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NOTICE OF PUBLIC MEETING – PHARMACY AND THERAPEUTICS COMMITTEE

AGENDA

Date of Publication: August 28, 2018

Date and Time of Meeting: Thursday, September 27, 2018 at 1:00 PM

Name of Organization: The State of Nevada, Department of Health and Human Services (DHHS), Division of Health Care Financing and Policy (DHCFP)

Place of Meeting:
Springs Preserve
333 S. Valley View Blvd.
Las Vegas, Nevada 89107

Please check with staff to verify room location

There will not be a North Location for this meeting.

Webinar Registration: https://optum.webex.com/optum/onstage/g.php?MTID=ef960c11cad07d87baa20f41da6a911dd

OR

www.webex.com, select "Join," enter Meeting Number 645 588 030, your name and email and then select, "Join."

A Password should not be necessary, but if asked, enter "Medicaid1!"

OR

Audio Only: (763) 957-6300

Event Number: 645 588 030
Follow the instructions that appear on your screen to join the teleconference. Audio will also be broadcast over the internet (VoIP).

Reasonable efforts will be made to assist and accommodate physically challenged persons desiring to attend the meeting. Please call Wendy Montgomery at: (775) 684-3722 or email wmontgomery@dhcfp.nv.gov in advance, but no later than two working days prior to the meeting, so that arrangements may be conveniently made.

Items may be taken out of order.
Items may be combined for consideration by the public body.
Items may be pulled or removed from the agenda at any time.

Public comment is limited to five minutes per individual, organization or agency, but may be extended at the discretion of the Chairperson.

AGENDA

1. Call to Order and Roll Call

2. Public Comment

3. Administrative

a. **For Possible Action:** Review and Approve Meeting Minutes from June 28, 2018

b. Status Update by DHCFP

1. Public Comment

4. Proposed New Classes

a. Respiratory Agents – Long-acting/maintenance therapy

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

b. Respiratory Agents – Short-acting/rescue

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

5. Annual Review – Established Drug Classes Being Reviewed Due to the Release of New Drugs

a. Antihistamines – H1 blockers – Non-Sedating H1 Blockers

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

b. Biologic Response Modifiers – Immunomodulators – Targeted Immunomodulators

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

c. Cardiovascular Agents – Antihypertensive Agents – Beta-Blockers

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups

4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

d. Cardiovascular Agents – Antilipemics – HMG-CoA Reductase Inhibitors (Statins)

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

e. Hematological Agents – Erythropoiesis-Stimulating Agents

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

f. Neurological Agents – Alzheimer's Agents

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

g. Neurological Agents – Anti-Migraine Agents – Serotonin-Receptor Agonists

1. Public Comment

2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

h. Ophthalmic Agents – Ophthalmic Anti-infective/Anti-inflammatory Combinations

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

i. Otic Agents – Otic Anti-infectives – Otic Quinolones

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

6. Annual Review – Established Drug Classes

a. Anti-infective Agents – Antivirals – Anti-Herpetic Agents

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP

5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

b. Anti-infective Agents – Antivirals – Influenza Agents

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

c. Anti-infective Agents – Quinolones – Quinolones – 3rd Generation

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

d. Cardiovascular Agents – Antihypertensive Agents – Vasodilators – Oral

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

e. Dermatological Agents – Antipsoriatic Agents – Topical Vitamin D Analogs

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action

a. Approve Clinical/Therapeutic Equivalency of Agents in Class
b. Identify Exclusions/Exceptions for Certain Patient Groups

4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

f. Dermatological Agents – Topical Anti-infectives – Topical Antifungals (onychomycosis)

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

g. Electrolytic and Renal Agents – Phosphate Binding Agents

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

h. Genitourinary Agents – Benign Prostatic Hyperplasia (BPH) Agents – 5-Alpha Reductase Inhibitors

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

i. Hematological Agents – Anticoagulants – Injectable

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

j. Hematological Agents – Anticoagulants – Oral

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

k. Hormones and Hormone Modifiers – Antidiabetic Agents – Alpha-Glucosidase Inhibitors/Amylin analogs/Misc.

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

l. Hormones and Hormone Modifiers – Antidiabetic Agents – Incretin Mimetics

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups

4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

m. Musculoskeletal Agents – Bone Resorption Inhibitors – Bisphosphonates

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

n. Musculoskeletal Agents – Bone Resorption Inhibitors – Nasal Calcitonins

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

o. Ophthalmic Agents – Ophthalmic Antihistamines

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

p. Ophthalmic Agents – Ophthalmic Anti-infectives – Ophthalmic Macrolides

1. Public Comment

2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

q. Ophthalmic Agents – Ophthalmics for Dry Eye Disease

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

7. Annual Review – Drug Classes Without Proposed Changes

a. Public Comment
b. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP Without Changes
   1. Analgesics - Analgesic/Miscellaneous - Neuropathic Pain/Fibromyalgia Agents
   2. Analgesics - Analgesic/Miscellaneous - Tramadol and Related Drugs
   3. Analgesics - Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) - Oral
   4. Analgesics - Opiate Agonists
   5. Analgesics - Opiate Agonists - Abuse Deterrent
   6. Anti-infective Agents - Aminoglycosides - Inhaled Aminoglycosides
   7. Anti-infective Agents - Antivirals - Alpha Interferons
   8. Anti-infective Agents - Antivirals - Anti-Hepatitis Agents - Polymerase Inhibitors/Combination Products
   9. Anti-infective Agents - Antivirals - Anti-Hepatitis Agents - Ribavirins
   10. Anti-infective Agents - Cephalosporins - Second-Generation Cephalosporins
   11. Anti-infective Agents - Cephalosporins - Third-Generation Cephalosporins
   12. Anti-infective Agents - Macrolides
   13. Anti-infective Agents - Quinolones - Quinolones - 2nd Generation
   14. Autonomic Agents - Sympathomimetics - Self-Injectable Epinephrine
   15. Biologic Response Modifiers - Multiple Sclerosis Agents - Injectable
   16. Biologic Response Modifiers - Multiple Sclerosis Agents - Oral
   17. Biologic Response Modifiers - Multiple Sclerosis Agents - Specific Symptomatic Treatment

18. Cardiovascular Agents - Antihypertensive Agents - Angiotensin II Receptor Antagonists
19. Cardiovascular Agents - Antihypertensive Agents - Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors)
20. Cardiovascular Agents - Antihypertensive Agents - Calcium-Channel Blockers
21. Cardiovascular Agents - Antihypertensive Agents - Direct Renin Inhibitors
22. Cardiovascular Agents - Antihypertensive Agents - Vasodilators - Inhaled
23. Cardiovascular Agents - Antilipemics - Bile Acid Sequestrants
24. Cardiovascular Agents - Antilipemics - Cholesterol Absorption Inhibitors
25. Cardiovascular Agents - Antilipemics - Fibric Acid Derivatives
26. Cardiovascular Agents - Antilipemics - Niacin Agents
27. Cardiovascular Agents - Antilipemics - Omega-3 Fatty Acids
28. Dermatological Agents - Topical Anti-infectives - Acne Agents: Topical, Benzoyl Peroxide, Antibiotics and Combination Products
29. Dermatological Agents - Topical Anti-infectives - Impetigo Agents: Topical
30. Dermatological Agents - Topical Anti-infectives - Topical Antivirals
31. Dermatological Agents - Topical Anti-infectives - Topical Scabicides
32. Dermatological Agents - Topical Anti-inflammatory Agents - Immunomodulators: Topical
33. Dermatological Agents - Topical Antineoplastics - Topical Retinoids
34. Gastrointestinal Agents - Antiemetics - Miscellaneous
35. Gastrointestinal Agents - Antiemetics - Serotonin-receptor antagonists/Combo
36. Gastrointestinal Agents - Antiulcer Agents - H2 blockers
37. Gastrointestinal Agents - Antiulcer Agents - Proton Pump Inhibitors (PPIs)
38. Gastrointestinal Agents - Functional Gastrointestinal Disorder Drugs
39. Gastrointestinal Agents - Gastrointestinal Anti-inflammatory Agents
40. Gastrointestinal Agents - Gastrointestinal Enzymes
41. Genitourinary Agents - Benign Prostatic Hyperplasia (BPH) Agents - Alpha-Blockers
42. Genitourinary Agents - Bladder Antispasmodics
43. Hematological Agents - Platelet Inhibitors
44. Hormones and Hormone Modifiers - Androgens
45. Hormones and Hormone Modifiers - Antidiabetic Agents - Biguanides
46. Hormones and Hormone Modifiers - Antidiabetic Agents - Dipeptidyl Peptidase-4 Inhibitors
47. Hormones and Hormone Modifiers - Antidiabetic Agents - Insulins (Vials, Pens and Inhaled)
48. Hormones and Hormone Modifiers - Antidiabetic Agents - Meglitinides
49. Hormones and Hormone Modifiers - Antidiabetic Agents - Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors
50. Hormones and Hormone Modifiers - Antidiabetic Agents - Sulfonylureas
51. Hormones and Hormone Modifiers - Antidiabetic Agents - Thiazolidinediones
52. Hormones and Hormone Modifiers - Pituitary Hormones - Growth hormone modifiers
53. Hormones and Hormone Modifiers - Progestins for Cachexia
54. Musculoskeletal Agents - Antigout Agents
55. Musculoskeletal Agents - Restless Leg Syndrome Agents
56. Musculoskeletal Agents - Skeletal Muscle Relaxants

57. Neurological Agents - Anticonvulsants - Barbiturates
58. Neurological Agents - Anticonvulsants - Benzodiazepines
59. Neurological Agents - Anticonvulsants - Hydantoins
60. Neurological Agents - Antiparkinsonian Agents - Non-ergot Dopamine Agonists
61. Ophthalmic Agents - Antiglaucoma Agents - Carbonic Anhydrase Inhibitors/Beta-Blockers
62. Ophthalmic Agents - Antiglaucoma Agents - Ophthalmic Prostaglandins
63. Ophthalmic Agents - Ophthalmic Anti-infectives - Ophthalmic Quinolones
64. Ophthalmic Agents - Ophthalmic Anti-inflammatory Agents - Ophthalmic Corticosteroids
65. Ophthalmic Agents - Ophthalmic Anti-inflammatory Agents - Ophthalmic Nonsteroidal Anti-inflammatory Drugs (NSAIDs)
66. Psychotropic Agents - ADHD Agents
67. Psychotropic Agents - Antidepressants - Other
68. Psychotropic Agents - Antidepressants - Selective Serotonin Reuptake Inhibitors (SSRIs)
69. Psychotropic Agents - Antipsychotics - Atypical Antipsychotics - Oral
70. Psychotropic Agents - Anxiolytics, Sedatives, and Hypnotics
71. Psychotropic Agents - Psychostimulants - Narcolepsy Agents
72. Respiratory Agents - Nasal Antihistamines
73. Respiratory Agents - Respiratory Anti-inflammatory Agents - Leukotriene Receptor Antagonists
74. Respiratory Agents - Respiratory Anti-inflammatory Agents - Nasal Corticosteroids
75. Respiratory Agents - Respiratory Anti-inflammatory Agents - Phosphodiesterase Type 4 Inhibitors
76. Toxicology Agents - Antidotes - Opiate Antagonists
77. Toxicology Agents - Substance Abuse Agents - Mixed Opioid Agonists/Antagonists

c. **For Possible Action**: Committee Discussion and Approval of the Drug Classes without Changes

8. Report by OptumRx on New Drugs to Market, New Generic Drugs to Market, and New Line Extensions

9. Closing Discussion

a. Public comments on any subject
b. Date and location of the next meeting
c. Adjournment

PLEASE NOTE: Items may be taken out of order at the discretion of the chairperson. Items may be combined for consideration by the public body. Items may be pulled or removed from the agenda at any time. If an action item is not completed within the time frame that has been allotted, that action item will be continued at a future time designated and announced at this meeting by the chairperson. All public comment may be limited to five minutes.

This notice and agenda have been posted at http://dhcfp.nv.gov/ and notice.nv.gov/.

Notice of this meeting and draft copies of the changes will be available on or after the date of this notice at the DHCFP Web site http://dhcfp.nv.gov/, Carson City Central office and Las Vegas DHCFP. The agenda posting of this meeting can be viewed at the following locations: Nevada State Library; Carson City Library; Churchill County Library; Las Vegas Library; Douglas County Library; Elko County Library; Lincoln County Library; Lyon County Library; Mineral County Library; Tonopah Public Library; Pershing County Library; Goldfield Public Library; Eureka Branch Library; Lander County Library; Storey County Library; Washoe County Library; and White Pine County Library and may be reviewed during normal business hours.

If requested in writing, a draft copy of the changes will be mailed to you. Requests and/or written comments on the proposed changes may be sent to the Wendy Montgomery at the Division of Health Care Financing and Policy, 1100 E. William Street, Suite 101, Carson City, NV 89701.

All persons that have requested in writing to receive the Public Hearings agenda have been duly notified by mail or e-mail.

We are pleased to make accommodations for members of the public who have disabilities and wish to attend the meeting. If special arrangements are necessary, notify the Division of Health Care Financing and Policy as soon as possible and at least ten days in advance of the meeting, by e-mail at: wmontgomery@dhcfp.nv.gov, in writing, at 1100 East William Street, Suite 101, Carson City, Nevada 89701 or call Wendy Montgomery at (775) 684-3722.

Preferred Products	PA Criteria	Non-Preferred Products
Analgesics		
Analgesic/Miscellaneous		
Neuropathic Pain/Fibromyalgia Agents		
DULOXETINE * GABAPENTIN LYRICA® * SAVELLA® * (Fibromyalgia only)	* PA required *No PA required for drugs in this class if ICD-10 - M79.1; M60.0-M60.9, M61.1.*	CYMBALTA® * GRALISE® LIDODERM® * HORIZANT®
Tramadol and Related Drugs		
TRAMADOL TRAMADOL/APAP		CONZIPR® NUCYNTA® RYZOLT® RYBIX® ODT TRAMADOL ER ULTRACET® ULTRAM® ULTRAM® ER
Opiate Agonists		
MORPHINE SULFATE SA TABS (ALL GENERIC EXTENDED RELEASE) QL FENTANYL PATCH QL BUTRANS®	**PA required for Fentanyl Patch** **General PA Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-59.pdf	AVINZA® QL BUPRENORPHINE PATCH DOLOPHINE® DURAGESIC® PATCHES QL EXALGO® KADIAN® QL METHADONE METHADOSE® MS CONTIN® QL NUCYNTA® ER OPANA ER® OXYCODONE SR QL OXYMORPHONE SR XARTEMIS XR® QL ZOHYDRO ER® QL
Opiate Agonists - Abuse Deterrent		
EMBEDA® HYSINGLA ER® MORPHABOND® (NEW)		ARYMO® ER (NEW) OXYCONTIN® QL XTAMPZA ER®

Preferred Products	PA Criteria	Non-Preferred Products
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) - Oral		
DICLOFENAC POTASSIUM DICLOFENAC TAB DR FLURBIPROFEN TAB IBUPROFEN SUSP IBUPROFEN TAB INDOMETHACIN CAP KETOROLAC TAB MELOXICAM TAB NABUMETONE TAB NAPROXEN SUSP NAPROXEN TAB NAPROXEN DR TAB PIROXICAM CAP SULINDAC TAB		CAMBIA ® POWDER CELECOXIB CAP DICLOFENAC SODIUM TAB ER DICLOFENAC W/ MISOPROSTOL TAB DUEXIS TAB ETODOLAC CAP ETODOLAC TAB ETODOLAC ER TAB INDOMETHACIN CAP ER KETOPROFEN CAP MEFENAM CAP MELOXICAM SUSP NAPRELAN TAB CR NAPROXEN TAB CR OXAPROZIN TAB TIVORBEX CAP VIMOVO TAB ZIPSOR CAP ZORVOLEX CAP
Antihistamines		
H1 blockers		
Non-Sedating H1 Blockers		
CETIRIZINE D OTC CETIRIZINE OTC LORATADINE D OTC LORATADINE OTC	A two week trial of one of these drugs is required before a non-preferred drug will be authorized.	ALLEGRA® CLARITIN® CLARINEX® DESLORATADINE FEXOFENADINE SEMPREX® XYZAL®
Anti-infective Agents		
Aminoglycosides		
Inhaled Aminoglycosides		
BETHKIS® KITABIS® PAK TOBI PODHALER® TOBRAMYCIN NEBULIZER		
Antivirals		
Alpha Interferons		
PEGASYS® PEGASYS® CONVENIENT PACK		

Preferred Products	PA Criteria	Non-Preferred Products
PEG-INTRON® and REDIPEN		
Anti-hepatitis Agents		
Polymerase Inhibitors/Combination Products		
EPCLUSA® HARVONI® MAVYRET® SOVALDI® ZEPATIER®	**PA required: (see below)** http://dhcfp.nv.gov/uploadedFiles/dhcfpnvgov/content/Resources/AdminSupport/Manuals/MSMCh1200Packet6-11-15(1).pdf https://www.medicaid.nv.gov/Downloads/provider/Pharmacy_Announcement_Viekira_2015-0721.pdf	DAKLINZA® OLYSIO® TECHNIVIE® VIEKIRA® PAK VOSEVI®
Ribavirins		
RIBAVIRIN		RIBASPHERE RIBAPAK® MODERIBA® REBETOL®
Anti-Herpetic Agents		
ACYCLOVIR FAMVIR® VALCYCLOVIR		
Influenza Agents		
AMANTADINE TAMIFLU® RIMANTADINE RELENZA®		OSELTAMIVIR CAP RAPIVAB
Cephalosporins		
Second-Generation Cephalosporins		
CEFACLOR CAPS and SUSP CEFACLOR ER CEFUROXIME TABS and SUSP CEFPROZIL SUSP		CEFTIN® CECLOR® CECLOR CD® CEFZIL
Third-Generation Cephalosporins		
CEFDINIR CAPS / SUSP CEFPODOXIME TABS and SUSP		CEDAX® CAPS and SUSP CEFDITOREN OMNICEF® SPECTRACEF® SUPRAX® VANTIN®
Macrolides		
AZITHROMYCIN TABS/SUSP		BIAXIN®

Preferred Products	PA Criteria	Non-Preferred Products
CLARITHROMYCIN TABS/SUSP ERYTHROMYCIN BASE ERYTHROMYCIN ESTOLATE ERYTHROMYCIN ETHYLSUCCINATE ERYTHROMYCIN STEARATE		DIFICID® ZITHROMAX® ZMAX®
Quinolones		
Quinolones - 2nd Generation		
CIPROFLOXACIN TABS CIPRO® SUSP		FLOXIN® OFLOXACIN
Quinolones - 3rd Generation		
AVELOX® AVELOX ABC PACK® LEVOFLOXACIN		LEVAQUIN® MOXIFLOXACIN BAXDELA®
Autonomic Agents		
Sympathomimetics		
Self-Injectable Epinephrine		
EPINEPHRINE AUTO INJ EPINEPHRINE®	* PA required	ADRENACLICK® QL AUVI-Q® *
Biologic Response Modifiers		
Immunomodulators		
Targeted Immunomodulators		
ACTEMRA® CIMZIA® COSENTYX® ENBREL® HUMIRA® INFLECTRA® KINERET® ORENCIA® OTEZLA® SIMPONI® XELJANZ®	Prior authorization is required for all drugs in this class https://www.medicaid.nv.gov/Downloads/provider/FA-61.pdf	DUPIXENT® ENTYVIO® ILARIS® KEVZARA® REMICADE® RENFLEXIS® SILIQ® STELARA® TALTZ® TREMFYA®
Multiple Sclerosis Agents		
Injectable		
AVONEX® AVONEX® ADMIN PACK BETASERON® COPAXONE® QL EXTAVIA® OCREVUS®	*Trial of only one agent is required before moving to a non-preferred agent*	GLATOPA® LEMTRADA® PLEGRIDY® ZINBRYTA®

	Preferred Products	PA Criteria	Non-Preferred Products
	REBIF® QL TYSABRI®		
Oral			
	AUBAGIO® GILENYA® TECFIDERA®		
Specific Symptomatic Treatment			
	AMPYRA® QL	PA required	
Cardiovascular Agents			
Antihypertensive Agents			
Angiotensin II Receptor Antagonists			
	DIOVAN® DIOVAN HCTZ® LOSARTAN LOSARTAN HCTZ		ATACAND® AVAPRO® BENICAR® CANDESARTAN COZAAR® EDARBI® EDARBYCLOR® EPROSARTAN HYZAAR® IRBESARTAN MICARDIS® TELMISARTAN TEVETEN® VALSARTAN
Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors)			
	BENAZEPRIL BENAZEPRIL HCTZ CAPTOPRIL CAPTOPRIL HCTZ ENALAPRIL ENALAPRIL HCTZ EPANED® £ LISINOPRIL LISINOPRIL HCTZ RAMIPRIL	£ PREFERRED FOR AGES 10 AND UNDER ǂ NONPREFERRED FOR OVER 10 YEARS OLD	ACCURETIC® EPANED® ǂ FOSINOPRIL MAVIK® MOEXIPRIL QUINAPRIL QUINARETIC® QBRELIS® TRANDOLAPRIL UNIVASC®
Beta-Blockers			
	ACEBUTOLOL ATENOLOL ATENOLOL/CHLORTH BETAXOLOL BISOPROLOL BISOPROLOL/HCTZ BYSTOLIC®*	*Restricted to ICD-10 codes J40-J48	SOTYLIZE®

Preferred Products	PA Criteria	Non-Preferred Products
CARVEDILOL LABETALOL METOPROLOL (Reg Release) NADOLOL PINDOLOL PROPRANOLOL PROPRANOLOL/HCTZ SOTALOL TIMOLOL		
Calcium-Channel Blockers		
AFEDITAB CR® AMLODIPINE CARTIA XT® DILTIA XT® DILTIAZEM ER DILTIAZEM HCL DYNACIRC CR® EXFORGE® EXFORGE HCT® FELODIPINE ER ISRADIPINE LOTREL® NICARDIPINE NIFEDIAC CC NIFEDICAL XL NIFEDIPINE ER NISOLDIPINE ER TAZTIA XT® VERAPAMIL VERAPAMIL ER		
Vasodilators		
Inhaled		
VENTAVIS® TYVASO®		
Oral		
ORENITRAM® SILDENAFIL TRACLEER®		ADCIRCA® ADEMPAS® LETAIRIS® OPSUMIT® REVATIO ® UPTRAVI®
Antilipemics		
Bile Acid Sequestrants		
COLESTIPOL		QUESTRAN®

Preferred Products	PA Criteria	Non-Preferred Products
CHOLESTYRAMINE WELCHOL®		
Cholesterol Absorption Inhibitors		
ZETIA®		EZETIMIBE
Fibric Acid Derivatives		
FENOFIBRATE FENOFIBRIC GEMFIBROZIL		ANTARA® FENOGLIDE® FIBRICOR® LIPOFEN® LOFIBRA® TRICOR® TRIGLIDE® TRILIPIX®
HMG-CoA Reductase Inhibitors (Statins)		
ATORVASTATIN CRESTOR® QL FLUVASTATIN LOVASTATIN PRAVASTATIN SIMVASTATIN		ADVICOR® ALTOPREV® AMLODIPINE/ATORVASTATIN CADUET® EZETIMIBE-SIMVASTATIN LESCOL® LESCOL XL® LIPITOR® LIPTRUZET® LIVALO® MEVACOR® PRAVACHOL® ROSUVASTATIN SIMCOR® VYTORIN® ZOCOR®
Niacin Agents		
NIASPAN® (Brand only) NIACIN ER (ALL GENERICS)		NIACOR®
Omega-3 Fatty Acids		
LOVAZA® VASCEPA®		OMEGA-3-ACID OMTRYG®
Dermatological Agents		
Antipsoriatic Agents		
Topical Vitamin D Analogs		
SORILUX® (FOAM) TACLONEX® VECTICAL® (OINT)		CALCITENE® CALCIPOTRIENE CALCIPOTRIENE OINT/BETAMETHAZONE

Preferred Products	PA Criteria	Non-Preferred Products
		DOVONEX® CREAM ENSTILAR ® (AER)
Topical Analgesics		
CAPSAICIN FLECTOR® LIDOCAINE LIDOCAINE HC LIDOCAINE VISCOUS LIDOCAINE/PRILOCAINE PENNSAID® VOLTAREN® GEL		DICLOFENAC (gel/sol) EMLA® LIDODERM® QL LIDAMANTLE®
Topical Anti-infectives		
Acne Agents: Topical, Benzoyl Peroxide, Antibiotics and Combination Products		
ACANYA® AZELEX® 20% cream BENZACLIN® BENZOYL PEROXIDE (2.5, 5 and 10% only) CLINDAMYCIN ONEXTON GEL®	PA required if over 21 years old	ACZONE GEL® BENZOYL PER AEROSOL CLINDAMYCIN AEROSOL CLINDAMYCIN/BENZOYL PEROXIDE GEL DUAC CS® ERYTHROMYCIN ERYTHROMYCIN/BENZOYL PEROXIDE SODIUM SODIUM SULFACETAMIDE/SULFUR SULFACETAMIDE
Impetigo Agents: Topical		
MUPIROCIN OINT		ALTABAX® CENTANY® MUPIROCIN CREAM
Topical Antifungals (onychomycosis)		
CICLOPIROX SOLN TERBINAFINE TABS	PA required	JUBLIA® KERYDIN® PENLAC® ITRACONAZOLE
Topical Antivirals		
ABREVA® XERESE® CREAM ZOVIRAX®, OINTMENT		ACYCLOVIR OINT DENAVIR®
Topical Scabicides		
NIX® PERMETHRIN	* PA required	EURAX® LINDANE

Preferred Products	PA Criteria	Non-Preferred Products
RID® SKLICE® ULESFIA®		MALATHION NATROBA® * OVIDE® SPINOSAD
Topical Anti-inflammatory Agents		
Immunomodulators: Topical		
ELIDEL® QL EUCRISA® PROTOPIC® QL	Prior authorization is required for all drugs in this class	TACROLIMUS
Topical Antineoplastics		
Topical Retinoids		
RETIN-A MICRO®(Pump and Tube) TAZORAC® ZIANA®	Payable only for recipients up to age 21.	ADAPALENE GEL AND CREAM ATRALIN® AVITA® DIFFERIN® EPIDUO® TRETINOIN TRETIN-X® VELTIN®
Electrolytic and Renal Agents		
Phosphate Binding Agents		
CALCIUM ACETATE ELIPHOS® RENAGEL® RENVELA®		AURYXIA ® FOSRENOL® PHOSLO® PHOSLYRA® SEVELAMER CARBONATE VELPHORO®
Gastrointestinal Agents		
Antiemetics		
Miscellaneous		
Diclegis® OTC Doxylamine 25mg/Pyridoxine 10mg		BONJESTA® (NEW)
Serotonin-receptor antagonists/Combo		
GRANISETRON QL ONDANSETRON QL	PA required for all medication in this class	AKYNZEO® ANZEMET® QL KYTRIL® QL SANCUSO® ZOFRAN® QL ZUPLENZ® QL
Antiulcer Agents		
H2 blockers		
FAMOTIDINE RANITIDINE	*PA not required for < 12 years	

Preferred Products	PA Criteria	Non-Preferred Products
RANITIDINE SYRUP*		
Proton Pump Inhibitors (PPIs)		
NEXIUM® CAPSULES NEXIUM® POWDER FOR SUSP* PANTOPRAZOLE	PA required if exceeding 1 per day *for children ≤ 12 yrs.	ACIPHEX® DEXILANT® ESOMEPRAZOLE LANSOPRAZOLE OMEPRAZOLE OTC TABS PREVACID® PRILOSEC® PRILOSEC® OTC TABS PROTONIX®
Functional Gastrointestinal Disorder Drugs		
AMITIZA® * LINZESS®	* PA required for Opioid Induced Constipation	MOVANTIK® * RELISTOR® * SYMPROIC® TRULANCE®
Gastrointestinal Anti-inflammatory Agents		
APRISO® ASACOL HD® ASACOL®SUPP BALSALAZIDE® CANASA® DELZICOL® LIALDA ® MESALAMINE ENEMA SUSP PENTASA® SULFASALAZINE DR SULFASALAZINE IR		COLAZAL® GIAZO® MESALAMINE (GEN LIALDA) MESALAMINE (GEN ASACOL HD)
Gastrointestinal Enzymes		
CREON® ZENPEP®		PANCREAZE® PANCRELIPASE PERTZYE® ULTRESA® VIOKACE®
Genitourinary Agents		
Benign Prostatic Hyperplasia (BPH) Agents		
5-Alpha Reductase Inhibitors		
AVODART® FINASTERIDE		DUTASTERIDE/TAMSULOSIN JALYN® PROSCAR®
Alpha-Blockers		
DOXAZOSIN		ALFUZOSIN

Preferred Products	PA Criteria	Non-Preferred Products
TAMSULOSIN TERAZOSIN		CARDURA® FLOMAX® MINIPRESS® PRAZOSIN RAPAFLO® UROXATRAL®
Bladder Antispasmodics		
BETHANECHOL OXYBUTYNIN TABS/SYRUP/ER TOVIAZ® VESICARE®		DETROL® DETROL LA® DITROPAN XL® ENABLEX® FLAVOXATE GELNIQUE® MYRBETRIQ® OXYTROL® SANCTURA® TOLTERODINE TROSPIUM
Hematological Agents		
Anticoagulants		
Oral		
COUMADIN® ELIQUIS® * JANTOVEN® PRADAXA® * QL SAVAYSA®* WARFARIN XARELTO ® *	* No PA required if approved diagnosis code transmitted on claim	BEVYXXA®
Injectable		
ARIXTRA® ENOXAPARIN FRAGMIN®		FONDAPARINUX INNOHEP® LOVENOX®
Erythropoiesis Stimulating Agents		
ARANESP® QL PROCRIT® QL	PA required Quantity Limit	EPOGEN® QL OMONTYS® QL
Platelet Inhibitors		
AGGRENOX® ANAGRELIDE ASPIRIN BRILINTA® * QL CILOSTAZOL® CLOPIDOGREL DIPYRIDAMOLE	* PA required	ASPIRIN/DIPYRIDAMOLE DURLAZA® EFFIENT® * QL PLAVIX® PRASUGREL ZONTIVITY® YOSPRALA®

Preferred Products	PA Criteria	Non-Preferred Products
Hormones and Hormone Modifiers		
Androgens		
ANDROGEL® ANDRODERM®	**PA required** **PA Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-72.pdf	AXIRON® FORTESTA® NATESTO® STRIANT® TESTIM® TESTOSTERONE GEL VOGELXO®
Antidiabetic Agents		
Alpha-Glucosidase Inhibitors/Amylin analogs/Misc.		
ACARBOSE (Precose®) GLYSET® PRECOSE® SYMLIN® (PA required)		CYCLOSET®
Biguanides		
FORTAMET® GLUCOPHAGE® GLUCOPHAGE XR® METFORMIN EXT-REL (Glucophage XR®) GLUMETZA® METFORMIN (Glucophage®) RIOMET®		METFORMIN (GEN GLUMETZA)
Dipeptidyl Peptidase-4 Inhibitors		
JANUMET® JANUMET XR® JANUVIA® JENTADUETO® KOMBIGLYZE XR® ONGLYZA® TRADJENTA®		ALOGLIPTIN ALOGLIPTIN-METFORMIN ALOGLIPTIN-PIOGLITAZONE KAZANO® NESINA® OSENI®
Incretin Mimetics		
BYDUREON® * BYETTA® * OZEMPIC® (NEW) TANZEUM® TRULICITY® VICTOZA® *	* PA required	ADLYXIN® SOLIQUA® XULTOPHY®
Insulins (Vials, Pens and Inhaled)		
APIDRA®		ADMELOG® (NEW)

Preferred Products	PA Criteria	Non-Preferred Products
HUMALOG® HUMULIN® LANTUS® LEVEMIR ® NOVOLIN® NOVOLOG® TRESIBA FLEX INJ		AFREZZA® BASAGLAR® FIASP® (NEW) HUMALOG® U-200 TOUJEO SOLO® 300 IU/ML
Meglitinides		
NATEGLINIDE (Starlix®) PRANDIMET® PRANDIN® STARLIX®		
Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors		
FARXIGA® INVOKANA® JARDIANCE®		GLYXAMBI® INVOKAMET® INVOKAMET® XR QTERN® (NEW) SEGLUROMET® (NEW) STEGLATRO® (NEW) STEGLUJAN™ (NEW) SYNJARDY® SYNJARDY® XR XIGDUO XR®
Sulfonylureas		
AMARYL® CHLORPROPAMIDE DIABETA® GLIMEPIRIDE (Amaryl®) GLIPIZIDE (Glucotrol®) GLUCOTROL® GLUCOVANCE® GLIPIZIDE EXT-REL (Glucotrol XL®) GLIPIZIDE/METFORMIN (Metaglip®) GLYBURIDE MICRONIZED (Glynase®) GLYBURIDE/METFORMIN (Glucovance®) GLUCOTROL XL® GLYBURIDE (Diabeta®) GLYNASE® METAGLIP® TOLAZAMIDE		

Preferred Products	PA Criteria	Non-Preferred Products
TOLBUTAMIDE		
Thiazolidinediones		
ACTOPLUS MET XR® ACTOS® ACTOPLUS MET® AVANDAMET® AVANDARYL® AVANDIA® DUETACT®		
Pituitary Hormones		
Growth hormone modifiers		
GENOTROPIN® NORDITROPIN®	**PA required for entire class** https://www.medicaid.nv.gov/Downloads/provider/FA-67.pdf	HUMATROPE® NUTROPIN AQ® OMNITROPE® NUTROPIN® SAIZEN® SEROSTIM® SOMAVERT® TEV-TROPIN® ZORBTIVE®
Progestins for Cachexia		
MEGESTROL ACETATE, SUSP		MEGACE ES®
Monoclonal Antibodies for the treatment of Respiratory Conditions (NEW)		
NUCALA® (NEW) XOLAIR® (NEW)		CINQAIR® (NEW) FASENRA® (NEW)
Musculoskeletal Agents		
Antigout Agents		
ALLOPURINOL COLCHICINE TAB/CAP PROBENECID PROBENECID/COLCHICINE ULORIC®		COLCRYS® TAB MITIGARE® CAP ZURAMPIC® ZYLOPRIM®
Bone Resorption Inhibitors		
Bisphosphonates		
ALENDRONATE TABS FOSAMAX PLUS D®		ACTONEL® ALENDRONATE SOLUTION ATELVIA® BINOSTO® BONIVA® DIDRONEL® ETIDRONATE IBANDRONATE SKELID®

Preferred Products	PA Criteria	Non-Preferred Products
Nasal Calcitonins		
MIACALCIN®		FORTICAL® CALCITONIN-SALMON
Restless Leg Syndrome Agents		
PRAMIPEXOLE REQUIP XL ROPINIROLE		HORIZANT® MIRAPEX® MIRAPEX® ER REQUIP
Skeletal Muscle Relaxants		
BACLOFEN CHLORZOXAZONE CYCLOBENZAPRINE DANTROLENE METHOCARBAMOL METHOCARBAMOL/ASPIRIN ORPHENADRINE CITRATE ORPHENADRINE COMPOUND TIZANIDINE		
Neurological Agents		
Alzheimers Agents		
DONEPEZIL DONEPEZIL ODT EXELON® PATCH EXELON® SOLN MEMANTINE NAMENDA® XR TABS RIVASTIGMINE CAPS		ARICEPT® 23mg ARICEPT® GALANTAMINE GALANTAMINE ER NAMENDA® TABS NAMZARIC® RAZADYNE® RAZADYNE® ER
Anticonvulsants		
BANZEL® BRIVIACT® CARBAMAZEPINE CARBAMAZEPINE XR CARBATROL ER® CELONTIN® DEPAKENE® DEPAKOTE ER® DEPAKOTE® DIVALPROEX SODIUM DIVALPROEX SODIUM ER EPITOL® ETHOSUXIMIDE FELBATOL®	PA required for members under 18 years old	APTIOM® OXTELLAR XR® POTIGA® QUDEXY XR® TROKENDI XR® SPRITAM®

Preferred Products	PA Criteria	Non-Preferred Products
FYCOMPA® GABAPENTIN GABITRIL® KEPPRA® KEPPRA XR® LAMACTAL ODT® LAMACTAL XR® LAMICTAL® LAMOTRIGINE LEVETIRACETAM LYRICA® NEURONTIN® OXCARBAZEPINE SABRIL® STAVZOR® DR TEGRETOL® TEGRETOL XR® TOPAMAX® TOPIRAGEN® TOPIRAMATE (IR AND ER) TRILEPTAL® VALPROATE ACID VIMPAT® ZARONTIN® ZONEGRAN® ZONISAMIDE		
Barbiturates		
LUMINAL® MEBARAL® MEPHOBARBITAL SOLFOTON® PHENOBARBITAL MYSOLINE® PRIMIDONE	PA required for members under 18 years old	
Benzodiazepines		
CLONAZEPAM CLORAZEPATE DIASTAT® DIAZEPAM DIAZEPAM rectal soln KLONOPIN® TRANXENE T-TAB® VALIUM®	PA required for members under 18 years old	ONFI®

Preferred Products	PA Criteria	Non-Preferred Products
Hydantoins		
CEREBYX® DILANTIN® ETHOTOIN FOSPHENYTOIN PEGANONE® PHENYTEK® PHENYTOIN PRODUCTS	PA required for members under 18 years old	
Anti-Migraine Agents		
Serotonin-Receptor Agonists		
RELPAX® RIZATRIPTAN ODT SUMATRIPTAN NASAL SPRAY SUMATRIPTAN INJECTION SUMATRIPTAN TABLET	PA required for exceeding Quantity Limit	AMERGE® AXERT® FROVA® ELETRIPTAN IMITREX® MAXALT® TABS MAXALT® MLT NARATRIPTAN SUMAVEL® TREXIMET® ZECUITY® TRANSDERMAL ZOMIG® ZOMIG® ZMT
Antiparkinsonian Agents		
Non-ergot Dopamine Agonists		
PRAMIPEXOLE ROPINIROLE ROPINIROLE ER		MIRAPEX® MIRAPEX® ER NEUPRO® REQUIP® REQUIP XL®
Ophthalmic Agents		
Antiglaucoma Agents		
ALPHAGAN P® AZOPT® BETAXOLOL BETOPTIC S® BRIMONIDINE CARTEOLOL COMBIGAN® DORZOLAM DORZOLAM / TIMOLOL LATANOPROST LEVOBUNOLOL		ALPHAGAN® BETAGAN® BETOPTIC ® BIMATOPROST (NEW) COSOPT PF® COSOPT® OCUPRESS® OPTIPRANOLOL® TIMOPTIC XE® TIMOPTIC® TRAVOPROST

Preferred Products	PA Criteria	Non-Preferred Products
LUMIGAN® METIPRANOLOL RHOPRESSA® (NEW) SIMBRINZA® TIMOLOL DROPS/ GEL SOLN TRAVATAN Z® TRAVATAN®		TRUSOPT® VYZULTA® (NEW) XALATAN® ZIOPTAN®
Ophthalmic Antihistamines		
ALAWAY® BEPREVE® KETOTIFEN PAZEO® ZADITOR OTC®		AZELASTINE ALOMIDE ALOCRIL ELESTAT® EMADINE® EPINASTINE LASTACRAFT® OLOPATADINE (drop/sol) OPTIVAR® PATADAY® PATANOL®
Ophthalmic Anti infectives		
Ophthalmic Macrolides		
ERYTHROMYCIN OINTMENT		
Ophthalmic Quinolones		
BESIVANCE® CIPROFLOXACIN LEVOFLOXACIN MOXEZA® VIGAMOX®		CILOXAN® MOXIFLOXACIN OFLOXACIN® ZYMAXID®
Ophthalmic Anti infective/Anti-inflammatory Combinations		
NEO/POLY/DEX PRED-G SULF/PRED NA SOL OP TOBRADEX OIN TOBRADEX SUS ZYLET SUS		BLEPHAMIDE MAXITROL NEO/POLY/BAC OIN /HC NEO/POLY/HC SUS OP TOBRA/DEXAME SUS TOBRADEX SUS TOBRADEX ST SUS
Ophthalmic Anti inflammatory Agents		
Ophthalmic Corticosteroids		
ALREX® DEXAMETHASONE DUREZOL® FLUOROMETHOLONE		FLAREX® FML® FML FORTE® MAXIDEX®

Preferred Products	PA Criteria	Non-Preferred Products
LOTEMAX® PREDNISOLONE		OMNIPRED® PRED FORTE® PRED MILD® VEXOL®
Ophthalmic Nonsteroidal Anti-inflammatory Drugs (NSAIDs)		
DICLOFENAC FLURBIPROFEN ILEVRO® KETOROLAC NEVANAC®		ACULAR® ACULAR LS® ACUVAIL® BROMDAY® BROMFENAC® PROLENSA®
Ophthalmics for Dry Eye Disease		
RESTASIS®		XIIDRA®
Otic Agents		
Otic Anti-infectives		
Otic Quinolones		
CIPRODEX® CIPRO HC® OTIC SUSP OFLOXACIN		CIPROFLOXACIN SOL 0.2% CETRAXAL® OTOVEL® SOLN
Psychotropic Agents		
ADHD Agents		
ADDERALL XR® ADZENYS® AMPHETAMINE SALT COMBO IR DEXMETHYLPHENIDATE DEXTROAMPHETAMINE SA TAB DEXTROAMPHETAMINE TAB DEXTROSTAT® DYANAVEL® FOCALIN XR® GUANFACINE ER METADATE CD® METHYLIN® METHYLIN ER® METHYLPHENIDATE METHYLPHENIDATE ER (All forms generic extended release) METHYLPHENIDATE SOL PROCENTRA®	**PA required for entire class** **Children's Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-69.pdf **Adult Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-68.pdf	ADDERALL® AMPHETAMINE SALT COMBO XR APTENSIO XR® ATOMOXETINE CONCERTA® COTEMPLA XR®-ODT DAYTRANA® DESOXYN® DEXEDRINE® DEXTROAMPHETAMINE SOLUTION EVEKEO® FOCALIN® INTUNIV® KAPVAY® METADATE ER® MYDAYIS® RITALIN® ZENZEDI®

Preferred Products	PA Criteria	Non-Preferred Products
QUILLICHEW® QUILLIVANT® XR SUSP RITALIN LA® STRATTERA® VYVANSE®		
Antidepressants		
Other		
BUPROPION BUPROPION SR BUPROPION XL DULOXETINE * MIRTAZAPINE MIRTAZAPINE RAPID TABS PRISTIQ® TRAZODONE VENLAFAXINE (ALL FORMS)	PA required for members under 18 years old * PA required *No PA required if ICD-10 - M79.1; M60.0-M60.9, M61.1.*	APLENZIN® BRINTELLIX® CYMBALTA® * DESVENLAFAXINE FUMARATE EFFEXOR® (ALL FORMS) FETZIMA® FORFIVO XL® KHEDEZLA® VIIBRYD® WELLBUTRIN®
Selective Serotonin Reuptake Inhibitors (SSRIs)		
CITALOPRAM ESCITALOPRAM FLUOXETINE PAROXETINE PEXEVA® SERTRALINE	PA required for members under 18 years old	CELEXA® FLUVOXAMINE QL LEXAPRO® LUVOX® PAXIL® PROZAC® SARAFEM® ZOLOFT®
Antipsychotics		
Atypical Antipsychotics - Oral		
ARIPIPRAZOLE CLOZAPINE FANAPT® LATUDA® NUPLAZID®* OLANZAPINE QUETIAPINE QUETIAPINE XR REXULTI® RISPERIDONE SAPHRIS®	**PA required for Ages under 18 years old** **PA Forms:** https://www.medicaid.nv.gov/Downloads/provider/FA-70A.pdf (ages 0-5)	ABILIFY® CLOZARIL® FAZACLO® GEODON® INVEGA® PALIPERIDONE RISPERDAL®

Preferred Products	PA Criteria	Non-Preferred Products
	https://www.medicaid.nv.gov/Downloads/provider/FA-70B.pdf (ages 6-18)	SEROQUEL®
VRAYLAR®		SEROQUEL XR®
ZIPRASIDONE	*(No PA required Parkinson's related psychosis ICD code on claim)	ZYPREXA®
Anxiolytics, Sedatives, and Hypnotics		
ESTAZOLAM FLURAZEPAM ROZEREM® TEMAZEPAM TRIAZOLAM ZALEPLON ZOLPIDEM	No PA required if approved diagnosis code transmitted on claim (All agents in this class)	AMBIEN® AMBIEN CR® BELSOMRA® DORAL® ESZOPICLONE EDLUAR® HETLIOZ® INTERMEZZO® LUNESTA® SILENOR® SOMNOTE® SONATA® ZOLPIDEM CR ZOLPIMIST®
	PA required for members under 18 years old	
Psychostimulants		
Narcolepsy Agents		
Provigil® *	* (No PA required for ICD-10 code G47.4)	MODAFINIL NUVIGIL® XYREM®
Respiratory Agents		
Nasal Antihistamines		
DYMISTA® PATANASE®		ASTEPRO® AZELASTINE OLOPATADINE
Respiratory Anti-inflammatory Agents		
Leukotriene Receptor Antagonists		
MONTELUKAST ZAFIRLUKAST ZYFLO® ZYFLO CR®		ACCOLATE® SINGULAIR® ZILEUTON ER
Respiratory Corticosteroids		
ARNUITY ELLIPTA® ASMANEX® FLOVENT DISKUS® QL FLOVENT HFA® QL PULMICORT FLEXHALER® PULMICORT RESPULES®*	*No PA required if < 4 years old	ALVESCO® AEROSPAN HFA® ARMONAIR® BUDESONIDE NEBS* QVAR® REDIHALER™ (NEW)

Preferred Products	PA Criteria	Non-Preferred Products
QVAR®		
Nasal Corticosteroids		
FLUTICASONE TRIAMCINOLONE ACETONIDE (NEW)		BECONASE AQ® FLONASE® FLUNISOLIDE NASACORT AQ® NASONEX® (NEW) OMNARIS® QNASL® RHINOCORT AQUA® VERAMYST® XHANCE™ (NEW) ZETONNA®
Phosphodiesterase Type 4 Inhibitors		
DALIRESP® QL	PA required	
Respiratory Antimuscarinics		
ATROVENT® COMBIVENT RESPIMAT® IPRATROPIUM/ALBUTEROL NEBS QL IPRATROPIUM NEBS SPIRIVA®	Only one agent per 30 days is allowed	INCRUSE ELLIPTA ® SEEBRI NEOHALER® SPIRIVA RESPIMAT® TRELEGY ELLIPTA® (NEW) TUDORZA®
Respiratory Beta-Agonists		
Long-Acting Respiratory Beta-Agonist		
FORADIL® SEREVENT DISKUS® QL STRIVERDI RESPIMAT®		ARCAPTA NEOHALER® BROVANA® PERFOROMIST NEBULIZER®
Short-Acting Respiratory Beta-Agonist		
ALBUTEROL NEB/SOLN LEVALBUTEROL* NEBS PROVENTIL® HFA XOPENEX® HFA* QL	* PA required	LEVALBUTEROL* HFA PROAIR® HFA PROAIR RESPICLICK® VENTOLIN HFA® XOPENEX® Solution* QL
Respiratory Corticosteriod/Long-Acting Beta-Agonist Combinations		
ADVAIR DISKUS® ADVAIR HFA® DULERA® SYMBICORT®		AIRDUO® BREO ELLIPTA® FLUTICASONE PROPIONATE/SALMETEROL
Respiratory Long-Acting Antimuscarinic/Long-Acting Beta-Agonist Combinations		
ANORO ELLIPTA® BEVESPI® STIOLTO RESPIMAT®		UTIBRON NEOHALER ®

	Preferred Products	PA Criteria	Non-Preferred Products
Toxicology Agents			
Antidotes			
Opiate Antagonists			
	EVZIO ® NALOXONE NARCAN® NASAL SPRAY		
Substance Abuse Agents			
Mixed Opiate Agonists/Antagonists			
	BUNAVAIL® SUBOXONE® ZUBSOLV®	PA required for class	BUPRENORPHINE / NALOXONE

2. Standard Preferred Drug List Exception Criteria
Drugs that have a “non-preferred” status are a covered benefit for recipients if they meet the coverage criteria.
a. Coverage and Limitations
1. Allergy to all preferred medications within the same class;
2. Contraindication to or drug-to-drug interaction with all preferred medications within the same class;
3. History of unacceptable/toxic side effects to all preferred medications within the same class;
4. Therapeutic failure of two preferred medications within the same class.
5. If there are not two preferred medications within the same class therapeutic failure only needs to occur on the one preferred medication;
6. An indication which is unique to a non-preferred agent and is supported by peer-reviewed literature or a FDA-approved indication;
7. Antidepressant Medication – Continuity of Care.
Recipients discharged from acute mental health facilities on a nonpreferred antidepressant will be allowed to continue on that drug for up to 90 days following discharge. After 90 days, the recipient must meet one of the above five (5) PDL Exception Criteria; or
8. For atypical or typical antipsychotic, anticonvulsant and antidiabetic medications the recipient demonstrated therapeutic failure on one preferred agent.
b. Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms/aspx.

NRS 422.4025 List of preferred prescription drugs used for Medicaid program; list of drugs excluded from restrictions; role of Pharmacy and Therapeutics Committee; availability of new pharmaceutical products and products for which there is new evidence. [Effective through June 30, 2015.]

1. The Department shall, by regulation, develop a list of preferred prescription drugs to be used for the Medicaid program.

2. The Department shall, by regulation, establish a list of prescription drugs which must be excluded from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs established pursuant to subsection 1. The list established pursuant to this subsection must include, without limitation:

(a) Prescription drugs that are prescribed for the treatment of the human immunodeficiency virus or acquired immunodeficiency syndrome, including, without limitation, protease inhibitors and antiretroviral medications;

(b) Antirejection medications for organ transplants;

(c) Antihemophilic medications; and

(d) Any prescription drug which the Committee identifies as appropriate for exclusion from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs.

3. The regulations must provide that the Committee makes the final determination of:

(a) Whether a class of therapeutic prescription drugs is included on the list of preferred prescription drugs and is excluded from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs;

(b) Which therapeutically equivalent prescription drugs will be reviewed for inclusion on the list of preferred prescription drugs and for exclusion from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs;

(c) Which prescription drugs should be excluded from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs based on continuity of care concerning a specific diagnosis, condition, class of therapeutic prescription drugs or medical specialty; and

(d) The criteria for prescribing an atypical or typical antipsychotic medication, anticonvulsant medication or antidiabetic medication that is not on the list of preferred drugs to a patient who experiences a therapeutic failure while taking a prescription drug that is on the list of preferred prescription drugs.

4. Except as otherwise provided in this subsection, the list of preferred prescription drugs established pursuant to subsection 1 must include, without limitation, every therapeutic prescription drug that is classified as an anticonvulsant medication or antidiabetic medication that was covered by the Medicaid program on June 30, 2010. If a therapeutic prescription drug that is included on the list of preferred prescription drugs pursuant to this subsection is prescribed for a clinical indication other than the indication for which it was approved as of June 30, 2010, the Committee shall review the new clinical indication for that drug pursuant to the provisions of subsection 5.

5. The regulations adopted pursuant to this section must provide that each new pharmaceutical product and each existing pharmaceutical product for which there is new clinical evidence supporting its inclusion on the list of preferred prescription drugs must be made available pursuant to the Medicaid program with prior authorization until the Committee reviews the product or the evidence.

6. The Medicaid program must make available without prior authorization atypical and typical antipsychotic medications that are prescribed for the treatment of a mental illness, anticonvulsant medications and antidiabetic medications for a patient who is receiving services pursuant to Medicaid if the patient:

(a) Was prescribed the prescription drug on or before June 30, 2010, and takes the prescription drug continuously, as prescribed, on and after that date;

(b) Maintains continuous eligibility for Medicaid; and

(c) Complies with all other requirements of this section and any regulations adopted pursuant thereto.

(Added to NRS by 2003, 1317; A 2010, 26th Special Session, 36; 2011, 985)

NRS 422.4025 List of preferred prescription drugs used for Medicaid program; list of drugs excluded from restrictions; role of Pharmacy and Therapeutics Committee; availability of new pharmaceutical products and products for which there is new evidence. [Effective July 1, 2015.]

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2. The Department shall, by regulation, establish a list of prescription drugs which must be excluded from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs established pursuant to subsection 1. The list established pursuant to this subsection must include, without limitation:

(a) Atypical and typical antipsychotic medications that are prescribed for the treatment of a mental illness of a patient who is receiving services pursuant to Medicaid;

(b) Prescription drugs that are prescribed for the treatment of the human immunodeficiency virus or acquired immunodeficiency syndrome, including, without limitation, protease inhibitors and antiretroviral medications;

(c) Anticonvulsant medications;

(d) Antirejection medications for organ transplants;

(e) Antidiabetic medications;

(f) Antihemophilic medications; and

(g) Any prescription drug which the Committee identifies as appropriate for exclusion from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs.

3. The regulations must provide that the Committee makes the final determination of:

(a) Whether a class of therapeutic prescription drugs is included on the list of preferred prescription drugs and is excluded from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs;

(b) Which therapeutically equivalent prescription drugs will be reviewed for inclusion on the list of preferred prescription drugs and for exclusion from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs; and

(c) Which prescription drugs should be excluded from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs based on continuity of care concerning a specific diagnosis, condition, class of therapeutic prescription drugs or medical specialty.

4. The regulations must provide that each new pharmaceutical product and each existing pharmaceutical product for which there is new clinical evidence supporting its inclusion on the list of preferred prescription drugs must be made available pursuant to the Medicaid program with prior authorization until the Committee reviews the product or the evidence.

(Added to NRS by 2003, 1317; A 2010, 26th Special Session, 36; 2011, 985, effective July 1, 2015)

Definition of "Therapeutic Alternative"

A "Therapeutic Alternative" is defined by the AMA as: "Drug products with different chemical structures but which are of the same pharmacological and/or therapeutic class and usually can be expected to have similar therapeutic effects and adverse reaction profiles when administered to patients in therapeutically equivalent doses."

BRIAN SANDOVAL
Governor

RICHARD WHITLEY, MS
Director

MARTA JENSEN
Administrator

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PHARMACY AND THERAPEUTICS COMMITTEE

Draft Meeting Minutes

Date and Time of Meeting: **Thursday, June 28, 2018 at 1:00 PM**

Name of Organization: **The State of Nevada, Department of Health and Human Services (DHHS), Division of Health Care Financing and Policy (DHCFP)**

Place of Meeting:

North Nevada Location:
Division of Public & Behavioral Health
4150 Technology Way, Room 303
Carson City, NV 89706

South Nevada Location:
Springs Preserve
333 S Valley View Blvd
Las Vegas, NV 89107

Attendees

Board Members (Present Las Vegas)
Shamim Nagy, MD, Chair
Mark Decerbo, Pharm.D.
Adam Zold, Pharm.D.
Evelyn Chu, Pharm.D.
Sapandeep Khurana, MD

Board Members (Absent)
Michael Hautekeet, RPh
Joseph Adashek, MD
Chris Highley, DO

Board Members (Present Carson City)
Kate Ward, Pharm.D.

DHCFP (Las Vegas):
Holly Long, Social Services Program Specialist III
Gabe Lither, DAG

DHCFP (Carson City):
Jack Zenteno, DHCFP

DXC (Carson City):
Beth Slamowitz, Pharm.D.

OptumRx (Las Vegas):
Carl Jeffery, Pharm.D.
Kevin Whittington, RPh

Public (Las Vegas):
Nate Bailey, Pfizer
Danny McNatty, Janssen
William Crawford, DSI
Bryan Rodriguez, DSI
Michael Sans, Otsuka
Samantha Sweeney, Otsuka
Mike Stroud, Novo Nordisk
Pauline Whelan, Orexo
William Lam, Boehringer Ingelheim
Phil Walsh, Sunovian
Leon Ravin, DPBH
Alice Swett, Alexion
Mark Schwartz, GSK
Cynthia Albert, Merck,
Charissa Anne, J&J
Allen Quan, DSI
Keri Smith, VIIV
Christy Lemons, Orexo
Nana Numapay, BI
Todd Gavin, Indivior
Georgette C., Indivior

Public (Carson City):
Lea Cartwright, JK Belz
Paige Barnes, Crowley & Ferrato

Public (Teleconference):
Stephanie Ferrell, DXC
Bruce Smith, GSK
Melissa Wagenbrenner, Aerie
Gary Okano, BMS
Brad Fuller, Aerie

AGENDA

1. Call to Order and Roll Call

Meeting called to order at 1:00 PM.

Holly Long
Carl Jeffery
Kevin Whittington
Sapandeep Khurana
Adam Zold
Mark Decerbo
Gabe Lither
Evelyn Chu

Shamim Nagy
Beth Slamowitz
Kate Ward

2. Public Comment

3. Administrative

a. **For Possible Action**: Review and Approve Meeting Minutes from December 7, 2017

b. Status Update by DHCFP

Holly Long: The Nevada Medicaid Drug Use Review Board has voted to adopt prior authorization changes at the October 19 meeting with the public hearing on April 26, 2018. These changes include revised prior authorization criteria for Xolair for pediatric patients, new prior authorization criteria for Austedo, Brineura, Ingrezza, Emflaza and Xadago. The DUR Board also recommended new prior authorization criteria for codeine and Tramadol for pediatric patients. For provider type 33, which is durable medical equipment, they added a HCPCS code with a zero rate, which will require prior authorization. This is effective for claims with a date of service on or after April 1, 2018. I have a list of the codes available if anyone is interested. All this information is also on the website on June 20, 2018. That concludes the update.

i. Public Comment (indiscernible speakers)

Shamim Nagy: Motion for approval of the meeting minutes. We need a motion of approval.
Evelyn Chu: I move to accept the minutes from the last meeting.
Adam Zold: Second
Motion approved.

4. Proposed New Drug Classes

a. Monoclonal Antibodies for the Treatment of Respiratory Conditions

No public comment.

Carl Jeffery: This is a new proposed class we have for the Board. It's kind of a confusing class because all of these need to be administered in the doctor's office so they're all have to be administered that way, but we're seeing a lot of claims coming through the pharmacy system so we thought we would introduce you, put these on the preferred drug list and have the benefits with having them listed on the preferred drug list. There's three medications currently in this class. We have these that the DUR Board added criteria so there's all clinical criteria on these but it's very limited to just what the labeled indication is. There's no crazy criteria on it. You'll see the Xolair is a little bit different. It's an IGE so it's binds up the IGE. The other one's kind of the same way. They're IL-5 modulated so they're a little bit different but they all have the same effect on reducing the antibodies that cause some of the reactive asthma disease. The comparative study, there's not a whole lot out there. There's a few that I looked at that compared the Nucala and the Xolair. Statistically not really different. There's a trend towards the benefit of the Nucala and in another review, with all of them, and they're all very effective for patients

that qualify to receive them, but there's really no huge difference between them. I broke down kind of the different indications. You can see Xolair has more indications. We're recommending Nucala be preferred anyway so this doesn't really apply as with other eosinophilic granulomatosis added on there, too. The other ones have similar indications. The dosing is on here. I don't know how familiar the Board is with these medications. I know it's something we see too much, but most of them are every 4 weeks. The newest one on the market here is the Fasenra. It's dosage is every 8 weeks after the first 3 doses so there's a slight advantage and then the Cinqair which I'll show you in a second, we don't have any utilization of that one as that one has to be infused over 15 minutes so we don't see that one in the pharmacy claims. So here's our first quarter 2018 utilization. We have 71 claims for the Xolair and then 10 claims for Nucala. Xolair has by far been out much longer than the other one so it kind of makes sense, the Cinqair, we may never see claims for this because those are the ones that IV infusion they may only be billed through the doctor's office so we may never see those but the Fasenra, I would expect to see a few claims once it gets more established in the marketplace. So, Optum makes the recommendation that this class be considered clinically and therapeutically equivalent.

A motion and second to accept as clinically and therapeutically equivalent. The board voted unanimously, the motion carries.

Carl Jeffery: Optum makes the recommendation since again it's a new class, we don't have any of these drugs that apparently are on the preferred drug list, but we would recommend the Nucala and Xolair be added to preferred and the Cinqair and Fasenra as non-preferred, and this just because the breadth of the indications and the current utilization trends, I think it kind of makes sense.

Mark Decerbo: Since the proposed PDL, is there any functional difference from Medicaid whether it's still preferred at home or a certain physician's office or is that not (indiscernible).

Carl Jeffery: My understanding is these aren't allowed to be administered at home. I think there's still a period of observation even after a dose that is needed so I think potentially they could be done through Home Health, but I think what we're mostly seeing is they're administered at the doctor's office.

Mark Decerbo: But unlike the IV product, there's a different mechanism or would fall under to be consider for PDL?

Carl Jeffery: There's a lot of different ways doctors' offices bill and so one they can just order the product in themselves and they'd have the stock on hand. I think what's happening with these and why we're seeing a utilization come through the pharmacy program is the doctors are ordering from the pharmacy, the pharmacy is filling it and billing it and then shipping it to the doctor's office for administration and I think that's where we're seeing the benefits of having the preferred drug list on here.

Kevin Whittington: We did see some Cinqair come through in 2017.

Motion to accept PDL as presented and second. The Board votes unanimously, the motion carries.

5. Established Drug Classes

a. Cardiovascular Agents - Antihypertensive Agents - Direct Renin Inhibitors

No public comment.

Carl Jeffery: Optum recommends that the Board remove this class of medications from the PDL. This is a class that's not frequently used. We're not seeing any benefit from having it on here. What removal does for this class is essentially just open up access. So potentially makes it all preferred because there's no restriction as when we have something in a class, it essentially makes it non-preferred. But what this will do is it makes everything where the rules don't apply anymore. Here's the utilization up here. We have a total of 4 claims over the quarter, so I think we've got one member is on the Tekturna still. They're pretty good about getting their prescription filled every 3 months and then there's one Tekturna HCT. So, there's really no utilization and we're not getting any benefit from having this class managed. I think we can skip the clinically and therapeutically equivalent portion of it and Optum recommends that this class of medication be removed from the PDL.

Open for discussion.

Mark Decerbo: I don't disagree with the recommendation, clinically these agents have not brought any benefit to the table. If I'm John Q Public and wondering what is preferred, is there any harm in leaving this as all preferred to give a reference of what is available. What is the difference between removing the class and leaving all the drugs as preferred?

Carl Jeffery: Well, yeah, there's really no advantage of it. The advantage of having it not listed is we don't have to manage it; it's not something we have to update and review every year, so it's something we have to come back and we have put this out as something that from the rebate perspective, we have to go back and talk to the manufacturer's about. So by not having it in the class, we can skip all of that and that work on our side, too.

Kate Ward: Can you please repeat the comment?

Carl Jeffery: Yeah, so Dr. Decerbo asked if there's any harm on just making all the products on here as preferred and just leaving the class on there versus deleting the whole class from the list.

Kate Ward: The question I had, those four members, will this impact them?

Carl Jeffery: They will remain on, so essentially what it does is make everything preferred.

Kate Ward: Ok, thank you.

Shamim Nagy: So these would be moved to a different class?

Carl Jeffery: No, this would be off the preferred. They wouldn't be listed at all. They would all be essentially listed as preferred because they're not restricted at all so Medicaid has an open formulary so everything that's not listed on the preferred drug list is open access as far as the preferred drug list goes. So anything that we add to the preferred drug list, those would be the only classes that we manage and so for example, there's a lot of oncology medications that are on the market. We don't manage that class on our preferred drug list. We don't have any non-preferred or preferred oncology medications because that's not a managed class. They're essentially all preferred because there's no restriction.

Shamim Nagy: Do we need a motion for this?

Kate Ward: So they won't be listed, so how will members be able to get them?

Carl Jeffery: The PDL policy would no longer apply to them. So for this specific class, we don't have any other restrictions like on any other kind of clinical edit around here so these would just be open access.

Shamim Nagy: I need a motion to delete this class and make it open.

Carl Jeffery: We're asking for a motion to delete this class.

Motion and second. Voting. Motion passed.

6. Established Drug Classes Being Reviewed Due to the Release of New Drugs

a. Analgesics - Opiate Agonists – Abuse Deterrent

Allen Quan: Good afternoon. Thank you for giving me to opportunity to speak. My name is Allen Quan. I'm a pharmacist and a medical liaison for DSI. It's been over 6 months since I was last here to present this information so I just want to highlight some of the finer points, Morphabond extended release as well as opiate crisis. As you all know, there is an opioid crisis going on. So, in general, morphine is the most frequently prescribed ER opioid and is often abused. Morphabond extended release is bioequivalent to MS-Contin has a direct 1 to 1 conversion along with a q 8 and q 12-hour dosing interval. Morphabond extended release is the only ER for extended release morphine abuse deterrent formulation to prevent dose dumping by maintaining its extended release properties even if manipulated via intranasal or IV route. And how does this do this? Well Morphabond-ER is formulated with a proprietary Sentry Bond technology that is composed of chemical properties that contribute to the abuse deterrent. Morphabond-ER technology is expected to deter abuse by intranasal and IV route with administration as demonstrated by categories I, II, and III studies required by the FDA for abuse deterrence. Also, in addition to these properties, the active ingredient is contained within a polymer matrix of inactive ingredient; so active ingredients mixed in with the polymer matrix inactive ingredients. The active ingredient is difficult to visibly distinguish or physically separate from the polymer matrix so this slows the release of active ingredients compared to related extended release morphine and results in a maintenance of Morphabond extended release properties even though it can be manipulated via the intranasal route. As with all these agents with abuse deterrent, they're not abuse preventative so there is the caveat that all these agents including Morphabond can be abused by intranasal, oral, and IV route is still possible. Thank you for your time.

Carl Jeffery: This is a class that the Board asked us to bring back again after our last meeting and we've got another medication on the list here. It's Arymo, that's what prompted us to bring it back to the Board. I want to remind the Board I've got a list here. I think it's been a year and a half now I think is when the Board decided to make a class specific to have the FDA label abuse deterrent property medications that would just be included in this class. There are some other "abuse deterrent" property medications out there that haven't been approved by the FDA. Those are not included in our class. Right now there are no generics for any of the FDA-approved abuse deterrent medications. Still, the most common form of abuse with these is still just swallowing them whole. So despite having all the

abuse deterrent properties, people can still abuse them so they're not abuse proof. Arymo is the one that I brought up here to talk about this class again. We've got a couple different strengths of it. It's every 8 to 12 hours, similar with the other morphine products. This one's a little bit sketchy. If you read the package insert, it's not real clear about what properties they use and they do that on purpose. They don't want to advertise to drug abusers how they can get around their systems, but the other ones are usually a little bit more detailed. This one's very vague about what is has in the package insert. The abuse by injection, oral or nasal route is still possible with these. It's just difficult to crush. So this is a list of currently available abuse deterrent labeled medications. The RoxyBond is on here. It just got approved so it got loaded in our system but I heard it's not going to be available until October or so. It's a ways out from being on the market. But that's an immediate release abuse deterrent medication. Everything else we have on the list is extended release so this one may be included in a different class at some point but here's all the other ones. We've got a couple of other ones that it seems like they've potentially been coming out for a while now but they're not available yet. When you look at the utilization, I've got quarter 4 2015 versus quarter 1 2018. OxyContin used to be the big king of all the other medications in this class partly because most of these other ones weren't available at that time, but we had looked at the OxyContin utilization and it's still holding pretty steady but it has gone from 96% market share down to 53% market share, so there are some other medications that are coming in this class including Morphabond which we just heard about. I think they are doing a good job. Not only is it a decent medication but they're doing a good job of marketing out there, too; 105 claims to that in the first quarter of 2018. So you can see despite that being non-preferred, OxyContin is also non-preferred under that drug list and still has 400 claims to that. Optum makes the recommendation this class be considered clinically and therapeutically equivalent.

Adam Zold: I'll make the motion that this class is therapeutically and clinically equivalent.

Second and voting. Motion approved.

Carl Jeffery: So, Optum is going to recommend a couple of changes here and I just want to throw an idea that kind of we had out to the Board and see what they thoughts would be, and this wouldn't happen at this meeting but for future meetings. Combining not breaking out the abuse deterrent property medications but combining all of the opioids into a single class. I don't know what the Board thinks about that? Maybe mull it over, we'll bring it back at the next meeting and if that's the direction you guys want to take, I think maybe it's an advantage to do that. The next class we have is the regular release, we're going to discuss it. We've got some utilization numbers. We can look at those and see if that's something because I think the Board has an opportunity to drive the utilization to these potentially safer agents. I think if you have to be seen and if the public really benefits from having these out here. I'm not convinced that these are really that much of a benefit, but anyway, currently what we have is abuse deterrent property medications. Optum would recommend that Morphabond be considered added as preferred and then the new medication, the Arymo be added to the non-preferred.

Shamim Nagy: So we are just voting on the inclusion of these agents, not combining the classes?

Carl Jeffery: Right, not combining, we will agendize that in the future if we're going do that, but I just wanted to throw it out as an idea to the Board and maybe get some input on what they think about that or nothing we have to discuss today but I just wanted to see what the Board thought.

Adam Zold: I think we should make a motion to bring that up at the next meeting.

Mark Decerbo: It is worthy of discussion. I think it may be a little premature to comingle both these classes, but it would be a good discussion.

Carl Jeffery: Okay, I don't think we need a motion. I'll just add that to the agenda.

Shamim Nagy: I need a motion for inclusion of these.

Adam Zold: I motion to go to Optum's recommendation.

Mark Decerbo: Just for the minutes, thank you for the utilization numbers. I think they are helpful for our discussion.

Second, voting. Motion carries.

b. Analgesics - Opiate Agonists

Shamim Nagy: Next topic is analgesic – opiate agonists.

Gabe Lither: Are there any new medications on that Carl?

Carl Jeffery: No, and it was the Board's request that we bring this back with some numbers, the utilization numbers and that's why we have it back to the Board here. We don't have any recommended changes so if the Board just wants to cruise through this and take a look at the numbers, there's no voting necessary if they're not going to make any changes, but we just put it on the agenda as it was requested at one of the last meetings.

Shamim Nagy: Any discussion?

Mark Decerbo: Just numbers is fine.

Carl Jeffery: So here's the utilization of this last year. The morphine sulfate which is the generic MS-Contin certainly by far the most utilization here. If you look at the bottom of the total, what we're seeing is a general trend on quarter 4 2015 to quarter 1 2018, which I think is a testament of several factors that we have added some criteria, some pretty strict quantity limits on opioids and then we've also just with the public and prescribers being educated on the dangers of the opioids that I think we've seen a decrease of it. Still the morphine sulfate, methadone and we don't have the specifics on what these are used for but if I had to guess, it's still being used for drug addiction treatment centers. And then the other preferred medication that's up there is the fentanyl. We also have Butrans is the other preferred one and we've seen a little bit of uptick in the utilization since that's been added to preferred but it's still not real widely used. It's kind of limited on its utilization so really only indicated for mild to moderate pain.

Mark Decerbo: Our fee for service covered lives, from 2015 to now, is it about the same?

Carl Jeffery: We've probably seen a pretty good-sized increase. If I'm remembering right, we're running maybe 120 to 130 in 2015; 130,000 in 2015. Now we're running right around 170,000 lives so it has increased pretty significantly. Part of that's because of the ACA expansion and picked up some lives there. But we want to go through the class. I don't think we need to vote on anything if the Board doesn't desire to make any changes.

Shamim Nagy: There's no change.

Gabe Lither: Anyone in front of the Board could recommend to make any motion now and we'd have something but in the absence of that, we'll move on. So this is your chance to speak up with a motion. Otherwise, we move to the next class. Alright, going, going, gone.

c. Hormones and Hormone Modifiers - Antidiabetic Agents - Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors and Combination

No public comments.

Carl Jeffery: Okay, so we have another one. We have a couple new medications on here. We've tried to do this at the March meeting and that didn't happen so we'll get a repeat here. These are slides from March so I'll have to refresh my memory what they were about, but Qtern is a combination medication of dapagliflozin and saxagliptin so it's essentially Farxiga and Onglyza combined together so a DPP4 and incretin mimetic. Similar medications for type 2 diabetes, specific dose combination taken once daily. Found to be effective reducing A1c by 0.5% when added to the establishment metformin with the dapagliflozin already versus placebo so it's found to be effective. There's another new chemical entity, the ertugliflozin, another SLG-2. Again, shown to be effective reducing A1c in treatment group versus placebo. Similar when added to Metformin and other medications. As predicted, and we have chemical entity with all the combination agents here, too, so combined with the sitagliptin, a DPP4. Again you expect to see a similar A1c reduction and then just in another combo with Metformin. So I see the utilization numbers here. Jardiance definitely the number one utilization for the first quarter. Invokana and Farxiga are in there too, I think it has to do with the CV studies that are out there, the EMPAREG and the other studies that are out there now. If there's any comments or questions about the utilization.

Motion to accept as clinically and therapeutically equivalent. Motion carried.

Carl Jeffery: Optum's recommendation is to make all the new medications in this class with all the combos and the new standalone agent non-preferred. We feel there's enough with the options with the other agents there that they would provide enough options for patients on Medicaid.

Motion to accept recommendation. Motion carried.

d. Hormones and Hormone Modifiers – Antidiabetic Agents – Insulins (Vials, Pens and Inhaled)

No public comments.

Carl Jeffery: We have a couple new agents in this class and it prompted us to review it. There's two, Fiasp and Admelog, you can look at their generic names and see that they look somewhat familiar. Similar indications. Improved glycemic control in adults with diabetes. The Admelog has the indication for children, as well. Fiasp is similar active ingredient as NovoLog but it has two ingredients added to it so it's got B3 that they say increases absorption and then the L-arginine increases stability of this product. A lot of studies show that it is effective. What it essentially is, they measured the time it takes

to get into the bloodstream, so 2-1/2 minutes versus 5.2 minutes. So, take that for its therapeutic value if that's really that critical. Onset studies show that it's non-inferior to NovoLog. The other one is the Admelog, it's our first follow-on biologic which is similar to the biosimilar agent so it's not necessarily "generic" but a rapid-acting insulin so similar to Humalog. Two trials versus Humalog showing that it's non-inferior. We look at the utilization of this one and we've got kind of all over the board, Lantus. It's a little confusing graph, because we see both the long acting basal insulins as well as the rapid-acting insulin so it's all kind of combined on here but you can see the Lantus and NovoLog and Humalog are certainly high up there with the other long-acting agents kind of following up in there.

Adam Zold: How long has the Fiasp been out?

Carl Jeffery: That's a good question. Kevin do you know?

Kevin Whittington: I don't know exactly, six months to a year at most.

Motion to accept as clinically and therapeutically equivalent. Motion carried.

Carl Jeffery: Optum is making the recommendation that Admelog and Fiasp are added as non-preferred.

Adam Zold: I have a patient on Fiasp that has been doing really well on it. I know it's a little early to maybe make this recommendation but I would like to see this brought back up at another meeting.

Carl Jeffery: Yes, the September meeting is our next meeting and that'll be our annual one where we review all the classes so we can certainly bring that back up. Are there other products coming out? You've got another insulin. We can bring this back as a discussion for next time.

Gabe Lither: You're welcome to make a different motion, also, at this time, you don't have to wait or if you want to accept this now or wait.

Carl Jeffery: Well I'm just curious, were they on NovoLog before and they're doing better now on the Fiasp versus the NovoLog.

Adam Zold: Yeah, they're someone who had the hyperglycemia and they were able to get their blood sugars down faster which has a great effect on their A1c, I would assume, so they're able to have better control quicker even though its seconds going into the bloodstream, overall they have improved life I think.

Carl Jeffery: Yeah and so what this class leads to is that we just ask that they try; it's not off limits, they can still get the Fiasp, we ask that they try one of the preferred agents first before they move to that one.

Evelyn Chu: What is the difference between Fiasp and the NovoLog? I might have missed that.

Carl Jeffery: The Fiasp has the same active ingredient as the NovoLog, it just has that B3 and L-arginine in there that increases the rate of absorption.

Motion to accept the PDL as presented. Motion carried.

e. Hormones and Hormone Modifiers – Antidiabetic Agents – Incretin Mimetics

Public Comments:

Ryan Flugge – Hello I'm Ryan Flugge with Novo Nordisk, a pharmacist, a medical liaison and to answer your previous questions, Fiasp was brought to market the first quarter of this year so that would have been the first quarter it was available on the market. I wanted to discuss some highlights with you regarding the Ozempic which is the GLP-1 receptor agonist in this class indicated for type 2 patients as an adjunct to diet and exercise to improve glycemic control. It does carry a box warning and a contraindication for patients who have a personal or family history of medullary thyroid carcinoma or MEN type 2 syndrome. There is no REMs associated with this product. Not indicated for type 1 or diabetic ketoacidosis and has not been studied in patients with a history of pancreatitis. The safety and efficacy has been established in the sustain program. Dosing information can be found in the package insert. GI side effects are the most common with nausea being the most commonly reported mild to moderate intensity and does diminish over time like we see with the other GLP-1 agents. It has shown A1c reductions from 1.2 to 1.5% with a 0.5 mg and 1.4 to 1.6% with the 1 mg and the sustained 1 through 5 trial. While not indicated for weight loss, weight effect was a secondary endpoint. It demonstrated 7 to 9.2 pound loss with a 0.5 mg and 10.3 to 13.2 pound loss with 1 mg. There's two head-to-head trials comparing it to other once-weekly GLP-1 agents, sustained 3 comparing those Ozempic to Bydureon and sustained 7 comparing Ozempic to Trulicity. Both trials do show Ozempic statistically significant and superior A1c reductions and weight loss and sustained 3 comparing to Bydureon, the difference of A1c reduction between Ozempic 1 mg and Bydureon 2 mg was 1.5 compared to 0.9% decrease. The weight difference was 12.3 pounds lost with Ozempic and 4.1 pound loss with Bydureon. More subjects did experience nausea with Ozempic compared to Bydureon. In sustained 7 comparing those Ozempic to Trulicity, the difference of A1c reduction was 0.4% meeting superiority and non-inferiority both prespecified endpoints in favor of Ozempic. Weight loss was also superior with Ozempic in that trial. Cardiovascular safety information is included in the label with data from the sustained 6 trial. Ozempic met the primary endpoint as not inferiority for MACE events compared to placebo on the background of standard of care. The hazard ratio was 0.74 with a 95% confidence interval of 0.58 and 0.95. It's available in a one-pen cartridge and a two-pen cartridge. One pen being for the titration and 0.5 mg maintenance dose and the two-pen for the 1 mg maintenance dose. Both packaging does include the needles but there is no need for an additional prescription. Given this information and the sustained 3 trials I kindly ask you consider placement of Ozempic on your PDL.

Carl Jeffery: Alright, so as we just heard about, Ozempic is our new one on here and as we heard about all the different studies, it was well studied. Here a lot of sustained trials kind of summarized down here. It was shown to be some benefit over a lot of the other medications so I'm not going to sugarcoat it. It looks like it's a promising medication, again, I think we heard about the CV risk reduction studies and it's my understanding, from what I thought was ongoing but maybe some more details that are available now. You can see the utilization here with incretin mimetic here. The Victoza is still in the preferred one and Trulicity is following up with a close second. So, the Bydureon number there, also includes the new form with BCise, so they reformulated the Bydureon as it's a little bit easier to administer but all the numbers are included in there. We weren't going to pull out the BCise separately from the Bydureon but it's all just included in there. Tanzeum as you probably know is being slowly weaned off the market so probably at the next meeting, I don't think we'll see any of the utilization anymore of it and we can eventually remove that name from our drug list but it's still there. We have a

few claims for it. Optum makes the recommendation that this class be considered clinically and therapeutically equivalent.

Motion to accept as clinically and therapeutically equivalent. Motion carried.

Carl Jeffery: Optum recommends that the new medication, Ozempic, to be added to the list of non-preferred and the rest of the class remain the same.

Mark Decerbo: You brought up the Tanzeum and I think it will be any day now they will stop making it. Are we fine letting it ride as preferred?

Carl Jeffery: So the question was, is it okay to leave the Tanzeum on the list the next time. I don't see a problem with leaving the Tanzeum until it's completely off the market.

Mark Decerbo: Any insight from Optum on the Ozempic, similar weekly dosing like Trulicity, any reason why starting as non-preferred?

Carl Jeffery: It's a tough call. It's a good medication, but it's just that from the information we have, this is our recommendation.

Motion made to add Ozempic as preferred and keep the rest of the class the same. Motion presented.

Carl Jeffery: So in summary, I'll repeat the motion so everybody hears it, so the motion is to add Ozempic to the preferred side.

Mark Decerbo: I don't have any problems with the motion. We will have some lives coming off Tanzeum that will have to go somewhere else, Ozempic once weekly like Trulicity, potentially better. So I don't have a problem with that.

Carl Jeffery: So to just review and make sure you understand the motion, the motion is to add Ozempic as preferred so if not accept our recommendation.

Kate Ward: What was the discussion?

Carl Jeffery: I'm sorry, so the motion is to make Ozempic as preferred.

Beth Slamowitz: What was the discussion that occurred, we couldn't hear it.

Carl Jeffery: Yeah, sure, I think it was just Dr. Zold who made the recommendation that he thought it to be entered as preferred. There really wasn't all that discussion behind that other than just, there was some discussion of parliamentary procedures about taking care that we follow the right rules, but it was just the recommendation from Dr. Zold and Dr. Decerbo and Dr. Chu.

Gabe Lither: Dr. Decerbo said that he thought it was a good decision.

Carl Jeffery: Yes, Dr. Decerbo thought it was a good decision.

Motion carried.

f. Respiratory Agents - Respiratory Anti-inflammatory Agents - Nasal Corticosteroids

Carl Jeffery: Okay, so we have a new medication in this class, Xhance, fluticasone spray. It's a pretty funky delivery system. It's only indicated for nasal polyps but I'm not sure how it's actually going to be administered but it has a nozzle to go into your nostril and then a mouthpiece we blow on it and it actually blows it in. It's supposed to be deposit it deeper into your nasal passage to get to the polyps, but right now it only has indication for the nasal polyps. It's just one spray twice daily, two sprays can be effective. So, a couple of studies show it's effective. Probably shouldn't really be used, probably it's a little overkill for the allergies of most of the other classes were used for. There's some other medications in this class that have an indication, Nasonex and Beconase AQ also have the indication for the nasal polyps. Our utilization by far predominant with the generic fluticasone spray and we've had that as preferred for a while now. The other preferred one, we have got a list there, is the Nasonex and it really hasn't picked up too much market share and I think there's a few more generics that have come on the market now so I think we've got an opportunity to maybe make some modifications to our current list. It's really not too much else that's on here that's remarkable. Optum makes the recommendation this class be considered clinically and therapeutically equivalent.

Motion to accept as clinically and therapeutically equivalent. Motion carried.

Carl Jeffery: Okay, with the addition of the additional generics for the Nasonex, we thought this is a good opportunity to maybe mix up the class a little bit, but fluticasone will remain preferred, that is our number one utilizer anyway but we'll add the triamcinolone acetonide as preferred we'll move brand Nasonex as non-preferred so we'll just have the two generic medications available as preferred and the new medication Xhance since it is limited on indications be non-preferred, as well.

Mark Decerbo: Did we lose mometasone?

Carl Jeffery: I don't see it; maybe I didn't include it on the list but mometasone will be included as non-preferred, too.

Evelyn Chu: It had the second highest market share didn't it?

Carl Jeffery: It's third, it's not preferred already so this is a new one and I didn't get it added on here so it's already considered non-preferred since it's new.

Mark Decerbo: Both the brand and generic mometasone are non-preferred.

Carl Jeffery: That's right.

Mark Decerbo: With the addition of generic mometasone to the non-PL as clinically and therapeutically equivalent.

Evelyn Chu: Second.

Carl Jeffery: And just to repeat the motion, the motion was to accept it as presented with the addition of the generic mometasone added to the non-preferred.

Motion carried.

g. Respiratory Agents - Respiratory Anti-inflammatory – Agents Respiratory Corticosteroids

No public comments.

Carl Jeffery: Qvar has a new delivery mechanism, it's a RediHaler. Same medication just with a different delivery system here. It's been compared to the MDI and has been shown to have really no calculated difference except maybe some fewer adverse reactions with the RediHaler versus the MDI. Market share here shows that we're still seeing the Qvar was still going to be on the market. It's not going away anytime real soon. I think it may eventually go away but the regular metered dose Qvar is still our number one utilizer. It's followed by the Flovent, but we have a lot of preferred medications over here in kind of ascending order starting with the Qvar at the highest percent there. Optum recommends this class be considered clinically and therapeutically equivalent.

Motion to accept class as clinically and therapeutically equivalent. Motion carried.

Carl Jeffery: So Optum recommends that the new dosing form of Qvar RediHaler be added to non-preferred and the rest of the class remain the same.

Motion to accept the recommendation. Motion carried.

h. Respiratory Agents - Respiratory Antimuscarinic Combinations.

Public Comment

Carl Jeffery: Alright new medication. This one's Trelegy. It's a combination of three agents. It's fluticasone, umeclidinium and vilanterol, all 3 medications that are typically used in your most severe COPD patients. So, there's been studies. The agents, either one or two combinations versus one. There's been a lot of companies with this study showing that it's effective and I think it's well known even the GOLD guidelines if you follow those guidelines of A, B, C, and D but when you get up to D, you're on triple therapy anyway and this just combines them into a single inhaler. So, by the time you get up to the triple therapy, you're looking at some pretty severe COPD patients so they're either in a C category that they're adding an ICS or they're preferably in the D category as they're the most severe COPD patients. It's only indicated for COPD at this time, I don't know that they're looking at it for asthma, but it will have a bigger impact probably on the med-D population which we don't have any impact over. The Medicaid population, I don't know that we're going to see a whole lot of utilization of this anyway. So, when we look at the numbers of the utilization of this class, this class doesn't really fit. We're going to rename the class to antimuscarinic combinations to include the beta-agonists and the inhaled corticosteroids so at some point in the future, we may have to come back and discuss the class again and see how we want to put these in here. We put them in the antimuscarinic class, because this made the most sense on how people progress through the utilization of the COPD treatment algorithm there but still the ipratropium and albuterol is still number one so we still get a lot of people that use the short acting, maybe a few with the Spiriva inhalers and then move on from there. Optum makes the recommendation this be considered clinically and therapeutically equivalent.

Motion for therapeutically and clinically equivalent. Motion carried.

Carl Jeffery: So because Trelegy is so limited and it's really only for the most severe, it just makes sense that is be non-preferred drugs, they're going to try to use other agents first before they get there anyway, so it shouldn't be used first line and Optum recommends that it be non-preferred.

Motion to accept preferred drug list as presented. Motion carries.

i. Gastrointestinal Agents – Antiemetics – Miscellaneous

No public comments.

Carl Jeffery: Another new one to talk about. This is one we will be brief. Bonjesta, just like the currently available product, it's double the dose and extended release. I was looking through there to see what kind of efficacy trial they have to see if it's more effective, statement on their package insert. There have been no efficacy or safety trials for Bonjesta, which makes me a little nervous, but I know it's the same with the other medications and there's just pyridoxine and doxylamine so they are pretty benign but it makes me a little nervous. Pharmacokinetic studies were showing the bio-equivalent to getting the same levels as the Diclegis. So this one you start at one pill at a time and goes up to twice a day so it still has that option. You see our utilization. We don't have a lot of claims with it, even we made Diclegis preferred a little while ago, several meetings ago, and two years. So it's still not usually used. Dr. Adashek missed this meeting and he would probably have an opinion on this one. Optum recommends the class be considered clinically and therapeutically equivalent. I just want to point out real quick, so we had Emend on here because we just didn't know where else to put it. It's preferred on there. I think it doesn't belong in here, so we're going to remove the Emends. It'll still be preferred; it just won't be listed on the list. I just wanted to make sure the Board is aware of that one, too. Just to review, Optum recommends Board consider these clinically and therapeutically equivalent.

Motion to accept as clinically and therapeutically equivalent. Motion carried.

Carl Jeffery: Optum recommends the new Bonjesta be entered as not preferred. Like I said, we'll remove the Emend. We still have, I think we've had a request from the DUR Board, we have the OTC products, at least the listed there so to give people an option so I guess it would be amenable. But the Bonjesta would be non-preferred Diclegis and the OTC products would remain as preferred.

Shamim Nagy: The last one you are removing, it will moving to another list?

Carl Jeffery: Yeah, the Emend will still be available and without restrictions. After further review, it probably doesn't belong with this class because these are for antiemetics for hyperemesis gravidarum.

Mark Decerbo: I learned today about the open access, so removing the Emend from the list will provide open access since this is used for chemotherapy. The OTC agents, is there any nuance to OTC's with Medicaid?

Carl Jeffery: So, yeah for OTC coverage, doctors still need to write a prescription for Medicaid to pay for it and that's to allow the pharmacy to run through their system. A patient can't just grab it off the shelf and ask the pharmacy to run it through and pay for it. It still needs to be a prescription but other than that, it's open access.

Motion accept the list as presented. Motion carried.

j. Ophthalmic Agents – Antiglaucoma Agents

Public comment:

Nama Numapay: My name is Nana Numapay with BI, I just have a quick question as I think we need to see the Stiolto on the other list in terms of the respiratory agent. I thought it was going to be the next one, but I still didn't see it so I just wanted to make sure it was not an oversight.

Carl Jeffery: The Stiolto, we didn't bring that because the category is the long-acting respiratory, long-acting beta-agonist combination. This is what I talked about. We may use in the future to combine these because we weren't real sure where to put it but we ended up putting the Trelegy into this other long-acting respiratory beta-agonist.

Nama Numapay: So it's going to be as preferred? .

Carl Jeffery: Yes, we were not talking about it today. The Stiolto is preferred now and we're not discussing it. As I kind of eluded to, there is confusion on what class to put these in because we've got the class of medications called respiratory long-acting antimuscarinic agents/long-acting beta-agonists combination. Then we've got respiratory corticosteroids, long-acting beta-agonists combinations, and we even have another one called long-acting respiratory beta-agonists and then we've got respiratory antimuscarinic so we've got all these classes and so rather than at this time redo all of the classes, we tried to kind of shoe in the Trelegy the best place we thought it would fit and that was with the other antimuscarinics.

Mark Decerbo: I had a question on that. If we have a class, does there need to be preferred agent or can we have a class where everything is non-preferred? I'm just trying to think ahead as we resort these.

Kevin Whittington: You have to have at least one preferred.

Carl Jeffery: The answer is we have to have at least one preferred agent. So, if we have a class, we can't have the whole class of non-preferred medications. We need at least one preferred agent. We can bring this back in the future. I think we've kind of planned on it

anyway but I think the next meeting will be a good time to talk about maybe reorganizing these classes. It will be the annual meeting. We will have an opportunity to discuss these other ones.

No public comment.

Carl Jeffery: We have a couple new agents in this one. Rhopressa is the really novel one that is on the market. It's a new class of medications called a ROCK inhibitor and it decreases the intraocular pressure through a different mechanism. I was reading the package insert and they kind of know what it does but they don't know why it does what it does. The exact mechanism is still unknown. But you can see there's a couple studies on there, rocket 1, rocket 2. The rocket 1 was kind of discouraging. I think it wasn't able to show it noninferior to Timolol but rocket 2 was able to it was not inferior to Timolol. You can see the different doses up there of how many patients were in each of the classes. But I think numerically, things are trending correctly. The rocket 1 from my understanding is it wasn't powered correctly to really get the benefits in there. The other new one is on here, the Vyzulta. It's another prostaglandin analog. This one has some pretty good data behind it, too. Same indication, intraocular pressure reduction. Shown to be superior to Timolol, and latanoprost for reducing the intraocular pressure. Still the guidelines for the association of ocular, I don't know what the A stands for; still, they don't really recommend one agent over the other. The AAO guidelines do recommend the prostaglandin as kind of the first order of treatment because I think they're well tolerated, they're effective, and so that's kind of what this kind of does here. You can see that it looks different because this is one where we did combine the classes so we did have these broken out for the beta-blockers first and then the prostaglandins and then with this new one, Rhopressa, where are we going to put this one. This is one where it did work out okay to combine the classes and we'll just have an antiglaucoma agent class because really the way these are prescribed, it's really individual by the patient and the doctor who is prescribing it so there's really not such a guideline as to which to be tried in combinations and there's all sorts of stuff in here. So you can see. We took a snapshot of kind of the newer agents on here with the utilization of the Vyzulta and the Rhopressa of course having not been out that long, there's no utilization but the Lumigan is our number one here and is preferred. Also, new generic bimatoprost, so that one's on here too. So with the addition here, and I know this gets a little confusing because you have to understand how the treatment works so of all the agents, they're not same mechanism of action but they all treat intraocular pressure and I think that's their goal here. Optum makes the recommendation that all these medications be considered clinically and therapeutically equivalent.

Mark Decerbo: Trying to digest all these different agents in the same class, going to back to what was said earlier, if something isn't listed as open access, cosmetic use like Latisse, I don't see it listed as the brand, if it is not listed, does that mean it is open to people on Medicaid? Is it worth adding to non-preferred?

Carl Jeffery: So the question is like Latisse and medications, so the Latisse will be covered kind of listed separately under cosmetics. So cosmetics are excluded from Medicaid coverage and so it's also like

Botox cosmetics. Those aren't covered. They're in a different class of medications that are excluded from coverage.

Motion to accept as clinically and therapeutically equivalent presented. Motion carried.

Carl Jeffery: Optum recommends with the new, I'll get another slide and we can talk about some of the drugs in the future, but I think Rhopressa is the first of the class of the new some agents that are coming out so I think there is another ROCK agent that's coming out with this one, but Optum recommends that Rhopressa be added as preferred and the generic, bimatoprost, and the Vyzulta be added as non-preferred.

Motion to accept the recommendation as presented. Motion carried.

7. Report by OptumRx on New Drugs to Market, New Generic Drugs to Market, and New Line Extensions

Carl Jeffery: We've got a couple new recently approved medications. I think they're interesting and I think, I don't know if they may show up in the future. The first cannabinoid medication to treat LGS. I think it's interesting. We'll have to see how this pans out. I think that it could open access to some other therapies. I'm not sure how it's going to work out so we'll see. The generic for the sublingual test for the Suboxone. I think that will be a discussion in a future meeting for sure because this is a class medication that we do have on our preferred drug list and the new one I think is kind of exciting too, but Aimovig for migraines. There is another one that's in the works pending drug approval so this could be another class that we include on our preferred drug list. I think it would give us some opportunities. I just wanted to mention briefly, if there's a new medication for ADHD, Dasotraline. So those are all pending so may be at our November/December meeting.

8. Closing Discussion

Carl Jeffery: Next meeting September 27, Thursday. We have this room booked for the South, we will work on a meeting room for the North. We like to get all people together so maybe we'll have the people from the North come down here, too, so we'll go look at some options to make the next meeting. That's usually an extensive agenda.

Meeting adjourned at 2:43 PM

INTRODUCTION

- The inhaled anticholinergics class includes short- and long-acting agents. Short-acting agents include Atrovent HFA (ipratropium bromide) inhalation aerosol, and ipratropium bromide solution for nebulization (available generically). Long-acting agents, also called long-acting muscarinic antagonists (LAMAs), include Spiriva Handihaler (tiotropium bromide) inhalation powder, Spiriva Respimat (tiotropium bromide) inhalation spray, and Incruse Ellipta (umeclidinium) inhalation powder, which are all administered once daily; Lonhala Magnair (glycopyrrolate) solution for nebulization is administered twice daily. Other relatively long-acting agents are Tudorza Pressair (aclidinium bromide) inhalation powder and Seebri Neohaler (glycopyrrolate) inhalation powder, which are administered twice daily. The predominant use of inhaled anticholinergics is for the treatment of chronic obstructive pulmonary disease (COPD); Spiriva Respimat is also indicated for selected patients with asthma.
- COPD is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities. The abnormalities are usually caused by exposure to noxious particles or gases. Airflow limitation is caused by a combination of small airway disease (eg, obstructive bronchiolitis) and parenchymal destruction (emphysema); the relative contributions of each component vary between patients. The most common symptoms of COPD include dyspnea, cough, and sputum production (*Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2018*).
- COPD affects 6.4% of the United States population and is the major contributor to mortality from chronic lower respiratory diseases, the third leading cause of death in the United States (Centers for Disease Control and Prevention 2017). Globally, COPD is the fourth leading cause of death and is expected to be the third leading cause of death by 2020; the burden of COPD continues to increase due to continued exposure to risk factors and aging of the population (*GOLD 2018*).
- Cigarette smoking is the main risk factor for COPD; other risk factors include biomass fuel exposure (such as from cooking and heating in poorly ventilated dwellings) and air pollution. Host factors such as genetic abnormalities, abnormal lung development, and accelerated aging can predispose individuals to COPD development (*GOLD 2018*).
- Patients with COPD may experience exacerbations, which are periods of acute worsening of respiratory symptoms (*GOLD 2018*).
- Pharmacologic therapy for COPD can reduce symptoms, reduce the risk and severity of exacerbations, and improve patients' health status and exercise tolerance. There is no conclusive evidence that COPD medications modify the long-term decline in lung function characteristic of COPD (*GOLD 2018*).
- Pharmacologic options for COPD treatment comprise several classes, including beta-agonists, anticholinergics, methylxanthines, various combination products (including bronchodilators with inhaled corticosteroids [ICSs]), and the phosphodiesterase (PDE)-4 inhibitor, roflumilast. Pharmacologic treatments should be individualized based on symptom severity, risk of exacerbations, side effects, comorbidities, drug availability, and cost, as well as the patient's response, preference, and ability to use various drug delivery devices (*GOLD 2018*).
- In 2015, tiotropium inhalation spray became the first LAMA to be Food and Drug Administration (FDA)-approved for the treatment of asthma (See Table 2). Asthma is a chronic lung disease that inflames and narrows the airways, making it difficult to breathe. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing. Asthma affects people of all ages, but most often starts during childhood. In the United States, more than 25 million people are known to have asthma, including about 7 million children (*National Heart, Lung, and Blood Institute [NHLBI] 2014*).
- The most effective, commonly recommended long-term control medications for the treatment of asthma are ICSs. Alternative long-term control monotherapy medications, such as leukotriene modifiers, mast-cell stabilizers, and methylxanthines, are considered less effective as monotherapy compared to ICSs. Long-acting beta$_2$-agonists (LABAs) should not be used as monotherapy for asthma due to increased risk for serious adverse events including death; however, they are considered the most effective adjunctive therapy in patients not adequately controlled with an ICS alone. Tiotropium is an option for add-on therapy in certain patients requiring an additional controller medication. An interleukin-5 (IL-5) antagonist or the immunoglobulin E (IgE) antagonist, omalizumab, may be added if patients require a higher level of care. Omalizumab is used in patients with moderate to severe allergic asthma while IL-5 antagonists are used for severe eosinophilic asthma. Short-acting beta$_2$-agonists (SABAs) are the medication of choice for the relief of

bronchospasm during acute asthma exacerbations (*Xolair prescribing information 2017, Global Initiative for Asthma [GINA] 2018, NHLBI, 2007*).

- This review includes single-agent LAMAs. While some inhaled anticholinergics are available in combination with other bronchodilators such as SABAs and LABAs, combination agents are not included within this review.
- Medispan class: Bronchodilators – Anticholinergics

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Atrovent HFA (ipratropium bromide)	-
Incruse Ellipta (umeclidinium bromide)	-
ipratropium bromide solution	✔
Lonhala Magnair (glycopyrrolate)	-
Seebri Neohaler (glycopyrrolate)	-
Spiriva Handihaler (tiotropium bromide)	-
Spiriva Respimat (tiotropium bromide)	-
Tudorza Pressair (aclidinium bromide)	-

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Atrovent HFA (ipratropium bromide)	Incruse Ellipta (umeclidinium)	ipratropium bromide solution	Lonhala Magnair (glycopyrrolate)	Seebri Neohaler (glycopyrrolate)	Spiriva Handihaler (tiotropium)	Spiriva Respimat (tiotropium)	Tudorza Pressair (aclidinium)
Maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema	✔		✔					
Long-term maintenance treatment of airflow obstruction/ bronchospasm in patients with COPD		✔ *		✔	✔	✔ *	✔ *	✔
Reducing COPD exacerbations						✔	✔	
Long-term, once-daily maintenance treatment of asthma in patients ≥ 6 years of age							✔	

*Once-daily maintenance treatment

(*Prescribing information: Atrovent HFA 2012, Incruse Ellipta 2017, ipratropium solution 2013, Lonhala Magnair 2018, Seebri Neohaler 2017, Spiriva Handihaler 2018, Spiriva Respimat 2017, Tudorza Pressair 2017*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

COPD

- Efficacy of the LAMAs for the management of COPD is well established through placebo-controlled trials and a number of systematic reviews and meta-analyses. The primary endpoint in most trials has focused on lung function, including measures of the forced expiratory volume in 1 second (FEV_1). Several studies have also evaluated the impact of LAMAs on measures of quality of life and health status, and frequency of COPD exacerbations.
  - All of the LAMAs have demonstrated improved FEV_1 compared to placebo (*Karner et al 2014, Kerwin et al 2016, Kerwin et al 2017, LaForce et al 2016, Ni et al 2014, Ni et al 2017, Pleasants et al 2016*).

- All of the LAMAs have demonstrated improvement in health status and/or COPD symptoms (*Karner et al 2014, Kerwin et al 2016, Kerwin et al 2017, LaForce et al 2016, Ni et al 2014, Ni et al 2017, Pleasants et al 2016*).
- Tiotropium and umeclidinium have demonstrated a significant reduction in moderate COPD exacerbations (*Karner et al 2014, Ni et al 2017, Pleasants et al 2016*).

Placebo-controlled trials

- Tiotropium administered via the Handihaler device has been compared to placebo in several randomized controlled trials.
  - A randomized double-blind trial (N = 623) demonstrated that tiotropium 18 mcg daily significantly improved trough forced expiratory volume in one second (FEV_1) over placebo. Improvements were also demonstrated in peak expiratory flow (PEF) rate, transitional dyspnea index (TDI) focal scores, and St. George's Respiratory Questionnaire (SGRQ) scores compared to placebo (*Donohue et al 2002*).
  - Another randomized double-blind trial (N = 1207) demonstrated that tiotropium 18 mcg daily compared to placebo led to a delayed time to first COPD exacerbation, fewer hospital admissions, fewer days in which patients could not perform their usual daily activities, improved TDI focal scores, and improved results on the SGRQ (*Brusasco et al 2003*).
  - A randomized double-blind trial (N = 457) in maintenance treatment-naïve patients with COPD GOLD stage II demonstrated that tiotropium 18 mcg daily compared to placebo significantly improved FEV_1 and physician's global assessments of overall health status (*Troosters et al 2014*).
  - In a small randomized double-blind trial (N = 105), patients receiving tiotropium 18 mcg daily showed a longer exercise endurance time compared to patients receiving placebo (*Casaburi et al 2005*).
  - A large, randomized, double-blind, four-year trial (N = 5993) (UPLIFT) demonstrated that tiotropium 18 mcg daily was associated with a significant delay in the time to first exacerbation and time to first hospitalization for an exacerbation. Although the improvement in FEV_1 with tiotropium was maintained throughout the trial, tiotropium did not lead to a significant difference in the rate of decline in FEV_1 over time. Improvements in SGRQ were demonstrated, but were less than what is generally accepted as clinically significant. Mortality was 14.9% in the tiotropium group and 16.5% in the placebo group (*Tashkin et al 2008*). A predefined subgroup analysis of UPLIFT demonstrated that for patients with moderate COPD (GOLD Stage II), the rate of decline for post-bronchodilator FEV_1 was lower in the tiotropium group compared to the placebo group. However, the rate of decline of pre-bronchodilator FEV_1 did not differ between groups (*Decramer et al 2009*).
  - A multicenter, randomized, double-blind trial in patients (N = 841) with mild or moderate COPD (ie, GOLD stage 1 or 2) demonstrated that tiotropium 18 mcg daily significantly improved change in FEV_1 before bronchodilator use from baseline to 24 months compared to placebo (between-group difference, 157 mL; 95% confidence interval [CI], 123 to 192; p<0.001) (*Zhou et al 2017*). Annual decline in FEV_1 after bronchodilator use was lower with tiotropium vs placebo (difference, 22 mL per year; 95% CI, 6 to 37; p = 0.006) but the annual decline in FEV_1 before bronchodilator use was not significantly different between groups.
- Tiotropium administered via the Respimat inhaler has also been compared to placebo in several randomized controlled trials.
  - Two one-year studies (total N = 1990) evaluated tiotropium 5 mcg or 10 mcg compared to placebo. Combined results for the 5 mcg dose demonstrated the following:
    - improved response on FEV_1 (difference, 127 mL; p < 0.0001)
    - improved response on SGRQ (difference, -3.5 units; p < 0.0001)
    - improved response on TDI focal score (difference, 1.05 units; p < 0.0001)
    - reduced exacerbations (odds ratio [OR], 0.75; p < 0.01) (*Bateman et al 2010a*)
  - A one-year study (N = 3991) compared tiotropium 5 mcg to placebo and demonstrated the following:
    - improved response on FEV_1 (difference, 102 mL; p < 0.0001)
    - a delayed time to first exacerbation (hazard ratio [HR], 0.69; p < 0.0001) (*Bateman et al 2010b*)
- A systematic review summarized the data on exacerbation risk reduction with tiotropium compared to placebo (as well as compared to other COPD maintenance treatments). A total of 29 articles were included, of which 20 compared tiotropium to placebo (16 with the Handihaler and 4 with the Respimat device). Although a formal meta-analysis was not conducted as part of this review, overall, the data demonstrated that tiotropium was associated with a longer time to first exacerbation and fewer exacerbations, including severe exacerbations, compared to placebo. Exacerbations were generally comparable with the Handihaler and Respimat formulations (*Halpin et al 2016*).

- A systematic review and meta-analysis of 22 trials and 23,309 participants evaluated the efficacy of tiotropium (delivered via the Respimat or Handihaler device) vs placebo. The analysis showed that tiotropium led to statistically and clinically significant improvements in quality of life vs placebo, as measured by SGRQ. Compared to placebo, tiotropium significantly reduced the number of exacerbations and led to fewer hospitalizations due to exacerbations, but no significant difference was found for all-cause hospitalization or mortality.Pooled analysis showed an improvement in trough FEV_1 with tiotropium vs placebo (mean difference, 119 mL; 95% CI, 113 to 125) (*Karner et al 2014*).
- Aclidinium has also been evaluated in a number of placebo-controlled trials.
  - In a large, randomized double-blind study (N = 828), patients were randomized to receive aclidinium 200 or 400 mcg twice daily or placebo over 24 weeks. The mean change from baseline in trough FEV_1, the primary endpoint, was significantly larger in patients treated with aclidinium 200 or 400 mcg compared to patients treated with placebo. In addition, a significantly higher proportion of patients treated with aclidinium 200 or 400 mcg experienced a clinically significant improvement in SGRQ score and TDI score when compared to patients treated with placebo (*Jones et al 2012*).
  - In the 12-week double-blind ACCORD COPD I study (N = 561), patients randomized to receive aclidinium 200 or 400 mcg twice daily experienced a statistically significant increase from baseline in trough FEV_1 compared to patients in the placebo group. Statistically significant improvements on SGRQ were demonstrated for both dose groups, but on average were less than those considered clinically meaningful. A higher proportion of patients receiving aclidinium achieved a clinically meaningful improvement in TDI scores compared to those in the placebo group (*Kerwin et al 2012*).
  - In the 12-week double-blind ACCORD COPD II study (N = 544), patients randomized to receive aclidinium 200 or 400 mcg twice daily experienced a statistically significant increase from baseline in trough FEV_1 compared to patients in the placebo group. SGRQ scores improved in all groups, but differences between aclidinium and placebo were not significant. A higher proportion of patients receiving aclidinium achieved a clinically meaningful improvement in TDI scores compared to those in the placebo group (*Rennard et al 2013*).
- A systematic review and meta-analysis of 12 multicenter randomized trials (total N = 9547) evaluated aclidinium vs placebo in patients with stable COPD. The analysis found that aclidinium resulted in a significant improvement in pre-dose FEV_1 compared to placebo (MD, 90 mL; 95% CI, 80 to 100 mL), a reduction in the number of patients with exacerbations requiring hospitalization (OR, 0.64; 95% CI, 0.46 to 0.88), and a reduced SGRQ score (MD, -2.34; 95% CI, -3.18 to -1.51]). However, no difference was demonstrated in all-cause mortality or in the number of patients with exacerbations requiring oral steroids and/or antibiotics (*Ni et al 2014*). A similar meta-analysis included seven trials (total N = 7001) evaluating aclidinium vs placebo for a duration of ≥ 12 weeks. This analysis found that compared to placebo, aclidinium did not significantly reduce the incidence of exacerbations (OR, 0.90; 95% CI, 0.75 to 1.07; P = 0.22) or all-cause mortality (OR, 0.92; 95% CI, 0.43 to 1.94; P = 0.82). However, a significant difference was demonstrated for the rate of hospitalization due to exacerbation (OR, 0.64; 95% CI, 0.47 to 0.89; P = 0.008) and improvement in SGRQ (MD, -2.34; 95% CI, -3.18 to
-1.51). Secondary endpoints, including FEV_1, forced vital capacity (FVC), and TDI, supported the efficacy of aclidinium on lung function and dyspnea symptoms (*Zou et al 2016*).
- Umeclidinium has been evaluated for the treatment of COPD in several Phase 3, multicenter, randomized, placebo-controlled trials.
  - One trial (N = 206) compared two doses of umeclidinium, 62.5 mcg and 125 mcg daily, to placebo over a period of 12 weeks. Patients receiving an ICS at baseline continued treatment at a stable dose. No other long-acting bronchodilators were permitted. Improvements in the primary endpoint, the least squares mean (LSM) change from baseline in FEV_1, were observed for umeclidinium 62.5 mcg daily vs placebo (127 mL; 95% CI, 52 to 202; $p < 0.001$) and for umeclidinium 125 mcg daily vs placebo (152 mL; 95% CI, 76 to 229; $p < 0.001$). Improvements were also noted for dyspnea, rescue medication use (62.5 mcg strength only), and SGRQ (*Trivedi et al 2014*).
  - A second trial (N = 1,536) compared umeclidinium 62.5 mcg daily, vilanterol 25 mcg daily, umeclidinium/vilanterol 62.5 mcg/25 mcg daily, and placebo over a period of 24 weeks. Concomitant use of ICSs at a stable dose was permitted. Improvements in the primary endpoint, the LSM change from baseline in FEV_1, were observed for all active treatments. For umeclidinium 62.5 mcg daily, the improvement vs placebo was 115 mL (95% CI, 76 to 155). Improvements were also noted for dyspnea and time to first COPD exacerbation (*Donohue et al 2013*).

- Two additional randomized, double-blind trials (published together, N = 862 and N = 872) evaluated the addition of umeclidinium to fluticasone propionate/salmeterol in patients with COPD. Patients received once-daily umeclidinium 62.5 mcg, umeclidinium 125 mcg, or placebo added to twice-daily fluticasone propionate/salmeterol 250/50 mcg for 12 weeks. In both studies, improvement in the primary endpoint, the trough FEV_1 on day 85, was significantly better in both umeclidinium groups vs placebo, with differences of 147 mL (95% CI, 107 to 187) and 127 mL (95% CI, 89 to 164) for the 62.5 mcg strength and 138 (95% CI, 97 to 178) and 148 (95% CI, 111 to 185) for the 125 mcg strength. Significant improvements were also demonstrated for the weighted mean FEV_1 over 0 to 6 hours post-dose and rescue albuterol use, while results on SGRQ and the COPD Assessment Test were mixed (*Siler et al 2016*).

- A review and meta-analysis evaluated the use of umeclidinium compared to placebo (as well as compared to active controls). The meta-analysis included randomized trials with a duration of ≥ 12 weeks. A total of 10 trials were included. Key results from this meta-analysis were as follows (*Pleasants et al 2016*):
  - The weighted mean difference in FEV_1 change from baseline (primary endpoint) for umeclidinium 62.5 mcg vs placebo was 120 mL (95% CI, 100 to 130) (based on data from 7 studies).
  - The weighted mean difference in TDI change from baseline for umeclidinium 62.5 mcg vs placebo was 0.61 (95% CI, -0.17 to 1.39) (based on data from 2 studies).
  - The weighted mean difference in SGRQ change from baseline for umeclidinium 62.5 mcg vs placebo was -2.34 (95% CI, -4.59 to 0.08) (based on data from 5 studies).
  - Umeclidinium 62.5 mcg significantly improved the time to first COPD exacerbation, with an HR of 0.61 (95% CI, 0.41 to 0.90) (based on data from 1 study).
- A systematic review and meta-analysis of 4 randomized controlled trials with a duration ≥ 12 weeks evaluated umeclidinium compared to placebo in patients with moderate to severe COPD (n = 37,98). Key results from this meta-analysis were as follows (*Ni et al 2017*):
  - Odds of moderate exacerbations requiring steroids and/or antibiotics were reduced with umeclidinium vs placebo (OR, 0.61; 95% CI, 0.46 to 0.80), but there was no difference in odds of severe exacerbations requiring hospitalization between groups (based on data from 4 studies).
  - Umeclidinium reduced SGRQ total score compared to placebo (MD, -4.79 units; 95% CI, -8.84 to -0.75) and the odds of having an improvement ≥ 4 units in SGRQ total score was higher with umeclidinium vs placebo (OR, 1.45; 95% CI, 1.16 to 1.82) (based on data from 3 studies).
  - TDI focal score was improved with umeclidinium vs placebo (MD, 0.76 units; 95% CI, 0.43 to 1.09 units) (based on data from 3 studies).
  - Change from baseline in trough FEV_1 was higher with umeclidinium vs placebo (MD, 0.14 L; 95% CI, 0.12 to 0.17 L) (based on data from 4 studies).
- Glycopyrrolate has been evaluated for the treatment of COPD in Phase 3, randomized, multicenter, double-blind, placebo-controlled trials.
  - Two 12-week trials (N = 441 and 428) evaluated the efficacy of glycopyrrolate inhalation powder 15.6 mcg twice daily vs placebo. Both trials met their primary endpoint, demonstrating differences from placebo in the mean change from baseline in FEV_1 area under the curve (AUC) from 0 to 12 hours (FEV_1 AUC_{0-12}) of 139 mL (95% CI, 95 to 184; $p < 0.001$) and 123 mL (95% CI, 81 to 165; $p < 0.001$), respectively. Improvement in several secondary endpoints was also demonstrated, including trough FEV_1, and SGRQ score. The difference in the TDI score was significant in one of the two studies (*Clinicaltrials.gov 2015, Kerwin et al 2016, LaForce et al 2016*).
  - The efficacy of nebulized glycopyrrolate was evaluated in two replicate 12-week randomized controlled trials (GOLDEN 3 and 4; N = 653 and N = 641, respectively) in patients with moderate to very severe COPD. Compared with placebo, patients in the intention to treat analysis who were randomized to nebulized glycopyrrolate 25 mcg or 50 mcg twice daily experienced significant increases in the primary endpoint, FEV_1 from baseline (mean placebo-adjusted differences, 0.096 and 0.104, respectively, in GOLDEN 3; 0.081 and 0.074, respectively, in GOLDEN 4; all $p < 0.0001$). Improvements from baseline were also observed with both doses of nebulized glycopyrrolate vs placebo in FVC and SGRQ scores (*Kerwin et al 2017*).

Comparisons between different anticholinergics and formulations

- A small number of clinical trials have compared tiotropium to ipratropium.
  - A randomized, double-blind, double-dummy study (N = 288) compared tiotropium 18 mcg daily to ipratropium 40 mcg four times daily over 15 weeks. This study demonstrated that the FEV_1 response was significantly greater for tiotropium compared to ipratropium at all time points ($p < 0.05$). Differences in trough FEV_1 values were most

pronounced, whereas differences in peak FEV_1 did not reach statistical significance. Improvements were also greater for tiotropium for morning and evening PEF rate and use of rescue albuterol (*van Noord et al 2000*).
  - A second double-blind, double-dummy study (N = 535) also compared tiotropium 18 mcg daily to ipratropium 40 mcg four times daily. At the end of one year, trough FEV_1 was significantly better in the tiotropium group (difference, 150 mL; $p < 0.001$). FVC results paralleled those for FEV_1. Tiotropium also led to improved PEF rates and reduced use of rescue albuterol (*Vincken et al 2002*).
  - Two identical double-blind, double-dummy 12-week trials (total N = 719) compared tiotropium Respimat in both 5 mcg and 10 mcg daily doses to placebo and to ipratropium bromide. Results for the 5 mcg dose demonstrated that trough FEV_1 was improved significantly more with tiotropium vs placebo (difference, 118 mL; $p < 0.0001$) and compared to ipratropium (difference, 64 mL; $p < 0.01$) (*Voshaar et al 2008*).
- A meta-analysis demonstrated that compared to patients receiving ipratropium, patients receiving tiotropium were more likely to experience improvement in SGRQ scores and TDI scores. Patients receiving tiotropium also experienced a reduced rate of exacerbations compared to patients receiving ipratropium (*Yohannes et al 2011*).
- A systematic review and meta-analysis (N = 2 studies; 1073 patients) evaluated the safety and efficacy of tiotropium compared to ipratropium (*Cheyne et al 2015*). In one study, patients used tiotropium by Handihaler for 12 months, and in the other, patients used tiotropium by Respimat for 12 weeks. Primary endpoints included the trough FEV_1 at three months and serious adverse events.
  - Trough FEV_1 at three months was significantly increased with tiotropium compared to ipratropium (MD, 109 mL; 95% CI, 81 to 137; $I^2 = 62\%$).
  - Fewer patients experienced one or more non-fatal serious adverse events with tiotropium compared to ipratropium (OR, 0.5; 95% CI, 0.34 to 0.73). Patients taking tiotropium were also less likely to experience a COPD-related serious adverse event (OR, 0.59; 95% CI, 0.41 to 0.85).
  - Benefits were also demonstrated for tiotropium compared to ipratropium for secondary endpoints including exacerbations, hospital admissions, and quality of life. There was no significant difference in mortality between the two treatments.
- The large, randomized, double-blind TIOSPIR trial (N = 17,135) compared tiotropium Respimat at a dose of 2.5 mcg or 5 mcg daily to tiotropium Handihaler (18 mcg daily). During a mean follow-up of 2.3 years, tiotropium via Respimat and Handihaler were shown to have similar safety and efficacy profiles (*Wise et al 2013*).
  - Risk of death for tiotropium Respimat 5 mcg daily vs Handihaler: HR, 0.96; 95% CI, 0.84 to 1.09.
  - Risk of first exacerbation for tiotropium Respimat 5 mcg daily vs Handihaler: HR, 0.98; 95% CI, 0.93 to 1.03.
- A systematic review evaluated tiotropium Respimat 5 mcg daily vs tiotropium Handihaler 18 mcg daily on pharmacokinetic, efficacy, and safety data. Data were included from a total of 22 comparative studies (10 published studies, one submitted manuscript, and 11 Congress abstracts). Key results from this review were as follows (*Dahl et al 2016*):
  - Several clinical trials demonstrated similar pharmacokinetic profiles between the two formulations. Although it had previously been suggested that systemic exposure may be greater with tiotropium Respimat, a recent study showed that exposure may actually be slightly lower with the Respimat formulation.
  - Results of several randomized trials demonstrated that the efficacy and safety profiles are comparable between the two formulations, and results from post-hoc and pooled analyses provide further support for similarity on lung function, exacerbations, and safety outcomes in various patient subtypes.
  - Similar results for health-related quality of life were demonstrated with each formulation based on the SGRQ total score.
- A double-blind, double-dummy, randomized Phase 3b trial (N = 414) compared tiotropium 18 mcg daily to aclidinium 400 mcg twice daily. This trial demonstrated no significant differences between active treatments at week 6 in the change from baseline in FEV_1 AUC over 24 hours (AUC_{0-24}). FEV_1 AUC_{0-12} was numerically greater with tiotropium vs aclidinium, and AUC_{12-24} was numerically greater with aclidinium vs tiotropium; however, differences between active treatments were not statistically significant. The two groups also had comparable results for most COPD symptom measures (*Beier et al 2013*).
- A 48-week, open-label trial (GOLDEN 5; N = 1086) compared glycopyrrolate nebulizer solution 50 mcg twice daily to tiotropium 18 mcg daily in 1086 patients with moderate to very severe COPD. The trial demonstrated that the rates of treatment-emergent adverse events were generally similar between groups, while rates of respiratory events were somewhat higher with glycopyrrolate vs tiotropium (35.2% vs 28.8%, respectively); the authors attributed this in part to incorrect nebulizer technique early in treatment. There were no significant differences between groups in the change

from baseline in FEV_1 or SGRQ. There was a similar and numerically lower incidence of exacerbations with glycopyrrolate nebulizer solution vs tiotropium (18.5% and 22.5%, respectively) (*Ferguson et al 2017*).

- Results were reported in abstract form of an open-label randomized control trial comparing tiotropium 18 mcg daily with aclidinium 400 mcg twice daily in addition to background therapy in adults with moderate to severe COPD. After 8 weeks of treatment, the primary endpoint, FEV_1 AUC_{0-3} was not significantly different between groups. Secondary outcomes evaluating other measures of lung function were not significantly different; however, SGRQ and Modified Medical Research Council scores were significantly improved with aclidinium (*Nakamura et al 2017*).
- A network meta-analysis (N = 21 studies; 22,542 patients) demonstrated no significant differences between tiotropium 18 mcg daily and aclidinium 400 mcg twice daily in FEV_1, SGRQ, or TDI score (*Karabis et al 2013*).
- A 12-week, blinded, double-dummy, randomized trial (N = 1107) compared umeclidinium 62.5 mcg daily delivered via the Ellipta device and tiotropium 18 mcg daily delivered via the Handihaler device (*Feldman et al 2016*). The primary endpoint, LSM change from baseline in trough FEV_1 at day 85 in the per-protocol population (N = 976), was greater with umeclidinium vs tiotropium (difference, 59 mL; 95% CI, 29 to 88; $p < 0.001$). Similar results were seen in the intention-to-treat population (difference, 53 mL; 95% CI, 25 to 81; $p < 0.001$). Improvements in the weighted mean FEV_1 over 0 to 24 hours post-dose were similar between treatments, but greater with umeclidinium vs tiotropium over 12 to 24 hours post-dose (difference, 70 mL; 95% CI, 14 to 127; $p = 0.015$). No differences were observed between umeclidinium and tiotropium in patient-reported outcomes (TDI and SGRQ), and the safety profiles were similar with both treatments. More patients preferred the Ellipta device compared to the Handihaler, including an overall device preference and scores for ease of use.
  - There were several limitations to this trial, including a short duration and incomplete blinding (markings differed among active tiotropium capsules and placebo, and stickers were used to obscure inhaler markings).
- A network meta-analysis (N = 24 studies; 21,311 participants) compared tiotropium 18 mcg daily to aclidinium 400 mcg twice daily, glycopyrronium 50 mcg daily (not the FDA-approved dosing), and umeclidinium 62.5 mcg daily in patients with COPD. All active treatments demonstrated favorable outcomes vs placebo for 12-week trough FEV_1, 24-week trough FEV_1, 24-week SGRQ, 24-week TDI, and 24-week rescue inhaler use (*Ismaila et al 2015*).
  - Based on 17 studies (11,935 participants) for the primary endpoint, the mean change from baseline in trough FEV_1 vs placebo at 12 weeks ranged from 101.4 to 136.7 mL, and was greatest for umeclidinium, followed by glycopyrronium, tiotropium, and aclidinium. However, the 95% credible interval (CrI) crossed zero in all between-treatment comparisons, so superiority was not demonstrated for any single LAMA over another.
- A network meta-analysis (N = 27 studies; 48,140 participants) compared tiotropium, aclidinium, and glycopyrronium for preventing COPD exacerbations (*Oba et al 2015*). All of the studied LAMAs reduced moderate-to-severe exacerbations compared to placebo; however, there were no significant differences demonstrated among the active treatments.
  - The analysis also evaluated the rate of severe exacerbations. Tiotropium dry powder inhaler was the only LAMA demonstrated to reduce severe exacerbations vs placebo (HR, 0.73; 95% CI, 0.6 to 0.86). However, the 95% CrI crossed zero in all between-treatment comparisons. The authors concluded that there were no statistically significant differences among LABAs in preventing COPD exacerbations.

Comparisons between anticholinergics and $beta_2$-agonists or ICS/LABA combinations

- In a meta-analysis of 4 trials, there was no statistically significant difference in short-term FEV_1 changes (up to 90 minutes post dose) between individuals receiving ipratropium compared to a $beta_2$-adrenergic agonist (albuterol, metaproterenol, or fenoterol) (*McCrory et al 2002*).
- Tiotropium has been compared to the LABAs salmeterol and indacaterol in several large comparative trials.
  - Two placebo-controlled trials of tiotropium 18 mcg daily also included an active control arm in which patients received salmeterol 50 mcg twice daily. In the first trial (N = 623), the improvement in trough FEV_1 at 24 weeks was greater with tiotropium compared to salmeterol (difference, 52 mL; $p < 0.01$). Differences also favored tiotropium for FVC (difference, 112 mL; $p < 0.01$) and PEF rate (difference, 5.9 L/minute; $p < 0.01$). Tiotropium was also better than salmeterol in improving TDI focal score (difference, 0.78 units; $p < 0.05$). The difference between active treatments in SGRQ was not statistically significant (*Donohue et al 2002*). In the second trial (N = 1207), improvements in FEV_1, FEV_1 area under the curve over three hours (AUC_{0-3}), and FVC were greater for tiotropium vs salmeterol; however, there were no significant differences among active treatment groups for time to first COPD exacerbation, hospital admissions, or TDI focal scores (*Brusasco et al 2003*).
  - A large double-blind randomized trial (N = 7348) (POET-COPD) demonstrated that tiotropium 18 mcg daily increased the time to first COPD exacerbation, the risk of moderate exacerbations, and the risk of severe exacerbations

compared to treatment with salmeterol (*Vogelmeier et al 2011*). Prolongation of time to the first exacerbation was also demonstrated in prespecified subgroups of patients with GOLD stage II COPD and patients who were maintenance-therapy-naïve (*Vogelmeier et al 2013*).
  - A randomized trial (N = 1683) compared two doses of the once-daily LABA indacaterol (150 mcg and 300 mcg) to tiotropium 18 mcg daily and to placebo. In this trial, patients receiving placebo or indacaterol were blinded, but tiotropium was open-label because blinded tiotropium was not available. The primary endpoint, trough FEV_1 at 12 weeks, was greater for indacaterol (both doses) than for tiotropium (difference, 40 mL; $p \leq 0.01$). Greater improvements were also demonstrated for indacaterol vs tiotropium for the proportions of patients achieving a clinically important improvement in TDI total score ($p \leq 0.01$), use of rescue albuterol ($p \leq 0.001$), and change from baseline in morning and evening PEF ($p < 0.05$). Rates of exacerbations did not differ among active treatment groups (*Donohue et al 2010*).
  - A randomized, double-blind, double-dummy trial compared tiotropium 18 mcg daily to indacaterol 150 mcg daily. In this trial, trough FEV_1 with tiotropium was determined to be non-inferior to indacaterol, but not superior (treatment difference, 0 mL; 95% CI, -20 to 20). However, FEV_1 and FVC were demonstrated to be greater with indacaterol on day one when evaluated five minutes, 30 minutes, and one hour after dosing. More patients receiving indacaterol compared to those taking tiotropium experienced a clinically significant improvement in TDI scores (OR, 1.49; $p < 0.001$) and SGRQ scores (OR, 1.43; $p < 0.001$). In addition, use of rescue medication was lower in the indacaterol group (*Buhl et al 2011*).
- Tiotropium has also been compared to combination ICS/LABAs.
  - Tiotropium 18 mcg daily has been compared to fluticasone/salmeterol 250 mcg/50 mcg in a randomized, double-blind, double-dummy, two-year trial (N = 1323). The primary endpoint in this trial, the rate of exacerbations over two years, was comparable in the tiotropium (1.32/year) and fluticasone/salmeterol (1.28/year) groups ($p = 0.656$). Patients randomized to tiotropium were significantly more likely to withdraw from the study than those randomized to fluticasone/salmeterol (HR, 1.29; 95% CI, 1.08 to 1.54; $p = 0.005$). In addition, mortality was significantly lower in the fluticasone/salmeterol group (3%) than in the tiotropium group (6%) (HR, 0.48; 95% CI, 0.27 to 0.85; $p = 0.012$) (*Wedzicha et al 2008*).
  - Tiotropium 18 mcg daily has also been compared to fluticasone furoate/vilanterol 100/25 mcg daily in a randomized, double-blind, double-dummy, 12-week trial (N = 623) in patients with COPD and cardiovascular disease (CVD) or CVD risk (≥ 1 risk factor of hypertension, hypercholesterolemia, or treated diabetes). The primary endpoint, change from baseline in weighted mean FEV_1 over 24 hours at 12 weeks, was similar in the two treatment arms (LSM change, 95 mL and 117 mL in the tiotropium and fluticasone furoate/vilanterol groups, respectively, with a difference of 22 mL [95% CI, -12 to 55; $p = 0.201$]). Trough FEV_1 after 12 weeks was improved to a similar extent in both groups. Some secondary endpoints seemed to favor tiotropium (change from baseline in FVC and inspiratory capacity), while other endpoints seemed to favor fluticasone furoate/vilanterol (onset of bronchodilation, rescue medication use, dyspnea, SGRQ, and COPD Assessment Test scores). Safety was generally similar, although pneumonia was reported more frequently in the fluticasone furoate/vilanterol group. Cardiovascular monitoring did not demonstrate an increased cardiovascular risk. The cardiovascular safety profile was similar between groups; however, there were 2 deaths from cardiovascular events in the tiotropium group (both patients had hypertension and one smoked and had a family history of CVD). Fewer patients experienced a COPD exacerbation in the fluticasone furoate/vilanterol group (2%) than the tiotropium group (4%) (*Covelli et al 2015*).
- Meta-analyses comparing tiotropium to LABAs do not consistently demonstrate superiority on key endpoints for either treatment. One meta-analysis (N = 7 trials; 12,223 participants) demonstrated a reduction in the proportion of patients experiencing one or more exacerbations with tiotropium compared to a LABA; however, one trial contributed the most weight to this analysis (Chong et al 2012).
- A systematic review and network meta-analysis (N = 71 trials; 73,062 participants) evaluated the efficacy of various treatment options for patients with COPD that could not be controlled by short-acting therapies alone. This analysis ranked ICS/LABA combinations first for results on SGRQ and trough FEV_1. LAMAs and LABAs were ranked second and third for each measure, and these two categories of medications had similar effects overall (*Kew et al 2014*).
- A systematic review and network meta-analysis (N = 10 trials; 10,894 participants) compared the effects of LABA/tiotropium combination therapy vs either therapy alone (*Farne et al 2015*).
  - Compared to tiotropium alone, combination treatment resulted in a slightly larger improvement in SGRQ (MD, -1.34; 95% CI, -1.87 to -0.8; 6709 participants; 5 studies). There were no significant differences in hospital admissions (4 studies; 4,856 participants) or all-cause mortality (10 studies; 9633 participants). The improvement in pre-

bronchodilator FEV_1 at the end of the study showed a statistically significant increase in the combination group compared to the tiotropium group (MD, 60 mL; 95% CI, 50 to 70; 10 studies; 9573 participants). Results for exacerbations were not pooled due to clinical heterogeneity.
  - Compared to LABA alone, combination treatment resulted in a small but statistically significant improvement in SGRQ (MD, -1.25; 95% CI, -2.14 to -0.37; 3378 participants; 4 studies). There were no significant differences in all-cause hospitalizations, hospitalizations for exacerbations, or all-cause mortality (3 studies; 3514 participants for all endpoints). The improvement in pre-bronchodilator FEV_1 at the end of the study showed a statistically significant increase in the combination group compared to the LABA group (MD, 70 mL; 95% CI, 60 to 90; 4 studies; 3513 participants). There was a significantly lower risk of exacerbation with combination treatment vs LABA monotherapy (OR, 0.8; 95% CI, 0.69 to 0.93; 3 studies; 3514 participants).
- There is little data on the use of aclidinium compared to $beta_2$-agonists. A small study (N = 79) compared various doses of aclidinium to the LABA formoterol in a crossover study in which each treatment was given for seven days. The primary endpoint, difference in FEV_1 $AUC_{0\text{-}12}$ on day seven, was not significantly different in the aclidinium 400 mcg twice daily and formoterol 12 mcg twice daily groups (208 mL and 210 mL, respectively). There also was no difference between treatment with aclidinium 400 mcg and formoterol with regard to changes in FEV_1 $AUC_{0–24}$; however, patients treated with aclidinium 400 mcg experienced a statistically significant improvement in FEV_1 $AUC_{12–24}$ compared to treatment with formoterol (56 mL; $p < 0.01$) *(Singh et al 2012*).

ASTHMA

- Clinical trials have demonstrated efficacy with the tiotropium Respimat vs placebo in patients with asthma not well controlled on baseline therapy that included at least an ICS.
- Efficacy of tiotropium for the treatment of asthma has also been established through many systematic reviews and meta-analyses.
  - A series of systematic reviews and meta-analyses have reported the efficacy of tiotropium in the treatment of asthma (*Rodrigo et al 2015a, Rodrigo et al 2015, Rodrigo et al 2017*). These analyses demonstrated the ability of tiotropium to improve lung function endpoints, including FEV_1 and/or PEF, while the impact on overall asthma control, asthma-related quality of life, and asthma exacerbations were mixed.
  - Focused meta-analyses have also demonstrated the efficacy of tiotropium for the management of asthma when added to an ICS compared to use of the ICS alone (*Anderson et al 2015, Wang et al 2018*), and when added to an ICS/LABA compared to ICS/LABA alone (*Kew et al 2016*). Studies generally supported the efficacy of tiotropium based on lung function, with less evidence for an impact on exacerbations and asthma-related quality of life.
  - A meta-analysis compared the addition of a LAMA (tiotropium) to addition of a LABA (salmeterol) in patients not adequately controlled on an ICS (*Kew et al 2015*). No significant differences were demonstrated in the rate of exacerbations requiring oral corticosteroids.

Placebo-controlled and trials

- Clinical trials have compared tiotropium Respimat to placebo in patients with asthma not well controlled on baseline therapy that included at least an ICS.
- A 12-week, Phase 3, multicenter, randomized trial (N = 465) compared tiotropium Respimat 2.5 mcg daily, 5 mcg daily, and placebo in adults with asthma who were symptomatic despite treatment with a low- to medium-dose ICS (200 to 400 mcg budesonide or equivalent), which was continued during the trial. The primary endpoint, change from baseline in peak FEV_1 within 3 hours of dosing (FEV_1 [0 to 3 hr]), was greater for both tiotropium doses compared to placebo, with adjusted MDs of 159 mL and 128 mL for the 2.5 mcg and 5 mcg doses, respectively ($p < 0.001$ for both comparisons vs placebo). Both doses of tiotropium were also superior to placebo with regard to the secondary endpoints of adjusted mean trough FEV_1 and FEV_1 $AUC_{0\text{ to }3}$ responses, and the other endpoints of morning and evening PEF. Adverse events were comparable across the treatment groups (*Paggiaro et al 2016*).
- Two 24-week, Phase 3, multicenter, randomized trials (total N = 2103) compared tiotropium Respimat 2.5 mcg daily, 5 mcg daily, salmeterol 50 mcg twice daily, or placebo in adults with asthma who were symptomatic despite treatment with a medium-dose ICS (400 to 800 mcg budesonide or equivalent) alone or in combination with a $beta_2$-agonist. During the study, patients continued their ICS, but pre-study LABAs were discontinued. Co-primary endpoints were the peak FEV_1 (0 to 3 hr), trough FEV_1, and responder rate according to the seven-question Asthma Control Questionnaire (ACQ-7). Pooled data demonstrated the following (*Kerstjens et al 2015*):

- The differences vs placebo in peak FEV_1 were 223 mL (95% CI, 185 to 262) in the tiotropium 2.5 mcg group, 185 mL (95% CI, 146 to 223) in the tiotropium 5 mcg group, and 196 mL (95% CI, 158 to 234) in the salmeterol group (all p < 0.0001 vs placebo).
- The differences in trough FEV_1 were 180 mL (95% CI, 138 to 221) in the tiotropium 2.5 mcg group, 146 mL (95% CI, 105 to 188) in the tiotropium 5 mcg group, and 114 mL (95% CI, 73 to 155) in the salmeterol group (all p < 0.0001 vs placebo).
- There were more ACQ-7 responders (improvement of ≥ 0.5) in the tiotropium 2.5 mcg group (OR, 1.33; 95% CI, 1.03 to 1.72; p = 0.031), tiotropium 5 mcg group (OR, 1.32; 95% CI, 1.02 to 1.71; p = 0.035), and salmeterol group (OR, 1.46; 95% CI, 1.13 to 1.89; p = 0.0039), than in the placebo group.
- Severe asthma exacerbations were recorded in 4%, 6%, 6%, and 8% of patients in the tiotropium 2.5 mcg, 5 mcg, salmeterol, and placebo groups, respectively. At least one episode of asthma worsening was recorded in 22%, 28%, 25%, and 32% of patients, respectively. The investigators noted a statistically significant reduction in risk of first severe exacerbation with tiotropium 2.5 mcg (p = 0.0084) and of first asthma worsening with tiotropium 2.5 mcg and salmeterol (p = 0.0007 and 0.013, respectively) vs placebo.
- The numbers of adverse events and serious adverse events were comparable among groups.

- Additional support for the safety and efficacy of tiotropium for asthma treatment was provided by the results of two 48-week, Phase 3, multicenter, randomized trials (total N = 912) comparing tiotropium Respimat 5 mcg daily to placebo in adults with asthma not adequately controlled on an ICS (≥ 800 mcg budesonide or equivalent) and a LABA. Tiotropium was superior to placebo for endpoints including mean change in peak FEV_1, trough FEV_1, and the time to first severe exacerbation. Adverse events were similar in the two groups. However, it should be noted that this study only evaluated a dose that is higher than the FDA-approved dose for asthma (*Kerstjens et al 2012*).
- Two randomized Phase 3 trials evaluated the use of tiotropium Respimat in adolescents 12 to 17 years of age.
  - A 12-week trial (N = 392) compared tiotropium Respimat 2.5 mcg daily, 5 mcg daily, and placebo in patients with severe asthma who were on background treatment of an ICS plus one or more controller medications, such as a LABA. The difference vs placebo for the primary endpoint, peak FEV_1 (0 to 3 hr), was 111 mL (95% CI, 2 to 220) for the 2.5 mcg dose and 90 mL (95% CI, -19 to 198) for the 5 mcg dose (*Hamelmann et al 2017*).
  - A 48 week trial (N = 398) compared tiotropium Respimat 2.5 mcg daily, 5 mcg daily, and placebo in patients with moderate asthma who were on background treatment of at least an ICS. The difference vs placebo in the primary endpoint, peak FEV_1 (0 to 3 hr) was 134 mL (95% CI, 34 to 234) for the 2.5 mcg dose and 174 mL (95% CI, 76 to 272) for the 5 mcg dose (*Clinicaltrials.gov 2014, Spiriva Respimat prescribing information 2017*).
- According to the prescribing information, efficacy of tiotropium in pediatric patients 6 to 11 years of age was based on extrapolation of efficacy in adults, and on two randomized, double-blind, placebo-controlled trials of 12 and 48 weeks duration. A total of 801 patients aged 6 to 11 years were enrolled in the two trials (271 receiving tiotropium 2.5 mcg daily 265 receiving tiotropium 5 mcg daily, and 265 receiving placebo). The primary endpoint in both trials was the change from baseline in the peak FEV_1 (0 to 3 hr), with the evaluation defined at week 12 in the 12-week trial and at week 24 in the 48-week trial (*Spiriva Respimat prescribing information 2017*).
  - The 12-week trial enrolled patients with severe asthma who were on background treatment of ICS plus ≥ 1 controller medication (eg, LABA). The mean difference vs placebo in the primary endpoint was 40 mL (95% CI, -30 mL to 100 mL; not significant).
  - The 48-week trial enrolled patients with moderate asthma on background treatment of at least an ICS. The mean difference vs placebo in the primary endpoint was 170 mL (95% CI, 110 to 230).
- An additional trial in children aged 6 to 11 years with severe symptomatic asthma randomized patients to double-blind tiotropium 5 mcg, 2.5 mcg, or placebo administered via a Respimat device in addition to background therapy with medium-dose ICS. After 12 weeks, tiotropium 5 mcg, but not 2.5 mcg, improved the primary end point, peak FEV_1 within 3 hours after dosing compared with placebo (MD, 139 mL; 95% CI, 75 to 203 and 35 mL; 95% CI, -28 to 99 for 5 and 2.5 mcg doses, respectively). Results were similar for the key secondary endpoint, trough FEV_1 *(Szefler et al 2017*).

Systematic reviews and network meta-analyses

- A systematic review and meta-analysis (N = 13 studies; 4966 patients) evaluated the efficacy and safety of tiotropium in patients with asthma. Tiotropium was given via the Respimat device in most studies, and the duration of the included studies ranged from 4 to 52 weeks (*Rodrigo et al 2015a*).
  - In 10 studies evaluating the addition of tiotropium to an ICS vs ICS alone in patients with mild or moderate asthma, the analysis demonstrated significant improvements in morning and evening PEF (MD, 22 to 24 L/min; p < 0.00001)

and peak and trough FEV_1 (MD, 150 mL; 95% CI, 110 to 180 and 140 mL; 95% CI, 110 to 160, respectively) with the addition of tiotropium. Tiotropium also significantly improved ACQ-7 and Asthma Quality of Life Questionnaire (AQLQ) scores from baseline (MD, -0.14 units; 95% CI, -0.19 to -0.09 and 0.07 units; 95% CI, 0.01 to 0.13, respectively). Tiotropium was also associated with a decrease in the number of patients with ≥ 1 asthma exacerbation (10.5% vs 13.3%; relative risk [RR], 0.74; 95% CI, 0.57 to 0.95).
    - In four studies comparing the addition of either tiotropium or LABA to an ICS in patients with moderate asthma, tiotropium improved morning PEF more than LABA, but the magnitude of the difference was small (6.6 L/min). There were no significant differences in evening PEF or peak or trough FEV_1. The addition of tiotropium was inferior to the addition of LABA for AQLQ (MD, -0.12 units; 95% CI, -0.06 to -0.18). There were no significant differences in ACQ-7 total score or the number of patients with ≥ 1 exacerbation.
    - In three studies comparing triple therapy (tiotropium with ICS/LABA) vs LABA with a high-dose ICS in patients with severe asthma, the analysis demonstrated significant improvements with triple therapy in morning and evening PEF (MD, 16 L/min; $p < 0.0004$ and 20 L/min; $p < 0.00001$, respectively). Peak and trough FEV_1 was also significantly greater with triple therapy (MD, 120 mL; 95% CI, 90 to 160 and 80 mL; 95% CI, 40 to 110, respectively). Triple therapy was associated with significant improvements in ACQ-7 and AQLQ (MD, -0.2 units; 95% CI, -0.25 to -0.09 and 0.12 units; 95% CI, 0.05 to 0.18, respectively). Patients treated with triple therapy also had a lower likelihood of experiencing ≥ 1 exacerbation (18.2% vs 24%; RR, 0.7; 95% CI, 0.53 to 0.94).
- A systematic review and meta-analysis (N = 3 studies; 895 patients) evaluated the use of tiotropium Respimat in adolescents aged 12 to 18 years with moderate to severe asthma. Patients were also receiving an ICS or ICS/LABA and the duration of the studies ranged from 4 to 48 weeks. Primary outcomes were peak and trough FEV_1 (*Rodrigo et al 2015b*).
    - Tiotropium was associated with significant improvements in peak and trough FEV_1 with mean changes from baseline of 120 mL and 100 mL vs placebo, respectively ($p < 0.001$ for both comparisons).
    - Benefits were also shown with tiotropium for the secondary endpoint of exacerbation risk. There were no significant differences in the rate of ACQ-7 response, rescue medication use, withdrawals, adverse events, or serious adverse events.
- A systematic review and meta-analysis (N = 3 studies; approximately 900 patients) evaluated the use of tiotropium Respimat in children aged 6 to 11 years with moderate to severe symptomatic asthma. Patients were also receiving maintenance therapy with ICS or ICS plus ≥ 1 controller medication and the duration of the studies ranged from 4 to 48 weeks. Primary outcomes were peak and trough FEV_1 (*Rodrigo et al 2017*).
    - Tiotropium demonstrated significant improvements in peak FEV_1 of 102 mL and trough FEV_1 of 82 mL vs placebo ($p < 0.0001$ for both comparisons).
    - Tiotropium significantly increased the rate of ACQ-7 responders ($p = 0.04$) and decreased the number of patients ≥ 1 exacerbations ($p = 0.002$) vs placebo.
    - There were no significant differences in rescue medication use, study withdrawals, adverse events, or withdrawals due to adverse events.
- A systematic review and meta-analysis (N = 5 studies; 2563 patients) evaluated the safety and efficacy of an ICS plus LAMA vs ICS alone in patients with asthma. The LAMA used was tiotropium Respimat in all studies, and the duration of treatment ranged from 12 to 52 weeks. All studies used a double-blind, double-dummy design. The primary outcomes included exacerbations requiring oral corticosteroids, quality of life, and all-cause serious adverse events (*Anderson et al 2015*).
    - Based on 4 studies in 2277 patients, the rate of exacerbations requiring oral corticosteroids was lower in patients taking a LAMA add-on than in those receiving the same dose of ICS alone (OR, 0.65; 95% CI, 0.46 to 0.93; $I^2 = 0\%$).
    - Based on 3 studies in 1713 patients, scores on the AQLQ were slightly higher for those taking a LAMA add-on compared to ICS alone (MD, 0.05; 95% CI, -0.03 to 0.12; $I^2 = 0\%$), but the difference was not statistically significant and was less than the established minimal clinically important difference of 0.5.
    - Based on five studies in 2,562 participants, patients taking a LAMA reported fewer serious adverse events, but the effect was too inconsistent and imprecise to suggest a definite benefit over an ICS alone (OR, 0.6; 95% CI, 0.23 to 1.57; $I^2 = 59\%$).
    - Benefits were also demonstrated with add-on LAMA therapy compared to ICS alone for the secondary endpoints including FEV_1 and PEF. Differences were not statistically significant for ACQ results or the number of exacerbations requiring hospitalization.

- A systematic review and meta-analysis compared the use of a LAMA vs a LABA when added to an ICS in patients with asthma. A total of seven trials were included in the narrative review, and four of these trials (N = 2049) were included in the meta-analysis. All of the studies included in the meta-analysis used tiotropium as the LAMA and salmeterol as the LABA, and the duration of the trials ranged from 14 to 24 weeks. The primary outcomes included exacerbations requiring oral corticosteroids, quality of life, and serious adverse events (*Kew et al 2015*).
  - Based on 3 studies in 1753 patients, there was no significant difference in the rate of exacerbations requiring oral corticosteroids between the LAMA and LABA groups (OR, 1.05; 95% CI, 0.50 to 2.18).
  - Based on 4 studies in 1,745 patients, those treated with a LAMA scored slightly worse than those treated with a LABA for quality of life measured on the AQLQ (MD, -0.12; 95% CI, -0.18 to -0.05). The difference was statistically significant, but both results fell below the established minimal clinically important difference of 0.5.
  - There was no difference detected in the rate of serious adverse events (OR, 0.84; 95% CI, 0.41 to 1.73); however, the rate of serious adverse events was too low for this result to be considered reliable.
  - Secondary endpoints showed little or no difference between the LAMA and LABA groups; these included FEV_1, PEF, FVC, exacerbations requiring hospitalization, and ACQ results.
- A systematic review and meta-analysis evaluated the addition of a LAMA to adults with asthma not well controlled by an ICS/LABA. Three double-blind trials (total N = 1197) comparing LAMA to placebo were included, and all trials evaluated tiotropium (mostly 5 mcg once daily via Respimat) (*Kew et al 2016*).
  - Based on two studies enrolling 907 patients, it was found that patients taking tiotropium plus an ICS/LABA had numerically fewer exacerbations requiring oral corticosteroids than those taking an ICS/LABA alone, but the confidence intervals did not rule out lack of a difference (OR, 0.75; 95% CI, 0.57 to 1.07). No benefit on quality of life was seen with the addition of tiotropium, based on results from the AQLQ (MD, 0.09; 95% CI, -0.03 to 0.20).
  - Secondary endpoints demonstrated a benefit on lung function, but no significant improvement in exacerbations requiring hospital admission or scores on asthma control measured by the ACQ.
- A meta-analysis of 4 randomized controlled trials evaluated tiotropium when added to low- to medium-dose ICS in adults with moderate uncontrolled asthma, and found significant improvement with tiotropium in FEV percent predicted (3.46%; 95% CI, 2.20 to 4.63), peak FEV_1 (146.85 mL; (114.89 to 178.82), trough FEV_1 (122.03 mL; 95% CI, 92.92 to 151.13). These results were consistent among subgroups treated with different doses of tiotropium (*Wang et al 2018*).

CLINICAL GUIDELINES

COPD

- The 2018 GOLD guidelines state that the management strategy for stable COPD should be predominantly based on an assessment of the patient's symptoms and risk of exacerbations; the risk of exacerbations is based on a patient's exacerbation history. Key recommendations from the GOLD guidelines are as follows (*GOLD 2018*):
  - Inhaled bronchodilators are central to symptom management in COPD and commonly given on a regular basis to prevent or reduce symptoms.
    - Inhaled bronchodilators are recommended over oral bronchodilators.
  - LAMAs and LABAs significantly improve lung function, dyspnea, and health status, and reduce exacerbation rates.
    - LAMAs and LABAs are preferred over short-acting agents except for patients with only occasional dyspnea.
    - LAMAs have a greater effect on exacerbation reduction compared to LABAs and decrease hospitalizations.
  - Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on one bronchodilator, treatment should be escalated to two bronchodilators.
  - Combination treatment with a LABA and LAMA:
    - Reduces exacerbations compared to monotherapy or ICS/LABA.
    - Increases FEV_1 and reduces symptoms compared to monotherapy.
  - Long-term monotherapy with ICSs is not recommended. Long-term treatment with ICSs may be considered in association with LABAs for patients with a history of exacerbations despite treatment with long-acting bronchodilators.
  - Triple inhaled therapy of LAMA/LABA/ICS improves lung function, symptoms, and health status and reduces exacerbations compared to ICS/LABA or LAMA monotherapy.
  - Treatment recommendations are given for patients with COPD based on their GOLD patient group (see Table 3 below).
    - Group A: Patients should be offered bronchodilator treatment (short- or long-acting). This should be continued if symptomatic benefit is documented.
    - Group B: Initial therapy should consist of a long-acting bronchodilator (LAMA or LABA). For patients with persistent breathlessness on monotherapy, use of 2 bronchodilators is recommended (LAMA + LABA). For patients with

severe breathlessness, initial therapy with 2 bronchodilators may be considered. If the addition of a second bronchodilator does not improve symptoms, it is suggested that treatment could be stepped down to a single bronchodilator.

- Group C: Initial therapy should be a LAMA. Patients with persistent exacerbations may benefit from adding a second long-acting bronchodilator (LAMA + LABA, preferred) or using an ICS + LABA.
- Group D: It is recommended to start therapy with a LAMA + LABA combination. In some patients, initial therapy with an ICS + LABA may be the first choice; these patients may have a history and/or findings suggestive of asthma-COPD overlap. In patients who develop further exacerbations on LAMA + LABA therapy, alternative pathways include escalation to a LAMA + LABA + ICS (preferred) or a switch to an ICS + LABA. If patients treated with a LAMA + LABA + ICS still have exacerbations, options for selected patients may include addition of roflumilast, addition of a macrolide, or stopping the ICS.

Table 3. Assessment of symptoms and risk of exacerbations to determine GOLD patient group

Exacerbation history	Symptoms	
	mMRC 0 to 1 CAT < 10	mMRC ≥ 2 CAT ≥ 10
≥ 2 (or ≥ 1 leading to hospital admission)	C	D
0 or 1 (not leading to hospital admission)	A	B

Abbreviations: CAT = COPD assessment test; mMRC = modified British Medical Research Council questionnaire

- Guidelines for the prevention of acute exacerbations of COPD from the American College of Chest Physicians and the Canadian Thoracic Society state that a LAMA is recommended over either a short-acting muscarinic antagonist or a LABA. The guidelines state that certain combination bronchodilators or bronchodilator/ICS combinations may reduce exacerbations, but does not state that any combination is superior to LAMA monotherapy in patients with stable COPD (*Criner et al 2015*).

Asthma

- The National Asthma Education and Prevention Program (NAEPP) guideline from the NHLBI states that the initial treatment of asthma should correspond to the appropriate asthma severity category, and it provides a stepwise approach to asthma management. Long-term control medications such as ICSs, long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline, and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. ICSs are the most potent and consistently effective long-term asthma control medication. Quick-relief medications such as SABAs and anticholinergics are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness, and wheezing. Systemic corticosteroids are important in the treatment of moderate or severe exacerbations because these medications prevent progression of the exacerbation, speed recovery, and prevent relapses (*NHLBI 2007*).
  - Ipratropium provides additive benefit to a SABA in moderate-to-severe asthma exacerbations, and may be used as an alternative bronchodilator for patients who do not tolerate a SABA.
  - The guideline states that ipratropium and tiotropium have not demonstrated effectiveness in the long-term management of asthma; however, it should be noted that this guideline has not been updated since 2007.
- The GINA guideline also provides a stepwise approach to asthma management. It recommends an ICS as a preferred initial controller medication choice, with an increased ICS dose and/or addition of a LABA for increasing symptom severity (higher steps). At the highest step, it is recommended that the patient be referred for add-on treatment (eg, tiotropium, anti-IgE, or anti-IL5 agent) (*GINA 2018*).

- Tiotropium by mist inhaler is recommended as an add-on controller option in patients at higher steps (4 and 5). At step 4, it is recommended under “other controller options” (not preferred), and at step 5, it is recommended as one of several preferred add-on treatment options. In this setting, tiotropium is recommended as an add-on treatment for patients with a history of exacerbations; however, the guideline states that tiotropium is not for use in children less than 12 years of age.
- Add-on tiotropium by mist inhaler improves lung function and increases the time to severe exacerbation.

- A guideline on the definition, evaluation, and treatment of severe asthma is available from the European Respiratory Society (ERS) and the American Thoracic Society (ATS) (*Chung et al 2014*).
  - The guideline notes that ipratropium is commonly used in severe asthma patients in an attempt to reduce the daily use of beta$_2$-agonists, as well as in the treatment of asthma exacerbations. Although considered to be less effective, ipratropium is well tolerated and may be used alternately with beta$_2$-agonists for as-needed use throughout the day.
  - Tiotropium has been shown to improve lung function and symptoms in moderate-to-severe asthma patients not controlled on a moderate- to high-dose ICS with or without a LABA. In patients taking high doses of an ICS and a LABA, the addition of tiotropium has provided improvements in FEV_1, reduced as-needed SABA use, and modestly reduced the risk of a severe exacerbation. However, there have been no studies of tiotropium in children with asthma.

SAFETY SUMMARY

- Ipratropium solution and Atrovent HFA are contraindicated in patients with hypersensitivity to ipratropium, atropine and its derivatives, or components of the product. Incruse Ellipta and Tudorza Pressair are contraindicated in patients with severe hypersensitivity to milk proteins or hypersensitivity to any ingredient. Seebri Neohaler is contraindicated in patients with known hypersensitivity to glycopyrrolate or any of the product ingredients. Spiriva Handihaler and Spiriva Respimat are contraindicated in patients with hypersensitivity to tiotropium, ipratropium, or components of the product.
- Key warnings and precautions are similar among the anticholinergics, and include hypersensitivity, paradoxical bronchospasm, urinary retention, and ocular effects/narrow-angle glaucoma. It should also be noted that anticholinergics are for maintenance treatment and are not for initial treatment of acute episodes of bronchospasm where rescue therapy is required.
- The most common adverse effects reported for each anticholinergic are as follows:
  - Atrovent HFA (> 5% incidence): bronchitis, COPD exacerbation, dyspnea, and headache
  - Ipratropium solution (> 5% incidence): bronchitis, upper respiratory tract infection, dyspnea, and headache
  - Incruse Ellipta (≥ 2% incidence): nasopharyngitis, upper respiratory tract infection, cough, arthralgia
  - Seebri Neohaler (≥ 2% incidence): upper respiratory tract infection and nasopharyngitis
  - Spiriva Handihaler (> 5% incidence): upper respiratory tract infection, dry mouth, sinusitis, pharyngitis, non-specific chest pain, urinary tract infection, dyspepsia, and rhinitis
  - Spiriva Respimat (> 3% incidence in COPD): pharyngitis, cough, dry mouth, and sinusitis;
    Spiriva Respimat (> 2% incidence in asthma, adults): pharyngitis, sinusitis, bronchitis, and headache
  - Tudorza Pressair (> 5% incidence): headache and nasopharyngitis
- Although earlier trials raised some concerns about increased mortality with tiotropium when administered by the Respimat inhaler, a large, randomized, double-blind trial revealed no increased mortality for patients treated with tiotropium Respimat compared to tiotropium Handihaler (*Wise et al 2013*).
- Spiriva Handihaler, Tudorza, Incruse, and Seebri are Pregnancy Category C, while Atrovent HFA and ipratropium solution are pregnancy category B; Spiriva Respimat and Lonhala Magnair are not currently assigned a Pregnancy Category.

DOSING AND ADMINISTRATION

- Administration devices vary among products, and ease of use may vary based on patients’ dexterity and coordination. Notably, Seebri Neohaler and Spiriva Handihaler require inserting individual capsules into the inhaler prior to each dose, and Spiriva Respimat requires coordination of inhalation with actuation of the device. The patient’s ability to use an inhalation device is an important consideration in product selection.

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Atrovent HFA (ipratropium bromide)	Inhalation aerosol	Inhalation	Four times a day	• May use additional inhalations as required; maximum 12 inhalations per 24 hours • Canister-style inhaler; requires inserting the canister and priming before use • Hand/breath coordination is required
Incruse Ellipta (umeclidinium)	Inhalation powder	Inhalation	Once daily	• Disc-shaped inhaler with self-contained foil blister strips; opening the inhaler prepares a dose • Breath-activated; hand/breath coordination not required
ipratropium bromide solution	Inhalation solution	Inhalation (with nebulizer)	Three to 4 times per day	• May be mixed in nebulizer with albuterol or metaproterenol if used within 1 hour
Lonhala Magnair (glycopyrrolate)	Inhalation solution	Inhalation (with nebulizer)	Twice daily	• Lonhala should only be administered with the Magnair device. • Supplied in vials with complete Magnair nebulizer system (starter kit) or refill handset (refill kit) • 2 to 3 minutes to administer, plus cleaning/prep time
Seebri Neohaler (glycopyrrolate)	Inhalation powder	Inhalation	Twice daily	• Capsules should not be swallowed • Dry powder inhaler; requires insertion of a capsule into the inhaler and piercing before each dose • Breath-activated; hand/breath coordination not required
Spiriva Handihaler (tiotropium bromide)	Inhalation powder	Inhalation	Once daily	• Capsules should not be swallowed • Dry powder inhaler; requires insertion of a capsule into the inhaler and piercing before each dose • Breath-activated; hand/breath coordination not required
Spiriva Respimat (tiotropium bromide)	Inhalation spray	Inhalation	Once daily	• Inhaler should be primed before first use and if not used for > 3 days • Maximum benefits in asthma treatment may take up to 4 to 8 weeks • Canister-style inhaler; requires inserting the canister and priming before use • Twisting the canister prepares a dose for inhalation • Hand/breath coordination is required
Tudorza Pressair (aclidinium bromide)	Inhalation powder	Inhalation	Twice daily	• Dry powder inhaler; pressing a button prepares a dose • Breath-activated; hand/breath coordination not required

See the current prescribing information for full details

CONCLUSION

- The inhaled anticholinergics are used predominantly for the management of COPD, with an additional asthma indication specific to Spiriva Respimat (tiotropium).
  - Short-acting inhaled anticholinergics include Atrovent HFA (ipratropium bromide) inhalation aerosol and ipratropium bromide solution for nebulization.
  - The LAMAs include 4 molecular entities in 6 formulations: Incruse Ellipta (umeclidinium) inhalation powder, Lonhala Magnair (glycopyrrolate) inhalation solution and Seebri Neohaler (glycopyrrolate) inhalation powder, Spiriva

Handihaler (tiotropium) inhalation powder and Spiriva Respimat (tiotropium) inhalation spray, and Tudorza Pressair (aclidinium) inhalation powder.

- All LAMAs are indicated for the long-term maintenance treatment of airflow obstruction in patients with COPD, while Spiriva Handihaler and Respimat are also indicated to reduce COPD exacerbations. Spiriva Respimat is additionally indicated for the maintenance treatment of asthma.
  - Spiriva Handihaler (tiotropium bromide), Spiriva Respimat (tiotropium bromide), and Incruse Ellipta (umeclidinium) are all administered once daily, while the Seebri Neohaler and Tudorza Pressair are administered twice daily.
  - Lonhala Magnair is administered twice daily via the Magnair nebulizer. This product is appropriate for a small percentage of COPD patients who are unable to effectively use other inhalation devices.
  - Devices and administration methods vary among products, and some may be favored over others for patients with dexterity issues, suboptimal peak inspiratory flow rate, and/or difficulty with coordinating actuation of the device with inhalation.
- Current clinical evidence supports the efficacy of all products in this class for their FDA-approved indications, and efficacy is well established through placebo-controlled trials and systematic reviews and meta-analyses. Improvement in lung function, health status and/or respiratory symptoms vs placebo has been demonstrated for all products.
  - Limited comparisons among LAMAs have been conducted. Some have demonstrated differences, particularly for the lung function endpoints (ie, FEV_1), but no clear differences in symptoms or other patient-reported outcomes.
  - Tiotropium and umeclidinium have evidence supporting a reduction in COPD exacerbations; however, only tiotropium is indicated to reduce exacerbations per FDA-approved labeling.
- Safety is comparable among products. Key warnings/precautions include paradoxical bronchospasm, urinary retention, and ocular effects/narrow-angle glaucoma. Spiriva Handihaler, Tudorza, Incruse, and Seebri are pregnancy category C, while Atrovent HFA and ipratropium solution are pregnancy category B; Spiriva Respimat and Lonhala Magnair are not currently assigned a Pregnancy Category.
- GOLD guidelines recommend LAMAs for most patients with COPD, as they improve lung function, dyspnea, and health status, and reduce exacerbations.
  - There is no preference stated for one LAMA compared to another; however, the choice of agent should be based on an assessment of the patient's symptoms and risk of exacerbations.
  - LAMAs have a greater effect on exacerbation reduction compared to LABAs.
  - Guidelines emphasize that the use of long-acting bronchodilators is recommended over short-acting bronchodilators except for patients with only occasional dyspnea, and inhaled therapy is preferred.
- GINA guidelines recommend tiotropium Respimat be considered in patients aged ≥ 12 years whose asthma is not well controlled with an ICS/LABA combination; its FDA-approved indication extends its use to patients aged ≥ 6 years.

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Publication Date: June 1, 2018

INTRODUCTION

- Inhaled beta$_2$-agonist combination agents include a beta$_2$-agonist combined with an inhaled corticosteroid (ICS), inhaled anticholinergic, or both. Beta$_2$-agonists can be short-acting beta$_2$-agonists (SABA) or long-acting beta$_2$-agonists (LABA); most combinations contain a LABA. Similarly, inhaled anticholinergics, also known as muscarinic antagonists, can be short-acting muscarinic antagonists (SAMA) or long-acting muscarinic antagonists (LAMA); most combinations contain a LAMA.
- Individual beta$_2$-agonist combinations are Food and Drug Administration (FDA) approved for the treatment of asthma, chronic obstructive pulmonary disease (COPD), or both.
  - All combinations of a beta$_2$-agonist and an ICS are indicated for the treatment of asthma, and some are additionally indicated for the treatment of COPD.
  - Combinations of a beta$_2$-agonist and an anticholinergic medication are indicated for COPD, as is the one available LAMA/LABA/ICS triple combination.
  - Refer to Tables 2A, 2B, and 2C for specific indications for each product.
- Asthma is a chronic lung disease that inflames and narrows the airways. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing. Asthma affects people of all ages, but most often starts during childhood. In the United States (U.S.), more than 25 million people are known to have asthma, including about 7 million children (*National Heart, Lung, and Blood Institute [NHLBI] 2017*).
- COPD is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities. The abnormalities are usually caused by exposure to noxious particles or gases, and cigarette smoking is a key risk factor. Airflow limitation is caused by a combination of small airway disease (eg, obstructive bronchiolitis) and parenchymal destruction (emphysema). The most common symptoms of COPD include dyspnea, cough, and sputum production (*Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2018*). COPD affects 6.4% of the U.S. population and is a major contributor to mortality from chronic lower respiratory diseases, the third leading cause of death in the U.S. (*Centers for Disease Control and Prevention 2017*).
- Medispan class/subclass: Sympathomimetics/Adrenergic Combinations

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Beta$_2$-agonist & corticosteroid combinations	
Advair Diskus & Advair HFA (fluticasone propionate/salmeterol)	-
AirDuo RespiClick (fluticasone propionate/salmeterol)	✔ *
Breo Ellipta (fluticasone furoate/vilanterol)	-
Dulera (mometasone furoate/formoterol fumarate dihydrate)	-
Symbicort (budesonide/formoterol fumarate dihydrate)	-
Beta$_2$-agonist & anticholinergic combinations	
Anoro Ellipta (umeclidinium/vilanterol)	-
Bevespi Aerosphere (glycopyrrolate/formoterol fumarate)	-
Combivent Respimat (ipratropium/albuterol)	-
ipratropium/albuterol solution	✔
Stiolto Respimat (tiotropium/olodaterol)	-
Utibron Neohaler (glycopyrrolate/indacaterol)	-
Triple combination	
Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol)	-

*Authorized generic
†Branded product DuoNeb is no longer marketed.

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2A. FDA-Approved Indications for Beta$_2$-agonist/Corticosteroid Combination Agents

Indication	Advair Diskus	Advair HFA	AirDuo RespiClick	Breo Ellipta	Dulera	Symbicort
Treatment of asthma	✔ (age ≥ 4 years)	✔ (age ≥ 12 years)	✔ (age ≥ 12 years)	✔ (age ≥ 18 years)	✔ (age ≥ 12 years)	✔ (age ≥ 6 years)
Maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema	✔ (250/50 strength only)			✔ (100/25 strength only)		✔ (160/4.5 strength only)
To reduce exacerbations of COPD in patients with a history of exacerbations	✔ (250/50 strength only)			✔ (100/25 strength only)		✔ (160/4.5 strength only)

(*Prescribing information: Advair HFA 2017, Advair Diskus 2017, AirDuo RespiClick 2018, Breo Ellipta 2017, Dulera 2018, Symbicort 2017*)

Table 2B. FDA-Approved Indications for Beta$_2$-agonist/Anticholinergic Combination Agents

Indication	Anoro Ellipta	Bevespi Aerosphere	Combivent Respimat	ipratropium/ albuterol solution	Stiolto Respimat	Utibron Neohaler
Long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema	✔				✔	
Long-term, twice-daily, maintenance treatment of airflow obstruction in patients with COPD		✔				✔
For use in patients with COPD on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator			✔			
For the treatment of bronchospasm associated with COPD in patients requiring more than 1 bronchodilator				✔		

(*Prescribing information: Anoro Ellipta 2017, Bevespi Aerosphere 2017, Combivent Respimat 2016, ipratropium/albuterol solution 2015, Stiolto Respimat 2016, Utibron Neohaler 2017*)

Table 2C. FDA-Approved Indication for Triple Combination Agent

Indication	Trelegy Ellipta
For the long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. Trelegy Ellipta is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations.	✔

(*Trelegy Ellipta prescribing information 2018*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Beta$_2$-agonist/corticosteroid combinations for asthma and COPD

Comparisons to placebo, monotherapy, combined use of individual components, varied treatments, or usual care:

- Numerous trials have compared the combination ICS/LABA products to their respective individual components as monotherapy, and in general, results have demonstrated that administration of the combination product is more effective than monotherapy for improving lung function and/or achieving control of symptoms in asthma and COPD (*Bateman et al 2001, Bateman et al 2004, Bateman et al 2006, Bateman et al 2014, Berger et al 2010, Bernstein et al 2015, Bleecker et al 2014, Calverley et al 2003, Corren et al 2007, Eid et al 2010, FDA AirDuo RespiClick Medical Review 2017, Gappa et al 2009, Hanania et al 2003, Jenkins et al 2006, Kerwin et al 2009, Kerwin et al 2013, Kuna et al 2006, Lalloo et al 2003, Lundback et al 2006, Martinez et al 2013, Meltzer et al 2012, Morice et al 2007, Murphy et al 2008, Nelson et al 2003a, Nathan et al 2006, Noonan et al 2006, O'Byrne et al 2014, Pearlman et al 2004, Pearlman et al 2017, Pohl et al 2006, Raphael et al 2018, Rennard et al 2009, Rodrigo et al 2016, Rodrigo et al 2017, Sharafkaneh et al 2012, Sher et al 2017, Tal et al 2002, Tashkin et al 2008, Vaessen-Verberne et al 2010, Vestbo et al 2005, Weinstein et al 2010*). Results for reducing COPD exacerbations have been inconsistent (*Dransfield et al 2013, Ohar et al 2014*).
- Although a synergistic effect of combination inhalers has been suggested by some data, overall there are similar efficacy between the administration of the combination ICS/LABA products and their individual components used in combination (*Chapman et al 1999, Jenkins et al 2006, Marceau et al 2006, Nelson et al 2003b, Noonan et al 2006, Perrin et al 2010, Rosenhall et al 2002*). Improved adherence with combination inhalers has also been suggested but not been shown conclusively (*Marceau et al 2006, Perrin et al 2010*).
- A large, double-blind, randomized trial (N = 6112) compared fluticasone propionate/salmeterol 500/50 mcg twice daily to its individual components and to placebo over a 3-year period in patients with COPD (*Calverley et al 2007*). The primary endpoint, time to death from any cause, for the combination vs placebo failed to reach statistical significance (12.6% vs 15.2%; p = 0.052). However, the difference in mortality between the combination therapy and fluticasone monotherapy did reach statistical significance (12.6% vs 16%; p = 0.007). Treatment with the combination regimen resulted in significantly fewer exacerbations, improved health status, and improved lung function compared with placebo.
- A large, double-blind, randomized trial (SUMMIT; N = 16,590) evaluated the use of fluticasone furoate/vilanterol vs fluticasone furoate alone, vilanterol alone, or placebo in a population of patients with moderate COPD and heightened cardiovascular risk (age ≥ 60 years and receiving medication for >2 of the following: hypercholesterolemia, hypertension, diabetes mellitus, or peripheral arterial disease) (*Vestbo et al 2016a*). Compared with placebo, there was no significant benefit or worsening in all-cause mortality with combination therapy (hazard ratio [HR], 0.88 [95% confidence interval (CI), 0.74 to 1.04; p = 0.137]) or with the components (fluticasone furoate HR, 0.91 [95% CI, 0.77 to 1.08; p = 0.284]; vilanterol HR, 0.96 [95% CI, 0.81 to 1.14; p = 0.655]). Composite cardiovascular events were also similar in the 4 groups (3.9% to 4.4%). All treatments reduced the risk of moderate to severe COPD exacerbations compared to placebo, with percent reductions of 29% (95% CI, 22 to 35), 12% (95% CI, 4 to 19), and 10% (95% CI, 2 to 18) in the fluticasone furoate/vilanterol, fluticasone furoate, and vilanterol groups, respectively.
- A 12-month, randomized, open-label trial (Salford Lung Study; N = 2799) compared the use of fluticasone furoate/vilanterol 100/25 mcg daily to continuation of usual care in a real-world patient population in the United Kingdom (*Vestbo et al 2016b*). Enrolled patients had COPD, had had ≥ 1 exacerbations in the previous 3 years, and were taking regular maintenance inhaler therapy (≥ 1 long-acting bronchodilators; ICS alone or in combination with a long-acting bronchodilator; or a combination of ICS, LABA, and LAMA). The primary endpoint, the rate of moderate or severe exacerbations among patients who had had an exacerbation within 1 year before the trial, was 1.74 per year in the

fluticasone furoate/vilanterol group and 1.90 per year in the usual-care group, for a difference of 8.4% (95% CI, 1.1 to 15.2; p = 0.02). Serious adverse events, including pneumonia, were similar between the 2 groups.

- A meta-analysis of 19 trials evaluated the use of ICS/LABA combinations compared to placebo in patients with COPD, and demonstrated a significant reduction in exacerbation rate between fluticasone propionate/salmeterol and placebo and between budesonide/formoterol and placebo (*Nannini et al 2013a*). For the number of patients who experienced ≥ 1 exacerbations, the differences between fluticasone propionate/salmeterol vs placebo and mometasone furoate/formoterol 200/10 mcg strength vs placebo were not statistically significant; however, the mometasone furoate/formoterol 400/10 mcg strength was associated with a lower proportion of patients experiencing ≥ 1 exacerbation. This meta-analysis also demonstrated that when results for all combined inhalers vs placebo were pooled, there was an overall reduction in mortality (odds ratio [OR], 0.82; 95% CI, 0.68 to 0.99).
- A meta-analysis of 14 trials evaluated the use of ICS/LABA combinations compared to use of the same LABA as monotherapy in patients with COPD (*Nannini et al 2012*). This analysis demonstrated that exacerbation rates were reduced with ICS/LABA combination therapy compared to LABA monotherapy (rate ratio, 0.76; 95% CI, 0.68 to 0.84). However, there was a significant increase in the incidence of pneumonia with combination therapy compared to LABA monotherapy (OR, 1.55; 95% CI, 1.2 to 2.01).
- A meta-analysis of 15 trials evaluated the use of ICS/LABA combinations compared to use of ICS monotherapy in patients with COPD (*Nannini et al 2013b*). This analysis demonstrated that exacerbation rates were significantly reduced with ICS/LABA combination therapy vs ICS monotherapy (rate ratio, 0.87; 95% CI, 0.80 to 0.94). Adverse events were similar between treatments; pneumonia rates as diagnosed by chest x-ray were lower than those reported in earlier trials.
- A meta-analysis of 14 trials (total N = 6641) compared fluticasone furoate/vilanterol to placebo, fluticasone furoate monotherapy, fluticasone propionate monotherapy, vilanterol monotherapy, or fluticasone propionate/salmeterol in patients with asthma (*Dwan et al 2016*). Primary endpoints included health-related quality of life (HRQoL) and severe asthma exacerbations (defined by hospital admission or treatment with oral corticosteroids). Fewer than half of the studies reported on these primary endpoints, and there were few opportunities to combine results from the included studies. One of the 14 studies evaluated HRQoL (as measured by the Asthma Quality of Life Questionnaire [AQLQ]) for fluticasone furoate/vilanterol 100/25 mcg vs placebo; it identified a significant advantage of fluticasone furoate/vilanterol (mean difference, 0.30; 95% CI, 0.14 to 0.46). Two studies compared fluticasone furoate/vilanterol 100/25 mcg vs placebo with respect to exacerbations; both studies reported no exacerbations in either treatment arm. No comparisons relevant to the primary outcomes were found for fluticasone furoate/vilanterol at a higher dose (200/25 mcg) vs placebo. There was insufficient evidence to assess whether once-daily fluticasone furoate/vilanterol had better or worse safety or efficacy compared to twice-daily fluticasone propionate/salmeterol. The authors stated that firm conclusions could not be drawn due to the limited number of studies, variety of endpoints, and short duration of most trials.
- Several large studies focused primarily on safety endpoints, with efficacy endpoints as secondary (*Peters et al 2016, Stempel et al 2016a, Stempel et al 2016b*). The studies compared the use of ICS/LABA combinations to ICS monotherapy in patients with asthma. These studies each demonstrated non-inferiority of the ICS/LABA combination to ICS monotherapy for the risk of serious asthma-related events, offering reassurance for the safety of these agents.
  - A randomized, double-blind study (AUSTRI; N = 11,679) enrolled adults and adolescents (age ≥ 12 years) with persistent asthma and a history of exacerbation within the previous year (*Stempel et al 2016a*). Patients were randomized to receive fluticasone propionate/salmeterol or fluticasone propionate monotherapy for 26 weeks. Patients were stratified by their baseline asthma control questionnaire (ACQ)-6 score and current asthma medication to determine the fluticasone propionate dose (100, 250, or 500 mcg twice daily) and were randomized to receive this dose with or without concomitant salmeterol.
    - The primary safety endpoint was the first serious asthma-related event, a composite endpoint that included death, endotracheal intubation, and hospitalization. There were 36 events in 34 patients in the fluticasone propionate/salmeterol group and 38 events in 33 patients in the fluticasone propionate group (HR, 1.03; 95% CI, 0.64 to 1.66). Fluticasone propionate/salmeterol was shown to be non-inferior to fluticasone propionate for this endpoint. There were no asthma-related deaths.
    - The main efficacy endpoint was the first severe asthma exacerbation, defined as asthma deterioration leading to the use of systemic glucocorticoids for ≥ 3 days or an asthma-related hospitalization or emergency department visit leading to the use of systemic glucocorticoids. At least 1 severe asthma exacerbation was reported in 480 patients (8%) in the fluticasone propionate/salmeterol group and in 597 patients (10%) in the fluticasone propionate group (HR, 0.79; 95% CI, 0.70 to 0.89; p < 0.001).

- A similarly designed trial (VESTRI; N = 6208) enrolled pediatric patients 4 to 11 years of age (*Stempel et al 2016b*). Enrolled patients had a history of exacerbation within the previous year and consistent use of asthma medication during the 4 weeks before enrollment. Patients were randomized, on the basis of pretrial medication, Childhood Asthma Control Test (C-ACT) score, and exacerbation history, to receive fluticasone propionate/salmeterol 100/50 mcg or 250/50 mcg or fluticasone propionate alone 100 mcg or 250 mcg twice daily for 26 weeks.
  - The primary safety endpoint, the first serious asthma-related event (death, intubation, or hospitalization), occurred in 27 patients in the fluticasone propionate/salmeterol group and 21 patients in the fluticasone propionate group (HR, 1.28; 95% CI, 0.73 to 2.27); this demonstrated non-inferiority for fluticasone propionate/salmeterol compared to fluticasone propionate (p = 0.006). All of the events were asthma-related hospitalizations; there were no deaths or asthma-related intubations in either group.
  - The primary efficacy endpoint was the first severe asthma exacerbation, defined as asthma deterioration leading to the use of systemic glucocorticoids for ≥ 3 days or a depot injection of glucocorticoids. One or more severe asthma exacerbations occurred in 8.5% of patients in the fluticasone propionate/salmeterol group and 10.0% of patients in the fluticasone propionate group (HR, 0.86; 95% CI, 0.73 to 1.01).
- An additional randomized, double-blind trial (N = 11,693) compared the safety of formoterol/budesonide to budesonide alone in patients ≥ 12 years of age (*Peters et al 2016*). Enrolled patients were receiving daily asthma medication and had had ≥ 1 exacerbation in the previous year. Patients were stratified to a dose level of budesonide on the basis of asthma control and prior treatment. Patients were then randomized to receive budesonide/formoterol (2 actuations of 80/4.5 mcg or 160/4.5 mcg) or budesonide alone (2 actuations of 80 mcg or 160 mcg) twice daily for 26 weeks.
  - The primary safety endpoint, the first serious adverse event (death, intubation, or hospitalization), occurred in 43 of 5,846 patients receiving budesonide/formoterol and 40 of 5,847 patients receiving formoterol alone (HR, 1.07; 95% CI, 0.70 to 1.65); this demonstrated non-inferiority for budesonide/formoterol vs budesonide alone. Two of the events (both in the budesonide/formoterol group) were asthma-related deaths; the remaining events were asthma-related hospitalizations.
  - The primary efficacy endpoint, the first asthma exacerbation (defined as a deterioration of asthma requiring systemic glucocorticoids for ≥ 3 days, inpatient hospitalization for asthma, or an emergency department visit for asthma that resulted in receipt of systemic glucocorticoids) occurred in 9.2% of patients in the budesonide/formoterol group and 10.8% of patients in the budesonide group (HR, 0.84; 95% CI, 0.74 to 0.94).

Comparisons between different ICS/LABA combinations

- There are some data available comparing different combination ICS/LABA products for the treatment of COPD.
  - One crossover study comparing budesonide/formoterol to fluticasone propionate/salmeterol demonstrated no significant difference between products for the primary endpoint, the increase from baseline in peak expiratory flow 5 minutes after the morning dose (*Partridge et al 2009*). However, the mean morning forced expiratory volume in 1 second (FEV_1) improved more with budesonide/formoterol at 5 minutes and 15 minutes post-dose compared to fluticasone propionate/salmeterol.
  - Several published trials compared fluticasone furoate/vilanterol to fluticasone propionate/salmeterol in patients with COPD. Three of the trials were published together; pooled results demonstrated a greater improvement with fluticasone furoate/vilanterol 100/25 mcg once daily compared to fluticasone propionate/salmeterol 250/50 mcg twice daily on the primary endpoint, the weighted mean (wm) FEV_1 (0 to 24 hr) (*Dransfield et al 2014*). However, 2 of these 3 trials did not demonstrate a significant difference on this endpoint. An additional trial compared fluticasone furoate/vilanterol 100/25 mcg daily to fluticasone propionate/salmeterol 500/50 mcg twice daily, and found no significant difference between groups on the wm FEV_1 (0 to 24 hr) (*Agusti et al 2014*).
- There have been several trials comparing combination ICS/LABA products to one another for the treatment of asthma.
  - Several head-to-head trials have compared budesonide/formoterol to fluticasone propionate/salmeterol. The trials varied in their design and the doses of medications. In general, these head-to-head trials have failed to demonstrate that one product is consistently superior to the other. Some trials showed benefits for fluticasone propionate/salmeterol on some endpoints (*Dahl et al 2006, Fitzgerald et al 2005, Price et al 2007*); some showed benefits for budesonide/formoterol (*Aalbers et al 2004, Palmqvist et al 2001*), and another showed no significant differences between the 2 products (*Busse et al 2008*).
  - A meta-analysis of 5 trials comparing fluticasone propionate/salmeterol 250/50 mcg twice daily vs varied doses of budesonide/formoterol twice daily failed to demonstrate significant differences in exacerbations, asthma-related

serious adverse events, FEV_1, rescue medication use, symptom scores, or peak expiratory flow (*Lasserson et al 2011*).
  - A head-to-head trial comparing mometasone/formoterol to fluticasone propionate/salmeterol demonstrated non-inferiority for mometasone/formoterol for the primary endpoint of FEV_1 area under the curve (AUC) (0 to 12 hr) (*Bernstein et al 2011*). Treatment with mometasone/formoterol demonstrated a rapid onset of action, with significantly greater effects on FEV_1 at all time points up to 30 minutes post-dose compared to fluticasone propionate/salmeterol. Other secondary endpoints were not significantly different between groups.
  - A head-to-head trial comparing fluticasone furoate/vilanterol 100/25 mcg daily to fluticasone propionate/salmeterol 250/50 mcg twice daily demonstrated no significant differences between treatments on the primary endpoint, the wm FEV_1 (0 to 24 hr) (Woodcock et al 2013). There were also no significant differences in key secondary endpoints, including the time to onset of bronchodilator effect, percentage of patients obtaining ≥ 12% and ≥ 200 mL increase from baseline in FEV_1 at 12 hours and 24 hours, and change from baseline in trough FEV_1. Another trial comparing fluticasone furoate/vilanterol with fluticasone propionate/salmeterol demonstrated noninferiority of fluticasone furoate/vilanterol to fluticasone propionate/salmeterol in evening trough FEV_1 at week 24 (*Bernstein et al 2018*).

ICS/LABA compared to tiotropium or in combination with tiotropium for COPD

- A double-blind, double-dummy, 2-year trial (N = 1323) compared the use of fluticasone propionate/salmeterol 250/50 mcg twice daily to tiotropium 18 mcg daily in patients with COPD (*Wedzicha et al 2008*). This trial demonstrated no significant difference between groups in the rate of exacerbations or post-dose FEV_1. The study demonstrated higher mortality in the tiotropium group (6%) compared to the fluticasone propionate/salmeterol group (3%). This study was limited by the high number of withdrawals, which were unevenly distributed between the study arms.
- A double-blind, double-dummy, 12-week trial (N = 494) compared the use of umeclidinium/vilanterol 62.5/25 mcg daily to tiotropium 18 mcg daily in patients with COPD who had been treated with tiotropium monotherapy at the time of enrollment (*Kerwin et al 2017a*). The primary endpoint, trough FEV_1, showed improved efficacy in the group that stepped up to combination therapy, with a between-group difference of 88 mL (95% CI, 45 to 131; $p < 0.001$). Improvements with umeclidinium/vilanterol were also observed in some secondary endpoints, including the use of rescue medication use and transition dyspnea index (TDI) score.
- A double-blind, double-dummy, 12-week trial (N = 623) evaluated the use of fluticasone furoate/vilanterol 100/25 mcg daily and tiotropium 18 mcg daily in patients with moderate-to-severe COPD and an increased cardiovascular risk (*Covelli et al 2015*). There was no significant difference in the primary endpoint, the change from baseline in wm FEV_1 (0 to 24 hr). Minor differences were noted in some secondary efficacy endpoints and in the safety profiles. Pneumonia occurred more frequently in the fluticasone furoate/vilanterol group, and 2 patients in the tiotropium group died following cardiovascular events. The duration of this trial was not long enough to allow any firm conclusions about the relative efficacy and safety of fluticasone furoate/vilanterol vs tiotropium.
- Several trials have evaluated the potential benefits of adding a combination ICS/LABA to tiotropium vs the use of tiotropium alone in patients with COPD. These trials generally demonstrated an improvement in FEV_1 and some other lung function, symptom score, and quality-of-life endpoints (*Hanania et al 2012, Lee et al 2016, Rojas-Reyes et al 2016, Welte et al 2009*). Some trials (*Lee et al 2016, Welte et al 2009*) also demonstrated a reduction in the risk of COPD exacerbations or severe exacerbations; however, other trials and a meta-analysis have not confirmed a significant benefit for exacerbations (*Aaron et al 2007, Hanania et al 2012, Karner et al 2011, Rojas-Reyes et al 2016*).

Beta$_2$-agonist/anticholinergic combinations for COPD

Comparisons of combination beta$_2$-agonist/anticholinergic products to bronchodilator monotherapy:

- Numerous trials have compared the combination beta$_2$-agonist/anticholinergic products to their respective individual components as monotherapy, and in general, results have demonstrated that administration of the combination product is more effective than monotherapy for improving lung function and/or achieving control of symptoms in COPD (*Beeh et al 2015, Bone et al 1994, Buhl et al 2015, Decramer et al 2014, Donohue et al 2013, Dorinsky et al 1999, Friedman et al 1999, Hanania et al 2017, Mahler et al 2015, Martinez et al 2017*).
- A systematic review of 23 studies of beta$_2$-agonist/anticholinergic combinations compared to their monocomponents and to other single-agent treatments in patients with COPD was conducted (*Price et al 2016*). The analysis demonstrated that beta$_2$-agonist/anticholinergic combinations significantly improved lung function compared to their individual components. These combinations generally improved other outcomes compared to monotherapies as well, including

symptoms and health status, but there were some discrepancies between lung function results and these patient-reported outcomes.

Comparisons of combination beta$_2$-agonist/anticholinergic products to each other or to other bronchodilator combinations

- Two head-to-head trials between different LAMA/LABA combinations have been published.
  - An 8-week, open-label, crossover trial compared Anoro Ellipta (umeclidinium/vilanterol) and Stiolto Respimat (tiotropium/olodaterol) in 236 patients with COPD (*Feldman et al 2017*). The primary endpoint, change from baseline in trough FEV$_1$, was shown to be greater for umeclidinium/vilanterol, with a difference of 52 mL (95% CI, 28 to 77; p < 0.001 for superiority in the intention-to-treat population). Effects on secondary endpoints were mixed, with umeclidinium/vilanterol demonstrating a small improvement in rescue medication use but no significant differences in COPD Assessment Test (CAT) scores (a health status questionnaire) or EXACT Respiratory Symptoms (E-RS) scores at most weekly assessments.
  - Two 12-week, double-blind, crossover trials compared Utibron Neohaler (glycopyrrolate/indacaterol) to Anoro Ellipta (umeclidinium/vilanterol) in a total of 712 patients with COPD (*Kerwin et al 2017*). The primary endpoint, FEV$_1$ AUC (0 to 24 hr), was similar between treatment arms in both studies, with differences for glycopyrrolate/indacaterol vs umeclidinium/vilanterol of -11.5 mL (95% CI, -26.9 to 3.8) and -18.2 mL (95% CI, -34.2 to -2.3) in Studies 1 and 2, respectively. Although the trials failed to demonstrate noninferiority of glycopyrrolate/indacaterol to umeclidinium/vilanterol due to the noninferiority margin used in the study methodology, the differences between treatments were not considered clinically meaningful.
- A 12-week, non-inferiority, randomized, double-blind, triple-dummy, parallel group study (N = 967) compared umeclidinium/vilanterol (62.5/25 mcg once daily) to tiotropium (18 mcg once daily) plus indacaterol (150 mcg once daily) (*Kalberg et al 2016*). When comparing trough FEV$_1$ on day 85, umeclidinium/vilanterol demonstrated non-inferiority to combination treatment with tiotropium and indacaterol. Other measures, including rescue medication use, TDI focal scores, and St. George's Respiratory Questionnaire (SGRQ) scores, were also similar between both treatment groups on day 85 (p values not provided).
- A meta-analysis of 26 randomized controlled trials comparing the efficacy of umeclidinium/vilanterol, indacaterol/glycopyrrolate, formoterol plus tiotropium, salmeterol plus tiotropium, or indacaterol plus tiotropium to tiotropium alone found that umeclidinium/vilanterol was comparable to other LAMA/LABA fixed dose combination agents with respect to trough FEV$_1$, SGRQ scores, TDI focal scores, and need for rescue medication use (*Huisman et al 2015*).
- Three systematic reviews/meta-analyses compared various LAMA/LABA combinations (*Calzetta et al 2016, Schlueter et al 2016, Sion et al 2017*). Limitations to these analyses included the fact that trials evaluated some formulations/dose regimens not available in the U.S., and comparisons between different combinations were based on indirect data.
  - Overall, these meta-analyses demonstrated that all LAMA/LABA combinations showed improved lung function vs monocomponents, with few differences among products across lung function and patient-reported endpoints.
  - The analysis by *Sion et al* noted that both Utibron Neohaler (glycopyrrolate/indacaterol) and Anoro Ellipta (umeclidinium/vilanterol) appeared to improve lung function to a greater extent than Stiolto Respimat (tiotropium/olodaterol) at 12 weeks, with differences in trough FEV$_1$ of 52 mL (95% credible interval [CrI], 18 to 86) and 38 mL (95% CrI, 13 to 63), respectively.
  - The *Schlueter et al* meta-analysis included 27 trials (N = 30,361) including 4 LAMA/LABA fixed-dose combination agents (aclidinium/formoterol 400/12 mcg [not FDA approved for use in the U.S.], glycopyrrolate/indacaterol 110/50 mcg, tiotropium/olodaterol 5/5 mcg, and umeclidinium/vilanterol 62.5/25 mcg), and showed non-significant differences in efficacy, exacerbations, and discontinuation rates (*Schlueter et al 2016*). Safety profiles were also similar among the products.

ICS/LABA compared to LAMA/LABA combinations for COPD

- A randomized, double-blind, 12-week trial (N = 717) compared umeclidinium/vilanterol 62.5/25 mcg once daily to fluticasone propionate/salmeterol 500/50 mcg twice daily in patients with moderate to severe COPD and no exacerbations in the previous year (*Singh et al 2015*). It should be noted that the dose of fluticasone propionate was higher than what is recommended in the U.S. for treatment of COPD. Treatment with umeclidinium/vilanterol resulted in greater improvement in lung function than fluticasone propionate/salmeterol, with a difference of 80 mL (95% CI, 46 to 113) in the wm FEV$_1$ (0 to 24 hr) and a difference of 90 mL (95% CI, 55 to 125) in trough FEV$_1$. Effects on rescue bronchodilator use, mean TDI focal score, and SGRQ total scores, and the incidence of adverse events, were similar between groups.

- Two randomized, double-blind, 12-week trials (N = 707 and N = 700; reported together) compared umeclidinium/vilanterol 62.5/25 mcg daily to fluticasone propionate/salmeterol 250/50 mcg twice daily in patients with moderate to severe COPD without exacerbations in the previous year (*Donohue et al 2015*). These trials also demonstrated a greater improvement in lung function endpoints for umeclidinium/vilanterol compared to fluticasone propionate/salmeterol, with differences in wm FEV_1 (0 to 24 hr) and trough FEV_1 ranging from 74 to 101 mL ($p < 0.001$ for all comparisons). Adverse event rates and effects on TDI score and SGRQ were similar between groups.
- A randomized, double-blind, 26-week trial (ILLUMINATE; N = 523) compared indacaterol/glycopyrrolate 110/50 mcg daily to fluticasone propionate/salmeterol 500/50 mcg twice daily in patients with COPD and a history of ≥ 1 exacerbation during the previous year (*Vogelmeier et al 2013*). The dosing regimens for indacaterol/glycopyrrolate and fluticasone propionate/salmeterol evaluated in this study are different from those available and/or recommended for COPD in the U.S. The primary endpoint, FEV_1 AUC (0 to 12 hr), was significantly higher with indacaterol/glycopyrrolate than fluticasone propionate/salmeterol, with a treatment difference of 138 mL (95% CI, 100 to 176; $p < 0.0001$). Benefits were also seen for indacaterol/glycopyrrolate for some secondary endpoints, including additional lung function measures, change from baseline in rescue medication use, and TDI focal score; the difference in SGRQ was not statistically significant.
- A large, randomized, double-blind, 52-week trial (FLAME; N = 3362) compared indacaterol/glycopyrrolate 110/50 mcg daily to fluticasone propionate/salmeterol 500/50 mcg twice daily in patients with COPD and a history of ≥ 1 exacerbation during the previous year (*Wedzicha et al 2016*). Again, these dosing regimens varied from U.S. recommendations. The primary endpoint, the annual rate of all COPD exacerbations, was 11% lower in the indacaterol/glycopyrrolate group than in the fluticasone propionate/salmeterol group (3.59 vs 4.03; rate ratio, 0.89; 95% CI, 0.83 to 0.96; $p = 0.003$). Lung function was also improved to a greater extent with indacaterol/glycopyrrolate, with a difference in trough FEV_1 of 62 mL between groups ($p < 0.001$).
- A randomized, double-blind, crossover trial (N = 229) evaluated the use of tiotropium/olodaterol 2.5/5 mcg and 5/5 mcg once daily and fluticasone propionate/salmeterol 250/50 mcg and 500/50 mcg twice daily in patients with moderate to severe COPD; each patient received each of the 4 treatments for 6 weeks separated by 3-week washout periods (*Beeh et al 2016*). The lower dose of each combination is the dose available/recommended for COPD in the U.S. The primary endpoint, FEV_1 AUC (0 to 12 hr), was greater for the tiotropium/olodaterol regimens (range, 295 to 317 mL) than for the fluticasone propionate/salmeterol regimens (range, 188 to 192 mL) ($p < 0.0001$). FEV_1 AUC (12 to 24 hr) and FEV_1 AUC (0 to 24 hr) also favored tiotropium/olodaterol. Rates of adverse events were similar among the treatments.

Triple combination for COPD

- Fluticasone furoate/umeclidinium/vilanterol is the first FDA-approved “closed triple” inhaler – an inhaler containing 3 active ingredients: an ICS, a LAMA, and a LABA. FDA approval was based primarily on the coadministration of umeclidinium plus the fluticasone furoate/vilanterol combination.
- Two 12-week randomized studies (N = 619 and N = 620; published together) evaluated the efficacy and safety of double-blind treatment with umeclidinium 62.5 mcg, umeclidinium 125 mcg, or placebo when added to open-label fluticasone furoate/vilanterol 100/25 mcg (*Siler et al 2015*). In both studies, the primary endpoint, trough FEV_1, was significantly improved with the addition of umeclidinium, with improvements ranging from 111 to 128 mL ($p < 0.001$ for all comparisons vs placebo). Improvement was also demonstrated on the secondary endpoint of wm FEV_1 (0 to 6 hr), with improvements ranging from 125 to 153 mL ($p < 0.001$ for all comparisons vs placebo). SGRQ results were inconsistent. No substantial benefit was observed with umeclidinium 125 mcg over 62.5 mcg, which is consistent with findings in the umeclidinium monotherapy studies.
- Once-daily triple therapy with fluticasone furoate/umeclidinium/vilanterol has also been compared to twice-daily budesonide/formoterol 400/12 mcg in a 24-week, double-blind, double-dummy randomized trial (FULFIL; N = 1810) (Lipson et al 2017). The formulation/dosing regimen of budesonide/formoterol in this trial is different from the formulation available in the U.S. The trial demonstrated improvements in the change from baseline in trough FEV_1 (difference, 171 mL; 95% CI, 148 to 194; $p < 0.001$), SGRQ (difference, -2.2; 95% CI, -3.5 to -1.0; $p < 0.001$), and the rate of moderate/severe exacerbations (rate ratio, 0.65; 95% CI, 0.49 to 0.86; $p = 0.002$). Although the comparator regimen is not available in the U.S., this trial further supports the efficacy of triple inhaler therapy with fluticasone furoate/umeclidinium/vilanterol.
- Once-daily triple therapy with fluticasone furoate/umeclidinium/vilanterol was compared to fluticasone furoate/vilanterol and umeclidinium/vilanterol in a 52-week, double-blind, randomized trial among patients with COPD (IMPACT; *Lipson et al 2018*). The primary endpoint of moderate or severe exacerbations was significantly lower with triple therapy in

comparisons both with fluticasone furoate/vilanterol (rate ratio, 0.85; 95% CI, 0.80 to 0.90) and with umeclidinium/vilanterol (rate ratio, 0.75; 95% CI, 0.70 to 0.81). The annual rate of severe exacerbation resulting in hospitalization was also significantly lower with triple therapy vs umeclidinium/vilanterol (rate ratio, 0.66; 95% CI, 0.56 to 0.78), but not vs fluticasone furoate/vilanterol. The mean change from baseline in trough FEV_1 was significantly increased with triple therapy by 97 and 54 mL vs fluticasone furoate/vilanterol and umeclidinium/vilanterol, respectively. The risk of pneumonia was significantly higher with triple therapy vs umeclidinium/vilanterol (HR, 1.53; 95% CI, 1.22 to 1.92), but not vs fluticasone furoate/vilanterol. Significant improvements in SGRQ total scores also occurred with triple therapy vs fluticasone furoate/vilanterol (mean difference, -1.8; 95% CI, -2.4 to -1.1) and vs umeclidinium/vilanterol (mean difference, -1.8; 95% CI, -2.6 to -1.0).

CLINICAL GUIDELINES

Asthma

- The National Asthma Education and Prevention Program (NAEPP) guideline from the NHLBI states that the initial treatment of asthma should correspond to the appropriate asthma severity category, and it provides a stepwise approach to asthma management. Long-term control medications such as ICS, long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline, and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. ICS are the most potent and consistently effective long-term asthma control medication. Quick-relief medications such as SABAs and anticholinergics are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness, and wheezing. Systemic corticosteroids are important in the treatment of moderate or severe exacerbations because these medications prevent progression of the exacerbation, speed recovery, and prevent relapses (*NHLBI 2007*).
  - LABAs are used in combination with ICS for long-term control and prevention of symptoms in moderate or severe persistent asthma.
  - Of the adjunctive treatments available, a LABA is the preferred option to combine with an ICS in patients 12 years of age and older. This combination is also an option in selected patients 5 to 12 years of age.
- The Global Initiative for Asthma (GINA) guideline also provides a stepwise approach to asthma management. It recommends an ICS as a preferred controller medication choice, with an increased ICS dose and/or addition of a LABA for increasing symptom severity (higher steps). At the highest step, it is recommended that the patient be referred for add-on treatment (eg, tiotropium, omalizumab, mepolizumab) (*GINA 2018*).
- The available asthma guidelines are generally similar; however, one difference among them is the recommendation of ICS/formoterol as both maintenance and rescue therapy by the GINA guidelines. The NHLBI do not recommend LABA medications for the management of acute asthma symptoms or exacerbations (*GINA 2018, NHLBI 2007*).
  - A meta-analysis of 16 randomized controlled trials evaluating the use of a LABA/ICS as single maintenance and reliever therapy found that it was associated with a significant reduction in the risk of asthma exacerbations compared with controller therapy with the same dose of ICS and LABA (relative risk, 0.68; 95% CI, 0.58 to 0.80) (*Sobieraj et al 2018*). Of the 16 trials, 15 studied budesonide/formoterol in a dry powder inhaler. Results were similar in comparisons with doses of ICS and LABA controller therapy that were higher than the combined LABA/ICS, and in comparison with ICS controller therapy only.

COPD

- The 2018 GOLD guidelines state that the management strategy for stable COPD should be predominantly based on an assessment of the patient's symptoms and future risk of exacerbations. The risk of exacerbations is now based solely on the exacerbation history, whereas in previous versions of the guideline, risk assessment also included consideration of airflow limitation assessed by spirometry. Key recommendations from the GOLD guidelines are as follows (*GOLD 2018*):
  - Inhaled bronchodilators are recommended over oral bronchodilators.
  - LAMA and LABA are preferred over short-acting agents except for patients with only occasional dyspnea.
  - Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on 1 bronchodilator, treatment should be escalated to 2 bronchodilators.
  - Combination treatment with a LABA and LAMA reduces exacerbations compared to monotherapy or ICS/LABA.
  - LAMAs have a greater effect on exacerbation reduction compared to LABA and decrease hospitalizations.
  - Combination treatment with a LABA and LAMA increases FEV_1 and reduces symptoms compared to monotherapy.
  - Combinations of LAMA and LABA in a single inhaler improve lung function compared to placebo; the improvement is greater than long-acting bronchodilator monotherapy, but less than fully additive of effects for the individual

components. In studies where patient-reported outcomes are the primary endpoint or in pooled analyses, combination bronchodilators have a greater impact on these endpoints compared to monotherapies.
- Long-term monotherapy with ICS is not recommended. Long-term treatment with ICS may be considered in association with LABA for patients with a history of exacerbations despite treatment with long-acting bronchodilators.
- An ICS combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD. However, regular treatment with ICS increases the risk of pneumonia, especially in those with severe disease.
- Triple inhaled therapy of ICS/LAMA/LABA improves lung function, symptoms, and health status and reduces exacerbations compared to ICS/LABA or LAMA monotherapy.
- Treatment recommendations are given for patients with COPD based on their GOLD patient group (see Table 3 below).
  - Group A: Patients should be offered bronchodilator treatment (short- or long-acting). This should be continued if symptomatic benefit is documented.
  - Group B: Initial therapy should consist of a long-acting bronchodilator (LAMA or LABA). For patients with persistent breathlessness on monotherapy, use of 2 bronchodilators is recommended (LAMA + LABA). For patients with severe breathlessness, initial therapy with 2 bronchodilators may be considered. If the addition of a second bronchodilator does not improve symptoms, it is suggested that treatment could be stepped down to a single bronchodilator.
  - Group C: Initial therapy should be a LAMA. Patients with persistent exacerbations may benefit from adding a second long-acting bronchodilator (LAMA + LABA, preferred) or using an ICS + LABA.
  - Group D: It is recommended to start therapy with a LAMA + LABA combination. In some patients, initial therapy with an ICS + LABA may be the first choice; these patients may have a history and/or findings suggestive of asthma-COPD overlap. In patients who develop further exacerbations on LAMA + LABA therapy, alternative pathways include escalation to a LAMA + LABA + ICS (preferred) or a switch to an ICS + LABA. If patients treated with a LAMA + LABA + ICS still have exacerbations, options for selected patients may include addition of roflumilast, addition of a macrolide, or stopping the ICS.

Table 3. Assessment of Symptoms and Risk of Exacerbations to Determine GOLD Patient Group

Moderate/Severe Exacerbation history	Symptoms	
	mMRC 0 to 1 CAT <10	mMRC ≥ 2 CAT ≥10
≥ 2 (or ≥ 1 leading to hospital admission)	C	D
0 or 1 (not leading to hospital admission)	A	B

Abbreviations: CAT = COPD assessment test; mMRC = modified British Medical Research Council questionnaire

- Guidelines from the American College of Chest Physicians and the Canadian Thoracic Society for prevention of acute exacerbations of COPD state that LAMA/LABA combinations are effective in reducing acute COPD exacerbations, but do not state that this combination is superior to LAMA monotherapy (*Criner et al 2015*).

SAFETY SUMMARY

Beta$_2$-agonist/corticosteroid combinations

- Beta$_2$-agonist/ICS combinations are generally contraindicated for the primary treatment of status asthmaticus or other acute episodes of asthma/COPD where intensive measures are required.
- Advair Diskus, AirDuo RespiClick, and Breo Ellipta are contraindicated in patients with a severe hypersensitivity to milk proteins.
- Previously, ICS/LABA combinations had a boxed warning about an increased risk of asthma-related death, which had been observed with the LABA salmeterol. However, the boxed warning was removed from the prescribing information for ICS/LABA combinations in December 2017 based on an FDA review of 4 large clinical safety trials, which demonstrated that these combinations do not result in a significantly increased risk of asthma-related death, hospitalizations, or the need for intubation compared to ICS alone. There is still a warning/precaution in the prescribing information of ICS/LABA combinations related to the increased risk of asthma-related death with LABA monotherapy. A

description of the clinical safety trials with ICS/LABA combinations has been added to the prescribing information for these products (*FDA 2017*).

- Other key warnings and precautions include:
  - Significant cardiovascular effects and fatalities with excessive use of beta$_2$-agonists
  - Cardiovascular and/or central nervous system effects from beta-adrenergic stimulation (seizures, angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia)
  - Paradoxical bronchospasm
  - Hypercorticism and adrenal suppression due to systemic absorption of the corticosteroid
  - The need for caution when transferring patients from systemic corticosteroid therapy (deaths due to adrenal insufficiency have occurred)
  - Lower respiratory tract infections/pneumonia
  - Local infections of the mouth and pharynx with *Candida albicans*
  - Reduced growth velocity in pediatric patients
  - The potential for drug interactions with strong CYP3A4 inhibitors; concomitant use is not recommended due to the potential for increased systemic effects
  - The potential for developing glaucoma, increased intraocular pressure, blurred vision, central serous chorioretinopathy, or cataracts
  - Immunosuppression
  - Hypersensitivity
  - Reduction in bone mineral density
- It is also important to note that ICS/LABA combinations should not be initiated in the setting of disease deterioration or potentially life-threatening episodes.
- Commonly reported adverse events (≥ 5% for at least 1 medication in the class) include oral candidiasis, hoarseness/dysphonia, nasopharyngitis/pharyngitis, pharyngolaryngeal/oropharyngeal pain, sinusitis, upper respiratory tract infection, upper respiratory tract inflammation, bronchitis, cough, headache, gastrointestinal discomfort, and nausea/vomiting.

Beta$_2$-agonist/anticholinergic combinations

- Both albuterol/ipratropium combination products are contraindicated in patients with hypersensitivity to atropine or its derivatives. Anoro Ellipta is contraindicated in patients with hypersensitivity to any component of the product, as well as in patients with severe hypersensitivity to milk proteins. Bevespi Aerosphere, Stiolto Respimat, and Utibron Neohaler are all contraindicated in patients with asthma without use of a long-term asthma control medication (and are not indicated for the treatment of asthma).
- There are no boxed warnings for the albuterol/ipratropium combination products. Anoro Ellipta, Bevespi Aerosphere, Stiolto Respimat and Utibron Neohaler have boxed warnings stating that LABA increase the risk of asthma-related death. Data from a large placebo-controlled U.S. trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including formoterol (an active ingredient in Bevespi Aerosphere), indacaterol (an active ingredient in Utibron Neohaler), vilanterol (an active ingredient in Anoro Ellipta), and olodaterol (an active ingredient in Stiolto Respimat). The safety and efficacy of Anoro Ellipta, Bevespi Aerosphere, Stiolto Respimat, and Utibron Neohaler in patients with asthma have not been established, and these products are not indicated for the treatment of asthma.
- Warnings and precautions are very similar among products, and include the following:
  - Paradoxical bronchospasm: May produce paradoxical bronchospasm, which can be life-threatening. If it occurs, the product should be discontinued and alternative therapy instituted.
  - Cardiovascular effect: Beta$_2$-agonists can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, and/or symptoms. If these symptoms occur, the product may need to be discontinued. In addition, electrocardiogram (ECG) changes may occur. These products should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
  - Ocular effects: Ipratropium and other anticholinergic agents may increase intraocular pressure, which may precipitate or worsen narrow-angle glaucoma. They should be used with caution in patients with narrow-angle glaucoma. In addition, patients should avoid spraying product into eyes, as this can cause eye pain and visual symptoms.

- Urinary retention: Ipratropium and other anticholinergic agents may cause urinary retention. Caution is advised when administering to patients with prostatic hyperplasia or bladder-neck obstruction.
- The recommended dose should not be exceeded: Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma.
- Hypersensitivity reactions: Urticaria, angioedema, rash, pruritus, bronchospasm, laryngospasm, oropharyngeal edema, and anaphylaxis may occur. If such a reaction occurs, therapy should be discontinued and alternative treatment considered.
- Coexisting conditions: Due to the beta$_2$-agonist component, caution is advised in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines.
- Hypokalemia: β-agonists may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.
- Drug interactions with strong CYP3A4 inhibitors; increased cardiovascular effects may occur (Anoro Ellipta only).
- Reports of anaphylactic reactions in patients with severe milk protein allergy (Anoro Ellipta only).
- Deterioration of disease and acute episodes; drug has not been studied in this setting and is not to relieve acute symptoms (Anoro Ellipta and Stiolto Respimat only).

- Adverse reactions are similar among products and include back pain, bronchitis, upper respiratory infection, lung disease, headache, dyspnea, nasopharyngitis/pharyngitis, and cough.
- In a 12-week trial comparing Combivent Respimat to Combivent inhalation aerosol, rates of adverse reactions were very similar between groups. In a 48-week safety trial, most adverse reactions were similar in type and rate between treatment groups; however, cough occurred more frequently in patients enrolled in the Combivent Respimat group (7%) than the Combivent inhalation aerosol group (2.6%).
- The choice of a specific LAMA/LABA fixed dose combination product is not based on any difference in the safety profile (*Matera et al 2016*).

Triple combination (beta$_2$-agonist/anticholinergic/corticosteroid)

- Trelegy Ellipta is contraindicated in patients with severe hypersensitivity to milk proteins or any ingredients in the formulation.
- Similar to other combination agents for COPD (and/or asthma), Trelegy Ellipta has a number of additional warnings and precautions; these include:
  - Increased risk of asthma-related death
  - Not indicated for treatment of asthma
  - Not initiating in patients with rapidly deteriorating COPD
  - Avoiding excessing use
  - Local effects of ICS
  - Risk of pneumonia
  - Immunosuppression
  - Using caution when transferring patients from systemic corticosteroid therapy
  - Hypercorticism and adrenal suppression
  - Drug interactions with strong CYP3A4 inhibitors
  - Paradoxical bronchospasm
  - Hypersensitivity reactions
  - Cardiovascular effects
  - Reduction in bone mineral density
  - Glaucoma and cataracts
  - Urinary retention
  - Using caution in patients with certain coexisting conditions such as convulsive disorders or thyrotoxicosis
  - Hypokalemia and hyperglycemia
- The most common adverse reactions with Trelegy Ellipta include headache, back pain, dysgeusia, diarrhea, cough, oropharyngeal pain, and gastroenteritis.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency
Beta$_2$-agonist & corticosteroid combinations			
Advair Diskus (fluticasone propionate/salmeterol)	Inhalation powder	Inhalation	2 times daily
Advair HFA (fluticasone propionate/salmeterol)	Aerosol inhaler	Inhalation	2 times daily
AirDuo RespiClick (fluticasone propionate/salmeterol)	Inhalation powder	Inhalation	2 times daily
Breo Ellipta (fluticasone furoate/vilanterol)	Inhalation powder	Inhalation	Once daily
Dulera (mometasone furoate/formoterol fumarate dihydrate)	Aerosol inhaler	Inhalation	2 times daily
Symbicort (budesonide/formoterol fumarate dihydrate)	Aerosol inhaler	Inhalation	2 times daily
Beta$_2$-agonist & anticholinergic combinations			
Anoro Ellipta (umeclidinium/vilanterol)	Inhalation powder	Inhalation	Once daily
Bevespi Aerosphere (glycopyrrolate/formoterol fumarate)	Inhalation spray	Inhalation	2 times daily
Combivent Respimat (ipratropium bromide/albuterol)	Inhalation spray	Inhalation	4 times daily
ipratropium bromide/albuterol	Nebulizer solution	Inhalation (nebulizer)	4 times daily
Stiolto Respimat (tiotropium bromide/olodaterol)	Inhalation spray	Inhalation	Once daily
Utibron Neohaler (indacaterol/glycopyrrolate)	Inhalation powder	Inhalation	2 times daily
Triple combination			
Trelegy Ellipta (fluticasone furoate/ umeclidinium/vilanterol)	Inhalation powder	Inhalation	Once daily

See the current prescribing information for full details.

CONCLUSION

- Inhaled medications, including bronchodilators and corticosteroids, are a mainstay of treatment for asthma and COPD, and a large amount of clinical evidence supports the safety and efficacy of combination beta$_2$-agonist agents for these indications.
  - Clinical trials have demonstrated that the combination products superior efficacy compared with the individual separate components when given as monotherapy for the treatment of both asthma and COPD. The combination products are generally well tolerated.
- Several single-ingredient inhalers containing beta$_2$-agonists, ICS, or anticholinergics are also available. Beta$_2$-agonist combinations offer improved convenience over the use of multiple separate inhalers.
  - Trelegy Ellipta is the first fixed-dose combination inhaler combining a LAMA, a LABA, and an ICS, and provides an alternative to the use of multiple inhalers for patients with COPD in whom triple therapy is indicated.
- GINA guidelines support the use of combination ICS/LABA products for long-term control and prevention of symptoms in patients with asthma who do not achieve sufficient symptom control with ICS monotherapy.
  - Single-agent LABA therapy should not be used for asthma management due to the increased risk of asthma-related death, as well as asthma-related hospitalization in pediatric and adolescent patients. However, recent drug safety information from the FDA states that no significantly increased risk of serious asthma outcomes has been seen with the use of ICS/LABA combinations, and boxed warnings about this potential risk have been removed from the prescribing information for the ICS/LABA combinations.
  - An advantage of the ICS/LABA combinations is that their use ensures that patients are not using a LABA without a concomitant ICS.
- GOLD guidelines recommend the use of combination ICS/LABA products as an option for some patients at higher risk of exacerbations; however, the use of 1 or more bronchodilator without an ICS is recommended as first-line treatment for most COPD patients.
  - LAMA/LABA combination therapy is recommended as a first- or second-line treatment in most patients with COPD, with the exception of low-risk patients with milder symptoms.
- None of the current asthma or COPD treatment guidelines recommend the use of one specific combination product over another.

- Administration instructions and inhalation devices vary among products and should be considered in product selection.

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Publication Date: June 1, 2018

INTRODUCTION

- Inhaled corticosteroids (ICSs) are approved by the Food & Drug Administration (FDA) for the treatment of asthma. These agents are effective in the treatment of asthma due to their wide range of inhibitory activities against multiple cell types (e.g., mast cells and eosinophils) and mediators (e.g., histamine and cytokines) involved in the asthmatic response.
- Asthma is a chronic lung disease that inflames and narrows the airways, making it difficult to breathe. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing. Asthma affects people of all ages, but most often starts during childhood. In the United States, more than 25 million people are known to have asthma, including about 7 million children (*National Heart, Lung, and Blood Institute [NHLBI] 2014*).
- The exact cause(s) of asthma are unknown. A combination of factors such as genetics, certain respiratory infections during childhood, and contact with airborne allergens can contribute to its development. Most patients with asthma have allergies (*NHLBI 2014*).
- Current pharmacologic options for asthma management are categorized as: (1) long-term control medications to achieve and maintain control of persistent asthma, and (2) quick-relief medications used to treat acute symptoms and exacerbations (*NHLBI 2007*).
- Long-term control medications include (*NHLBI 2007*):
  - Corticosteroids (ICSs for long-term control; short courses of oral corticosteroids to gain prompt control of disease, long-term oral corticosteroids for severe persistent asthma)
  - Cromolyn sodium and nedocromil
  - Immunomodulators (i.e., omalizumab)
  - Leukotriene modulators
  - Long-acting β-agonists (LABAs)
  - Methylxanthines (i.e., theophylline)
- Quick-relief medications include (*NHLBI 2007*):
  - Short-acting β-agonists (SABAs) as the therapy of choice for relief of acute symptoms and prevention of exercise-induced bronchospasm
  - Anticholinergics (i.e. ipratropium bromide), as an alternative bronchodilator for those not tolerating a SABA
  - Systemic corticosteroids, although not short-acting, are used for moderate and severe exacerbations as part of initial treatment.
- In recent years, additional medications have been made available for select subsets of patients with asthma, including the interleukin-5 (IL-5) antagonists benralizumab, mepolizumab, and reslizumab for the management of severe asthma with an eosinophilic phenotype *(Prescribing information: Cinqair 2016, Fasenra 2017, Nucala 2017)*. Additionally, tiotropium, long used for chronic obstructive pulmonary disease (COPD), has been FDA-approved for the treatment of asthma *(Spiriva Respimat prescribing information 2017)*.
- ICSs are the most effective and most commonly recommended long-term control medications used for the treatment of asthma. The LABAs should not be used as monotherapy for the management of asthma due to increased risk for serious adverse events including death. However, they are effective adjunctive therapy in patients who are not adequately controlled with an ICS alone. Theophylline and mast-cell stabilizers have weak to low efficacy in asthma. Theophylline has an unfavorable side-effect profile and may be life-threatening at high doses. Mast-cell stabilizers have a more favorable safety profile. Tiotropium is an option for add-on therapy in patients with a history of exacerbations. An IL-5 antagonist or the immunoglobulin E (IgE) antagonist, omalizumab, may be added if patients require a higher level of care. Omalizumab is used in patients with moderate to severe allergic asthma while IL-5 antagonists are used for severe eosinophilic asthma. SABAs are the medication of choice for the relief of bronchospasm during acute exacerbations of asthma (*Fasenra prescribing information 2017, NHLBI 2007, Global Initiative for Asthma [GINA] 2018*).

- This review includes single-agent ICSs. While corticosteroids are commonly available in combination with other bronchodilators such as LABAs, combination agents are not included within this review. Although inflammation is also a component of COPD pathogenesis, no single-entity ICS has been FDA-approved for use in COPD.
- Of note, QVAR RediHaler, a new breath-actuated inhalation formulation of beclomethasone dipropionate manufactured by Teva, was approved by the FDA in August 2017 and was launched in February 2018, replacing the existing QVAR product (*Teva 2018*). Additionally, in January 2018, Mylan informed the FDA of the discontinuation of Aerospan (flunisolide) due to business reasons (*FDA Drug Shortages 2018*).
- Medispan class: Steroid Inhalants

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Alvesco (ciclesonide)	-
ArmonAir RespiClick (fluticasone propionate)	-
Arnuity Ellipta (fluticasone furoate)	-
Asmanex HFA (mometasone furoate)	-
Asmanex Twisthaler (mometasone furoate)	-
Flovent Diskus (fluticasone propionate)	-
Flovent HFA (fluticasone propionate)	-
Pulmicort Flexhaler (budesonide)	-
Pulmicort Respules (budesonide)	✔
QVAR RediHaler (beclomethasone dipropionate)	-

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Drug	Maintenance treatment of asthma as prophylactic therapy
Alvesco (ciclesonide)	✔ (age ≥ 12 years)
ArmonAir RespiClick (fluticasone propionate)	✔ (age ≥ 12 years)
Arnuity Ellipta (fluticasone furoate)	✔ (age ≥ 5 years)
Asmanex HFA (mometasone furoate)	✔ (age ≥ 12 years)
Asmanex Twisthaler (mometasone furoate)	✔ (age ≥ 4 years)
Flovent Diskus & Flovent HFA (fluticasone propionate)	✔ (age ≥ 4 years)
Pulmicort Flexhaler (budesonide)	✔ (age ≥ 6 years)
Pulmicort Respules (budesonide)	✔ (age 12 months to 8 years)
QVAR RediHaler (beclomethasone dipropionate)	✔ (age ≥ 4 years)

(*Prescribing information: Alvesco 2018, ArmonAir RespiClick 2018, Arnuity Ellipta 2018, Asmanex HFA 2018, Asmanex Twisthaler 2018, Flovent Diskus 2017, Flovent HFA 2017, Pulmicort Flexhaler 2016, Pulmicort Respules 2016, QVAR RediHaler 2017*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Several trials demonstrate the efficacy of ICSs compared to placebo for preventing exacerbations, improving FEV_1 and peak expiratory flow (PEF), improving symptoms, reducing use of SABAs, reducing oral corticosteroid requirements,

and/or improving quality of life (*Amar et al 2017, Baker et al 1999, Bleecker et al 2014, Fish et al 2000, Karpel et al 2007, Lotvall et al 2014, Meltzer et al 2009, Meltzer et al 2012, Nathan et al 2010, Nelson et al 1999, Rowe et al 1999, Sheffer et al 2005*).

- Numerous head-to-head trials have compared various ICS regimens to one another. Several clinical trials demonstrated no significant differences between different ICSs:
  - A trial comparing budesonide 750 mcg twice daily to fluticasone propionate 375 mcg twice daily in children 5 to 16 years of age demonstrated no statistically significant differences between treatment groups in PEF, symptom scores, physician/patient/parent assessment of efficacy, or frequency of exacerbations (*Fitzgerald et al 1998*).
  - A trial comparing fluticasone propionate 250 mcg twice daily to various doses of mometasone furoate twice daily demonstrated comparable efficacy between fluticasone propionate and mometasone furoate for improvement in FEV_1, forced expiratory flow at 25 to 75% of forced vital capacity (FVC; i.e., forced expiratory flow $[FEF]_{25\text{ to }75\%}$), and PEF (*O'Connor et al 2001*).
  - A trial comparing fluticasone propionate 250 mcg twice daily to mometasone furoate 400 mcg every evening demonstrated no significant differences between groups in FEV_1, FVC, PEF, albuterol use, or asthma symptom scores (*Wardlaw et al 2004*).
  - A trial comparing fluticasone propionate 500 mcg twice daily to mometasone furoate 500 mcg twice daily demonstrated no significant differences in PEF, FEV_1, symptom scores, or rescue albuterol use (*Harnest et al 2008*).
  - A trial comparing beclomethasone dipropionate 168 mcg twice daily to mometasone furoate 100 or 200 mcg twice daily demonstrated no significant differences in FEV_1, PEF, asthma symptoms, nocturnal awakenings, or albuterol use (*Nathan et al 2001*). The beclomethasone product evaluated in the trial is no longer commercially available.
  - A trial comparing ciclesonide 160 mcg every evening to budesonide 400 mcg every evening in children aged 6 to 11 years demonstrated no significant differences between groups in FEV_1, morning PEF, asthma symptom score, or need for rescue medication (*Von Berg et al 2007*).
  - A trial comparing fluticasone furoate 100 mcg daily to placebo also included fluticasone propionate 250 mcg twice daily as a reference arm; comparable results were seen between fluticasone propionate and fluticasone furoate for FEV_1, percentage of rescue-free days, and severe asthma exacerbations (*Lotvall et al* 2014).
  - A trial comparing fluticasone furoate 200 mcg daily to fluticasone propionate 500 mcg twice daily demonstrated that fluticasone furoate was non-inferior to fluticasone propionate based on effect on FEV_1 (*O'Byrne et al 2014*).
- Overall, comparative trials have not conclusively demonstrated one ICS to be significantly more effective than another. However, in several individual trials, significant differences in some endpoints were observed. For example, comparative trials have demonstrated:
  - In a trial comparing fluticasone propionate 200 mcg twice daily to budesonide 400 mcg twice daily in children 4 to 12 years of age, patients treated with fluticasone propionate had superior results for mean morning PEF compared to patients receiving budesonide (271 ± 82 and 259 ± 75 L/minute, respectively, P=0.002) (*Ferguson et al 1999*).
  - In a trial comparing budesonide 200 mcg twice daily to fluticasone propionate 100 mcg twice daily in children 6 to 9 years of age, effectiveness measures were comparable between groups; however, the mean growth velocity was significantly greater in the fluticasone propionate group (5.5 cm/year) compared to the budesonide group (4.6 cm/year) (*Ferguson et al 2007*).
  - A trial comparing beclomethasone dipropionate 168 or 336 mcg twice daily to fluticasone propionate 88 to 220 mcg twice daily demonstrated greater improvement in FEV_1 for fluticasone propionate-treated patients than beclomethasone dipropionate-treated patients. At endpoint, mean FEV_1 values in the low- and medium-dose fluticasone propionate groups improved by 0.31 (14%) and 0.36 L (15%), respectively, compared to improvements of 0.18 (8%) and 0.21 L (9%) in the low-and medium-dose beclomethasone dipropionate treatment groups, respectively. Improvements were also superior in the fluticasone propionate group for $FEF_{25\text{ to }75\%}$, FVC, morning PEF, and use of albuterol (*Raphael et al 1999*). Of note, the beclomethasone product evaluated in the trial is no longer commercially available.
  - In a trial comparing budesonide 400 mcg twice daily to various doses of mometasone furoate twice daily, the FEV_1 was significantly improved from baseline in the mometasone furoate 200 and 400 mcg treatment groups compared to the budesonide treatment group. In addition, morning wheezing scores were significantly improved in the mometasone furoate 400 mcg twice daily group compared to the budesonide group, and patients treated with mometasone furoate 200 or 400 mcg twice daily required significantly less albuterol compared to patients treated with budesonide (*Bousquet et al 2000*).
  - In a trial comparing budesonide 400 mcg once daily to mometasone furoate 440 mcg once daily, the mometasone furoate group had superior results for the percent change in FEV_1, $FEF_{25\text{ to }75\%}$, FVC, evening asthma symptom

scores, albuterol use, percentage of asthma symptom-free days, and physician–evaluated response to therapy (*Corren et al 2003*).

- Meta-analyses have evaluated ciclesonide and mometasone furoate compared to other ICS agents:
  - A meta-analysis comparing ciclesonide to other ICS agents (budesonide or fluticasone propionate) in children with asthma demonstrated no significant differences between ciclesonide and budesonide on asthma symptom scores, symptom-free days, rescue medication-free days, or exacerbations. When ciclesonide and fluticasone propionate were compared, no significant differences were found in asthma symptoms or rescue medication-free days. One of the four studies of ciclesonide vs fluticasone propionate demonstrated a higher incidence of exacerbations with ciclesonide; however, the dose of fluticasone propionate was relatively higher in this study (*Kramer et al 2013*).
  - A meta-analysis comparing mometasone furoate to other ICS agents (beclomethasone dipropionate [Qvar formulation, which is no longer marketed], budesonide, or fluticasone propionate) in patients with moderate to severe asthma demonstrated superior results with mometasone furoate for pulmonary function measures (FEV_1, FVC, $FEF_{25 \text{ to } 75\%}$, and morning PEF). Mometasone furoate was also shown to be superior on some symptom indices (morning difficulty breathing scores and rescue medication use), but not others (morning wheeze scores, morning cough scores, and nocturnal awakenings). However, based on the pooled results for the comparative arms, it is not possible to make conclusions about the relative efficacy of mometasone furoate compared to other individual agents (*Yang et al 2012*).
- Fluticasone propionate has also been compared to a leukotriene receptor, montelukast, in several randomized controlled trials in both adults and children. Although differences were not detected for all endpoints, in general these trials demonstrated superior outcomes for fluticasone propionate for FEV_1, symptom-free days, asthma symptom scores, nighttime awakenings, rescue albuterol use, physician's global assessments, frequency of exacerbations, and/or quality of life measures (*Busse et al 2001, Garcia et al 2005, Sorkness et al 2007, Szefler et al 2005, Zeiger et al 2006*).
- The safety and efficacy of ArmonAir RespiClick were evaluated in 2,130 patients with asthma, including two 12-week confirmatory trials, a 26-week safety trial, and two dose-ranging trials. The efficacy of ArmonAir RespiClick is based primarily on the dose-ranging and confirmatory trials (*Bernstein et al 2017, Kerwin et al 2017, Mansfield et al 2017, Raphael el at 2017, Sher et al 2017*).
  - The first Phase 3 trial (n=647, of which 389 were randomized to ArmonAir RespiClick or placebo) was a randomized, double-blind, placebo-controlled efficacy and safety study that compared ArmonAir RespiClick 55 mcg and 113 mcg one inhalation twice daily, AirDuo RespiClick (fluticasone propionate/salmeterol) 55/14 mcg and 113/14 mcg one inhalation twice daily, and placebo in patients ≥12 years of age with persistent symptomatic asthma despite low-dose or mid-dose ICS or ICS/LABA therapy. For the primary endpoint of change from baseline in trough FEV_1, a significantly greater improvement was seen in ArmonAir RespiClick 55 mcg and 113 mcg as compared to placebo at the end of 12 weeks (least squares means [LSM] change of 0.172 L, 0.204 L, and 0.053 L, respectively). Secondary endpoints of weekly average of daily trough morning PEF, total daily use of rescue medication, and Asthma Quality of Life Questionnaire improvement were also evaluated and supported efficacy of ArmonAir RespiClick (*Raphael el at 2017*).
  - The second Phase 3 trial (n=728, of which 437 were randomized to ArmonAir RespiClick or placebo) was similarly designed, but evaluated an increased ICS dose: ArmonAir RespiClick 113 mcg and 232 mcg, AirDuo RespiClick 113/14 mcg and 232/14 mcg, and placebo. Results for the primary endpoint of change from baseline in trough FEV_1 mirrored that of Trial 1, with significantly greater improvement in the ArmonAir RespiClick 113 mcg and 232 mcg groups as compared to placebo at the end of 12 weeks (LSM change of 0.119 L, 0.179 L, and -0.004 L, respectively). Secondary endpoints of weekly average of daily trough morning PEF and total daily use of rescue medication also supported efficacy of ArmonAir RespiClick (*Sher et al 2017*).
- The safety and efficacy of QVAR RediHaler were evaluated in 1,858 patients with persistent symptomatic asthma, including two 12-week and one 6-week Phase 3 confirmatory trials in patients ≥12 years of age, and one 12-week Phase 3 confirmatory in patients 4 to 11 years of age (*Amar et al 2016, Hampel et al 2017, QVAR RediHaler prescribing information 2017, Vandewalker et al 2017*).
  - The first 12-week Phase 3 trial (N=270) was a randomized, double-blind, placebo-controlled trial study that compared QVAR RediHaler 40 mcg and 80 mcg twice daily vs placebo in patients who previously used low-dose ICS or non-corticosteroid therapy. For the primary endpoint of change from baseline in trough FEV_1 area under the effect curve 0 to 12 weeks ($AUEC_{0\text{-}12wk}$), a significantly greater improvement was seen with QVAR RespiClick 80 mcg and 160 mcg as compared to placebo (difference of LSM from placebo of 0.124 L and 0.116 L, respectively). Both doses of QVAR

RediHaler demonstrated improvements in asthma control as supported by significantly greater improvements in morning PEF and a reduction in asthma symptoms vs placebo (*Hampel et al 2017*).
  - The second 12-week Phase 3 trial (n=532) was a randomized, double-blind, placebo-controlled trial that compared QVAR RediHaler 160 mcg and 320 mcg twice daily vs QVAR 160 mcg and 320 mcg twice daily and placebo in patients who previously used mid- to high-dose ICS or ICS/LABA therapy. The baseline-adjusted trough morning FEV_1 $AUEC_{0\text{-}12wk}$ increased in all active treatment groups vs placebo, although the differences were not significant. Overall, the safety profiles of QVAR and QVAR RediHaler were comparable (*Amar et al 2016*).
  - The 6-week randomized, double-blind, parallel-group, placebo-controlled trial compared QVAR RediHaler 160 mcg and 320 mcg twice daily vs placebo, with a QVAR 160 mcg twice daily reference arm, in patients previously using non-corticosteroid, ICS ± LABA, or combination asthma therapy. For the primary endpoint of change from baseline in trough FEV_1 $AUEC_{0\text{-}6wk}$, a significantly greater improvement was seen with QVAR RespiClick 160 mcg and 320 mcg vs placebo (difference of LSM from placebo of 0.144 L and 0.150 L, respectively). Both doses of QVAR RediHaler demonstrated improvements in asthma control as supported by significantly greater improvements in morning PEF, reduced rescue medication use, and a reduction in asthma symptoms vs placebo, with similar results demonstrated with QVAR 160 mcg treatment (*QVAR RediHaler prescribing information 2017, Ostrom et al 2018*).
  - The 12-week randomized, double-blind, parallel-group, placebo-controlled trial in pediatric patients compared QVAR RediHaler 40 mcg and 80 mcg twice daily vs placebo in patients who previously used non-corticosteroid or low-dose ICS ± LABA therapy. Treatment with the QVAR RediHaler did not demonstrate a statistically significant difference vs placebo for the primary endpoint of FEV_1 $AUEC_{0\text{-}12wk}$; however, the change in weekly average of daily morning PEF was 11.3 L/min and 8.5 L/min for the 80 mcg/day and 160 mcg/day doses of QVAR RediHaler, respectively, with nominal significance (*QVAR RediHaler prescribing information 2017, Vandewalker et al 2017*).

CLINICAL GUIDELINES

- The National Asthma Education and Prevention Program (NAEPP) guideline from the NHLBI states that the initial treatment of asthma should correspond to the appropriate asthma severity category, and it provides a stepwise approach to asthma management. Long-term control medications such as ICSs, long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline, and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. ICSs are the most potent and consistently effective long-term asthma control medication. Quick-relief medications such as SABAs and anticholinergics are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness, and wheezing. Systemic corticosteroids are important in the treatment of moderate or severe exacerbations because these medications prevent progression of the exacerbation, speed recovery, and prevent relapses (*NHLBI 2007*).
  - LABAs are used in combination with ICSs for long-term control and prevention of symptoms in moderate or severe persistent asthma.
  - Of the adjunctive treatments available, a LABA is the preferred option to combine with an ICS in patients 12 years of age and older. This combination is also an option in selected patients 5 to 12 years of age.
- The GINA guideline also provides a stepwise approach to asthma management. It recommends an ICS as a preferred controller medication choice, with an increased ICS dose and/or addition of a LABA for increasing symptom severity (higher steps). At the highest step, it is recommended that the patient be referred for add-on treatment (e.g., tiotropium, omalizumab, mepolizumab, reslizumab, benralizumab) (*GINA 2018*).

SAFETY SUMMARY

- ICS agents are generally contraindicated in patients with hypersensitivity to components of the product. ArmonAir RespiClick, Arnuity Ellipta, Asmanex Twisthaler, Flovent Diskus, and Pulmicort Flexhaler are also contraindicated in patients with hypersensitivity to milk proteins. All ICSs are contraindicated as primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.
- ICSs have no boxed warnings. Key warnings and precautions are similar among products, and generally include:
  - The occurrence of *Candida albicans* infections in the mouth and pharynx
  - Eosinophilic conditions and Churg-Strauss Syndrome
  - Glaucoma, increased intraocular pressure, and cataracts
  - Hypercorticism and adrenal suppression
  - The risk of oral corticosteroid withdrawal or adrenal insufficiency in patients transitioning from oral to ICS agents
  - Paradoxical bronchospasm

- Reduction in bone mineral density with long-term use
- Reduction in growth velocity in pediatric patients

- Adverse effects are similar among products. Common adverse effects include allergic rhinitis, back pain, conjunctivitis, cough, bronchitis, diarrhea, dyspepsia, dysphonia, ear infections, epistaxis, fever, gastrointestinal discomfort, gastroenteritis, headache, increased asthma symptoms, musculoskeletal pain, nasal congestion, nasopharyngitis/pharyngitis, nausea and vomiting, oral candidiasis, pharyngolaryngeal pain, rash, sinusitis, throat irritation, and upper respiratory infection.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Alvesco (ciclesonide)	Inhalation Aerosol (HFA): 80 or 160 mcg per actuation	Inhalation	Patients treated previously with only bronchodilators: initial, 80 mcg twice daily; maximum, 160 mcg twice daily Patients treated previously with an ICS: initial, 80 mcg twice daily; maximum, 320 mcg twice daily Patients treated previously with oral corticosteroids: initial, 320 mcg twice daily; maximum, 320 mcg twice daily	Not indicated for children < 12 years of age.
ArmonAir RespiClick (fluticasone propionate)	Dry powder inhaler: 55, 113, or 232 mcg per inhalation	Inhalation	Patients ≥ 12 years of age: initial, 55, 113, or 232 mcg twice daily (dependent on asthma severity); maximum, 232 mcg twice daily	Not indicated for children < 12 years of age.
Arnuity Ellipta (fluticasone furoate)	Dry powder inhaler: 100 or 200 mcg per actuation	Inhalation	Patients not previously on an ICS: initial, 100 mcg once daily; maximum, 200 mcg once daily Patients treated previously with an ICS: Starting dose should be based on previous asthma drug therapy and disease severity, 100 mcg or 200 mcg once daily Age 5 to 11 years: 50 mcg once daily	Not indicated for children < 5 years of age.
Asmanex HFA (mometasone furoate)	Inhalation aerosol (HFA): 100 or 200 mcg per actuation	Inhalation	Patients previously receiving a medium-dose ICS: 100 mcg, 2 inhalations twice daily Patients previously receiving a high-dose ICS: 200 mcg, 2 inhalations twice daily Patients currently receiving oral corticosteroids: 200 mcg, 2 inhalations twice daily	Not indicated for children < 12 years of age.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Asmanex Twisthaler (mometasone furoate)	Dry powder inhaler: 110 or 220 mcg per actuation	Inhalation	Patients treated previously with bronchodilators alone or an ICS: initial, 220 mcg once daily in the evening; maximum, 440 mcg administered as once daily in the evening or as 220 mcg twice daily Patients treated previously with oral corticosteroids: initial, 440 mcg twice daily; maximum, 880 mcg per day	Children 4 to 11 years of age: initial, 110 mcg once daily in the evening; maximum, 110 mcg per day. When administered once daily, should be taken only in the evening.
Flovent Diskus (fluticasone propionate)	Dry powder inhaler: 50, 100, or 250 mcg per actuation	Inhalation	Patients who are not on an ICS: initial, 100 mcg twice daily; maximum, 1000 mcg twice daily For other patients and those who do not respond adequately to the starting dose after 2 weeks, higher dosages may provide additional control.	Children 4 to 11 years of age: initial, 50 mcg twice daily; maximum, 100 mcg twice daily
Flovent HFA (fluticasone propionate)	Inhalation Aerosol (HFA): 44, 110, or 220 mcg per actuation	Inhalation	Patients who are not on an ICS: initial, 88 mcg twice daily; maximum, 880 mcg twice daily For other patients and those who do not respond adequately to the starting dose after 2 weeks, higher dosages may provide additional control.	Children 4 to 11 years of age: 88 mcg twice daily
Pulmicort Flexhaler (budesonide)	Dry powder inhaler: 90 or 180 mcg per actuation	Inhalation	Patients ≥ 18 years of age: initial, 360 mcg twice daily (selected patients can be initiated at 180 mcg twice daily); maximum, 720 mcg twice daily	Children 6 to 17 years of age: initial, 180 mcg twice daily (selected patients can be initiated at 360 mcg twice daily); maximum, 360 mcg twice daily
Pulmicort Respules (budesonide)	Suspension for nebulization: 0.25 mg/2 mL, 0.5 mg/2 mL, or 1 mg/2 mL	Inhalation	Children 12 months to 8 years of age treated previously with only bronchodilators: initial, 0.5 mg total daily dose administered either once daily or divided into two doses; maximum, 0.5 mg total daily dose Children 12 months to 8 years of age treated previously with an ICS: initial, 0.5 mg total daily dose administered either once daily or divided into two doses; maximum, 1 mg total daily dose Children 12 months to 8 years of age treated previously with an oral	Not indicated in adults.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			corticosteroid: initial, 1 mg total daily dose administered either as 0.5 mg twice daily or 1 mg once daily; maximum, 1 mg total daily dose	
QVAR RediHaler (beclomethasone dipropionate)	Inhalation aerosol: 40 or 80 mcg per actuation	Inhalation	Patients ≥ 12 years of age, not previously on an ICS: 40 to 80 mcg twice daily; maximum, 320 mcg twice daily Patients ≥ 12 years of age, previously treated with an ICS: initial, 40, 80, 160, or 320 mcg twice daily (dependent on prior asthma therapy and asthma severity); maximum, 320 mcg twice daily	Children 4 to 11 years of age: initial, 40 mcg twice daily; maximum, 80 mcg twice daily

See the current prescribing information for full details.

CONCLUSION

- ICS agents are considered the cornerstone of drug therapy for long-term asthma control. Consensus guidelines emphasize the important role of ICS agents as long-term controller medications. The NHLBI and GINA asthma guidelines agree that ICSs are the preferred treatment for initiating therapy in children and adults with persistent asthma. It is important to note that the current consensus guidelines do not give preference to one ICS over another (*GINA 2018, NHLBI 2007*).
- Although individual head-to-head clinical trials have demonstrated some differences among ICS agents on certain endpoints, results have not conclusively demonstrated one agent to be significantly more effective than another in the management of asthma. Contraindications, warnings/precautions, and adverse effects are also similar among products.
- There are several differences among products with respect to their available formulations, dosing, and use in the pediatric population. Notably, some products are available as dry-powder formulations, while others are available as inhalation aerosols. Most ICSs are dosed twice daily; however, Arnuity Ellipta is administered once daily. Asmanex Twisthaler and Pulmicort Respules may be administered either once or twice daily. Also, while most ICSs are approved for use in children, the starting age varies among products. Table 5 summarizes some of these key characteristics.

Table 5. Characteristics of ICS agents

Drug	Formulation	Advantages	Disadvantages/Limitations
Alvesco (ciclesonide)	Inhalation aerosol	-	• Not approved in children <12 years of age • Pregnancy Category C
ArmonAir RespiClick (fluticasone propionate)	Dry powder inhaler	-	• Contraindicated with hypersensitivity to milk proteins • Not studied in pregnant women
Arnuity Ellipta (fluticasone furoate)	Dry powder inhaler	• Once daily dosing	• Not approved in children <12 years of age • Pregnancy Category C • Contraindicated with hypersensitivity to milk proteins
Asmanex HFA (mometasone furoate)	Inhalation aerosol	-	• Not approved in children <12 years of age • Not studied in pregnant women

Drug	Formulation	Advantages	Disadvantages/Limitations
Asmanex Twisthaler (mometasone furoate)	Dry powder inhaler	• Approved in children ≥4 years • May be given either once or twice daily	• Contraindicated with hypersensitivity to milk proteins • Pregnancy Category C
Flovent Diskus (fluticasone propionate)	Dry powder inhaler	• Approved in children ≥4 years	• Contraindicated with hypersensitivity to milk proteins • Not studied in pregnant women
Flovent HFA (fluticasone propionate)	Inhalation aerosol	• Approved in children ≥4 years	• Not studied in pregnant women
Pulmicort Flexhaler (budesonide)	Dry powder inhaler	• Approved in children ≥6 years • Pregnancy Category B	• Contraindicated with hypersensitivity to milk proteins
Pulmicort Respules (budesonide)	Suspension for nebulization	• Approved in children 12 months to 8 years • May be given either once or twice daily • Pregnancy Category B (although not indicated in adults) • Generic availability	• Pediatric only; not approved in ages >8 years
QVAR RediHaler (beclomethasone dipropionate)	Inhalation aerosol	• Approved in children ≥4 years	• Not studied in pregnant women

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Publication Date: July 3, 2018

Therapeutic Class Overview
Inhaled Beta-Agonists

INTRODUCTION

- Respiratory beta$_2$-agonists are primarily used to treat reversible airway disease. They are Food and Drug Administration (FDA)-approved for the treatment of asthma, chronic obstructive pulmonary disease (COPD), exercise-induced asthma/bronchospasm, and/or reversible bronchospasm.
- Asthma is a chronic lung disease that inflames and narrows the airways, making it difficult to breathe. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing. Asthma affects people of all ages, but most often starts during childhood. In the United States, more than 25 million people are known to have asthma, including about 7 million children. The exact cause(s) of asthma are unknown. A combination of factors such as genetics, certain respiratory infections during childhood, and contact with airborne allergens can contribute to its development. Most patients with asthma have allergies (*National Heart, Lung, and Blood Institute [NHLBI] 2014*).
  - Current pharmacologic options for asthma management are categorized as: (1) long-term control medications to achieve and maintain control of persistent asthma, and (2) quick-relief medications used to treat acute symptoms and exacerbations.
  - Long-term control medications for asthma include (*NHLBI 2007*):
    - Corticosteroids (inhaled corticosteroids [ICSs] for long-term control; short courses of oral corticosteroids to gain prompt control of disease, long-term oral corticosteroids for severe persistent asthma)
    - Cromolyn sodium and nedocromil
    - Immunomodulators (ie, omalizumab)
    - Leukotriene modulators
    - Long-acting beta$_2$-agonists (LABAs)
    - Methylxanthines (ie, theophylline)
  - Quick-relief medications for asthma include (*NHLBI 2007*):
    - Anticholinergics (ie, ipratropium bromide), as an alternative bronchodilator for those not tolerating a short-acting beta$_2$-agonist (SABA)
    - SABAs (therapy of choice for relief of acute symptoms and prevention of exercise-induced bronchospasm)
    - Systemic corticosteroids (not short-acting, but used for moderate and severe exacerbations)
  - In recent years, additional medications have been made available for select subsets of patients with asthma, including the interleukin-5 (IL-5) antagonists benralizumab, mepolizumab, and reslizumab for the management of severe asthma with an eosinophilic phenotype (*Prescribing information: Cinqair 2016, Fasenra 2017, Nucala 2017*). Additionally, tiotropium, long used for COPD, has been FDA-approved for the treatment of asthma (*Spiriva Respimat prescribing information 2017*).
  - ICSs are the most effective, most commonly recommended long-term control medications used for the treatment of asthma. The LABAs should not be used as monotherapy for the management of asthma due to increased risk for serious adverse events, including death. However, they are effective adjunctive therapy in patients who are not adequately controlled with an ICS alone. Theophylline and mast-cell stabilizers have weak to low efficacy in asthma. Theophylline has an unfavorable side-effect profile and may be life-threatening at high doses. Mast-cell stabilizers have a more favorable safety profile. Tiotropium is an option for add-on therapy in patients ≥ 12 years old with a history of exacerbations. An IL-5 antagonist or the immunoglobulin E (IgE) antagonist, omalizumab, may be added if patients require a higher level of care. Omalizumab is used in patients with moderate to severe allergic asthma while IL-5 antagonists are used for severe eosinophilic asthma. SABAs are the medication of choice for the relief of bronchospasm during acute exacerbations of asthma (*Fasenra prescribing information 2017, NHLBI 2007, Global Initiative for Asthma [GINA] 2018*).
- COPD is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities. The abnormalities are usually caused by exposure to noxious particles or gases. Airflow limitation is caused by a combination of small airway disease (eg, obstructive bronchiolitis) and parenchymal destruction (emphysema); the relative contributions of each component vary between patients. The most common symptoms of COPD include dyspnea, cough, and sputum production (*Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2018*).

- COPD affects 6.4% of the United States (U.S.) population and is the major contributor to mortality from chronic lower respiratory diseases, the third leading cause of death in the U.S. (*Centers for Disease Control and Prevention 2017*). Globally, COPD is the fourth leading cause of death and is expected to be the third leading cause of death by 2020; the burden of COPD continues to increase due to continued exposure to risk factors and aging of the population (*GOLD 2018*).
- Cigarette smoking is the main risk factor for COPD; other risk factors include biomass fuel exposure (such as from cooking and heating in poorly ventilated dwellings) and air pollution. Host factors such as genetic abnormalities, abnormal lung development, and accelerated aging can predispose individuals to COPD development (*GOLD 2018*).
- Patients with COPD may experience exacerbations, which are periods of acute worsening of respiratory symptoms (*GOLD 2018*).
- Pharmacologic therapy for COPD can reduce symptoms, reduce the frequency and severity of exacerbations, and improve patients' health status and exercise tolerance. There is no conclusive evidence that COPD medications modify the long-term decline in lung function characteristics of COPD (*GOLD 2018*).
- Pharmacologic options for COPD treatment comprise several classes, including beta$_2$-agonists, anticholinergics, methylxanthines, ICSs, various combination products, and the phosphodiesterase (PDE)-4 inhibitor, roflumilast. Pharmacologic treatments should be individualized based on symptom severity, risk of exacerbations, side effects, comorbidities, drug availability, and cost, as well as the patient's response, preference, and ability to use various drug delivery devices (*GOLD 2018*).
- Inhaled bronchodilators are central to COPD symptom management, and are usually given on a regular basis to prevent or reduce symptoms. Several long-acting inhaled bronchodilators are available, and use of short-acting bronchodilators on a regular basis is not generally recommended (*GOLD 2018*).
- Beta$_2$-agonists differ in their dosing requirements, pharmacokinetic parameters, and potential adverse effects. Several of the SABAs are available generically in at least 1 strength or formulation; however, there are no generic formulations for the LABAs.

- This review includes the single-agent inhaled and oral beta$_2$-agonists. Although several agents are also available in combination inhalers along with an ICS or an anticholinergic, the combination products are not included in this review.
  - Tables in this review are organized by whether the drug product is short- or long-acting. Note that extended-release albuterol is categorized as short-acting for the purposes of this review, along with the other albuterol products.
- Medispan class/subclass: Sympathomimetics/Beta Adrenergics

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Short-acting beta$_2$-agonists (oral and inhaled)	
albuterol inhalation aerosols and powder (ProAir HFA, ProAir RespiClick dry powder inhaler, Proventil HFA, Ventolin HFA)	-
albuterol solution for nebulization	✔
albuterol, oral tablets, extended-release tablets, and syrup	✔
levalbuterol inhalation aerosol (Xopenex HFA and generic)	-*
levalbuterol solution for nebulization (Xopenex and generics)	✔
metaproterenol, oral tablets and syrup	✔
terbutaline, oral tablets and injection	✔
Long-acting beta$_2$-agonists (inhaled)	
Arcapta Neohaler (indacaterol) inhalation powder	-
Brovana (arformoterol) solution for nebulization	-
Perforomist (formoterol) solution for nebulization†	-
Serevent Diskus (salmeterol) inhalation powder	-
Striverdi Respimat (olodaterol) inhalation spray	-

Abbreviations: HFA = hydrofluoroalkane
*No A-rated generics have been approved by the FDA; however, an authorized generic is available.
†Formoterol was previously available as a dry powder inhaler (Foradil Aerolizer); however, this formulation is no longer marketed.
(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Generic Name	Treatment and/or prevention of bronchospasm in patients with asthma/reversible obstructive airway disease	Prevention of exercise-induced bronchospasm	Maintenance treatment of bronchoconstriction/ airflow obstruction in patients with COPD	Treatment of reversible bronchospasm occurring in association with emphysema and bronchitis
Short-acting beta$_2$-agonists				
albuterol	✔ *	✔ *†		
levalbuterol	✔ ‡			
metaproterenol	✔			✔
terbutaline	✔ §			✔ §
Long-acting beta$_2$-agonists				
arformoterol			✔	
formoterol			✔	
indacaterol			✔ **	
olodaterol			✔ **	
salmeterol	✔ ‖ ¶	✔ ¶	✔	

Abbreviations: COPD = chronic obstructive pulmonary disease; HFA = hydrofluoroalkane
*Age ≥ 4 years (HFA inhalation aerosols and dry power inhaler); age ≥ 2 (solution for nebulization); age ≥ 2 years (syrup); age ≥ 6 years (tablets and extended-release tablets)
†Inhalation aerosols and dry powder inhaler only
‡Age ≥ 4 years (Xopenex HFA); age ≥ 6 years (Xopenex inhalation solution)
§Age ≥ 12 years
‖Only as a concomitant therapy with a long-term asthma control medication, such as an ICS
¶Age ≥ 4 years
**Indicated for long-term, once daily maintenance treatment
(*Prescribing information: albuterol solution 2014, albuterol syrup 2015, albuterol tablets 2014, albuterol extended-release tablets 2015, Arcapta Neohaler 2013, Brovana 2014, metaproterenol syrup 2014, metaproterenol tablets 2016, Perforomist 2017, ProAir HFA 2016, ProAir RespiClick 2016, Proventil HFA 2017, Serevent Diskus 2016, Striverdi Respimat 2018, terbutaline injection 2011, terbutaline tablets 2016, Ventolin HFA 2018, Xopenex HFA 2017, Xopenex inhalation solution 2017*)

- Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Clinical trials have demonstrated the efficacy of SABAs and LABAs in providing relief from asthma exacerbations, COPD exacerbations and exercise-induced asthma (EIA).

SABAs: Asthma and COPD

- In the clinical trials that evaluated SABAs for the treatment of mild asthma, all SABAs have been shown to be efficacious in improving forced expiratory volume in 1 second (FEV_1). In the clinical trials that compared albuterol to levalbuterol, inconsistent results were found (*Carl et al 2003, Gawchik et al 1999, Milgrom et al 2001, Nelson et al 1998, Nowak et al 2004, Nowak et al 2006, Qureshi et al 2005, Schreck et al 2005, Sepracor Trial 1, Sepracor Trial 2, Skoner et al 2001*).
  - In 2 studies (one retrospective, one prospective), levalbuterol resulted in a significantly lower hospitalization rate compared to albuterol (*Carl et al 2003, Schreck et al 2005*).

- In another trial, when the 2 agents were given in the emergency department, there was no significant difference in the time to discharge (*Skoner et al 2001*).
- *Nowak et al* also reported that there was no difference in the time to discharge from the emergency room with albuterol compared to levalbuterol (76 and 78.5 minutes; p = 0.74) (*Nowak et al 2006*).
- Overall, studies have shown no significant differences between the 2 agents in the peak change in FEV_1 and the number and incidence of adverse events experienced (*Carl et al 2003, Gawchik et al 1999, Milgrom et al 2001, Nelson et al 1998, Nowak et al 2004, Nowak et al 2006, Qureshi et al 2005, Schreck et al 2005, Sepracor Trial 1, Sepracor Trial 2, Skoner et al 2001*).
  - In an unpublished study, the difference in peak FEV_1 was statistically significant for albuterol hydrofluoroalkanes (HFA) compared to levalbuterol HFA (p = 0.018) (*Sepracor Trial 2*).

- Albuterol dry powder inhaler was compared to placebo dry powder inhaler in patients with asthma maintained on ICS treatment (*Raphael et al 2014*). Patients treated with albuterol dry powder inhaler had significantly improved FEV_1 area under the curve compared to placebo. In patients with exercise-induced bronchoconstriction undergoing treadmill exercise challenge, placebo-treated patients had a greater decrease in FEV_1 compared with albuterol dry powder inhaler-treated patients (*Ostrom et al 2014*). In a cumulative-dose, crossover study, albuterol dry powder inhaler was compared with albuterol HFA with similar between-group improvements in FEV_1 at 30 minutes (*Miller et al 2014*). Additionally, albuterol dry power inhaler demonstrated favorable FEV_1 improvement in EIA compared to placebo in a crossover study (*Ostrom et al 2015*).

LABAs: Asthma

- The LABAs salmeterol and formoterol have been found to improve FEV_1 in patients with mild to moderate asthma who require persistent use of SABAs. However, the SMART trial found that salmeterol had significant occurrences of combined respiratory-related deaths or respiratory-related life-threatening experiences compared to placebo ($p < 0.05$) (*Nelson et al 2006*). In a meta-analysis, salmeterol and formoterol both demonstrated an increase in severe exacerbations that required hospitalization, life-threatening exacerbations and asthma-related deaths in adults and children alike when compared to placebo (*Salpeter et al 2006*). Due to the results of these studies, all LABAs have a boxed warning stating that these agents may increase the risk of asthma-related death.

LABAs: COPD

- A systematic review concluded that in patients with COPD, there was no difference in the rate of mild exacerbations between patients treated with an ICS or LABA (odd ratio, 1.63; 95% confidence interval [CI], 0.49 to 5.39) or in the rate of moderate or severe COPD exacerbations (rate ratio, 0.96; 95% CI, 0.89 to 1.02) (*Spencer et al 2011*).
- The safety and efficacy of indacaterol were evaluated in randomized controlled trials that compared it to placebo and other agents used in the management of COPD (*Balint et al 2010, Buhl et al 2011, Chapman et al 2011, Dahl et al 2010, Donohue et al 2010, Feldman et al 2010, Korn et al 2011, Kornmann et al 2011, Magnussen et al 2010, Vogelmeier et al 2010*). Notably, most of these trials evaluated indacaterol in doses of 150, 300 and 600 mcg once daily, rather than the FDA-approved dosing of 75 mcg once daily (*Balint et al 2010, Buhl et al 2011, Chapman et al 2011, Dahl et al 2010, Donohue et al 2010, Feldman et al 2010, Korn et al 2011, Kornmann et al 2011, Magnussen et al 2010, Vogelmeier et al 2010*). However, results from placebo-controlled trials of indacaterol 75 mcg have also been published, lending support to the use of the 75 mcg dose (*Gotfried et al 2012, Kerwin et al 2011*).
- Overall, data from published clinical trials demonstrated that treatment with indacaterol consistently results in significantly higher mean trough FEV_1 after 12 weeks of treatment compared to placebo, formoterol, salmeterol and tiotropium. Patients treated with indacaterol also achieved significant improvements in COPD symptoms, as well as health-related quality of life compared to those treated with placebo. Compared to placebo, indacaterol significantly reduces the use of rescue medications, increases the days of no rescue medication use, and improves diary card-derived symptom variables (eg, nights with no awakenings, days with no daytime symptoms, days able to perform usual activities). In general, treatment with indacaterol is favored over other long-acting bronchodilators for these outcomes, but statistical superiority is not consistently achieved (*Balint et al 2010, Buhl et al 2011, Chapman et al 2011, Dahl et al 2010, Donohue et al 2010, Feldman et al 2010, Gotfried et al 2012, Kerwin et al 2011, Korn et al 2011, Kornmann et al 2011, Magnussen et al 2010, Vogelmeier et al 2010*). Recent meta-analyses comparing indacaterol to tiotropium and to twice-daily LABAs (salmeterol or formoterol) demonstrated that patients treated with indacaterol had higher trough FEV_1 and greater improvements in the use of rescue medications and achieving improvements in dyspnea and health status

compared to the alternative treatments. However, the trials included in this meta-analysis used indacaterol doses higher than FDA-approved daily doses of 75 mcg (*Cope et al 2013, Rodrigo et al 2012*).

- Placebo-controlled trials demonstrate that within 5 minutes after administration of indacaterol, significant improvements in bronchodilation are achieved (*Balint et al 2010, Donohue et al 2010, Gotfried et al 2012, Kerwin et al 2011, Magnussen et al 2010, Vogelmeier et al 2010*). These results have also been observed when comparing indacaterol to salmeterol, salmeterol/fluticasone, and tiotropium (*Buhl et al 2011, Korn et al 2011, Vogelmeier et al 2010*).
- In 2 studies, patients diagnosed with COPD were treated with arformoterol, salmeterol, or placebo. These studies found that both arformoterol and salmeterol significantly improved morning trough FEV_1 throughout the 12 weeks of daily treatment compared to placebo ($p < 0.001$ in both trials) (*Baumgartner et al 2007, Sepracor, 2005*). In a head-to-head study against salmeterol, formoterol was associated with a greater change from baseline in FEV_1 at 5 minutes post-dose on day 28 ($p = 0.022$) (*Cote et al 2009*). Currently, there is a lack of head-to-head randomized, double-blind clinical trials to determine a preferential status of one agent over another for the treatment of COPD.
- Two replicate, multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 studies investigated the long-term efficacy and safety of once-daily olodaterol via Respimat soft-mist inhaler vs placebo and formoterol over 48 weeks in patients with moderate to very severe COPD receiving usual-care background therapy. Patients were randomized to receive once-daily olodaterol 5 or 10 mcg, twice-daily formoterol 12 mcg, or placebo. Co-primary endpoints were FEV_1 area under the curve from 0 to 3 hours (AUC_{0-3}), trough FEV_1, and Mahler transition dyspnea index (TDI) total score after 24 weeks. Overall, in Study 1222.13 (N = 904) and Study 1222.14 (N = 934), patients who received treatment with olodaterol had significantly improved FEV_1 AUC_{0-3} vs placebo in both studies ($p < 0.0001$ for all comparisons) and trough FEV_1 vs placebo ($p < 0.01$). Formoterol also showed statistically significant differences in both Study 1222.13 ($p < 0.01$) and Study 1222.14 ($p < 0.05$) (*Koch et al 2014*).
- Two replicate, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 trials investigated the long-term safety and efficacy of olodaterol in patients with moderate to very severe COPD receiving usual-care background therapy. Patients received olodaterol 5 mcg or 10 mcg or placebo once daily for 48 weeks. Co-primary endpoints were FEV_1 AUC_{0-3} (change from baseline) and trough FEV_1 at 12 weeks. Overall, Study 1222.11 (N = 624) and Study 1222.12 (N = 642) showed that olodaterol 5 mcg and 10 mcg significantly improved the FEV_1 AUC_{0-3} response ($p < 0.0001$) and trough FEV_1 (Study 1222.11, $p < 0.0001$; Study 1222.12, $p < 0.05$, post hoc) at week 12. The incidence of adverse events was comparable with that of placebo (*Ferguson et al 2014*).
- Two replicate, multicenter, randomized, double-blind, double-dummy, placebo-controlled, 4-way cross-over group, Phase 3 studies investigated the long-term efficacy and safety of once-daily olodaterol via Respimat soft-mist inhaler vs placebo and formoterol over 6 weeks in patients with moderate to very severe COPD receiving usual-care background therapy. Patients were randomized to receive once-daily olodaterol 5 or 10 mcg, twice-daily formoterol 12 mcg, or placebo. Co-primary endpoints were FEV_1 area under the curve from 0 to 12 hours (AUC_{0-12}) and FEV_1 area under the curve from 12 to 24 hours (AUC_{12-24}) after 6 weeks. Overall, in Study 1222.24 (N = 99) and Study 1222.25 (N = 100), patients who received treatment with both doses of olodaterol and formoterol had significantly improved FEV_1 profiles (co-primary endpoints of FEV_1 AUC_{0-12} and FEV_1 AUC_{12-24} and the key secondary endpoint [FEV_1 AUC_{0-24}]) vs placebo in both studies (for all comparisons $p < 0.0001$). No statistically significant differences were reported between the 3 active comparators (*Feldman et al 2014*).
- A meta-analysis that compared LABAs (salmeterol, formoterol, and indacaterol) to tiotropium demonstrated that tiotropium was more effective than LABAs as a group in preventing COPD exacerbations and disease-related hospitalizations. However, overall hospitalization rates, mortality, symptom improvement, and changes in lung function were similar among groups (*Chong et al 2012*). Another meta-analysis compared the use of LABAs plus tiotropium to the use of either LABAs alone or tiotropium alone. The analysis demonstrated that there was a significant improvement in FEV_1 with combination therapy compared to tiotropium alone. There was also a small mean improvement in health-related quality of life for patients receiving a LABA plus tiotropium compared to tiotropium alone, but the clinical significance of this small difference is unclear. Hospital admissions and mortality were not significantly different between groups. Data comparing LABA plus tiotropium to LABA alone were somewhat limited, but demonstrated a significant improvement in health-related quality of life, FEV_1 and exacerbations (*Farne et al 2015*).

EIA

- For the treatment of EIA, albuterol, metaproterenol, and formoterol have demonstrated an improvement in FEV_1 compared to placebo (*Berkowitz et al 1986, Bonini et al 2013, Edelman et al 2000, Richter et al 2002, Shapiro et al 2002, Storms et al 2004*).
  - In 1 study, albuterol- and metaproterenol-treated patients had a lower incidence of exercise-induced bronchospasm compared to placebo (*Cote et al 2009*).
  - In another study comparing albuterol, formoterol and placebo for EIA, both active treatment groups provided a statistically significant decrease in mean maximum percent of FEV_1 compared to placebo ($p < 0.01$) (*Shapiro et al 2002*).

CLINICAL GUIDELINES

Asthma

- The National Asthma Education and Prevention Program (NAEPP) guideline from the NHLBI states that the initial treatment of asthma should correspond to the appropriate asthma severity category, and it provides a stepwise approach to asthma management. Long-term control medications such as ICSs, long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline, and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. ICSs are the most potent and consistently effective long-term asthma control medication. Quick-relief medications such as SABAs and anticholinergics are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness, and wheezing. Systemic corticosteroids are important in the treatment of moderate or severe exacerbations because these medications prevent progression of the exacerbation, speed recovery, and prevent relapses (*NHLBI 2007*).
  - LABAs are used in combination with ICSs for long-term control and prevention of symptoms in moderate or severe persistent asthma.
  - Of the adjunctive treatments available, a LABA is the preferred option to combine with an ICS in patients 12 years of age and older. This combination is also an option in selected patients 5 to 12 years of age.
- The Global Initiative for Asthma (GINA) guideline also provides a stepwise approach to asthma management. It recommends an ICS as a preferred controller medication choice, with an increased ICS dose and/or addition of a LABA for increasing symptom severity (higher steps). At the highest step, it is recommended that the patient be referred for add-on treatment (eg, tiotropium, omalizumab, mepolizumab) (*GINA 2018*).

COPD

- The 2018 GOLD guidelines state that the management strategy for stable COPD should be predominantly based on an assessment of the patient's symptoms and future risk of exacerbations. The risk of exacerbations is now based solely on the exacerbation history, whereas in previous versions of the guideline, risk assessment also included consideration of airflow limitation assessed by spirometry. Key recommendations from the GOLD guidelines are as follows (*GOLD 2018*):
  - Inhaled bronchodilators are recommended over oral bronchodilators.
  - LAMAs and LABAs are preferred over short-acting agents except for patients with only occasional dyspnea.
  - Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on 1 bronchodilator, treatment should be escalated to 2.
  - Long-term monotherapy with ICSs is not recommended. Long-term treatment with ICSs may be considered in association with LABAs for patients with a history of exacerbations despite treatment with long-acting bronchodilators.
  - Treatment recommendations are given for patients with COPD based on their GOLD patient group (see Table 3 below).
    - Group A: Patients should be offered bronchodilator treatment (short- or long-acting). This should be continued if symptomatic benefit is documented.
    - Group B: Initial therapy should consist of a long-acting bronchodilator (LAMA or LABA). For patients with persistent breathlessness on monotherapy, use of 2 bronchodilators is recommended (LAMA + LABA). For patients with severe breathlessness, initial therapy with 2 bronchodilators may be considered. If the addition of a second bronchodilator does not improve symptoms, it is suggested that treatment could be stepped down to a single bronchodilator.
    - Group C: Initial therapy should be a LAMA. Patients with persistent exacerbations may benefit from adding a second long-acting bronchodilator (LAMA + LABA, preferred) or using an ICS + LABA.
    - Group D: It is recommended to start therapy with a LAMA + LABA combination. In some patients, initial therapy with an ICS + LABA may be the first choice; these patients may have a history and/or findings suggestive of

asthma-COPD overlap. In patients who develop further exacerbations on LAMA + LABA therapy, alternative pathways include escalation to a LAMA + LABA + ICS (preferred) or a switch to an ICS + LABA. If patients treated with a LAMA + LABA + ICS still have exacerbations, options for selected patients may include addition of roflumilast, addition of a macrolide, or stopping the ICS.

Table 3. Assessment of symptoms and risk of exacerbations to determine GOLD patient group

Exacerbation history	Symptoms	
	mMRC 0 to 1 CAT < 10	mMRC ≥ 2 CAT ≥10
≥ 2 (or ≥ 1 leading to hospital admission)	C	D
0 or 1 (not leading to hospital admission)	A	B

Abbreviations: CAT = COPD assessment test; mMRC = modified British Medical Research Council questionnaire

- Guidelines for the prevention of acute exacerbations of COPD from the American College of Chest Physicians and the Canadian Thoracic Society state that a LAMA is recommended over either a short-acting muscarinic antagonist or a LABA. The guidelines state that certain combination bronchodilators or bronchodilator/ICS combinations may reduce exacerbations, but does not state that any combination is superior to LAMA monotherapy in patients with stable COPD (*Criner et al 2015*).

Exercise-induced bronchoconstriction

- For exercise-induced bronchoconstriction, guidelines from the American Thoracic Society recommend administration of an inhaled SABA 15 minutes prior to exercise. The guidelines also recommend a controller agent added whenever SABA therapy is used at least once daily. Additional guidelines are set forth for patients with symptoms despite using an inhaled SABA before exercise (*Parsons et al 2013*). Joint guidelines from the American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma & Immunology, and the American College of Allergy, Asthma & Immunology state that beta$_2$-agonists (SABAs or LABAs) are most effective at short-term protection against exercise-induced bronchoconstriction and for accelerating recovery from exercise-induced bronchoconstriction. However, daily use of a SABA or LABA will lead to tolerance. Additional or adjunctive options include daily use of leukotriene inhibitors or ICSs, cromolyn sodium before exercise, or ipratropium for patients who have not responded to other agents (*Weiler et al 2016*).

SAFETY SUMMARY

- Contraindications:
  - Serevent Diskus and ProAir RespiClick are contraindicated in patients with a severe hypersensitivity to milk proteins.
  - LABAs should generally not be used as a primary treatment of status asthmaticus or other acute episodes of asthma or COPD that require intensive measures; this is listed as a contraindication for Serevent Diskus.
  - All LABAs are contraindicated for use in patients with asthma without concomitant use of a long-term asthma control medication.
- Key warnings and precautions:
  - All LABAs have a boxed warning describing the increased risk of asthma-related deaths. Because of this risk, use of LABAs for the treatment of asthma without a concomitant long-term asthma control medication, such as an ICS, is contraindicated. LABAs should be used only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an ICS.
  - Beta$_2$-agonists may also lead to:
    - paradoxical bronchospasm
    - fatalities with excessive use
    - cardiovascular effects such as increased heart rate, blood pressure, and/or electrocardiogram changes
    - central nervous system effects and/or seizures
  - LABAs should not be used to treat acute symptoms or initiated in the setting of acutely deteriorating asthma or COPD.

- Adverse events
  - Commonly-reported adverse events (≥ 5% for at least 1 medication in the class) include chest pain, palpitations, tachycardia, dizziness, excitement, fatigue, headache, nervousness, shakiness, somnolence, tremor, rash, diarrhea, nausea, vomiting, pain, asthma exacerbation, bronchitis, cough, influenza, nasal congestion, nasopharyngitis/pharyngitis, respiratory disorder, rhinitis, throat irritation, upper respiratory tract infection, viral respiratory infection, accidental injury, fever, and viral infection.
- Albuterol, levalbuterol, metaproterenol, terbutaline, arformoterol, indacaterol, and salmeterol are Pregnancy Category C; formoterol and olodaterol are not currently assigned a Pregnancy Category.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Generic Name	Available Formulations	Route	Usual Recommended Frequency	Comments
Short-acting beta$_2$-agonists				
albuterol	Inhalation: metered dose aerosol inhaler (HFA), metered dose dry powder inhaler, solution for nebulization Oral: extended-release tablets, syrup, tablets	Inhalation, oral	Treatment or prevention of bronchospasm in patients with asthma: • Aerosol/dry powder inhaler: 1 to 2 inhalations every 4 to 6 hours • Solution for nebulization: 3 to 4 times daily • Extended-release tablets: twice daily • Syrup, tablets: 3 to 4 times daily Exercise-induced bronchospasm: • Aerosol/dry powder inhaler: 2 inhalations 15 to 30 minutes before exercise	
levalbuterol	Metered dose aerosol inhaler (HFA), solution for nebulization	Inhalation	Treatment or prevention of bronchospasm in patients with asthma: • Aerosol inhaler: 1 to 2 inhalations every 4 to 6 hours • Solution for nebulization: 3 times daily	
metaproterenol	Syrup, tablets	Oral	3 to 4 times daily	
terbutaline	Injection, tablets	Subcutaneous injection, oral	• Injection: 1 subcutaneous injection, may repeat in 15 to 30 minutes if improvement does not occur; maximum, 0.5 mg in 4 hours • Tablets: 3 times daily, 6 hours apart	Injection: Safety and efficacy in children < 12 years of age have not been established.
Long-acting beta$_2$-agonists				
arformoterol	Solution for nebulization	Inhalation	Twice daily	Safety and efficacy in children have not been established.
formoterol	Solution for nebulization	Inhalation	Twice daily	Safety and efficacy in children have not been established.

Generic Name	Available Formulations	Route	Usual Recommended Frequency	Comments
indacaterol	Capsule for inhalation	Inhalation	Once daily	Safety and efficacy in children have not been established.
olodaterol	Inhalation spray	Inhalation	Once daily	Safety and efficacy in children have not been established.
salmeterol	Dry powder inhaler	Inhalation	Treatment or prevention of bronchospasm in patients with asthma/maintenance treatment of bronchoconstriction in COPD 1 inhalation twice daily Exercise-induced bronchospasm: 1 inhalation at least 30 minutes before exercise	

Abbreviations: COPD = chronic obstructive pulmonary disease; HFA = hydrofluoroalkane

See the current prescribing information for full details

CONCLUSION

- Single-entity respiratory beta$_2$-agonist agents are FDA-approved for the treatment of asthma, COPD, reversible airway obstruction and/or exercise-induced bronchospasm.
  - Beta$_2$-agonists are classified as short- or long-acting based on their onset and duration of action, and are available in various dosage forms, including solution for nebulization, aerosol inhaler, dry powder inhaler, oral solution, immediate- and extended-release tablets, and solution for injection.
  - SABAs are generally dosed multiple times per day for the treatment or prevention of symptoms.
  - LABAs are typically administered twice daily for COPD, with the exception of indacaterol and olodaterol, which are administered once daily.
- Overall, SABAs have demonstrated similar efficacy and safety. Similarly, guidelines do not recommend one LABA over another, and head-to-head clinical trials have not determined the superiority of any one agent.
- All LABAs have a boxed warning stating that these agents may increase the risk of asthma-related death.
  - In the treatment of asthma, LABAs should not be used as monotherapy, but rather added on to another long-acting controller medication such as an ICS if patients are not adequately controlled on the ICS alone.
- GINA and NHLBI guidelines recommend SABAs for symptomatic relief in patients with asthma, which should generally be used on an as-needed or “rescue” basis. For chronic management of asthma, LABAs should be used as add-on therapy in patients not adequately controlled on an ICS as an alternative to maximizing the ICS dose.
  - LABAs may also be used for exercise-induced bronchospasm and provide a longer period of coverage (typically 12 hours or more) compared to the SABAs; however, daily use of a beta$_2$-agonist can lead to tolerance, and daily use of LABA monotherapy is not recommended.
- GOLD guidelines state that inhaled bronchodilators are a key component of COPD treatment, and long-acting agents are generally preferred over short-acting agents for maintenance therapy.
  - Depending on the COPD patient subtype, initial COPD management may include use of a beta$_2$-agonist and/or an anticholinergic agent.
- None of the current asthma or COPD treatment guidelines recommend the use of one specific inhaled beta$_2$-agonist product over another.
  - Administration instructions and inhalation devices vary among products and should be considered in product selection.

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Publication Date: June 01, 2018

Therapeutic Class Overview
Antihistamines, Second Generation

INTRODUCTION

- Oral antihistamines have been a mainstay in the treatment of allergic rhinitis and chronic idiopathic urticaria (CIU) since their development in the first half of the 20th century *(Janssen 1993)*.
- Although first-generation antihistamines are effective at ameliorating symptoms associated with allergic rhinitis and CIU, use in practice is limited by their lack of selectivity for the histamine 1 (H_1)-receptor and their ability to cross the blood-brain barrier, both resulting in adverse effects. Second-generation antihistamines were developed to maintain the efficacy of the first-generation agents, while reducing associated adverse effects. Due to a more complex chemical structure, the movement of second-generation antihistamines across the blood-brain barrier is reduced. In addition to a safer adverse event profile, second-generation agents have a longer duration of action, which allows for once- or twice-daily dosing for most products *(Lehman et al 2006)*.
- Despite the efficacy of second-generation antihistamines for the treatment of allergic rhinitis, they are not effective in the treatment of nasal congestion *(Lehman et al 2006, Seidman et al 2015)*. Because of this, they are often combined with a decongestant. Second-generation antihistamines combined with pseudoephedrine have been shown to improve symptoms and quality of life in patients with allergic rhinitis and nasal congestion compared to antihistamines alone *(Seidman et al 2015)*.
- This review focuses on the use of the second-generation antihistamines for the treatment of CIU, perennial allergic rhinitis (PAR), and seasonal allergic rhinitis (SAR).
- Several products formerly available by prescription (Rx) are now available over-the-counter (OTC). This review includes Rx products and those that are sold both by Rx and OTC. Products sold solely OTC are not included in this review. However, the clinical efficacy section retains some information on OTC products that were formerly available by Rx for informational purposes.
- Medispan Class: Antihistamines – Non-Sedating and Cough/Cold/Allergy Combinations

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Cetirizine*	
cetirizine oral solution/syrup (Rx/OTC)	√
OTC-only products include tablets, chewable tablets, liquid-filled capsules, and orally disintegrating tablets (ODT)	
Desloratadine	
Clarinex (desloratadine) oral solution/syrup (Rx only)	-†
Clarinex (desloratadine) tablet (Rx only)	√
desloratadine ODT (Rx only)	√
Fexofenadine*	
OTC-only products include tablets, oral suspension, and ODT	
Levocetirizine*	
levocetirizine tablet (Rx/OTC)	√
levocetirizine oral solution (Rx/OTC)	√
Loratadine*	
OTC-only products include tablets, capsules, chewable tablets, solution/syrup, and ODT	
Antihistamine – decongestant combinations*	
Clarinex-D 12 Hour (desloratadine/pseudoephedrine extended release tablet) (Rx only)	-
Clarinex-D 24 Hour (desloratadine/pseudoephedrine extended release tablet) (Rx only)‡	-†

Drug	Generic Availability
Semprex-D (acrivastine/pseudoephedrine capsule) (Rx only)	-
OTC-only combinations include fexofenadine/pseudoephedrine, loratadine/pseudoephedrine, and cetirizine/ pseudoephedrine extended release tablets	

*Medication or combination is available OTC in at least 1 dosage form or strength. OTC products are available in various brand and private label names.
†Generic product has been FDA-approved but is not currently marketed.
‡Clarinex-D 24 Hour is no longer marketed.

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018, Facts and Comparisons 2018*)

INDICATIONS

Table 2a. FDA-Approved Indications – Single Entity Agents*

Indication	Cetirizine†	Desloratadine‡	Levocetirizine
CIU	√ (age 6 months to 5 years)	√ (ages 6 months and older)	√ (age 6 months and older)
PAR	√ (age 6 to 23 months)	√ (ages 6 months and older)	√ (age 6 months and older)
SAR		√ (ages 2 years and older)	√ (ages 2 years and older)

*The indications listed in the table are based on current prescription labeling. All OTC single entity products are to be used for the temporary relief of runny nose; sneezing; itchy, watery eyes; or itching of the nose and throat due to hay fever or other upper respiratory allergies.
†Oral solution indications (other formulations are no longer available by prescription)
‡The CIU indication is for the tablets and oral solution/syrup only; the ODT formulation is indicated for PAR and SAR, and is not recommend for use in patients ≤ 6 years of age because the oral solution is better suited for these patients.

(*Clinical Pharmacology 2018, Facts and Comparisons 2018, Prescribing information: Cetirizine 2016, Clarinex 2018, Desloratadine 2017, Levocetirizine 2018*)

Table 2b. FDA-Approved Indications – Combination Agents*

Indication	Acrivastine/pseudoephedrine	Desloratadine/pseudoephedrine
Relief of symptoms of SAR, including nasal congestion, in adults and adolescents aged ≥ 12 years	√	√

*The indication listed in the table is based on current prescription labeling. All OTC combination agents are to be used for the temporary relief of runny nose; sneezing; itchy, watery eyes; or itching of the nose and throat due to hay fever or other upper respiratory allergies; they also temporarily relieve nasal congestion and reduce nasal passage swelling.

(*Clinical Pharmacology 2018, Facts and Comparisons 2018, Prescribing information: Clarinex-D [12 hour] 2018, Semprex-D 2018*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Clinical trials have demonstrated that second-generation antihistamines are more effective in treating and providing symptomatic relief of CIU, PAR, and SAR compared to placebo *(Kaplan et al 2005, Kapp et al 2006, Kim et al 2006, Monroe et al 2003, Nathan et al 2006, Nayak et al 2017, Nettis et al 2006, Potter et al 2003, Potter et al 2005, Okubo et al 2005, Ring et al 2001, Simons et al 2003)*.
- When agents within the class were compared, one agent did not consistently demonstrate greater efficacy over another *(Anuradha et al 2010, Boyle et al 2005, Ciprandi et al 2005, Day et al 1998, Day et al 2001, Day et al 2004, Garg et al 2007, Handa et al 2004, Lee et al 2009, Meltzer et al 1996, Nayak et al 2017, Potter et al 2009, Prenner et al 2000, Purohit et al 2004, Van Cauwenberge et al 2000)*.
- In a systematic review by Benninger et al, second-generation antihistamines were associated with a 23.5% reduction from baseline in total nasal symptom scores for SAR, and a 51.4% reduction in symptoms of PAR. Although intranasal

corticosteroids were more effective for SAR (40.7% reduction), they were not as effective as long-term oral antihistamines in patients with PAR (37.3% reduction) (*Benninger et al 2010*).

- In a comparative effectiveness review by the Agency for Healthcare Research and Quality (AHRQ), oral selective antihistamines were equivalent to montelukast for nasal and eye symptoms in patients with SAR. Based on evidence of safety, in order to avoid insomnia, an oral selective antihistamine was preferred over the combination of an oral selective antihistamine with a decongestant or monotherapy with a decongestant *(Glacy et al 2013)*.
- In a systematic review of 73 randomized controlled trials in CIU, at standard treatment doses, the second-generation antihistamines were effective when compared with placebo. Cetirizine 10 mg once daily in the short term and in the intermediate term was effective in completely suppressing urticaria. Evidence was limited for desloratadine given at 5 mg once daily in the intermediate term and at 20 mg in the short term. Levocetirizine at 5 mg was effective for complete suppression in the intermediate term but not in the short term. No single agent was demonstrated to be more effective than another, and there is a lack of available head-to-head trials *(Sharma et al 2014)*.

CLINICAL GUIDELINES

- According to the current clinical guidelines for the management of allergic rhinitis, intranasal corticosteroids should be considered first-line therapy in the majority of patients with moderate to severe allergic rhinitis and may also be effective in some forms of nonallergic rhinitis. Although intranasal corticosteroids are the most effective drugs for treating allergic rhinitis, second-generation antihistamines may be used in patients with mild-to-moderate disease, especially those with a preference for oral therapy and with complaints of sneezing and itching. Considering their safety profile, second-generation antihistamines should be considered as first-line symptomatic treatment for urticaria *(Bernstein et al 2014, Brozek et al 2017, Dykewicz et al 2017, Grattan et al 2007, Seidman et al 2015, Wallace et al 2008, Zuberbier et al 2014)*.

SAFETY SUMMARY

- Levocetirizine is contraindicated in patients with severe renal impairment and in pediatric patients 6 months to 11 years of age with impaired renal function.
- Due to the pseudoephedrine component, the combination agents are contraindicated in patients with narrow angle glaucoma, severe hypertension or coronary artery disease, or urinary retention. The combination agents should not be used when there has been treatment with a monoamine oxidase inhibitor within the last 14 days.
- The most common adverse effects are associated with sedation and fatigue.

DOSING AND ADMINISTRATION

- For the combination agents, at least 14 days must elapse after discontinuation of a monoamine oxidase inhibitor before starting treatment.
- Extended-release products should be swallowed whole; tablets should not be broken, chewed, or crushed.

Table 3. Dosing and Administration

Drug	Route	Usual Recommended Frequency	Comments
Single Entity Agents			
Cetirizine	Oral	Once or twice daily	Dosage adjustment in renal and hepatic impairment is required.
Desloratadine	Oral	Once daily	Dosage adjustment in renal and hepatic impairment is required.
Levocetirizine	Oral	Once daily in the evening	Dosage adjustment in renal impairment is required.
Combination Agents			
Acrivastine/ pseudoephedrine	Oral	4 times per day	Avoid use in patients with creatinine clearance ≤ 48 mL/minute.
Desloratadine/ pseudoephedrine	Oral	Once or twice daily (the once-daily product is not currently marketed)	Avoid use in patients with renal and hepatic impairment (combination product was not studied in these populations).

See the current prescribing information for full details.

CONCLUSION

- Second-generation antihistamines have been shown to significantly improve the symptoms of allergic rhinitis and CIU, without the unwanted adverse effects associated with the first-generation agents *(Sur et al 2010)*.
- Currently, all of the single entity second-generation antihistamines are available as generics and/or OTC in at least 1 dosage form. Cetirizine, fexofenadine, levocetirizine, and loratadine can be purchased OTC, and several different dosage forms are available for the OTC products *(Clinical Pharmacology 2018, Facts and Comparisons 2018, Micromedex 2018)*.
- Current evidence supports the use of second-generation antihistamines in the treatment of seasonal and perennial allergic rhinitis as well as CIU. In a systematic review by Benninger et al, second-generation antihistamines were associated with a 23.5% reduction from baseline in total nasal symptom scores for SAR, and a 51.4% reduction in symptoms of PAR *(Benninger et al 2010)*.
- Overall, clinical trials have not consistently demonstrated one single-entity second generation antihistamine agent to be more efficacious or safe than the others. Furthermore, there is a lack of head-to-head trials comparing the combination second generation antihistamine products, rendering a comparison of the agents difficult.
- Current consensus guidelines are consistent among organizations that antihistamines are somewhat less effective than intranasal corticosteroids, but may be used on a daily or as-needed basis. Second-generation antihistamines are recommended as they are less sedating and cause less central nervous system impairment compared to first-generation agents. Oral decongestants can be a useful addition to antihistamines in the treatment of nasal congestion *(Brozek et al 2017, Dykewicz et al 2017, Seidman et al 2015)*.
- Considering their efficacy and safety profile, second-generation antihistamines should be considered as first-line symptomatic treatment of urticaria. Additionally, patients should be offered the choice of at least 2 nonsedating antihistamines as response varies among individuals *(Bernstein et al 2014, Grattan et al 2007, Zuberbier et al 2014)*.

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Publication Date: June 25, 2018

Therapeutic Class Overview
Immunomodulators

INTRODUCTION

- Immunomodulators treat a wide variety of conditions, including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), plaque psoriasis (PsO), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC), hidradenitis suppurativa (HS), and uveitis (UV), as well as several less common conditions.
- T cells, B cells, and cytokines such as tumor necrosis factor (TNF), interleukin-1 (IL-1) and interleukin-6 (IL-6) play a key role in the inflammatory and immune process (*Choy et al 2001*). This has led to the development of biologic agents to target these areas. The Food and Drug Administration (FDA) has currently approved 5 originator TNF inhibitors: Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Remicade (infliximab), and Simponi/Simponi Aria (golimumab), as well as 6 biosimilar TNF inhibitors: Amjevita (adalimumab-atto), Erelzi (etanercept-szzs), Inflectra (infliximab-dyyb), Renflexis (infliximab-abda), Cyltezo (adalimumab-adbm), and Ixifi (infliximab-qbtx). Other agents targeting different cells and cytokines are also FDA-approved for RA treatment. These include Orencia (abatacept), which inhibits CD28-B7 mediated costimulation of the T-cell; Rituxan (rituximab), which targets CD20, a molecule that is found on the surface of B-cells; Actemra (tocilizumab) and Kevzara (sarilumab), which have activity directed against the IL-6 receptor; and Kineret (anakinra), which targets the IL-1 receptor. An oral agent on the market, Xeljanz and Xeljanz XR (tofacitinib), targets Janus-associated kinase (JAK) pathways. By inhibiting the JAK pathway, the ability of cytokines to produce inflammation is reduced.
- Other immunomodulators include Ilaris (canakinumab), which binds to the IL-1ß receptor and is approved to treat JIA; and Entyvio (vedolizumab), which binds to the α4β7 integrin and is approved to treat CD and UC. Otezla (apremilast), an oral, small-molecule phosphodiesterase 4 (PDE-4) inhibitor, and Stelara (ustekinumab), which targets the IL-12 and IL-23 cytokines, are each approved for the treatment of PsA and PsO; Stelara is additionally indicated for the treatment of CD. Cosentyx (secukinumab) and Taltz (ixekizumab) bind and neutralize IL-17A and are indicated for the treatment of PsO and PsA; Cosentyx is additionally indicated to treat PsA and AS. A related agent, Siliq (brodalumab), is an IL-17 receptor antagonist, and Tremfya (guselkumab), an IL-23 antagonist, are indicated for selected patients with PsO.
- Certain rare conditions for which immunomodulators are indicated are mentioned in this review but are not discussed in detail; these include:
    - Ilaris for the treatment of 1) cryopyrin-associated periodic syndromes (CAPS), specifically the subtypes familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS); 2) TNF receptor associated periodic syndrome (TRAPS); 3) hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD); and 4) familial Mediterranean fever (FMF)
    - Kineret for the treatment of CAPS, specifically neonatal-onset multisystem inflammatory disease (NOMID)
    - Actemra for giant cell arteritis (GCA) and cytokine release syndrome (CRS).
- Rituxan is also approved for non–Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), and granulomatosis with polyangiitis (GPA) (Wegener's granulomatosis) and microscopic polyangiitis (MPA). These indications will not be discussed in this review.
- Tysabri (natalizumab), an integrin receptor antagonist, is indicated for multiple sclerosis and CD for patients who have had an inadequate response to, or are unable to tolerate conventional therapies and TNF inhibitors; it is not included as a drug product in this review (*Tysabri prescribing information 2017*). Arcalyst (rilonacept), an interleukin-1 blocker indicated for CAPS, is also not included in this review (*Arcalyst prescribing information 2016*).
- Although FDA-approved, the launch plans for the biosimilar drugs Amjevita (adalimumab-atto), Erelzi (etanercept-szzs), Cyltezo (adalimumab-adbm) and Ixifi (infliximab-qbtx) are pending and may be delayed; therefore, these agents are not currently included in this review. The manufacturer of Ixifi to date does not have plans to launch Ixifi in the United States.
- Medispan Classes: Antineoplastic-Monoclonal Antibodies, Antipsoriatics, Antirheumatic-Enzyme Inhibitors, Anti-TNF-Alpha-Monoclonal Antibodies, Integrin Receptor Antagonists, Interleukin-1 Receptor Antagonists, Interleukin-1beta Receptor Inhibitors, Interleukin-6 Receptor Inhibitors, PDE-4 Inhibitors, Selective Costimulation Modulators, Soluble Tumor Necrosis Factor Receptor Agents, Tumor Necrosis Factor Alpha Blockers

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Biosimilar or Generic Availability	Type of Agent
Actemra (tocilizumab)	Genentech	01/08/2010	-	Human monoclonal antibody targeting the IL-6 receptor
Cimzia (certolizumab)	UCB	04/22/2008	-	TNFα inhibitor
Cosentyx (secukinumab)	Novartis	01/21/2015	-	Human monoclonal antibody to IL-17A
Enbrel (etanercept)	Amgen	11/02/1998	-*	sTNFR fusion protein, TNFα inhibitor
Entyvio (vedolizumab)	Takeda Pharmaceuticals America, Inc.	05/20/2014	-	Human monoclonal antibody binds to the α4β7 integrin
Humira (adalimumab)	AbbVie	12/31/2002	-*	TNFα inhibitor
Ilaris (canakinumab)	Novartis	06/17/2009	-	Human monoclonal antibody that binds to IL-1ß
Inflectra (infliximab-dyyb)	Celltrion/ Hospira/Pfizer	04/05/2016	N/A†	TNFα inhibitor
Kevzara (sarilumab)	Sanofi Genzyme Regeneron	05/22/2017	-	Human monoclonal antibody targeting IL-6 receptor
Kineret (anakinra)	Swedish Orphan Biovitrum	11/14/2001	-	IL-1 receptor antagonist
Orencia (abatacept)	Bristol Myers Squibb	12/23/2005	-	sCTLA-4-Ig recombinant fusion protein
Otezla (apremilast)	Celgene Corporation	03/21/2014	-	Small-molecule phosphodiesterase 4 inhibitor
Remicade (infliximab)	Janssen Biotech	8/24/1998	-†	TNFα inhibitor
Renflexis (infliximab-abda)	Merck	04/21/2017	N/A†	TNFα inhibitor
Rituxan (rituximab)	Genentech	11/26/1997	-	Anti-CD20 monoclonal antibody
Siliq (brodalumab)	Valeant	02/15/2017	-	Human monoclonal antibody directed against the IL-17 receptor A (IL-17RA)
Simponi/ Simponi Aria (golimumab)	Janssen Biotech	04/24/2009 and 07/18/2013	-	TNFα inhibitor
Stelara (ustekinumab)	Janssen Biotech	09/25/2009	-	Human monoclonal antibody targeting the IL-12 and IL-23 cytokines
Taltz (ixekizumab)	Eli Lilly	03/22/2016	-	Human monoclonal antibody to IL-17A
Tremfya (guselkumab)	Janssen Biotech	07/13/2017	-	Human monoclonal antibody to IL-23 cytokine
Xeljanz / Xeljanz XR (tofacitinib)	Pfizer	11/06/2012 and 02/23/2016	-	Small molecule Janus kinase (JAK) inhibitor

*Erelzi (etanercept-szzs) has been FDA-approved as a biosimilar to Enbrel (etanercept). Amjevita (adalimumab-atto) and Cyltezo (adalimumab-adbm) have been FDA-approved as biosimilars to and Humira (adalimumab). The specific launch dates for these products are pending and may be delayed. Further information on Erelzi, Amjevita, and Cyltezo will be included in this review after these products have launched.

†Inflectra (infliximab-dyyb) and Renflexis (infliximab-abda) have been FDA-approved as biosimilar agents to Remicade (infliximab), however, they are not FDA-approved as interchangeable biologics.

(Drugs@FDA, 2018; Prescribing information: Actemra, 2017; Cimzia, 2018; Cosentyx, 2018; Enbrel, 2017; Entyvio, 2018; Humira, 2017; Ilaris, 2017; Inflectra, 2017; Kevzara, 2017; Kineret, 2016; Orencia, 2017; Otezla, 2017; Remicade, 2017; Renflexis, 2017; Rituxan, 2014; Siliq, 2017; Simponi, 2018; Simponi Aria, 2018; Stelara, 2018; Taltz, 2017; Tremfya, 2017; Xeljanz/Xeljanz XR, 2017)

Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

INDICATIONS

Table 2. Food and Drug Administration Approved Indications (see footnotes for less common indications: CAPS, CRS, FMF, GCA, HIDS/MKD, and TRAPS)

Drug	Rheumatoid Arthritis (RA)	Crohn's Disease (CD)	Systemic Juvenile Idiopathic Arthritis (SJIA)	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Ankylosing Spondylitis (AS)	Ulcerative Colitis (UC)	Hidradenitis Suppurativa (HS)	Uveitis (UV)
Actemra[ŷ] (tocilizumab)	✔ *		✔ **	✔ **						
Cimzia (certolizumab)	✔	✔				✔	✔			
Cosentyx (secukinumab)					✔ ‡	✔	✔			
Enbrel (etanercept)	✔ †			✔ **	✔ ‡	✔ †	✔			
Entyvio (vedolizumab)		✔						✔		
Humira (adalimumab)	✔ ‡‡	✔ ⌐		✔ ∫	✔ ‡	✔ ∫∫	✔	✔	✔	✔ ▼
Ilaris" (canakinumab)			✔ **							

Drug	Rheumatoid Arthritis (RA)	Crohn's Disease (CD)	Systemic Juvenile Idiopathic Arthritis (SJIA)	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Ankylosing Spondylitis (AS)	Ulcerative Colitis (UC)	Hidradenitis Suppurativa (HS)	Uveitis (UV)
Inflectra (infliximab-dyyb)	✔ ⊥	✔ ⌐⌐			✔ ‡‡‡	✔	✔	✔ ⊥⊥		
Kevzara (sarilumab)	✔ *									
Kineret▼▼ (anakinra)	✔ ∞									
Orencia (abatacept)	✔ ∞∞			✔ ⌂		✔				
Otezla (apremilast)					✔ ‡	✔				
Remicade (infliximab)	✔ ⊥	✔ ⌐⌐			✔ ‡‡‡	✔	✔	✔ ⊥⊥		
Renflexis (infliximab-abda)	✔ ⊥	✔ ⌐⌐			✔ ‡‡‡	✔	✔	✔ ⊥⊥		

Drug	Rheumatoid Arthritis (RA)	Crohn's Disease (CD)	Systemic Juvenile Idiopathic Arthritis (SJIA)	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Ankylosing Spondylitis (AS)	Ulcerative Colitis (UC)	Hidradenitis Suppurativa (HS)	Uveitis (UV)
Rituxan‴ (rituximab)	✓ǂ									
Siliq (brodalumab)					✓ǂǂ					
Simponi (golimumab)	✓┤					✓┤┤	✓	✓˜		
Simponi Aria (golimumab)	✓┤					✓	✓			
Stelara (ustekinumab)		✓⌐⌐⌐			✓‡	✓				
Taltz (ixekizumab)					✓‡	✓				
Tremfya (guselkumab)					✓‡					

Drug	Rheumatoid Arthritis (RA)	Crohn's Disease (CD)	Systemic Juvenile Idiopathic Arthritis (SJIA)	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Ankylosing Spondylitis (AS)	Ulcerative Colitis (UC)	Hidradenitis Suppurativa (HS)	Uveitis (UV)
Xeljanz / Xeljanz XR (tofacitinib)	✔ ╪╪					✔				

ϒActemra is also indicated for treatment of giant cell arteritis in adults and chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome in adults and pediatric patients ≥ 2 years.
*Patients with moderately to severely active RA who have had an inadequate response (or intolerance [Kevzara]) to ≥ 1 Disease-Modifying Anti-Rheumatic Drugs (DMARDs).
**Patients 2 years and older.
†In combination with methotrexate (MTX) or used alone.
‡Indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe PsO who are candidates for systemic therapy or phototherapy, with the exception of Enbrel, which is indicated for the treatment of patients 4 years and older with chronic moderate to severe PsO who are candidates for systemic therapy or phototherapy, and Stelara, which is indicated for the treatment of patients 12 years and older with moderate to severe PsO.
‡‡Indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA. Can be used alone or in combination with MTX or other DMARDs.
‡‡‡ Indicated for the treatment of adult patients with chronic severe (ie, extensive and/or disabling) PsO who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.
∫Indicated for reducing signs and symptoms of JIA for patients 2 years of age and older. Can be used alone or in combination with MTX.
∫∫Indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA. Can be used alone or in combination with non-biologic DMARDs.
▼Treatment of non-infectious intermediate, posterior and panuveitis in adult patients.
▼▼Kineret is also indicated for the treatment of cryopyrin-associated periodic syndromes (CAPS) including neonatal-onset multisystem inflammatory disease (NOMID).
"Ilaris also indicated for the treatment of CAPS in adults and children 4 years of age and older including: familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS); tumor necrosis factor receptor associated periodic syndrome (TRAPS) in adult and pediatric patients; hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD) in adult and pediatric patients; and familial Mediterranean fever (FMF) in adult and pediatric patients.
∞Indicated for the reduction in signs and symptoms and slowing the progression of structural damage in moderately to severely active RA, in patients 18 years of age or older who have failed one or more DMARDs. Can be used alone or in combination with DMARDs other than TNF blocking agents.
∞∞Indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA. May be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.
⌂ Indicated for reducing signs and symptoms in pediatric patients 2 years and older with moderate to severely active PJIA. May be used as monotherapy or with MTX.
⌐For all patients 6 years of age and older, indicated for reducing signs and symptoms and inducing and maintaining clinical remission in patients who have had an inadequate response to conventional therapy. For adults, also indicated for reducing signs and symptoms and inducing clinical remission if patients have also lost a response to or are intolerant of infliximab.
⌐⌐Indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy and for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing CD. And for patients 6 years of age and older for reducing signs and symptoms and inducing and maintaining clinical remission with moderately to severely active disease who have had an inadequate response to conventional therapy.
⌐⌐⌐Indicated for treatment of adult patients with moderately to severely active CD who have: 1) failed or were intolerant to treatment with immunomodulators or corticosteroids but never failed a TNF blocker, or 2) failed or were intolerant to treatment with ≥ 1 TNF blockers
┴In combination with MTX, is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active RA.
┴┴For reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy. Also for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active disease who have had an inadequate response to conventional therapy (Remicade only). The biosimilars Inflectra and Renflexis did not receive FDA approval for pediatric UC due to existing marketing exclusivity for Remicade for this indication (not for clinical reasons).
'"Rituxan also indicated for Non–Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), and granulomatosis with polyangiitis (GPA) (Wegener's Granulomatosis) and microscopic polyangiitis (MPA).
╪In combination with MTX is indicated for the treatment of adult patients with moderately- to severely- active RA who have had an inadequate response to ≥ 1TNF antagonist therapies.
╪╪Treatment of moderate to severe PsO in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies.

┤In combination with MTX, is indicated for the treatment of adult patients with moderately to severely active RA.
┤┤Alone or in combination with MTX, is indicated for the treatment of adult patients with active PsA.
╪╪Indicated for the treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to MTX. It may be used as monotherapy or in combination with MTX or other nonbiologic DMARDs. Use in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.
˜Indicated in adult patients with moderately to severely active UC who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosalicylates, oral corticosteroids, azathioprine, or 6-mercaptopurine for: inducing and maintaining clinical response; improving endoscopic appearance of the mucosa during induction; inducing clinical remission; and achieving and sustaining clinical remission in induction responders.

CLINICAL EFFICACY SUMMARY

Rheumatoid arthritis (RA)

- The approval of the subcutaneous (SQ) formulation of Orencia (abatacept) was based on a double-blind, double-dummy, randomized trial demonstrating noninferiority to the intravenous (IV) formulation. The trial enrolled patients with RA who had an inadequate response to methotrexate (MTX). The proportion of patients achieving American College of Rheumatology 20% improvement (ACR 20) was not significantly different between the groups (*Genovese et al 2011*).
- Orencia (abatacept), Remicade (infliximab), and placebo were compared in a Phase 3, randomized, double-blind trial (n = 431). Enrolled patients had an inadequate response to MTX, and background MTX was continued during the trial. Although efficacy was comparable between abatacept and infliximab after 6 months of treatment, some differences in favor of abatacept were evident after 1 year of treatment. After 1 year, the mean changes from baseline in disease activity score based on erythrocyte sedimentation rate (DAS28-ESR) were -2.88 and -2.25 in the abatacept and infliximab groups, respectively (estimate of difference, -0.62; 95% confidence interval [CI], -0.96 to -0.29). Abatacept demonstrated greater efficacy vs infliximab on some (but not all) secondary endpoints, including the proportion of patients with a good European League Against Rheumatism (EULAR) response (32.0% vs 18.5%), low disease activity score (LDAS) (35.3% vs 22.4%), ACR 20 responses (72.4% vs 55.8%), and improvements in the Medical Outcomes Study short-form-36 (SF-36) physical component summary (PCS) (difference of 1.93). Overall, abatacept had a relatively more acceptable safety and tolerability profile, with fewer serious adverse events (AEs) and discontinuations due to AEs than the infliximab group (*Schiff et al 2008*).
- Treatment with Orencia (abatacept) was directly compared to treatment with Humira (adalimumab), when added to MTX, in a multicenter, investigator-blind, randomized controlled trial (n = 646) of RA patients with inadequate response to MTX. After 2 years, the proportions of patients achieving ACR 20 responses were comparable between abatacept and adalimumab treatment groups (59.7 and 60.1%, respectively; difference 1.8%; 95% CI, -5.6 to 9.2%). ACR 50 and ACR 70 responses were also similar between the 2 groups after 2 years of treatment. Rates of AEs were similar between treatment groups (*Schiff et al 2014*).
- The RAPID-1 and RAPID-2 studies compared Cimzia (certolizumab) in combination with MTX to placebo plus MTX in adults with active RA despite MTX therapy (*Keystone et al 2008, Smolen et al 2009a*). A significantly greater proportion of patients on certolizumab 400 mg plus MTX at weeks 0, 2, and 4 then 200 or 400 mg every 2 weeks attained greater ACR 20, ACR 50 and ACR 70 responses compared to patients on placebo and MTX, respectively, after 24 weeks ($p \leq 0.01$). The response rates were sustained with active treatment over 52 weeks (*Keystone et al 2008*). The Modified Total Sharp Score (mTSS) was significantly lower with certolizumab in combination with MTX compared to MTX in combination with placebo (*Keystone et al 2008, Smolen et al 2009a*). A trial evaluated Cimzia (certolizumab) monotherapy vs placebo in patients with active disease who had failed at least 1 prior DMARD. After 24 weeks, ACR 20 response rates were significantly greater with active treatment (45.5%) compared to placebo (9.3%; $p < 0.001$). Significant improvements in secondary endpoints (ACR 50, ACR 70, individual ACR component scores, and patient reported outcomes) were also associated with certolizumab therapy (*Fleischmann et al 2009*).
- More Cimzia (certolizumab)-treated patients achieved clinical disease activity index (CDAI) remission than placebo-treated patients (18.8% vs 6.1%, $p \leq 0.05$) in a randomized, double-blind, placebo-controlled trial of certolizumab over 24 weeks in 194 patients with RA who were on DMARD therapy with MTX, leflunomide, sulfasalazine and/or hydroxychloroquine for at least 6 months (*Smolen et al 2015a*).
- A randomized, double-blind, placebo-controlled trial (n = 316) conducted in Japan compared Cimzia (certolizumab) plus MTX to placebo plus MTX in MTX-naïve patients with early RA (≤ 12 months persistent disease) and poor prognostic factors: high anti-cyclic citrullinated peptide (anti-CCP) antibody and either positive rheumatoid factor and/or presence of bone erosions (*Atsumi et al 2016*). The primary endpoint was inhibition of radiographic progression (change from baseline in mTSS at week 52). The certolizumab plus MTX group showed significantly greater inhibition of radiographic progression vs MTX alone (mTSS change, 0.36 vs 1.58; $p < 0.001$). Clinical remission rates were higher in patients treated with certolizumab plus MTX vs MTX alone. The authors suggest that certolizumab plus MTX could be used as possible first-line treatment in this patient population. In a long-term extension, a higher percentage of patients treated with certolizumab plus MTX experienced inhibition of radiographic progression (change from baseline in mTSS) at week 104 vs MTX alone (84.2% vs 67.5%; $p < 0.001$) (*Atsumi et al 2017*).
- The FDA approval of Simponi (golimumab) for RA was based on 3 multicenter, double-blind, randomized, controlled trials in 1,542 patients ≥ 18 years of age with moderate to severe active disease. A greater percentage of patients from all 3 trials treated with the combination of golimumab and MTX achieved ACR responses at week 14 and week 24 vs patients treated with MTX alone (*Emery et al 2009, Keystone et al 2009, Smolen et al 2009b*). Additionally, the golimumab 50 mg groups demonstrated a greater improvement compared to the control groups in the change in

mean Health Assessment Questionnaire (HAQ) Disability Index (HAQ-DI) (*Keystone et al 2009, Smolen et al 2009b*). Response with golimumab + MTX was sustained for up to 5 years (*Keystone et al 2013a, Smolen et al 2015b*).

- Simponi Aria (golimumab) was studied in patients with RA. In 1 trial, 643 patients could receive golimumab 2 mg/kg or 4 mg/kg intravenously (IV) every 12 weeks with or without MTX, or placebo with MTX. The proportion of patients meeting the primary endpoint of ACR 50 response was not significantly different between the golimumab with or without MTX groups and the placebo group. However, significantly more patients receiving golimumab plus MTX achieved an ACR 20 response at week 14 compared with patients receiving placebo plus MTX (53 vs 28%; $p < 0.001$) (*Kremer et al 2010*). In the GO-FURTHER trial (n = 592), golimumab 2 mg/kg IV or placebo was given at weeks 0, 4 and then every 8 weeks. An increased percentage of patients treated with golimumab + MTX achieved ACR 20 response at week 14 (58.5% [231/395] of golimumab + MTX patients vs 24.9% [49/197] of placebo + MTX patients [$p < 0.001$]) (*Weinblatt et al 2013*). In an open-label extension period, treatment was continued through week 100, with placebo-treated patients crossing over to golimumab at week 16 (early escape) or week 24. Clinical response was maintained through week 100, with an ACR 20 response of 68.1%. There was a very low rate of radiographic progression throughout the study, and patients treated with IV golimumab plus MTX from baseline had significantly less radiographic progression to week 100 compared to patients who had initially received placebo plus MTX. No unexpected AEs occurred (*Bingham et al 2015*). In the GO-MORE trial, investigators treated patients with golimumab SQ for 6 months. If patients were not in remission, they could be randomized to receive golimumab SQ or IV. The percentages of patients who achieved DAS28-ESR remission did not differ between the combination SQ + IV group and the SQ golimumab group (*Combe et al 2014*).
- The efficacy and safety of Actemra (tocilizumab) were assessed in several randomized, double-blind, multicenter studies in patients age ≥ 18 years with active RA. Patients were diagnosed according to ACR criteria, with at least 8 tender and 6 swollen joints at baseline. Tocilizumab was given every 4 weeks as monotherapy (AMBITION), in combination with MTX (LITHE and OPTION) or other DMARDs (TOWARD) or in combination with MTX in patients with an inadequate response to TNF antagonists (RADIATE). In all studies, mild to moderate AEs were reported, occurring in similar frequencies in all study groups. The most common AEs in all studies were infections and gastrointestinal symptoms (*Emery et al 2008, Genovese et al 2008, Jones et al 2010, Kremer et al 2011, Smolen et al 2008*).
    - AMBITION evaluated the safety and efficacy of tocilizumab monotherapy vs MTX in patients with active RA for whom previous treatment with MTX or biological agents had not failed. A total of 673 patients were randomized to 1 of 3 treatment arms, tocilizumab 8 mg/kg every 4 weeks, MTX 7.5 mg/week and titrated to 20 mg/week within 8 weeks, or placebo for 8 weeks followed by tocilizumab 8 mg/kg. The primary endpoint was the proportion of patients achieving ACR 20 response at week 24. The results showed that tocilizumab monotherapy when compared to MTX monotherapy produced greater improvements in RA signs and symptoms, and a favorable benefit-risk ratio in patients who had not previously failed treatment with MTX or biological agents. Additionally, more patients treated with tocilizumab achieved remission at week 24 when compared to patients treated with MTX (*Jones et al 2010*).
    - LITHE evaluated 1,196 patients with moderate to severe RA who had an inadequate response to MTX. Patients treated with tocilizumab had 3 times less progression of joint damage, measured by Total Sharp Score, when compared to patients treated with MTX alone. Significantly more patients treated with tocilizumab 8 mg/kg were also found to achieve remission at 6 months as compared to MTX (33% vs 4%), and these rates continued to increase over time to 1 year (47% vs 8%) (*Kremer et al 2011*). These benefits were maintained or improved at 2 years with no increased side effects (*Fleishmann et al 2013*).
    - OPTION evaluated tocilizumab in 623 patients with moderate to severely active RA. Patients received tocilizumab 8 mg/kg, 4 mg/kg, or placebo IV every 4 weeks, with MTX at stable pre-study doses (10 to 25 mg/week). Rescue therapy with tocilizumab 8 mg/kg was offered at week 16 to patients with < 20% improvement in swollen and tender joint counts. The primary endpoint was ACR 20 at week 24. The findings showed that ACR 20 was seen in significantly more patients receiving tocilizumab than in those receiving placebo at week 24 ($p < 0.001$). Significantly more patients treated with tocilizumab achieved ACR 50 and ACR 70 responses at week 24 as well ($p < 0.001$). Greater improvements in physical function, as measured by the HAQ-DI, were seen with tocilizumab when compared to MTX (-0.52 vs -0.55 vs -0.34; $p < 0.0296$ for 4 mg/kg and $p < 0.0082$ for 8 mg/kg) (*Smolen et al 2008*).
    - TOWARD examined the efficacy and safety of tocilizumab combined with conventional DMARDs in 1220 patients with active RA. Patients remained on stable doses of DMARDs and received tocilizumab 8 mg/kg or placebo every 4 weeks for 24 weeks. At week 24, significantly more patients taking tocilizumab with DMARDs achieved an ACR 20 response than patients in the control group. The authors concluded that tocilizumab, combined with any of the DMARDs evaluated (MTX, chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine, and leflunomide), was safe and effective in reducing articular and systemic

symptoms in patients with an inadequate response to these agents. A greater percentage of patients treated with tocilizumab also had clinically meaningful improvements in physical function when compared to placebo (60% vs 30%; p value not reported) (*Genovese et al 2008).*

- RADIATE evaluated the safety and efficacy of tocilizumab in patients with RA refractory to TNF antagonist therapy. A total of 499 patients with inadequate response to ≥ 1TNF antagonists were randomly assigned to 8 or 4 mg/kg tocilizumab or placebo every 4 weeks with stable MTX doses (10 to 25 mg/week) for 24 weeks. ACR 20 responses and safety endpoints were assessed. This study found that tocilizumab plus MTX is effective in achieving rapid and sustained improvements in signs and symptoms of RA in patients with inadequate response to TNF antagonists and has a manageable safety profile. The ACR 20 response in both tocilizumab groups was also found to be comparable to those seen in patients treated with Humira (adalimumab) and Remicade (infliximab), irrespective of the type or number of failed TNF antagonists (*Emery et al 2008*). In the ADACTA trial, patients with severe arthritis who could not take MTX were randomized to monotherapy with tocilizumab or adalimumab. The patients in the tocilizumab group had a significantly greater improvement in DAS28 at week 24 than patients in the adalimumab group (*Gabay et al 2013*).

- More recently, results of a randomized, double-blind trial evaluating Actemra (tocilizumab) in early RA were published (*Bijlsma et al 2016*). Patients (n = 317) had been diagnosed with RA within 1 year, were DMARD-naïve, and had a DAS28 score of ≥ 2.6. Patients were randomized to 1 of 3 groups: tocilizumab plus MTX, tocilizumab plus placebo, or MTX plus placebo. Tocilizumab was given at a dose of 8 mg/kg every 4 weeks (maximum 800 mg per dose), and MTX was given at a dose of 10 mg orally per week, increased to a maximum of 30 mg per week as tolerated. Patients not achieving remission switched from placebo to active treatments, and patients not achieving remission in the tocilizumab plus MTX group switched to a standard of care group (usually a TNF inhibitor plus MTX). The primary endpoint was the proportion of patients achieving sustained remission (defined as DAS28 < 2.6 with a swollen joint count ≤4, persisting for at least 24 weeks). The percentages of patients achieving a sustained remission on the initial regimen were 86%, 84%, and 44% in the tocilizumab plus MTX, tocilizumab monotherapy, and MTX monotherapy groups, respectively (p < 0.0001 for both comparisons vs MTX). The percentages of patients achieving sustained remission during the entire study were 86%, 88%, and 77% in the tocilizumab plus MTX, tocilizumab monotherapy, and MTX monotherapy groups, respectively (p = 0.06 for tocilizumab plus MTX vs MTX; p = 0.0356 for tocilizumab vs MTX). The authors concluded that immediate initiation of tocilizumab is more effective compared to initiation of MTX in early RA.
- The FDA approval of the SQ formulation of Actemra (tocilizumab) was based on 1 multicenter, double-blind, randomized, controlled trial in patients (n = 1262) with RA. Weekly tocilizumab SQ 162 mg was found to be non-inferior to tocilizumab IV 8 mg/kg every 4 weeks through 24 weeks. A higher incidence of injection-site reactions were reported with the SQ formulation (*Burmester et al 2014a*). In an open-label extension period, patients in both treatment arms were re-randomized to receive either IV or SQ tocilizumab through week 97. The proportions of patients who achieved ACR 20/50/70 responses, DAS28 remission, and improvement from baseline in HAQ-DI ≥ 0.3 were sustained through week 97 and comparable across arms. IV and SQ treatments had a comparable safety profile with the exception of higher injection-site reactions with the SQ formulation (*Burmester et al 2016*). A placebo-controlled trial in 656 patients further confirmed the efficacy of SQ Actemra administered every other week (*Kivitz et al 2014*).
- A phase 3 trial (MONARCH) evaluating the efficacy of Kevzara (sarilumab) monotherapy vs Humira (adalimumab) monotherapy for the treatment of patients with active RA with an inadequate response or intolerance to MTX reported superiority of sarilumab over adalimumab based on change from baseline in DAS28-ESR at week 24 (-3.28 vs -2.20; difference, -1.08; 95% CI, -1.36 to -0.79; p < 0.0001) (*Burmester et al 2017*). DAS28-ESR remission, ACR 20/50/70 response rates, and improvements in HAQ-DI scores were also more likely with sarilumab. Aside from the MONARCH trial, sarilumab has not been directly compared to any other biologic or tofacitinib. Nonetheless, 2 pivotal trials have shown the agent to be superior in achievement of ACR 50 when compared to MTX plus placebo, in both MTX inadequate responders and TNF inhibitor inadequate responder patients (*Genovese et al 2015, Fleischmann et al 2017*). Additionally, a meta-analysis of 4 randomized controlled trials (RCTs) has shown that ACR 50 response rates were significantly higher with sarilumab 200 mg and sarilumab 200 mg plus MTX when compared to MTX plus placebo (OR, 4.05; 95% CI, 2.04 to 8.33 and OR, 3.75; 95% CI, 2.37 to 5.72, respectively). Ranking probability based on the surface under the cumulative ranking curve (SUCRA) suggested that sarilumab 200 mg was most likely to achieve ACR 50 response rate, followed by sarilumab 200 mg plus MTX, sarilumab 150 mg plus MTX, adalimumab 40 mg, and MTX plus placebo (*Bae et al 2017).*
- In a Phase 3 trial, the percentage of patients who met criteria for RA disease remission was not significantly different in the Xeljanz (tofacitinib) groups (5 mg and 10 mg twice daily) vs placebo. However, significantly more patients in the tofacitinib groups did meet criteria for decrease of disease activity. The tofacitinib groups also had significant decreases in fatigue and pain (*Fleishmann et al 2012*). In another Phase 3 study, Xeljanz (tofacitinib), when

administered with background MTX, was superior to placebo with respect to all clinical outcomes. Although not directly compared to Humira (adalimumab), the clinical efficacy of tofacitinib was numerically similar to that observed with adalimumab. Safety of tofacitinib continues to be monitored for long term effects (*van Vollenhoven et al 2012*). The ORAL Scan trial showed the ACR 20 response rates at month 6 for patients receiving tofacitinib 5 mg and 10 mg twice daily were 51.5% and 61.8%, respectively, vs 25.3% for patients receiving placebo ($p < 0.0001$ for both comparisons) (*van der Heijde et al 2013*). The ORAL START trial evaluated tofacitinib and MTX in 956 patients with active RA over 24 months. The primary endpoint of mean change from baseline in modified total Sharp score was significantly less with tofacitinib (0.6 for 5 mg; 0.3 for 10 mg) compared to MTX (2.1; $p < 0.001$) (*Lee et al 2014*). No radiographic progression was defined as a change from baseline in the modified total Sharp score of < 0.5 points. However, a minimal clinically important difference in modified total Sharp score is 4.6 points; this study did not meet this minimal clinical meaningful difference threshold.

- In the ORAL Step study, patients with RA who had an inadequate response to ≥ 1 TNF inhibitors were randomized to Xeljanz (tofacitinib) 5 mg or 10 mg twice daily or placebo; all patients were on MTX (*Burmester et al 2013a, Strand et al 2015a*). The primary outcome, ACR 20 response rate, was significantly higher with tofacitinib 5 mg (41.7%; 95% CI, 6.06 to 28.41; $p = 0.0024$) and 10 mg (48.1%; 95% CI, 12.45 to 34.92; $p < 0.0001$) compared to placebo (24.4%). Improvements in HAQ-DI was reported as -0.43 (95% CI, -0.36 to -0.157; $p < 0.0001$) for tofacitinib 5 mg and -0.46 (95% CI, -0.38 to -0.17; $p < 0.0001$) for tofacitinib 10 mg groups compared to -0.18 for placebo. Common AEs included diarrhea, nasopharyngitis, headache, and urinary tract infections in the tofacitinib groups.
- Inflectra (infliximab-dyyb) was evaluated and compared to Remicade (infliximab; European Union formulation) in PLANETRA (N=606), a double-blind, multicenter, randomized trial (*Yoo et al 2013, Yoo et al 2016, Yoo et al 2017*). The primary endpoint, ACR 20 at week 30, was achieved by 58.6% and 60.9% of patients in the Remicade and Inflectra groups, respectively (treatment difference [TD], 2%; 95% CI, -6% to 10%) (intention-to-treat population). Corresponding results in the per-protocol population were 69.7% and 73.4%, respectively (TD, 4%; 95% CI, -4% to 12%). Equivalence was demonstrated between the 2 products.
    - Secondary endpoints included several other disease activity scales and a quality-of-life scale; no significant differences were noted in any of these endpoints at either the 30-week or 54-week assessments.
    - In the extension study (n = 302) through 102 weeks, all patients received Inflectra. Response rates were maintained, with no differences between the Inflectra maintenance group and the group who switched from Remicade to Inflectra.
- Renflexis (infliximab-abda) was evaluated and compared to Remicade (infliximab; European Union formulation) in 584 patients in a double-blind, multicenter, randomized phase 3 trial (*Choe et al 2017*). The primary endpoint, ACR 20 at week 30, was achieved by 64.1% and 66.0% of patients in the Renflexis and Remicade groups, respectively (TD, -1.88%; 95% CI, -10.26% to 6.51%) (per-protocol population). Equivalence was demonstrated between the 2 products.
    - Secondary endpoints were also very similar between the 2 groups.
    - At week 54 of this trial, patients transitioned into the switching/extension phase, in which patients initially taking Remicade were re-randomized to continue Remicade or switch to Renflexis; patients initially taking Renflexis continued on the same treatment. Although slight numerical differences were observed, there was consistent efficacy over time across treatments and the proportions of patients achieving ACR responses were comparable between groups (*Renflexis FDA clinical review 2017*).
- Two studies, 1 double-blind and 1 open-label, evaluated Rituxan (rituximab) in patients who had failed treatment with a TNF blocker (*Cohen et al 2006, Haraoui et al 2011*). All patients continued to receive MTX. Both studies showed > 50% of patients achieving ACR 20 response. AEs were generally mild to moderate in severity.
- A Cochrane review (*Lopez-Olivo et al 2015*) examined Rituxan (rituximab) for the treatment of RA. Eight studies and a total of 2720 patients were included. Rituximab plus MTX, compared to MTX alone, resulted in more patients achieving ACR 50 at 24 weeks (29% vs 9%, respectively) and clinical remission at 52 weeks (22% vs 11%). In addition, rituximab plus MTX compared to MTX alone resulted in more patients having no radiographic progression (70% vs 59% at 24 weeks, with similar results at 52 through 56 and 104 weeks). Benefits were also shown for physical function and quality of life.
- In the open-label ORBIT study (n = 295), adults with active, seropositive RA and an inadequate response to DMARDs who were biologic-naïve were randomized to either Rituxan (rituximab) (n = 144) or a TNF inhibitor (physician/patient choice of Enbrel [etanercept] or Humira [adalimumab]; n = 151) (*Porter et al 2016*). Medication doses were generally consistent with FDA-approved recommendations. Patients were able to switch over to the alternative treatment due to side effects or lack of efficacy. The primary endpoint was the change in DAS28-ESR in the per-protocol population at 12 months.
    - The changes in DAS28-ESR were -2.6 and -2.4 in patients in the rituximab and TNF inhibitor groups, respectively. The difference of -0.19 (95% CI, -0.51 to 0.13) was within the prespecified non-inferiority margin of 0.6 units. The authors concluded that initial treatment with rituximab was non-inferior to initial TNF inhibitor

treatment in this patient population. However, interpretation of these results is limited due to the open-label study design and the high percentage of patients switching to the alternative treatment (32% in the TNF inhibitor group and 19% in the rituximab group). The indication for rituximab is limited to patients with an inadequate response to TNF inhibitor(s).

- A randomized, open-label trial evaluated biologic treatments in patients with RA who had had an inadequate response to a TNF inhibitor (*Gottenberg et al 2016*). Patients (n = 300) were randomized to receive a second TNF inhibitor (n = 150) or a non-TNF-targeted biologic (n = 150) of the prescriber's choice. The second TNF inhibitors, in order of decreasing frequency, included Humira (adalimumab), Enbrel (etanercept), Cimzia (certolizumab), and Remicade (infliximab), and the non-TNF biologics included Actemra (tocilizumab), Rituxan (rituximab), and Orencia (abatacept). The primary endpoint was the proportion of patients with a good or moderate EULAR response at week 24, defined as a decrease in DAS28-ESR of > 1.2 points resulting in a score of ≤ 3.2.
    - At week 24, 52% of patients in the second anti-TNF group and 69% of patients in the non-TNF group achieved a good or moderate EULAR response (p = 0.003 or p = 0.004, depending on how missing data were handled). Secondary disease activity scores also generally supported better efficacy for the non-TNF biologics; however, HAQ scores did not differ significantly between groups. Among the non-TNF biologics, the proportion of EULAR good and moderate responders at week 24 did not significantly differ between abatacept, rituximab, and tocilizumab (67%, 61%, and 80%, respectively). There were 8 patients (5%) in the second TNF inhibitor group and 16 patients (11%) in the non-TNF biologic group that experienced serious AEs (p = 0.10), predominantly infections and cardiovascular events. There were some limitations to this trial; notably, it had an open-label design, and adherence may have differed between groups because all non-TNF biologics were given as infusions under observation and most of the TNF inhibitor drugs were self-injected by patients. The authors concluded that among patients with RA inadequately treated with TNF inhibitors, a non-TNF biologic was more effective in achieving a good or moderate disease activity response at 24 weeks; however, a second TNF inhibitor was also often effective in producing clinical improvement.
- Another recent randomized trial (*Manders et al 2015*) evaluated the use of Orencia (abatacept) (n = 43), Rituxan (rituximab) (n = 46), or a different TNF inhibitor (n = 50) in patients (n =139) with active RA despite previous TNF inhibitor treatment. Actemra (tocilizumab) was not included. In this trial, there were no significant differences with respect to DAS28, HAQ-DI, or SF-36 over the 1-year treatment period, and AEs also appeared similar. A cost-effectiveness analysis was also included in this publication, but results are not reported in this review.
- A Cochrane review examined Orencia (abatacept) for the treatment of RA. ACR 50 response was not significantly different at 3 months but was significantly higher in the abatacept group at 6 and 12 months compared to placebo (relative risk [RR], 2.47; 95% CI, 2 to 3.07 and RR, 2.21; 95% CI, 1.73 to 2.82). Similar results were seen in ACR 20 and ACR 70 (*Maxwell et al 2009*).
- The safety and efficacy of Humira (adalimumab) for the treatment of RA were assessed in a Cochrane systematic review. Treatment with adalimumab in combination with MTX was associated with a RR of 1.52 to 4.63, 4.63 (95% CI, 3.04 to 7.05) and 5.14 (95% CI, 3.14 to 8.41) for ACR 20, ACR 50, and ACR 70 responses, respectively, at 6 months when compared to placebo in combination with MTX. Adalimumab monotherapy was also proven efficacious (*Navarro-Sarabia et al 2005*). In another study, patients received adalimumab 20 mg or 40 mg every other week for 1 year, and then could receive 40 mg every other week for an additional 9 years. At Year 10, 64.2%, 49%, and 17.6% of patients achieved ACR 50, ACR 70, and ACR 90 responses, respectively (*Keystone et al 2013b*).
- A Phase 3, open-label study evaluated the long-term efficacy of Humira (adalimumab) for RA. Patients receiving adalimumab in 1 of 4 early assessment studies could receive adalimumab for up to 10 years in the extension study. Of 846 enrolled patients, 286 (33.8%) completed 10 years of treatment. In patients completing 10 years, adalimumab led to sustained clinical and functional responses, with ACR 20, ACR 50, and ACR 70 responses being achieved by 78.6%, 55.5%, and 32.8% of patients, respectively. The authors stated that patients with shorter disease duration achieved better outcomes, highlighting the need for early treatment. No unexpected safety findings were observed. This study demonstrated that some patients with RA can be effectively treated with adalimumab on a long-term basis; however, the study is limited by its open-label design, lack of radiographic data, and the fact that only patients who continued in the study were followed (*Furst et al 2015*).
- A Cochrane review was performed to compare Kineret (anakinra) to placebo in adult patients with RA. Significant improvements in both primary (ACR 20, 38% vs 23%; RR, 1.61; 95% CI, 1.32 to 1.98) and secondary (ACR 50 and ACR 70) outcomes were detected. The only significant difference in AEs noted with anakinra use was the rate of injection site reactions (71% vs 28% for placebo) (*Mertens et al 2009*).
- In another Cochrane review, Enbrel (etanercept) was compared to MTX or placebo in adult patients with RA and found that at 6 months, 64% of individuals on etanercept 25 mg twice weekly attained an ACR 20 vs 15% of patients on either MTX alone or placebo (RR, 3.8; number needed to treat [NNT], 2). An ACR 50 and ACR 70 were achieved by 39% and 15%, respectively, in the etanercept group compared to 4% (RR, 8.89; NNT, 3) and 1% (RR, 11.31; NNT,

7) in the control groups, respectively. Etanercept 10 mg twice weekly was only associated with significant ACR 20 (51% vs 11% of controls; RR, 4.6; 95% CI, 2.4 to 8.8; NNT, 3) and ACR 50 responses (24% vs 5% of controls; RR, 4.74; 95% CI, 1.68 to 13.36; NNT, 5). Seventy-two percent of patients receiving etanercept had no increase in Sharp erosion score compared to 60% of MTX patients. Etanercept 25 mg was associated with a significantly reduced total Sharp score (weighted mean difference, -10.5; 95% CI, -13.33 to -7.67). The Sharp erosion scores and joint space narrowing were not significantly reduced by either etanercept dose (*Blumenauer et al 2003*). In a trial of 353 patients with RA, patients received a triple therapy combination of sulfasalazine, hydroxychloroquine and MTX or etanercept and MTX. Triple therapy was shown to be noninferior to etanercept + MTX (*O'Dell et al 2013*).

- A more recent Cochrane review (*Singh et al 2016a*) evaluated the benefits and harms of 10 agents for the treatment of RA in patients failing treatment with MTX or other DMARDs. Agents included Xeljanz (tofacitinib) and 9 biologics (Orencia [abatacept], Humira [adalimumab], Kineret [anakinra], Cimzia [certolizumab], Enbrel [etanercept], Simponi [golimumab], Remicade [infliximab], Rituxan [rituximab], and Actemra [tocilizumab]), each in combination with MTX or other DMARDS, compared to comparator agents such as DMARDs or placebo. Data from 79 randomized trials (total 32,874 participants) were included. Key results from this review are as follows:
    - ACR 50: Biologic plus MTX/DMARD was associated with a statistically significant and clinically meaningful improvement in ACR 50 vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics. Differences between treatments in individual comparisons were small.
    - HAQ: Biologic plus MTX/DMARD was associated with a clinically and statistically significant improvement in function measured by HAQ vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics.
    - Remission: Biologic plus MTX/DMARD was associated with clinically and statistically significantly greater proportion of patients achieving RA remission, defined by DAS < 1.6 or DAS28 < 2.6, vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics.
    - Radiographic progression: Radiographic progression was statistically significantly reduced in those on biologic plus MTX/DMARD vs comparator. The absolute reduction was small and clinical relevance is uncertain.
    - Safety: Biologic plus MTX/DMARD was associated with a clinically significantly increased risk of serious AEs; statistical significance was borderline. TNF inhibitors did not differ significantly from non-TNF biologics.
- A similar Cochrane review focused on the use of biologic or Xeljanz (tofacitinib) monotherapy for RA in patients with traditional DMARD failure (*Singh et al 2016b*). A total of 41 randomized trials (n = 14,049) provided data for this review. Key results are as follows:
    - Biologic monotherapy was associated with a statistically significant and clinically meaningful improvement in ACR 50 and HAQ vs placebo and vs MTX or other DMARDs.
    - Biologic monotherapy was associated with a statistically significant and clinically meaningful greater proportion of patients with disease remission vs placebo.
    - Based on a single study, the reduction in radiographic progression was statistically significant for biologic monotherapy compared to active comparators, but the absolute reduction was small and of unclear clinical relevance.
- Another Cochrane review evaluated the use of biologics or Xeljanz (tofacitinib) in patients with RA who had been unsuccessfully treated with a previous biologic (*Singh et al 2017[a]*). The review included 12 randomized trials (n = 3,364). Key results are as follows:
    - Biologics, compared to placebo, were associated with statistically significant and clinically meaningful improvement in RA as assessed by ACR 50 and remission rates. Information was not available for HAQ or radiographic progression.
    - Biologics plus MTX, compared to MTX or other traditional DMARDs, were associated with statistically significant and clinically meaningful improvement in ACR 50, HAQ, and RA remission rates. Information was not available for radiographic progression.
    - There were no published data for tofacitinib monotherapy vs placebo.
    - Based on a single study, tofacitinib plus MTX, compared to MTX, was associated with a statistically significant and clinically meaningful improvement in ACR 50 and HAQ. RA remission rates were not statistically significantly different, and information was not available for radiographic progression.
- In another meta-analysis, ACR 20 and ACR 70 response rates for Xeljanz (tofacitinib) 5 mg and 10 mg were comparable to the other monotherapies (Orencia [abatacept], Humira [adalimumab], Kineret [anakinra], Cimzia [certolizumab], Enbrel [etanercept], Simponi [golimumab], Remicade [infliximab], Actemra [tocilizumab]) at 24 weeks (*Bergrath et al 2017*). ACR 50 response rates were also comparable for tofacitinib 10 mg and other monotherapies. At 24 weeks, ACR 20/50/70 response rates for the combination of tofacitinib 5 mg or 10 mg plus conventional DMARD were comparable to other biologic plus conventional DMARD therapies except tofacitinib 5 mg plus conventional DMARD and tofacitinib 10 mg plus conventional DMARD were both superior to certolizumab 400 mg every 4 weeks

plus conventional DMARD for achieving ACR 70 response (OR, 59.16; [95% CI, 2.70 to infinity]; and OR, 77.40; [95% CI, 3.53 to infinity], respectively).

- Another recent Cochrane review (*Hazlewood et al 2016*) compared MTX and MTX-based DMARD combinations for RA in patients naïve to or with an inadequate response to MTX; DMARD combinations included both biologic and non-biologic agents. A total of 158 studies and over 37,000 patients were included. Evidence suggested that efficacy was similar for triple DMARD therapy (MTX plus sulfasalazine plus hydroxychloroquine) and MTX plus most biologic DMARDs or Xeljanz (tofacitinib). MTX plus some biologics were superior to MTX in preventing joint damage in MTX-naïve patients, but the magnitude of effect was small.
- An additional Cochrane review evaluated biologics for RA in patients naïve to MTX in 19 studies (*Singh et al 2017[b]*). Agents included in the review were Humira (adalimumab), Enbrel (etanercept), Simponi (golimumab), Remicade (infliximab), Orencia (abatacept), and Rituxan (rituximab). When combined with MTX, use of biologics showed a benefit in ACR 50 vs comparator (MTX/MTX plus methylprednisolone) (RR, 1.40; 95% CI, 1.30 to 1.49) and in RA remission rates (RR, 1.62; 95% CI, 1.33 to 1.98), but no difference was found for radiographic progression. When used without MTX, there was no significant difference in efficacy between biologics and MTX.
- A meta-analysis evaluated the efficacy of Remicade (infliximab) in combination with MTX compared to placebo plus MTX. There was a higher proportion of patients in the infliximab group that achieved an ACR 20 at 30 weeks compared to patients in the placebo group (RR, 1.87; 95% CI, 1.43 to 2.45). These effects were similar in the proportion of patients achieving ACR 50 and ACR 70 (RR, 2.68; 95% CI, 1.79 to 3.99 and RR, 2.68; 95% CI, 1.78 to 4.03) (*Wiens et al 2009*).
- Another meta-analysis of randomized controlled trials included Humira (adalimumab), Kineret (anakinra), Enbrel (etanercept), and Remicade (infliximab) with or without MTX. The odds ratio (OR) for an ACR 20 was 3.19 (95% CI, 1.97 to 5.48) with adalimumab, 1.7 (95% CI, 0.9 to 3.29) with anakinra, 3.58 (95% CI, 2.09 to 6.91) with etanercept and 3.47 (95% CI, 1.66 to 7.14) with infliximab compared to placebo. The OR to achieve an ACR 50 with adalimumab was 3.97 (95% CI, 2.73 to 6.07), 2.13 (95% CI, 1.27 to 4.22) with anakinra, 4.21 (95% CI, 2.74 to 7.43) and with etanercept 4.14 (95% CI, 2.42 to 7.46) compared to placebo. Further analysis of each agent against another was performed, and no significant difference was determined between individual agents in obtaining an ACR 20 and ACR 50. However, the TNF-blockers as a class showed a greater ACR 20 and ACR 50 response compared to anakinra (OR, 1.96; 95% CI, 1.03 to 4.01 and OR, 1.93; 95% CI,1.05 to 3.5; $p < 0.05$) (*Nixon et al 2007*).
- The Agency for Healthcare Research and Quality published a review of drug therapy to treat adults with RA (*Donahue et al 2012*). They concluded that there is limited head-to-head data comparing the biologics. Studies that are available are generally observational in nature or mixed treatment comparison meta-analysis. At this time, there appears to be no significant differences amongst the agents. Clinical trials have shown better efficacy with combination biologics and MTX and no additional increased risk of AEs. However, combinations of 2 biologic agents showed increased rate of serious AEs with limited or no increase in efficacy.
- A meta-analysis of 6 trials (n = 1,927) evaluated the efficacy of withdrawing biologics from patients with RA who were in sustained remission or had low disease activity (*Galvao et al 2016*). The biologics in the identified trials were TNF inhibitors, most commonly Enbrel (etanercept) or Humira (adalimumab). Compared to withdrawing the medication, continuing the biologic increased the probability of having low disease activity (RR, 0.66; 95% CI, 0.51 to 0.84) and remission (RR, 0.57; 95% CI, 0.44 to 0.74). Although outcomes were worse in patients withdrawing the biologic, the investigators noted that almost half of the patients maintained a low disease activity after withdrawal. The authors suggested that further research is necessary to identify subgroups for which withdrawal may be more appropriate.

Ankylosing spondylitis (AS)

- The FDA-approval of Humira (adalimumab) for the treatment of AS was based on 1 randomized, double-blind, placebo-controlled study (n = 315) in which a significantly greater proportion of patients achieved a 20% improvement in the Assessment of SpondyloArthritis International Society criteria (ASAS 20) (primary endpoint) with adalimumab (58% vs 21% with placebo; $p < 0.001$). A greater than 50% improvement in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score, a measure of fatigue severity, spinal and peripheral joint pain, localized tenderness, and morning stiffness which is considered clinically meaningful, was detected in 45% of adalimumab-treated patients compared to 16% of placebo-treated patients ($p < 0.001$) at week 12. This response was sustained through week 24, with 42% in the adalimumab group achieving a greater than or equal to 50% improvement in BASDAI score compared to 15% in the placebo group ($p < 0.001$) (*van der Heijde et al 2006*).
- In 2 double-blind, randomized, placebo-controlled trials, the efficacy of Enbrel (etanercept) was evaluated in patients with AS (*Calin et al 2004, Gorman et al 2002*). Etanercept had a significantly greater response to treatment compared to placebo ($p < 0.001$) (*Gorman et al 2002*). More patients achieved an ASAS 20 response compared to placebo ($p < 0.001$) (*Calin et al 2004*). An open-label extension study, evaluating the long-term safety and efficacy of etanercept in patients with AS, was conducted. Safety endpoints included AEs, serious AEs, serious infection, and death while

efficacy endpoints included ASAS 20 response, ASAS 5/6 response and partial remission rates. After up to 192 weeks of treatment, the most common AEs were injection site reactions, headache and diarrhea. A total of 71% of patients were ASAS 20 responders at week 96 and 81% of patients were responders at week 192. The ASAS 5/6 response rates were 61% at week 96 and 60% at week 144, and partial remission response rates were 41% at week 96 and 44% at week 192. Placebo patients who switched to etanercept in the open-label extension trial showed similar patterns of efficacy maintenance (*Davis et al 2008*). A multicenter, randomized, double-blind trial compared etanercept and sulfasalazine in adult patients with active AS that failed treatment with nonsteroidal anti-inflammatory drugs (NSAIDs). A significantly greater proportion of patients treated with etanercept compared to patients treated with sulfasalazine achieved the primary outcome of ASAS 20 at week 16 ($p < 0.0001$). There were also significantly more patients that achieved ASAS 40 and ASAS 5/6 in the etanercept group compared to the sulfasalazine group ($p < 0.0001$ for both) (*Braun et al 2011*).

- The FDA-approval of Simponi (golimumab) for AS was based on a multicenter, randomized, double-blind, placebo-controlled trial in adult patients with active disease for at least 3 months (n = 356). Golimumab with or without a DMARD was compared to placebo with or without a DMARD and was found to significantly improve the signs and symptoms of AS as demonstrated by the percentage of patients achieving an ASAS 20 response at week 14 (*Inman et al 2008*). Sustained improvements in ASAS 20 and ASAS 40 response rates were observed for up to 5 years in an open-label extension trial (*Deodhar et al 2015*). Safety profile through 5 years was consistent with other TNF inhibitors.
- The efficacy of Remicade (infliximab) in the treatment of AS was demonstrated in 12- and 24-week double-blind, placebo-controlled trials. There was significantly more patients that achieved a 50% BASDAI score in the infliximab group compared to the placebo group at 12 weeks ($p < 0.0001$)(*Braun et al 2002*), At 24 weeks, significantly more patients in the infliximab group achieved ASAS 20 compared to the placebo group ($p < 0.001$)(*van der Heijde et al 2005*).
- Inflectra (infliximab-dyyb) was evaluated alongside Remicade (infliximab; European Union formulation) for the treatment of AS in PLANETAS (n = 250), a double-blind, multicenter, randomized trial (*Park et al 2013, Park et al 2016, Park et al 2017*). The primary endpoints related to pharmacokinetic equivalence. Secondary efficacy endpoints supported similar clinical activity between Inflectra and Remicade. An ASAS 20 response was achieved by 72.4% and 70.5% of patients in the Remicade and Inflectra groups, respectively, at 30 weeks, and by 69.4% and 67.0% of patients at 54 weeks. Other disease activity endpoints and a quality-of-life scale were also similar between groups.
    - In the extension study (n = 174) through 102 weeks, all patients received Inflectra. From weeks 54 to 102, the proportion of patients achieving a clinical response was maintained at a similar level to that of the main study in both the maintenance and switch groups and was comparable between groups.
- The efficacy of Cimzia (certolizumab) for the treatment of AS was established in 1 randomized, double-blind, placebo-controlled study (n = 325) in which a significantly greater proportion of patients achieved ASAS 20 response with certolizumab 200 mg every 2 weeks and certolizumab 400 mg every 4 weeks compared to placebo at 12 weeks (*Landewe et at 2014*). Patient-reported outcomes measured by the SF-36, health-related quality of life (HRQoL), and reports of pain, fatigue and sleep were significantly improved with certolizumab in both dose groups (*Sieper et al 2015a*). A Phase 3, randomized, placebo-controlled trial found that 62.5% of patients on certolizumab maintained ASAS 20 response to week 96 in a population of patients with axial spondyloarthritis which includes AS (*Sieper et al 2015b*).
- The efficacy and safety of Cosentyx (secukinumab) were evaluated in the double-blind, placebo-controlled, randomized MEASURE 1 and 2 studies (*Baeten et al 2015*). MEASURE 1 enrolled 371 patients and MEASURE 2 enrolled 219 patients with active AS with radiologic evidence treated with NSAIDs. Patients were treated with secukinumab 75 or 150 mg SQ every 4 weeks (following IV loading doses) or placebo. The primary outcome, ASAS 20 response at week 16, was significantly higher in the secukinumab 75 mg (60%) and 150 mg (61%) groups compared to placebo (29%, $p < 0.001$ for each dose) for MEASURE 1. For MEASURE 2 at week 16, ASAS 20 responses were seen in 61% of the secukinumab 150 mg group, 41% of the 75 mg group, and 28% of the placebo group ($p < 0.001$ for secukinumab 150 mg vs placebo; $p = 0.10$ for secukinumab 75 mg vs placebo). Common AEs reported included nasopharyngitis, headache, diarrhea, and upper respiratory tract infections. Improvements were observed from week 1 and sustained through week 52. In a long-term extension of MEASURE 1, ASAS 20 response rates were 73.7% with secukinumab 150 mg and 68.0% with 75 mg at week 104 and in MEASURE 2, ASAS 20 response rates were 71.5% with both doses at week 104 (*Braun et al 2017, Marzo-Ortega et al 2017*). In a 3-year extension of MEASURE-1, ASAS 20/40 response rates were 80.2%/61.6% for secukinumab 150 mg and 75.5%/50.0% for secukinumab 75 mg at week 156 (*Baraliakos et al 2017*).
- In 2 systematic reviews of TNF blockers for the treatment of AS, patients taking Simponi (golimumab), Enbrel (etanercept), Remicade (infliximab), and Humira (adalimumab) were more likely to achieve ASAS 20 or ASAS 40 responses compared with patients from control groups. The RR of reaching ASAS 20 after 12 or 14 weeks was 2.21

(95% CI, 1.91 to 2.56) (*Machado et al 2013*). After 24 weeks, golimumab, etanercept, infliximab, and adalimumab were more likely to achieve ASAS 40 compared to placebo (*Maxwell et al 2015*). A systematic review and network meta-analysis evaluated biologic agents for the treatment of AS, including adalimumab, etanercept, golimumab, infliximab, Cosentyx (secukinumab), and Actemra (tocilizumab; not FDA-approved for AS) (*Chen et al 2016*). A total of 14 studies were included. Infliximab was ranked best and secukinumab second best for achievement of ASAS 20 response; however, differences among agents were not statistically significant with the exception of infliximab 5 mg compared to tocilizumab (OR, 4.81; 95% credible interval [CrI], 1.43 to 17.04). Safety endpoints were not included in this analysis.

Crohn's disease (CD)

- In a trial evaluating Remicade (infliximab) for induction of remission, significantly more patients achieved remission at 4 weeks with infliximab compared to placebo ($p < 0.005$)(*Targan et al 1997*). In a placebo-controlled trial, significantly more patients treated with infliximab 5 and 10 mg/kg had a reduction greater than or equal to 50% in the number of fistulas compared to patients treated with placebo ($p = 0.002$ and $p = 0.02$, respectively)(*Present et al 1999*). In an open-label trial evaluating the use of infliximab in pediatric CD patients, 88.4% responded to the initial induction regimen, and 58.6% were in clinical remission at week 10 (*Hyams et al 2007*).
- The safety and efficacy of Entyvio (vedolizumab) was demonstrated in 2 trials for CD in patients who responded inadequately to immunomodulator therapy, TNF blockers, and/or corticosteroids. In 1 trial, a higher percentage of Entyvio-treated patients achieved clinical response and remission at week 52 compared to placebo. However, in the second trial, Entyvio did not achieve a statistically significant clinical response or clinical remission over placebo at week 6 (*Sandborn et al 2013, Sands et al 2014*).
- A meta-analysis evaluating Cimzia (certolizumab) use over 12 to 26 weeks for the treatment of CD demonstrated that the agent was associated with an increased rate of induction of clinical response (RR, 1.36; $p = 0.004$) and remission (RR, 1.95; $p < 0.0001$) over placebo. However, risk of infection was higher with certolizumab use (*Shao et al 2009*).
- Additionally, Humira (adalimumab), Cimzia (certolizumab) and Remicade (infliximab) demonstrated the ability to achieve clinical response (RR, 2.69; $p < 0.00001$; RR, 1.74; $p < 0.0001$ and RR, 1.66; $p = 0.0046$, respectively) and maintain clinical remission (RR, 1.68; $p = 0.000072$ with certolizumab and RR, 2.5; $p = 0.000019$ with infliximab; adalimumab, data not reported) over placebo in patients with CD. Adalimumab and infliximab also had a steroid-sparing effect (*Behm et al 2008*). Other systematic reviews have further demonstrated the efficacy of these agents in CD (*Singh et al 2014, Fu et al 2017*).
- In a systematic review of patients with CD who had failed a trial with Remicade (infliximab), the administration of Humira (adalimumab) was associated with remission rates of 19 to 68% at 1 year. Serious cases of sepsis, cellulitis, and fungal pneumonia occurred in 0 to 19% of patients in up to 4 years of treatment (*Ma et al 2009*).
- A systematic review of 8 randomized clinical trials with TYSABRI (natalizumab) or Entyvio (vedolizumab) for the management of CD evaluated the rates of failure of remission induction (*Chandar et al 2015*). Fewer failures of remission induction were reported with natalizumab and vedolizumab compared to placebo (RR 0.87; 95% CI, 0.84 to 0.91; $I^2=0\%$). The summary effect sizes were similar for both natalizumab (RR 0.86; 95% CI, 0.80 to 0.93) and vedolizumab (RR 0.87; 95% CI, 0.79 to 0.95). No significant difference was detected between the 2 active treatments ($p = 0.95$). No significant differences between natalizumab and vedolizumab were observed for rates of serious AEs, infections (including serious infections), and treatment discontinuation. Rates of infusion reactions in induction trials were more common with natalizumab over vedolizumab ($p = 0.007$). Progressive multifocal leukoencephalopathy (PML) has been reported with natalizumab but has not been reported with vedolizumab.
- The use of Stelara (ustekinumab) for the treatment of CD was evaluated in the UNITI-1, UNITI-2, and IM-UNITI studies (*Feagan et al 2016*). All were Phase 3, double-blind, placebo-controlled trials.
    - UNITI-1 (n = 741) was an 8-week induction trial that compared single IV doses of ustekinumab 130 mg IV, weight-based ustekinumab (~6 mg/kg), and placebo in patients with nonresponse or intolerance to ≥ 1 TNF inhibitors. The primary endpoint was clinical response at week 6, which was defined as a decrease from baseline in the CDAI of ≥100 points or a CDAI score of < 150. A clinical response was achieved by 34.4%, 33.7%, and 21.5% of patients in the ustekinumab 130 mg, weight-based ustekinumab, and placebo groups, respectively ($p = 0.002$ for 130 mg dose vs placebo; $p = 0.003$ for weight-based dose vs placebo). Benefits were also demonstrated on all major secondary endpoints, which included clinical response at week 8, clinical remission (CDAI < 150) at week 8, and CDAI decrease of ≥70 points at weeks 3 and 6.
    - UNITI-2 (n = 628) had a similar design to UNITI-1, but was conducted in patients with treatment failure or intolerance to immunosuppressants or glucocorticoids (with no requirement for prior TNF inhibitor use). In this trial, a clinical response was achieved by 51.7%, 55.5%, and 28.7% of patients in the ustekinumab 130 mg, weight-based ustekinumab, and placebo groups, respectively ($p < 0.001$ for both doses vs placebo). Benefits were also demonstrated on all major secondary endpoints.

- IM-UNITI was a 44-week maintenance trial that enrolled patients completing UNITI-1 and UNITI-2. Of 1,281 enrolled patients, there were 397 randomized patients (primary population); these were patients who had had a clinical response to ustekinumab induction therapy and were subsequently randomized to ustekinumab 90 mg SQ every 8 or 12 weeks or placebo. The primary endpoint, clinical remission at week 44, was achieved by 53.1%, 48.8%, and 35.9% of patients in the ustekinumab every 8 week, ustekinumab every 12 week, and placebo groups, respectively (p = 0.005 for every 8 week regimen vs placebo; p = 0.04 for every 12 week regimen vs placebo). Numerical and/or statistically significant differences for ustekinumab vs placebo were observed on key secondary endpoints including clinical response, maintenance of remission, and glucocorticoid-free remission.

Hidradenitis suppurativa (HS)

- Two 36-week, Phase 3, double-blind, multicenter, placebo-controlled, randomized trials, PIONEER I and II, evaluated Humira (adalimumab) for the treatment of HS (*Kimball et al 2016*). A total of 633 adults (307 in PIONEER I and 326 in PIONEER II) with moderate to severe HS were enrolled. The study consisted of 2 treatment periods; in the first period, patients were randomized to placebo or weekly adalimumab for 12 weeks; in the second period, patients initially assigned to placebo received weekly adalimumab (PIONEER I) or placebo (PIONEER II) for 24 weeks and patients initially assigned to adalimumab were re-randomized to placebo, weekly adalimumab, or every-other-week adalimumab. The adalimumab dosage regimen was 160 mg at week 0, followed by 80 mg at week 2, followed by 40 mg doses starting at week 4.
  - The primary endpoint was HS clinical response (HiSCR) at week 12, defined as at least 50% reduction in total abscess and inflammatory nodule count with no increase in abscess count and no increase in draining fistula count compared to baseline. HiSCR rates at week 12 were significantly higher for the groups receiving adalimumab than for the placebo groups: 41.8% vs 26.0% in PIONEER I (p = 0.003) and 58.9% vs 27.6% in PIONEER II (p < 0.001).
  - Among patients with a clinical response at week 12, response rates in all treatment groups subsequently declined over time. During period 2, there were no significant differences in clinical response rates in either trial between patients randomly assigned to adalimumab at either a weekly dose or an every-other-week dose and those assigned to placebo, regardless of whether the patients had a response at week 12. For patients who received placebo in period 1, 41.4% of those assigned to adalimumab weekly in period 2 (PIONEER I) and 15.9% of those reassigned to placebo in period 2 (PIONEER II) had a clinical response at week 36.
  - The authors noted that the magnitude of improvement with adalimumab treatment was modest compared with adalimumab treatment in other disease states, and patients were unlikely to achieve complete symptom resolution.

Juvenile idiopathic arthritis (JIA)

- In a trial of pediatric patients (6 to 17 years of age) with JIA (extended oligoarticular, polyarticular, or systemic without systemic manifestations), the patients treated with placebo had significantly more flares than the patients treated with Orencia (abatacept) (p = 0.0003). The time to flare was significantly different favoring abatacept (p = 0.0002) (*Ruperto et al 2008*).
- Humira (adalimumab) was studied in a group of patients (4 to 17 years of age) with active polyarticular JIA who had previously received treatment with NSAIDs. Patients were stratified according to MTX use and received 24 mg/m^2 (maximum of 40 mg) of adalimumab every other week for 16 weeks. The patients with an American College of Rheumatology Pediatric 30 (ACR Pedi 30) response at week 16 were randomly assigned to receive adalimumab or placebo in a double-blind method every other week for up to 32 weeks. The authors found that 74% of patients not receiving MTX and 94% of those receiving MTX had an ACR Pedi 30 at week 16. Among those not receiving MTX, flares occurred in 43% receiving adalimumab and 71% receiving placebo (p = 0.03). In the patients receiving MTX, flares occurred in 37 and 65% in the adalimumab and placebo groups, respectively (p = 0.02). ACR Pedi scores were significantly greater with adalimumab than placebo and were sustained after 104 weeks of treatment (*Lovell et al 2008*).
- A double-blind, multicenter, randomized controlled trial compared Humira (adalimumab) and placebo in 46 children ages 6 to 18 years with enthesitis-related arthritis (*Burgos-Vargas et al 2015*). Patients were TNF inhibitor naïve. At week 12, the percentage change from baseline in the number of active joints with arthritis was significantly reduced with adalimumab compared to placebo (-62.6% vs -11.6%, p = 0.039). A total of 7 patients (3 placebo; 4 adalimumab) escaped the study early during the double-blind phase and moved to open-label adalimumab therapy. Analysis excluding these patients produced similar results (adalimumab, -83.3 vs placebo -32.1; p = 0.018). At week 52, adalimumab-treated patients had a mean reduction in active joint count from baseline of 88.7%. A total of 93.5% of patients achieved complete resolution of their swollen joints with a mean of 41 days of adalimumab therapy.

- In a trial involving 69 pediatric patients with active polyarticular JIA despite treatment with NSAIDs and MTX, Enbrel (etanercept) was associated with a significant reduction in flares compared to placebo (28% vs 81%; p = 0.003) (*Lovell et al 2000*). Ninety-four percent of patients who remained in an open-label 4 year extension trial met ACR Pedi 30; C-reactive protein (CRP) levels, articular severity scores, and patient pain assessment scores all decreased. There were 5 cases of serious AEs related to etanercept therapy after 4 years (*Lovell et al 2006*).
- The approval of Actemra (tocilizumab) for the indication of SJIA was based on a randomized, placebo-controlled trial (n = 112). Children age 2 to 17 years of age with active SJIA and inadequate response to NSAIDs and corticosteroids were included in the study. The primary endpoint was ACR 30 and absence of fever at week 12. At week 12, the proportion of patients achieving ACR 30 and absence of fever was significantly greater in the tocilizumab-treated patients compared to the placebo treated patients (85% vs 24%; p < 0.0001)(*De Benedetti et al 2012*). The double-blind, randomized CHERISH study evaluated tocilizumab for JIA flares in patients ages 2 to 17 years with JIA with an inadequate response or intolerance to MTX (*Brunner et al 2015*). Tocilizumab-treated patients experienced significantly fewer JIA flares at week 40 compared to patients treated with placebo (25.6% vs 48.1%; p < 0.0024).
- In 2 trials in patients with SJIA, Ilaris (canakinumab) was more effective at reducing flares than placebo. It also allowed for glucocorticoid dose tapering or discontinuation. More patients treated with canakinumab experienced infections than patients treated with placebo (*Ruperto et al 2012*).
- A meta-analysis of trials evaluating biologics for the treatment of SJIA included 5 trials; 1 each for Kineret (anakinra), Ilaris (canakinumab), and Actemra (tocilizumab), and 2 for rilonacept (not FDA-approved for JIA and not included in this review) (*Tarp et al 2016*). The primary endpoint, the proportion of patients achieving a modified ACR Pedi 30 response, was superior to placebo for all agents, but did not differ significantly among anakinra, canakinumab, and tocilizumab. However, comparisons were based on low-quality, indirect evidence and no firm conclusions can be drawn on their relative efficacy. No differences among drugs for serious AEs were demonstrated.

Plaque psoriasis (PsO)

- In a randomized, double-blind, double-dummy trial, Humira (adalimumab) was compared to MTX and placebo in patients with moderate to severe PsO despite treatment with topical agents. The primary outcome was the proportion of patients that achieved Psoriasis Area and Severity Index (PASI) 75 at 16 weeks. Significantly more patients in the adalimumab group achieved the primary endpoint compared to patients in the MTX (p < 0.001) and placebo (p < 0.001) groups, respectively (*Saurat et al 2008*).
- More than 2,200 patients were enrolled in 2 published, pivotal, phase III trials that served as the primary basis for the FDA approval of Stelara (ustekinumab) in PsO. PHOENIX 1 and PHOENIX 2 enrolled patients with moderate to severe PsO to randomly receive ustekinumab 45 mg, 90 mg or placebo at weeks 0, 4, and every 12 weeks thereafter (*Leonardi et al 2008, Papp et al 2008, Langley et al 2015*). In PHOENIX 1, patients who were initially randomized to ustekinumab at week 0 and achieved long-term response (at least PASI 75 at weeks 28 and 40) were re-randomized at week 40 to maintenance ustekinumab or withdrawal from treatment. Patients in the 45 mg ustekinumab and 90 mg ustekinumab groups had higher proportion of patients achieving PASI 75 compared to patients in the placebo group at week 12 (p < 0.0001 for both). PASI 75 response was better maintained to at least 1 year in those receiving maintenance ustekinumab than in those withdrawn from treatment at week 40 (p < 0.0001) (*Leonardi et al 2008*). In PHOENIX 2, the primary endpoint (the proportion of patients achieving a PASI 75 response at week 12) was achieved in significantly more patients receiving ustekinumab 45 and 90 mg compared to patients receiving placebo (p < 0.0001). Partial responders were re-randomized at week 28 to continue dosing every 12 weeks or escalate to dosing every 8 weeks. More partial responders at week 28 who received 90 mg every 8 weeks achieved PASI 75 at week 52 than did those who continued to receive the same dose every 12 weeks. There was no such response to changes in dosing intensity in partial responders treated with 45 mg. AEs were similar between groups (*Papp et al 2008*). A total of 70% (849 of 1212) of ustekinumab-treated patients completed therapy through week 244. At week 244, the proportions of patients initially randomized to ustekinumab 45 mg and 90 mg who achieved PASI 75 were 76.5% and 78.6%, respectively. A total of 50.0% and 55.5% of patients, respectively, achieved PASI 90 (*Langley et al 2015*).
- In a study comparing Enbrel (etanercept) and Stelara (ustekinumab), a greater proportion of PsO patients achieved the primary outcome (PASI 75 at week 12) with ustekinumab 45 (67.5%) and 90 mg (73.8%) compared to etanercept 50 mg (56.8%; p = 0.01 vs ustekinumab 45 mg; p < 0.001 vs ustekinumab 90 mg). In this trial, etanercept therapy was associated with a greater risk of injection site erythema (14.7% vs 0.7% of all ustekinumab patients) (*Griffiths et al 2010).*
- Approval of Otezla (apremilast) for moderate to severe PsO was based on results from the ESTEEM trials. In the trials, 1,257 patients with moderate to severe PsO were randomized 2:1 to apremilast 30 mg twice daily (with a titration period) or placebo. The primary endpoint was the number of patients with a 75% improvement on the PASI 75. In ESTEEM 1, significantly more patients receiving apremilast achieved PASI 75 compared to placebo (33.1% vs

5.3%; p < 0.0001) at 16 weeks. In ESTEEM 2, significantly more patients receiving apremilast also achieved PASI 75 compared to placebo (28.8% vs 5.8%; p < 0.0001) at 16 weeks (*Papp et al 2015, Paul et al 2015a*).
    - Additional analyses of the ESTEEM trials have been published. In 1 analysis (*Thaçi et al 2016*), the impact of apremilast on health-related quality of life, general function, and mental health was evaluated using patient-reported outcome assessments. The study demonstrated improvement with apremilast vs placebo, including improvements on the dermatology life quality index (DLQI) and SF-36 mental component summary (MCS) that exceeded minimal clinically important differences. In another analysis (*Rich et al 2016*), effects of apremilast on difficult-to-treat nail and scalp psoriasis were evaluated. At baseline in ESTEEM 1 and ESTEEM 2, respectively, 66.1% and 64.7% of patients had nail psoriasis and 66.7% and 65.5% had moderate to very severe scalp psoriasis. At week 16, apremilast produced greater improvements in Nail Psoriasis Severity Index (NAPSI) score vs placebo; greater NAPSI-50 response (50% reduction from baseline in target nail NAPSI score) vs placebo; and greater response on the Scalp Physician Global Assessment (ScPGA) vs placebo. Improvements were generally maintained over 52 weeks in patients with a PASI response at week 32.
- Cosentyx (secukinumab) was evaluated in 2 large, phase 3, double-blind trials in patients with moderate to severe PsO. The co-primary endpoints were the proportions of patients achieving PASI 75 and the proportions of patients with clear or almost clear skin (score 0 or 1) on the modified investigator's global assessment (IGA) at 12 weeks.
    - In ERASURE (n = 738), 81.6%, 71.6%, and 4.5% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 65.3%, 51.2%, and 2.4% achieved a score of 0 or 1 on the IGA (*Langley et al 2014*).
    - In FIXTURE (n = 1306), 77.1%, 67%, 44%, and 4.9% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, Enbrel (etanercept) at FDA-recommended dosing, and placebo, respectively, and 62.5%, 51.1%, 27.2%, and 2.8% achieved a score of 0 or 1 on the IGA (*Langley et al 2014*).
- Two smaller, phase 3, double-blind, placebo-controlled trials evaluated Cosentyx (secukinumab) given by prefilled syringe (FEATURE) or auto-injector/pen (JUNCTURE). Again, co-primary endpoints were the proportions of patients achieving PASI 75 and obtaining a score of 0 or 1 on the modified IGA at 12 weeks.
    - In FEATURE (n = 177), 75.9%, 69.5%, and 0% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 69%, 52.5%, and 0% achieved a score of 0 or 1 on the IGA (*Blauvelt et al 2015*).
    - In JUNCTURE (n = 182), 86.7%, 71.7%, and 3.3% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 73.3%, 53.3%, and 0% achieved a score of 0 or 1 on the IGA (*Paul et al 2015b*).
- Secondary endpoints, including the proportions of patients demonstrating a reduction of 90% or more on the PASI (PASI 90), a reduction of 100% (PASI 100), and change in the DLQI further support the efficacy of Cosentyx (secukinumab) (*Blauvelt et al 2015, Langley et al 2014, Paul et al 2015b*).
- In the CLEAR study, Cosentyx (secukinumab) 300 mg SQ every 4 weeks and Stelara (ustekinumab) 45 mg or 90 mg SQ (based on body weight) every 12 weeks were compared for safety and efficacy in a double-blind, randomized controlled trial in 676 patients with moderate to severe PsO (*Thaçi et al 2015*). The primary endpoint, proportion of patients achieving PASI 90 at week 16, was significantly higher with secukinumab compared to ustekinumab (79% vs 57.6%; p < 0.0001). Achievement of PASI 100 response at week 16 was also significantly higher with secukinumab over ustekinumab (44.3% vs 28.4%; p < 0.0001). Infections and infestations were reported in 29.3% of secukinumab- and 25.3% of ustekinumab-treated patients. Most infections were not serious and were managed without discontinuation. The most commonly reported AEs included headache and nasopharyngitis. Serious AEs were reported in 3% of each group.
- A meta-analysis of 7 Phase 3 clinical trials demonstrated the efficacy of Cosentyx (secukinumab) vs placebo and vs Enbrel (etanercept) in patients with PsO (*Ryoo et al 2016*). The ORs for achieving PASI 75 and for achieving IGA 0 or 1 were both 3.7 for secukinumab vs etanercept. Secukinumab 300 mg was significantly more effective than 150 mg. Secukinumab was well-tolerated throughout the 1-year trials.
- The use of Taltz (ixekizumab) for the treatment of PsO was evaluated in the UNCOVER-1, UNCOVER-2, and UNCOVER-3 trials. All were Phase 3, double-blind, randomized trials.
    - UNCOVER-1 (n = 1296) compared ixekizumab 160 mg loading dose then 80 mg every 2 weeks, ixekizumab 160 mg loading dose then 80 mg every 4 weeks, and placebo (*Gordon et al 2016, Taltz product dossier 2016*). Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving a physician's global assessment (PGA) score of 0 or 1 (clear or almost clear) at week 12. In the ixekizumab every 2 week, ixekizumab every 4 week, and placebo groups, PASI 75 was achieved by 89.1%, 82.6%, and 3.9% of patients, respectively (p < 0.001 for both doses vs placebo), and PGA 0 or 1 was achieved by 81.8%, 76.4%, and 3.2% of patients, respectively (p < 0.001 for both doses vs placebo).

Improvements for ixekizumab vs placebo were also seen in secondary endpoints including PASI 90, PASI 100, PGA 0, and change in DLQI.

- UNCOVER-2 (n = 1224) compared ixekizumab 160 mg loading dose then 80 mg every 2 weeks, ixekizumab 160 mg then 80 mg every 4 weeks, etanercept 50 mg twice weekly, and placebo (*Griffiths et al 2015*). Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving a PGA 0 or 1 at week 12. The proportions of patients achieving PASI 75 were 89.7%, 77.5%, 41.6%, and 2.4% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively ($p < 0.0001$ for all active treatments vs placebo and for both ixekizumab arms vs etanercept). The proportions of patients achieving PGA 0 or 1 were 83.2%, 72.9%, 36%, and 2.4% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively ($p < 0.0001$ for all active treatments vs placebo and for both ixekizumab arms vs etanercept). Improvements were also greater for ixekizumab vs placebo, etanercept vs placebo, and ixekizumab vs etanercept for all secondary endpoints including PGA 0, PASI 90, PASI 100, and DLQI.
- UNCOVER-3 (n = 1346) had the same treatment groups and primary and secondary endpoints as UNCOVER-2 (*Griffiths et al 2015*). The proportions of patients achieving PASI 75 were 87.3%, 84.2%, 53.4%, and 7.3% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively ($p < 0.0001$ for all active treatments vs placebo and for both ixekizumab arms vs etanercept). The proportions of patients achieving PGA 0 or 1 were 80.5%, 75.4%, 41.6%, and 6.7% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively ($p < 0.0001$ for all active treatments vs placebo and for both ixekizumab arms vs etanercept). Improvements were also greater for ixekizumab vs placebo, etanercept vs placebo, and ixekizumab vs etanercept for all secondary endpoints including PGA 0, PASI 90, PASI 100, and DLQI.
- Results through week 60 for UNCOVER-1, UNCOVER-2, and UNCOVER-3 have been reported (*Gordon et al 2016*). At week 12 in UNCOVER-1 and UNCOVER-2, patients responding to ixekizumab (PGA 0 or 1) were re-randomized to receive ixekizumab 80 mg every 4 weeks, ixekizumab 80 mg every 12 weeks, or placebo through week 60. Among the patients who were randomly reassigned at week 12 to receive 80 mg of ixekizumab every 4 weeks (the approved maintenance dosing), 80 mg of ixekizumab every 12 weeks, or placebo, a PGA score of 0 or 1 was maintained by 73.8%, 39.0%, and 7.0% of the patients, respectively, and high rates were maintained or attained for additional measures such as PASI 75, PASI 90, and PASI 100 (pooled data for UNCOVER-1 and UNCOVER-2). At week 12 in UNCOVER-3, patients entered a long-term extension period in which they received ixekizumab 80 mg every 4 weeks through week 60. At week 60, at least 73% had a PGA score of 0 or 1 and at least 80% had a PASI 75 response. In addition, most patients had maintained or attained PASI 90 or PASI 100 at week 60.

- The IXORA-S study (n = 676) was a head-to-head study that compared Taltz (ixekizumab) (160 mg LD, then 80 mg every 2 weeks for 12 weeks, then 80 mg every 4 weeks) to Stelara (ustekinumab) (45 mg or 90 mg weight-based dosing per label) (*Reich et al 2017[b]).* The primary endpoint, PASI 90 response at week 12, was achieved by 72.8% and 42.2% of patients in the ixekizumab and ustekinumab groups, respectively ($p < 0.001$); superior efficacy of ixekizumab was maintained through week 24. Response rates for PASI 75, PASI 100, and PGA 0 or 1 also favored ixekizumab over ustekinumab (adjusted $p < 0.05$).
- The use of Siliq (brodalumab) for the treatment of PsO was evaluated in the AMAGINE-1, AMAGINE-2, and AMAGINE-3 trials. All were Phase 3, double-blind, randomized trials.
  - AMAGINE-1 (n = 661) compared brodalumab 210 mg, brodalumab 140 mg, and placebo; each treatment was given at weeks 0, 1, and 2, followed by every 2 weeks to week 12 (*Papp et al 2016*). This 12-week induction phase was followed by a withdrawal/retreatment phase through week 52: patients receiving brodalumab who achieved PGA 0 or 1 (PGA success) were re-randomized to the placebo or induction dose, and patients randomized to brodalumab with PGA ≥ 2 and those initially receiving placebo received brodalumab 210 mg every 2 weeks. Patients in the withdrawal phase who had disease recurrence (PGA ≥ 3) between weeks 16 and 52 were retreated with their induction doses of brodalumab. Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving PGA success at week 12. PASI 75 was achieved by 83% (95% CI, 78 to 88), 60% (95% CI, 54 to 67), and 3% (95% CI, 1 to 6) of patients in the brodalumab 210 mg, brodalumab 140 mg, and placebo groups, respectively; PGA success was achieved by 76% (95% CI, 70 to 81), 54% (95% CI, 47 to 61), and 1% (95% CI, 0 to 4), respectively ($p < 0.001$ for all comparisons of brodalumab vs placebo). Differences in key secondary endpoints at week 12 also favored brodalumab vs placebo, including PASI 90, PASI 100, and PGA 0. In the randomized withdrawal phase, high response rates were maintained in those who continued brodalumab, while most patients re-randomized to placebo experienced return of disease (but were able to recapture disease control with retreatment).

- AMAGINE-2 (n = 1831) and AMAGINE-3 (n = 1881) were identical in design and compared brodalumab 210 mg, brodalumab 140 mg, Stelara (ustekinumab), and placebo (*Lebwohl et al 2015*). Brodalumab was given at weeks 0, 1, and 2, followed by every 2 weeks to week 12. Ustekinumab was given in weight-based doses per its FDA-approved labeling. At week 12, patients receiving brodalumab were re-randomized to receive brodalumab at a dose of 210 mg every 2 weeks or 140 mg every 2, 4, or 8 weeks; patients receiving ustekinumab continued ustekinumab; and patients receiving placebo were switched to brodalumab 210 mg every 2 weeks; maintenance continued though week 52. The primary endpoints included a comparison of both brodalumab doses vs placebo with regard to the proportion of patients achieving PASI 75 and the proportion of patients achieving PGA success (PGA 0 or 1) at week 12, as well as a comparison of brodalumab 210 mg vs ustekinumab with regard to the proportion of patients achieving PASI 100 at week 12.
  - In AMAGINE-2, the proportion of patients achieving PASI 75 was 86% (95% CI, 83 to 89), 67% (95% CI, 63 to 70), 70% (95% CI, 65 to 75), and 8% (95% CI, 5 to 12) in the brodalumab 210 mg, brodalumab 140 mg, ustekinumab, and placebo groups, respectively, and the proportion of patients achieving PGA success was 79% (95% CI, 75 to 82), 58% (95% CI, 54 to 62), 61% (95% CI, 55 to 67), and 4% (95% CI, 2 to 7), respectively ($p < 0.001$ for all comparisons of brodalumab vs placebo). The proportion of patients achieving PASI 100 was 44% (95% CI, 41 to 49), 26% (95% CI, 22 to 29), 22% (95% CI, 17 to 27), and 1% (95% CI, 0 to 2), respectively ($p < 0.001$ for both brodalumab doses vs placebo and for brodalumab 210 mg vs ustekinumab; $p = 0.08$ for brodalumab 140 mg vs ustekinumab).
  - In AMAGINE-3, the proportion of patients achieving PASI 75 was 85% (95% CI, 82 to 88), 69% (95% CI, 65 to 73), 69% (95% CI, 64 to 74), and 6% (95% CI, 4 to 9) in the brodalumab 210 mg, brodalumab 140 mg, ustekinumab, and placebo groups, respectively, and the proportion of patients achieving PGA success was 80% (95% CI, 76 to 83), 60% (95% CI, 56 to 64), 57% (95% CI, 52 to 63), and 4% (95% CI, 2 to 7), respectively ($p < 0.001$ for all comparisons of brodalumab vs placebo). The proportion of patients achieving PASI 100 was 37% (95% CI, 33 to 41), 27% (95% CI, 24 to 31), 19% (95% CI, 14 to 23), and 0.3% (95% CI, 0 to 2), respectively ($p < 0.001$ for both brodalumab doses vs placebo and for brodalumab 210 mg vs ustekinumab; $p = 0.007$ for brodalumab 140 mg vs ustekinumab).
  - In both studies, the 2 brodalumab doses were superior to placebo with regard to all key secondary endpoints. Patients receiving brodalumab 210 mg throughout the induction and maintenance phases demonstrated an increase in PASI response rates through week 12 and a stabilization during weeks 16 to 52. Based on PGA success rates, maintenance with brodalumab 210 mg or 140 mg every 2 weeks was superior to the use of the less frequent maintenance regimens, and the 210 mg regimen was superior to the 140 mg regimen.

- The use of Tremfya (guselkumab) for the treatment of moderate to severe PsO was evaluated in the VOYAGE 1, VOYAGE 2, and NAVIGATE trials. All were phase 3, double-blind, randomized trials.
  - Patients in both VOYAGE 1 and VOYAGE 2 were initially assigned to receive guselkumab (100 mg at weeks 0 and 4, then every 8 weeks), placebo, or Humira (adalimumab) (80 mg at week 0, 40 mg at week 1, then every 2 weeks). Patients in the placebo group were switched to guselkumab at week 16. The coprimary endpoints included the proportion of patients achieving an IGA score of 0 or 1 at week 16 as well as the proportion of patients achieving a PASI 90 response at week 16 in the guselkumab group compared with placebo. Comparisons between guselkumab and adalimumab were assessed as secondary endpoints at weeks 16, 24, and 48. To evaluate maintenance and durability of response in VOYAGE 2, subjects randomized to guselkumab at week 0 and who were PASI 90 responders at week 28 were re-randomized to either continue treatment with guselkumab every 8 weeks or be withdrawn from therapy (ie, receive placebo).
    - In VOYAGE 1 (n = 837), IGA 0 or 1 was achieved in more patients treated with guselkumab (85.1%) compared to placebo (6.9%) at week 16 ($p < 0.001$), and a higher percentage of patients achieved PASI 90 with guselkumab (73.3%) compared to placebo (2.9%; $p<0.001$) (*Blauvelt et al 2017*). Additionally, IGA 0 or 1 was achieved in more patients with guselkumab vs adalimumab at week 16 (85.1% vs 65.9%), week 24 (84.2% vs. 61.7%), and week 48 (80.5% vs 55.4%; $p < 0.001$). PASI 90 score was also achieved in a higher percentage of patients with guselkumab vs adalimumab at week 16 (73.3% vs 49.7%), week 24 (80.2% vs 53%), and week 48 (76.3% vs 47.9%; $p < 0.001$).
    - In VOYAGE 2 (n = 992), IGA 0 or 1 and PASI 90 were achieved by a higher proportion of patients who received guselkumab (84.1% and 70%) vs placebo (8.5% and 2.4%) ($p < 0.001$ for both comparisons). At week 16, IGA score of 0 or 1 and PASI 90 were achieved in more patients with guselkumab (84.1% and 70%) vs adalimumab (67.7% and 46.8%) ($p < 0.001$). PASI 90 was achieved in 88.6% of patients who continued on guselkumab vs 36.8% of patients who were rerandomized to

placebo at week 48. In patients who were nonresponders to adalimumab and switched to guselkumab, PASI 90 was achieved by 66.1% of patients.

- In NAVIGATE (n = 871), patients were assigned to open-label ustekinumab 45 or 90 mg at weeks 0 and 4 (*Langley et al 2017*). Patients with IGA 0 or 1 at week 16 were continued on ustekinumab, while patients with an inadequate response to ustekinumab at week 16 (IGA ≥ 2) were randomized to guselkumab 100 mg or ustekinumab. Patients treated with guselkumab had a higher mean number of visits with IGA of 0 or 1 and ≥ 2-grade improvement (relative to week 16) compared to randomized ustekinumab from week 28 to 40 (1.5 vs 0.7; p < 0.001). A higher proportion of patients achieved IGA of 0 or 1 with ≥ 2 grade improvement at week 28 with guselkumab (31.1%) vs randomized ustekinumab (14.3%; p = 0.001); at week 52, 36.2% of guselkumab-treated patients achieved this response vs 17.3% of the ustekinumab-treated patients. The proportion of patients with PASI 90 response at week 28 was 48.1% for the guselkumab group vs 22.6% for the ustekinumab group (p ≤ 0.001).

- For most immunomodulators that are FDA-approved for the treatment of PsO, the indication is limited to adults. In 2016, Enbrel (etanercept) received FDA approval for treatment of PsO in pediatric patients age ≥ 4 years. Limited information from published trials is also available on the use of Stelara (ustekinumab) in adolescent patients (age 12 to 17 years).
  - A 48-week, double-blind, placebo-controlled trial (n = 211) evaluated the use of etanercept in patients 4 to 17 years of age with moderate-to-severe PsO (*Paller et al 2008*). Patients received etanercept 0.8 mg SQ once weekly or placebo for 12 weeks, followed by 24 weeks of open-label etanercept; 138 patients underwent a second randomization to placebo or etanercept at week 36 to investigate effects of withdrawal and retreatment. The primary endpoint, PASI 75 at week 12, was achieved by 57% and 11% of patients receiving etanercept and placebo, respectively. A significantly higher proportion of patients in the etanercept group than in the placebo group achieved PASI 90 (27% vs 7%) and a PGA of 0 or 1 (53% vs 13%) at week 12 (p < 0.001). During the withdrawal period from week 36 to week 48, response was lost by 29 of 69 patients (42%) assigned to placebo at the second randomization. Four serious AEs (including 3 infections) occurred in 3 patients during treatment with open-label etanercept; all resolved without sequelae. The authors concluded that etanercept significantly reduced disease severity in this population. Results of a 5-year, open-label extension study (n = 182) demonstrated that etanercept was generally well tolerated and efficacy was maintained in those who remained in the study for up to 264 weeks (69 of 181 patients) (*Paller et al 2016*).
  - A 52-week, double-blind, placebo-controlled trial (n = 110) evaluated the use of ustekinumab in patients 12 to 17 years of age with moderate-to-severe PsO (*Landells et al 2015*). Patients received a weight-based standard dose (SD), a half-strength dose (HSD), or placebo. The primary endpoint, the proportion of patients achieving a PGA 0 or 1 at week 12, was significantly greater in the SD (69.4%) and HSD (67.6%) groups vs placebo (5.4%) (p < 0.001 for both doses vs placebo). The proportions of patients achieving PASI 75 at this time point were 80.6%, 78.4%, and 10.8% in the SD, HSD, and placebo groups, respectively (p < 0.001 for both doses vs placebo), and the proportions of patients achieving PASI 90 were 61.1%, 54.1%, and 5.4% in the SD, HSD, and placebo groups, respectively (p < 0.001 for both doses vs placebo). In both groups, the proportions of patients achieving these endpoints were maintained from week 12 through week 52. The authors concluded that ustekinumab appears to be a viable treatment option for moderate-to-severe PsO in the adolescent population. The standard dose provided a response comparable to that in adults with no unexpected AEs through 1 year of treatment.

- Combination therapy is commonly utilized, such as with different topical therapies, systemic plus topical therapies, and combinations of certain systemic therapies with phototherapy (*Feldman 2015*). Combinations of different systemic therapies have not been adequately studied; however, there are some data to show that combined therapy with Enbrel (etanercept) plus MTX may be beneficial for therapy-resistant patients (*Busard et al 2014; Gottlieb et al 2012*).
- In a meta-analysis evaluating the efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate to severe PsO, Humira (adalimumab) use was associated with a risk difference of 64% compared to placebo in achieving a PASI 75 response (p < 0.00001) while Enbrel (etanercept) 25 and 50 mg twice weekly were associated with a risk difference of 30 and 44% compared to placebo (p < 0.00001 for both strengths vs placebo). The Remicade (infliximab) group had the greatest response with a risk difference of 77% compared to the placebo group (p < 0.0001). The withdrawal rate was 0.5% with adalimumab, 0.4 to 0.5% with etanercept and 1.3% with infliximab (*Schmitt et al 2008*).
- Another meta-analysis evaluated the efficacy and safety of long-term treatments (≥24 weeks) for moderate-to-severe PsO (*Nast et al 2015a*). A total of 25 randomized trials (n = 11,279) were included. Compared to placebo, RRs for achievement of PASI 75 were 13.07 (95% CI, 8.60 to 19.87) for Remicade (infliximab), 11.97 (95% CI, 8.83 to 16.23) for Cosentyx (secukinumab), 11.39 (95% CI, 8.94 to 14.51) for Stelara (ustekinumab), 8.92 (95% CI, 6.33 to 12.57) for Humira (adalimumab), 8.39 (95% CI, 6.74 to 10.45) for Enbrel (etanercept), and 5.83 (95% CI, 2.58 to 13.17) for

Otezla (apremilast). Head-to-head studies demonstrated better efficacy for secukinumab and infliximab vs etanercept, and for infliximab vs MTX. The biologics and apremilast also had superior efficacy vs placebo for endpoints of PASI 90 and PGA 0 or 1. The investigators stated that based on available evidence, infliximab, secukinumab, and ustekinumab are the most efficacious long-term treatments, but noted that additional head-to-head comparisons and studies on safety and patient-related outcomes are desirable.

- In a meta-analysis of 41 RCTs that used hierarchical clustering to rate efficacy and tolerability, Humira (adalimumab), Cosentyx (secukinumab), and Stelara (ustekinumab) were characterized by high efficacy and tolerability, Remicade (infliximab) and Taltz (ixekizumab) were characterized by high efficacy and poorer tolerability, and Enbrel (etanercept), MTX, and placebo were characterized by poorer efficacy and moderate tolerability in patients with PsO (*Jabbar-Lopez et al 2017*).
- A Cochrane review evaluated biologics in patients with moderate to severe PsO in 109 studies (*Sbidian E et al 2017*) between 12 and 16 weeks after randomization. Agents included in the review were Humira (adalimumab), Enbrel (etanercept), Cimzia (certolizumab), Stelara (ustekinumab), Cosentyx (secukinumab), Taltz (ixekizumab), Siliq (brodalumab), Remicade (infliximab), and Tremfya (guselkumab). The network meta-analysis showed that all of the biologics were significantly more effective in achieving PASI 90 compared to placebo. Cosentyx (secukinumab), Taltz (ixekizumab), and Siliq (brodalumab) were significantly more effective than Remicade (infliximab), Humira (adalimumab), and Enbrel (etanercept), but not Cimzia (certolizumab). Stelara (ustekinumab) was superior to Enbrel (etanercept). There was no significant difference amongst the agents in the risk of serious adverse effects.

Psoriatic arthritis (PsA)

- In 2 trials, PsA patients receiving Humira (adalimumab) 40 mg every other week achieved an ACR 20 at a higher rate than with placebo. Thirty-nine percent in the active treatment group vs 16% in the placebo group achieved this endpoint by week 12 ($p = 0.012$) in a trial ($n = 100$); while 58 and 14% of patients, respectively, achieved this endpoint in a second trial ($p < 0.001$) (*Genovese et al 2007, Mease et al 2005*). Adalimumab use was also associated with an improvement in structural damage, as measured by the mTSS, compared to those receiving placebo (-0.2 vs 1; $p < 0.001$) (*Mease et al 2005*).
- In a 12-week trial in adult patients with PsA despite NSAID therapy, 87% of Enbrel (etanercept) treated patients met PsA response criteria, compared to 23% of those on placebo ($p < 0.0001$). A PASI 75 improvement and ACR 20 response were detected in 26 and 73% of etanercept-treated patients vs 0 ($p = 0.0154$) and 13% ($p < 0.0001$) of placebo-treated patients (*Mease et al 2000*). In a second trial, the mean annualized rate of change in the mTSS with Enbrel (etanercept) was -0.03 unit, compared to 1 unit with placebo ($p < 0.0001$). At 24 weeks, 23% of etanercept patients eligible for PsO evaluation achieved at least a PASI 75, compared to 3% of placebo patients ($p = 0.001$). Additionally, HAQ scores were significantly improved with etanercept (54%) over placebo (6%; $p < 0.0001$). Injection site reaction occurred at a greater rate with etanercept than placebo (36% vs 9%; $p < 0.001$) (*Mease et al 2004*).
- The FDA approval of Simponi (golimumab) for PsA was based on the GO-REVEAL study, a multicenter, randomized, double-blind, placebo-controlled trial in adult patients with moderate to severely active PsA despite NSAID or DMARD therapy ($n = 405$). Golimumab with or without MTX compared to placebo with or without MTX, resulted in significant improvement in signs and symptoms as demonstrated by the percentage of patients achieving a ACR 20 response at week 14. The ACR responses observed in the golimumab-treated groups were similar in patients receiving and not receiving concomitant MTX therapy (*Kavanaugh et al 2009*).
    - Subcutaneous golimumab for patients with active PsA demonstrated safety and efficacy over 5 years in the long-term extension of the GO-REVEAL study. Approximately one-half of patients took MTX concurrently. ACR 20 response rates at year 5 were 62.8 to 69.9% for golimumab SQ 50 or 100 mg every 4 weeks (*Kavanaugh et al 2014b*).
    - Post-hoc analyses of the 5-year GO-REVEAL results evaluated the relationship between achieving minimal disease activity (MDA; defined as the presence of ≥5 of 7 PsA outcomes measures [≤1 swollen joint, ≤1 tender joint, PASI ≤1, patient pain score ≤15, patient global disease activity score ≤20, HAQ disability index [HAQ DI] ≤0.5, and ≤1 tender enthesis point]) and long-term radiographic outcomes including radiographic progression. Among golimumab-treated patients, achieving long-term MDA was associated with better long-term functional improvement, patient global assessment, and radiographic outcomes. Radiographic benefit was more pronounced in patients using MTX at baseline. The authors conclude that in patients with active PsA, aiming for MDA as part of a treat-to-target strategy may provide long-term functional and radiographic benefits (*Kavanaugh et al 2016*).
- In another trial, more Remicade (infliximab) treated patients achieved ACR 20 at weeks 12 and 24 compared to placebo treated patients ($p < 0.001$) (*Antoni et al 2005*).
- The efficacy of Cimzia (certolizumab) in the treatment of PsA was established in 1 multicenter, double-blind, placebo controlled trial ($n = 409$). Patients were randomized to receive placebo, Cimzia 200 mg every 2 weeks, or Cimzia 400

mg every 4 weeks. At week 12, ACR 20 response was significantly greater in both active treatment groups compared to placebo (*Mease et al 2014*).

- The FDA-approval of Stelara (ustekinumab) for PsA was based on the results of 2 randomized, double-blind, placebo-controlled trials in adult patients with active PsA despite NSAID or DMARD therapy (PSUMMIT 1 and PSUMMIT 2). In PSUMMIT 1 (n = 615), a greater proportion of patients treated with ustekinumab 45 mg or 90 mg alone or in combination with MTX achieved ACR 20 response at week 24 compared to placebo (42.4% and 49.5% vs 22.8%; p < 0.0001 for both comparisons); responses were maintained at week 52 (*McInnes et al 2013*). Similar results were observed in the PSUMMIT 2 trial (n = 312) with 43.8% of ustekinumab-treated patients and 20.2% of placebo-treated patients achieving an ACR 20 response (p < 0.001) (*Ritchlin et al 2014*).
    - In PSUMMIT-1, patients taking placebo or ustekinumab 45 mg could adjust therapy at week 16 if they had an inadequate response, and all remaining patients in the placebo group at week 24 were crossed over to receive treatment with ustekinumab 45 mg (*McInnes et al 2013*). At week 100 (*Kavanaugh et al 2015a*), the ACR 20 responses were 63.6%, 56.7%, and 62.7% in the 90 mg, 45 mg, and placebo crossover groups, respectively. ACR 50 and ACR 70 responses followed a similar pattern and ranged from 37.3% to 46% and 18.6% to 24.7%, respectively. At week 100, the proportions of patients achieving PASI 75 were 71.3%, 72.5%, and 63.9% in the 90 mg, 45 mg, and placebo crossover groups, respectively. Improvements in physical function and health-related quality of life (HRQoL) were sustained over time, with median decreases in HAQ-DI scores from baseline to week 100 of 0.38, 0.25, and 0.38 in the 90 mg, 45 mg, and placebo crossover groups, respectively.
- Cosentyx (secukinumab) gained FDA approval for the treatment of PsA based on 2 multicenter, double-blind, placebo-controlled randomized controlled trials – FUTURE 1 and FUTURE 2 *(Mease et al 2015, McInnes et al 2015*). The FUTURE 1 study randomized patients to secukinumab 75 mg or 150 mg every 4 weeks (following IV loading doses) or placebo and evaluated ACR 20 at week 24. In the FUTURE 2 study, patients were randomized to secukinumab 75 mg, 150 mg, or 300 mg SQ every 4 weeks (following SQ loading doses given at weeks 0, 1, 2, 3, and 4) or placebo and evaluated at week 24 for ACR 20 response.
    - In FUTURE 1 at week 24, both the secukinumab 75 mg and 150 mg doses demonstrated significantly higher ACR 20 responses vs placebo (50.5% and 50.0% vs 17.3%, respectively; p < 0.0001 vs placebo).
    - All pre-specified endpoints including dactylitis, enthesitis, SF-36 PCS, HAQ-DI, DAS28-CRP, ACR 50, PASI 75, PASI 90, and mTSS score were achieved by week 24 and reached statistical significance.
    - At week 104 in a long-term extension study of FUTURE 1, ACR 20 was achieved in 66.8% of patients with secukinumab 150 mg and 58.6% of patients with secukinumab 75 mg (*Kavanaugh et al 2017*).
    - In FUTURE 2 at week 24, ACR 20 response rates were significantly greater with secukinumab than with placebo: 54.0%, 51.0%, and 29.3% vs 15.3% with secukinumab 300 mg, 150 mg, and 75 mg vs placebo, respectively (p < 0.0001 for secukinumab 300 mg and 150 mg; p < 0.05 for 75 mg vs placebo).
    - Improvements were seen with secukinumab 300 mg and 150 mg with regard to PASI 75/90 scores, DAS28-CRP, SF-36 PCS, HAQ-DI, dactylitis, and enthesitis. Efficacy was observed in both TNF-naïve patients and in patients with prior TNF inadequate response or intolerance.
- The efficacy of Otezla (apremilast) was demonstrated in 3 placebo-controlled trials in patients with PsA. At week 16, significantly more patients in the Otezla groups had ≥ 20% improvement in symptoms, as defined by ACR response criteria (*Cutolo et al 2013, Edwards et al 2016, Kavanaugh et al 2014a*). Clinical improvements observed at 16 weeks were sustained at 52 weeks (*Edwards et al 2016, Kavanaugh et al 2015b*).
- Orencia (abatacept) gained FDA approval for the treatment of PsA based on 2 double-blind, placebo-controlled clinical trials in patients with an inadequate response or intolerance to DMARD therapy (*Mease et al 2011, Mease et al 2017*). In a phase 2 dose-finding trial (n = 170), patients received abatacept 3 mg/kg, 10 mg/kg, or 30/10 mg/kg (2 doses of 30 mg/kg then 10 mg/kg) on days 1, 15, 29 and then every 28 days (*Mease et al 2011*). Compared to placebo (19%), the proportion of patients achieving ACR 20 was significantly higher with abatacept 10 mg/kg (48%; p = 0.006) and 30/10 mg/kg (42%; p = 0.022) but not 3 mg/kg (33%). A phase 3 trial (n = 424) randomized patients to abatacept 125 mg weekly or placebo (*Mease et al 2017*). At week 24, the proportion of patients with ACR 20 response was significantly higher with abatacept (39.4%) vs placebo (22.3%; p < 0.001).
- A small, single-center randomized trial (N = 100) compared Remicade (infliximab), Enbrel (etanercept), and Humira (adalimumab) in patients with PsA who had had an inadequate response to DMARDs (*Atteno et al 2010*). The investigators found that each of the agents effectively controlled the signs and symptoms of PsA, and ACR response rates were similar among agents. Patients receiving infliximab and adalimumab showed the greatest improvement in PASI scores, whereas patients receiving etanercept showed the greatest improvement on the tender joint count and HAQ. Limitations of this trial were lack of blinding and lack of a placebo group.
- A meta-analysis based on both direct and indirect comparisons evaluated the efficacy and safety of Humira (adalimumab), Enbrel (etanercept), Remicade (infliximab), and Simponi (golimumab) over 24 weeks for the treatment

of PsA (*Fénix et al 2013*). The investigators found no differences among products for the primary endpoint of ACR 50 or secondary endpoints of ACR 20 and ACR 70, except that etanercept was associated with a lower ACR 70 response. However, low sample sizes limited the power of the analysis.

- A meta-analysis of 9 randomized controlled trials and 6 observational studies evaluated Humira (adalimumab), Enbrel (etanercept), Simponi (golimumab), or placebo in the achievement of ACR 20, ACR 50, and ACR 70 endpoints in patients with moderate to severe PsA (*Lemos et al 2014*). Patients who used adalimumab, etanercept and golimumab were more likely to achieve ACR 20 and ACR 50 after 12 or 24 weeks of treatment. In long-term analysis (after all participants used anti-TNF for at least 24 weeks), there was no difference in ACR 20 and ACR 50 between the anti-TNF and control groups, but patients originally randomized to anti-TNF were more likely to achieve ACR 70.
- A meta-analysis of 8 studies evaluated Cosentyx (secukinumab), Taltz (ixekizumab), Siliq (brodalumab), and Stelara (ustekinumab) in the achievement of ACR 20, ACR 50, and ACR 70 endpoints in patients with PsA (*Bilal et al 2018*). Patients who used these agents were more likely to achieve ACR 20, ACR 50, and ACR70 after 24 weeks of treatment. Another network meta-analysis of 6 studies evaluated Cosentyx (secukinumab), Taltz (ixekizumab), and Stelara (ustekinumab) over 24 weeks in patients with active PsA (*Wu et al 2017*). The investigators found that all agents improved ACR20 and ACR50 at week 24 compared to placebo. A different network meta-analysis of 8 studies evaluated Orencia (abatacept), Otezla (apremilast), Stelara (ustekinumab), and Cosentyx (secukinumab) in the achievement of ACR 20 and ACR 50 in adults with moderate to severe PsA (*Kawalec et al 2018*). The investigators found a significant difference in ACR20 response rate between Cosentyx (secukinumab) 150 mg and Otezla (apremilast) 20 mg (RR, 2.55; 95% CI, 1.24 to 5.23) and Cosentyx (secukinumab) 300 mg and Otezla (apremilast) 20 mg (RR, 3.57; 95% CI, 1.48 to 8.64) or Otezla (apremilast) 30 mg (RR, 2.84; 95% CI, 1.18 to 6.86).
- Two indirect comparison meta-analyses sought to compare the efficacy of biologics for the treatment of PsA in patients with an inadequate response to prior therapies.
    - An analysis of 12 randomized trials compared various biologics in patients having an inadequate response to NSAIDs or traditional DMARDs (*Ungprasert et al 2016a*). The investigators determined that patients receiving older TNF inhibitors (evaluated as a group: Enbrel [etanercept], Remicade [infliximab], Humira [adalimumab], and Simponi [golimumab]) had a statistically significantly higher chance of achieving ACR 20 compared to patients receiving Cimzia (certolizumab), Otezla (apremilast), or Stelara (ustekinumab). Patients receiving Cosentyx (secukinumab) also had a higher chance of achieving ACR 20 compared to certolizumab, ustekinumab, and apremilast, but the relative risk did not always reach statistical significance. There was no statistically significant difference in this endpoint between secukinumab and the older TNF inhibitors, or between apremilast, ustekinumab, and certolizumab.
    - An analysis of 5 randomized trials compared various non-TNF inhibitor biologics (Orencia [abatacept], secukinumab, ustekinumab, and apremilast) in patients having an inadequate response or intolerance to TNF inhibitors (*Ungprasert et al 2016b*). The investigators found no difference for any between-agent comparison in the likelihood of achieving an ACR 20 response.
    - These meta-analyses had limitations, notably being based on a small number of trials, and should be interpreted with caution.

Ulcerative colitis (UC)

- Two trials (ACT 1 and ACT 2) evaluated Remicade (infliximab) compared to placebo for the treatment of UC. In both trials, clinical response at week 8 was significantly higher in infliximab 5 and 10 mg/kg treated patients compared to placebo treated patients (all $p < 0.001$). A significantly higher clinical response rate in both infliximab groups was maintained throughout the duration of the studies (*Rutgeerts et al 2005*). A randomized open-label trial evaluated infliximab at different dosing intervals for the treatment of pediatric UC. At week 8, 73.3% of patients met the primary endpoint of clinical response (95% CI, 62.1 to 84.5%) (*Hyams et al 2012*).
- In the ULTRA 2 study, significantly more patients taking Humira (adalimumab) 160 mg at week 0, 80 mg at week 2, and then 40 mg every other week for 52 weeks achieved clinical remission and clinical response vs patients taking placebo (*Sandborn et al 2012*). These long term results confirm the findings of ULTRA 1. This 8-week induction trial demonstrated that adalimumab in same dosage as ULTRA 2 was effective for inducing clinical remission (*Reinisch et al 2011*). In ULTRA 1, significant differences between the adalimumab and placebo groups were only achieved for 2 of the secondary end points at week 8, i.e., rectal bleeding and PGA subscores. Conversely, in ULTRA 2, significantly greater proportions of adalimumab-treated patients achieved almost all secondary end points at week 8. This may have been because of the high placebo response rates in ULTRA 1. A meta-analysis of 3 randomized trials comparing adalimumab to placebo demonstrated that adalimumab increased the proportion of patients with clinical responses, clinical remission, mucosal healing, and inflammatory bowel disease questionnaire responses in the induction and maintenance phases. It also increased the proportion of patients with steroid-free remission in the maintenance phase (*Zhang et al 2016*).

- Simponi (golimumab) was studied in 1,064 patients with moderate to severe UC. Patients receiving golimumab 200 mg then 100 mg or golimumab 400 mg then 200 mg at weeks 0 and 2 were compared to patients receiving placebo. At week 6, significantly greater proportions of patients in the golimumab 200/100 mg and golimumab 400/200 mg groups (51.8%, and 55%, respectively) were in clinical response than patients assigned to placebo (29.7%; $p < 0.0001$ for both comparisons) (*Sandborn et al 2014b*). In a study enrolling patients who responded in a prior study with golimumab, the proportion of patients who maintained a clinical response through week 54 was greater for patients treated with golimumab 100 mg and 50 mg compared to placebo (49.7 and 47 vs 31.2%; $p < 0.001$ and $p = 0.01$, respectively) (*Sandborn et al 2014a*).
- The safety and efficacy of Entyvio (vedolizumab) was evaluated in a trial for UC in patients who responded inadequately to previous therapy. A higher percentage of Entyvio-treated patients achieved or maintained clinical response and remission over placebo at weeks 6 and 52, as measured by stool frequency, rectal bleeding, endoscopic findings, and PGA (*Feagan et al 2013*). A systematic review and meta-analysis (n = 606; 4 trials) demonstrated that vedolizumab was superior to placebo for clinical response (RR, 0.82; 95% CI, 0.75 to 0.91), induction of remission (RR, 0.86; 95% CI, 0.80 to 0.91), and endoscopic remission (RR, 0.82; 95% CI, 0.75 to 0.91) (*Bickston et al 2014, Mosli et al 2015*).

Uveitis (UV)

- The safety and efficacy of Humira (adalimumab) were assessed in adult patients with non-infectious intermediate, posterior, and panuveitis in 2 randomized, double-masked, placebo-controlled studies, VISUAL I and VISUAL II.
    - VISUAL I (n = 217) enrolled adults with active noninfectious intermediate UV, posterior UV, or panuveitis despite having received prednisone treatment for ≥2 weeks (*Jaffe et al 2016*). Patients were randomized to adalimumab (80 mg loading dose then 40 mg every 2 weeks) or placebo; all patients also received a prednisone burst followed by tapering of prednisone over 15 weeks. The primary endpoint was the time to treatment failure (TTF) at or after week 6. TTF was a multicomponent outcome that was based on assessment of new inflammatory lesions, visual acuity, anterior chamber cell grade, and vitreous haze grade. The median TTF was 24 weeks in the adalimumab group and 13 weeks in the placebo group. Patients receiving adalimumab were less likely than those in the placebo group to have treatment failure (hazard ratio, 0.50; 95% CI, 0.36 to 0.70; $p < 0.001$).
    - VISUAL II (n = 226) had a similar design to VISUAL I; however, VISUAL II enrolled patients with inactive UV on corticosteroids rather than active disease (*Nguyen et al 2016a*). Patients were randomized to adalimumab (80 mg loading dose then 40 mg every 2 weeks) or placebo; all patients tapered prednisone by week 19. TTF was significantly improved in the adalimumab group compared with the placebo group (median not estimable [>18 months] vs 8.3 months; hazard ratio, 0.57, 95% CI, 0.39 to 0.84; $p = 0.004$). Treatment failure occurred in 61 (55%) of 111 patients in the placebo group compared with 45 (39%) of 115 patients in the adalimumab group.

Multiple indications

- The efficacy of infliximab-dyyb (European Union formulation) in patients (n = 481) with CD, UC, RA, PsA, spondyloarthritis, and PsO who were treated with the originator infliximab (European Union formulation) for ≥ 6 months was assessed in the NOR-SWITCH trial (*Jørgensen et al 2017*). Twenty-five percent of patients in the infliximab originator group experienced disease worsening compared to 30% of patients in the infliximab-dyyb group (TD, -4.4%; 95% CI, -12.7% to 3.9%; noninferiority margin, 15%). The authors concluded that infliximab-dyyb was noninferior to originator infliximab.

CAPS, CRS, FMF, GCA, HIDS/MKD, and TRAPs

- The efficacy of Kineret (anakinra) for NOMID was evaluated in a prospective, open-label, uncontrolled study in 43 patients treated for up to 60 months. The study demonstrated improvements in all disease symptoms comprising the disease-specific Diary Symptom Sum Score (DSSS), as well as in serum markers of inflammation. A subset of patients (n = 11) who went through a withdrawal phase experienced worsening of disease symptoms and inflammatory markers, which promptly responded to reinstitution of treatment (*Kineret prescribing information 2016*). A cohort study of 26 patients followed for 3 to 5 years demonstrated sustained improvement in disease activity and inflammatory markers (*Sibley et al 2012*).
- The efficacy and safety of Ilaris (canakinumab) has been evaluated for the treatment of CAPS, TRAPS, HIDS/MKD, and FMF.
    - Efficacy and safety in CAPS were evaluated in a trial in patients aged 9 to 74 years with the MWS phenotype and in a trial in patients aged 4 to 74 years with both MWS and FCAS phenotypes. Most of the trial periods were open-label. Trials demonstrated improvements based on physician's assessments of disease activity and assessments of skin disease, CRP, and serum amyloid A (*Ilaris prescribing information 2016*). Published

data supports the use of canakinumab for these various CAPS phenotypes (*Koné-Paut et al 2011, Kuemmerle-Deschner et al 2011, Lachmann et al 2009*).
    - Efficacy and safety in TRAPS, HIDS/MKD, and FMF were evaluated in a study in which patients having a disease flare during a screening period were randomized into a 16-week double-blind, placebo-controlled period. For the primary efficacy endpoint, canakinumab was superior to placebo in the proportion of TRAPS, HIDS/MKD, and FMF patients who resolved their index disease flare at day 15 and had no new flare for the duration of the double-blind period. Resolution of the flare was defined as a PGA score <2 (minimal or no disease) and CRP within normal range (or reduction ≥70% from baseline) (*Ilaris prescribing information 2016*).
- The efficacy and safety of Actemra (tocilizumab) has been evaluated for treatment of GCA and CRS.
    - Efficacy and safety of tocilizumab in GCA were evaluated in a double-blind, placebo-controlled phase 3 trial (GiACTA) in patients ≥ 50 years old with active GCA and a history of elevated ESR (*Stone et al 2017*). Patients received tocilizumab every week or every other week with a 26-week prednisone taper, or received placebo with a 26-week or 52-week prednisone taper. Patients who received tocilizumab every week and every other week experienced higher sustained remission rates at week 52 compared to placebo ($p < 0.01$).
    - The efficacy of tocilizumab in CRS was based on the result of a retrospective analysis of pooled outcome data from clinical trials of chimeric antigen receptor (CAR) T-cell therapies for hematological cancers (*Actemra prescribing information 2017*). Patients aged 3 to 23 years received tocilizumab with or without high-dose corticosteroids for severe or life-threatening CRS. Sixty-nine percent of patients treated with tocilizumab achieved a response. In a second study using a separate study population, CRS resolution within 14 days was confirmed.

Treatment Guidelines

- RA:
    - In patients with moderate or high disease activity despite DMARD monotherapy, the ACR recommends the use of combination DMARDs, a TNF inhibitor, or a non-TNF inhibitor biologic (tocilizumab, abatacept, or rituximab); tofacitinib is another option in patients with established RA, mainly in patients failing or intolerant to biologic DMARDs. If disease activity remains moderate or high despite use of a TNF inhibitor, a non-TNF biologic is recommended over another TNF inhibitor or tofacitinib. Anakinra was excluded from the ACR guideline because of its low use and lack of new data (*Singh et al 2016c*).
    - EULAR guidelines are similar to ACR guidelines. These guidelines state that if the treatment target is not reached with a conventional DMARD strategy in a patient with poor prognostic factors, addition of a biologic DMARD or a targeted synthetic DMARD (eg, tofacitinib) should be considered, with current practice being a biologic DMARD. Biologic and targeted synthetic DMARDs should be combined with a conventional DMARD, but in patients who cannot use a conventional DMARD concomitantly, a targeted synthetic DMARD or an IL-6 inhibitor (eg, tocilizumab) may have some advantages compared with other biologic DMARDs. The guideline notes that if a TNF inhibitor has failed, patients may receive another TNF inhibitor or an agent with another mode of action. An effective biologic should not be switched to another biologic for non-medical reasons (*Smolen et al 2017*).
    - The ACR released a position statement on biosimilars, which stated that the decision to substitute a biosimilar product for a reference drug should only be made by the prescriber. The ACR does not endorse switching stable patients to a different medication (including a biosimilar) of the same class for cost saving reasons without advance consent from the prescriber and knowledge of the patient (*ACR 2016*). Similarly, the Task Force on the Use of Biosimilars to Treat Rheumatological Disorders recommends that both healthcare providers and patients should take part in the decision-making process for switching amongst biosimilars (*Kay et al 2018*).
    - EULAR has released guidelines for use of antirheumatic drugs in pregnancy, which state that etanercept and certolizumab are among possible treatment options for patients requiring therapy (*Götestam Skorpen et al 2016*).
- JIA:
    - The American College of Rheumatology (ACR) published recommendations for the treatment of JIA in 2011, followed by an update in 2013 focusing on the management of SJIA (and tuberculosis screening) (*Beukelman et al 2011, Ringold et al 2013*).
        - According to the 2011 guideline, recommendations for JIA treatment vary based on factors such as disease characteristics and activity, current medication, and prognostic features. For patients with a history of arthritis in ≥ 5 joints (which includes extended oligoarthritis, polyarthritis, and some related subtypes), a TNF inhibitor is generally recommended in patients with continued disease activity after

receiving an adequate trial of a conventional DMARD. In patients with a history of ≥ 5 affected joints failing a TNF inhibitor, treatment approaches may include switching to a different TNF inhibitor or abatacept (*Beukelman et al 2011*).
    - According to the 2013 update, the inflammatory process in SJIA is likely different from that of other JIA categories, with IL-1 and IL-6 playing a central role. In patients with SJIA and active systemic features, recommendations vary based on the active joint count and the physician global assessment. Anakinra is 1 of the recommended first-line therapies; canakinumab, tocilizumab, and TNF-inhibitors are among the second-line therapies. In patients with SJIA and no active systemic features, treatments vary based on the active joint count. Abatacept, anakinra, tocilizumab, and TNF inhibitors are among the second-line treatments for these patients (*Ringold et al 2013*).
- UC:
    - For the treatment of UC, sulfasalazine is recommended by the American College of Gastroenterology (ACG) as first-line treatment of active disease. Balsalazide, mesalamine, olsalazine and sulfasalazine are recommended for maintenance of remission and reduction of relapses. If these therapies fail, infliximab should be considered (*Kornbluth et al 2010*). Note that other immunomodulators were not indicated for UC when these guidelines were written; an update is currently in process.
- CD:
    - The ACG states that the anti-TNF monoclonal antibodies adalimumab, certolizumab, and infliximab are effective in the treatment of moderate to severely active CD in patients who have not responded despite complete and adequate therapy with a corticosteroid or an immunosuppressive agent. These TNF inhibitors may also be used as alternatives to steroid therapy in selected patients in whom corticosteroids are contraindicated or not desired. Maintenance therapy with TNF inhibitors is effective. An update to these guidelines is currently in process (*Lichtenstein et al 2009*).
    - The American Gastroenterological Association (AGA) recommends using anti-TNF drugs to induce remission in patients with moderately severe CD (*Terdiman et al 2013*). The AGA supports the use of TNF inhibitors and/or thiopurines as pharmacologic prophylaxis in patients with surgically-induced CD remission (*Nguyen et al 2017*).
    - An AGA Institute clinical decision tool for CD notes the importance of controlling both symptoms and the underlying inflammation, and makes recommendations for treatments (budesonide, azathioprine, 6-mercaptopurine, prednisone, MTX, a TNF inhibitor, or certain combinations) based on the patient's risk level (*Sandborn 2014*).
    - The European Crohn's and Colitis Organisation (ECCO) recommends TNF inhibitors for patients with CD who have relapsed or are refractory to corticosteroids, depending on disease location and severity, and states that early TNF inhibitor therapy should be initiated in patients with high disease activity and features indicating a poor prognosis. Furthermore, the ECCO guideline states that all currently available TNF inhibitors seem to have similar efficacy in luminal CD and similar AE profiles; therefore the choice depends on availability, route of administration, patient preference, and cost. Vedolizumab is noted to be an appropriate alternative to TNF inhibitors for some patients (*Gomollón et al 2017*).
- Pregnancy in inflammatory bowel disease:
    - Consensus statements for the management of inflammatory bowel disease in pregnancy, coordinated by the Canadian Association of Gastroenterology, state that TNF inhibitor treatment does not appear to be associated with unfavorable pregnancy outcomes and should generally be continued during pregnancy. Because of the low risk of transfer across the placenta, certolizumab may be preferred in women who initiate TNF inhibitor therapy during pregnancy (*Nguyen et al 2016b*).
- PsO and PsA:
    - Consensus guidelines from the National Psoriasis Foundation Medical Board (that are currently in peer review with an anticipated updated publication in 2018) state that treatment of PsO includes topical agents; oral therapies such as acitretin, cyclosporine, and MTX; and biologic therapies (*Hsu et al 2012*).
    - Guidelines from the American Academy of Dermatology state that for the management of PsO, topical agents including corticosteroids are used adjunctively to either ultraviolet light or systemic medications for resistant lesions in patients with more severe disease (*Menter et al 2008, Menter et al 2009a, Menter et al 2009b, Menter et al 2010, Menter et al 2011*). Biologic agents are routinely used when ≥ 1 traditional systemic agents are not tolerated, fail to produce an adequate response, or are unable to be used due to patient comorbidities. First-line agents for PsO (> 5% BSA) with concurrent PsA include adalimumab, etanercept, golimumab, infliximab, MTX, or a combination of a TNF blocker and MTX.
    - Guidelines for PsO from the European Dermatology Forum, European Association for Dermatology and Venereology, and International Psoriasis Council (European S3 guidelines) state that adalimumab,

etanercept, infliximab, and ustekinumab are recommended as second-line medications for induction and long-term treatment if phototherapy and conventional systemic agents were inadequate, contraindicated, or not tolerated (*Nast et al 2015b*). In patients with PsA and active joint involvement despite use of NSAIDs and a potential poor prognosis due to polyarthritis, increased inflammatory markers and erosive changes, it is recommended to start synthetic DMARDs early to prevent progression of disease and erosive joint destruction. For inadequately responding patients with PsA after at least 1 synthetic DMARD, biologic DMARDS are recommended in combination with synthetic DMARDs or as monotherapy.
    - The American Academy of Dermatology recommends that moderate to severe PsA that is more extensive or aggressive in nature or that significantly impacts quality of life should be treated with MTX, TNF-blockers, or both (*Gottleib et al 2008, Menter et al 2009b, Menter et al 2011*).
    - EULAR 2015 PsA guidelines recommend TNF inhibitors in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, such as MTX. For patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, in whom a TNF inhibitor is not appropriate, biologics targeting IL-12/23 or IL-17 pathways may be considered. Apremilast is considered a treatment option in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, in whom biologics are not appropriate (*Gossec et al 2016, Ramiro et al 2016*).
    - The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommendations for PsA vary based on whether the arthritis is peripheral or axial and based on prior therapies, and may include DMARDS, NSAIDs, simple analgesics, a TNF inhibitor, an IL-12/23 inhibitor, or a PDE-4 inhibitor (*Coates et al 2016).*
- AS:
    - Joint recommendations for the management of axial spondyloarthritis are available from ASAS and EULAR. (Ankylosing spondylitis [AS] is synonymous with radiographic axial spondyloarthritis; these guidelines also include non-radiographic axial spondyloarthritis). The guidelines state that NSAIDs should be used first-line in patients with pain and stiffness; other analgesics might be considered if NSAIDs have failed or are contraindicated or poorly tolerated. Glucocorticoid injections may be considered but patients with axial disease should not receive long-term systemic glucocorticoids. Sulfasalazine may be considered in patients with peripheral arthritis, but patients with purely axial disease should normally not be treated with conventional DMARDs. Biologic DMARDs should be considered in patients with persistently high disease activity despite conventional treatments, and current practice is to start with a TNF inhibitor. If a TNF inhibitor fails, switching to another TNF inhibitor or to an IL-17 inhibitor should be considered (*van der Heijde et al 2017*).
    - The 2015 ACR, Spondylitis Association of America, and Spondyloarthritis Research and Treatment Network guidelines strongly recommend TNF inhibitors for patients who have active disease despite NSAIDs. No particular TNF inhibitor is preferred over another, except in patients with concomitant inflammatory bowel disease or recurrent iritis, in whom infliximab or adalimumab would be preferred over etanercept (*Ward et al 2016).*
- Ocular inflammatory disorders:
    - Expert panel recommendations for the use of TNF inhibitors in patients with ocular inflammatory disorders are available from the American Uveitis Society (*Levy-Clarke et al 2014*). Infliximab and adalimumab can be considered as first-line immunomodulatory agents for the treatment of ocular manifestations of Behçet's disease and as second-line immunomodulatory agents for the treatment of UV associated with juvenile arthritis. They also can be considered as potential second-line immunomodulatory agents for the treatment of severe ocular inflammatory conditions including posterior UV, panuveitis, severe UV associated with seronegative spondyloarthropathy, and selected patients with scleritis. Etanercept seems to be associated with lower rates of treatment success in these conditions.
- Additional indications:
    - Based upon guidelines from the European Dermatology Forum, adalimumab is recommended among first-line therapies for HS, and infliximab may be considered a second-line option (*Gulliver et al 2016, Zouboulis et al 2015*).
    - For the treatment of FMF, EULAR recommendations state that treatment with colchicine should begin as soon as FMF is diagnosed. Biologic treatment, such as anti-IL-1 therapy, is indicated in patients not responding to the maximum tolerated dose of colchicine. TNF inhibitors have also been used in colchicine-resistant patients, with good responses seen in observational studies (*Ozen et al 2016*).
    - No recent guidelines were identified for CAPS, CRS, GCA, HIDS/MKD, or TRAPS.

SAFETY SUMMARY

- Contraindications:

  - Actemra (tocilizumab), Cosentyx (secukinumab), Entyvio (vedolizumab), Ilaris (canakinumab), Inflectra (infliximab-dyyb), Kevzara (sarilumab), Kineret (anakinra), Otezla (apremilast), Remicade (infliximab), Renflexis (infliximab-abda), Stelara (ustekinumab), and Taltz (ixekizumab) use in patients with hypersensitivity to any component of the product.
  - Siliq in patients with Crohn's disease because Siliq may cause worsening of disease.
  - Enbrel (etanercept) in patients with sepsis.
  - Kineret (anakinra) in patients with hypersensitivity to *E coli*-derived proteins.
  - Remicade (infliximab), Inflectra (infliximab-dyyb), and Renflexis (infliximab-abda) in patients with hypersensitivity to murine proteins; and doses >5 mg/kg in patients with moderate to severe heart failure.
- Boxed Warnings:
  - Actemra (tocilizumab), Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Inflectra (infliximab-dyyb), Kevzara (sarilumab), Remicade (infliximab), Renflexis (infliximab-abda), Simponi / Simponi Aria (golimumab), and Xeljanz / Xeljanz XR (tofacitinib) all have warnings for serious infections such as active tuberculosis, which may present with pulmonary or extrapulmonary disease; invasive fungal infections; and bacterial, viral, and other infections due to opportunistic pathogens.
  - In addition, Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Inflectra (infliximab-dyyb), Remicade (infliximab), Renflexis (infliximab-abda), Simponi / Simponi Aria (golimumab), and Xeljanz (tofacitinib) all have warnings for increased risk of malignancies.
  - Rituxan (rituximab) can cause fatal infusion reactions, hepatitis B activation, severe mucocutaneous reactions, and progressive multifocal leukoencephalopathy (PML).
  - Siliq has a boxed warning that suicidal ideation and behavior, including completed suicides, have occurred in patients treated with Siliq. The prescriber should weigh potential risks and benefits in patients with a history of depression and/or suicidal ideation or behavior, and patients should seek medical attention if these conditions arise or worsen during treatment.
- Warnings/Precautions (applying to some or all of the agents in the class):
  - Reactivation of HBV or other viral infections
  - Serious infections including tuberculosis
  - New onset or exacerbation of central nervous system demyelinating disease and peripheral demyelinating disease
  - Pancytopenia
  - Worsening and new onset congestive heart failure
  - Hypersensitivity reactions
  - Lupus-like syndrome
  - Increased lipid parameters and liver function tests with Actemra (tocilizumab), Xeljanz / Xeljanz XR (tofacitinib) and Kevzara (sarilumab)
  - Increased incidence of CD and UC with Cosentyx (secukinumab) and Taltz (ixekizumab); risk of new-onset CD or exacerbation of CD with Siliq (brodalumab)
  - Diarrhea, nausea, and vomiting with Otezla (apremilast)
  - Gastrointestinal perforations with Xeljanz / Xeljanz XR (tofacitinib)
  - Consult prescribing information for other drug-specific warnings/precautions
- Adverse Reactions:
  - Infusion site reactions, diarrhea, nausea/vomiting, abdominal pain, infections, hypertension and headache.
  - Consult prescribing information for other drug-specific AEs
- Risks of Long-Term Treatment: As it becomes accepted practice to treat patients with these conditions for long-term, it is imperative to assess the long-term safety of these products. Because these agents suppress the immune system, serious infections and malignancies are a concern. Several long-term efficacy and safety studies support several agents in this class. The extension studies were performed in an open-label manner and were subject to attrition bias.
  - Rheumatoid Arthritis
    - Safety of adalimumab for RA has been supported in a 5-year study in RA and a 10-year study in patients with early RA (*Keystone et al 2014a, Burmester et al 2014b*). In the 5-year extension study, overall rates of serious AEs and serious infections were 13.8 events per 100 patient-years and 2.8 events per 100 patient-years, respectively. The rate of serious events was highest in the first 6 months and then declined. No new safety signals were reported in the 10-year study.
    - Certolizumab plus MTX had a consistent safety profile over 5 years in patients with RA (*Keystone et al 2014b*). The most frequently reported AEs included urinary tract infections (rate of 7.9 per 100 patient-years), nasopharyngitis (rate of 7.3 per 100 patient-years), and upper respiratory infections (rate of 7.3

per 100 patient-years). Serious AE rates were 5.9 events per 100 patient-years for serious infections and 1.2 events per 100 patient-years for malignancies.

- Abatacept has been evaluated in 2 long-term extension studies. Abatacept IV plus MTX demonstrated a similar safety profile between the 7 year follow-up and a 52-week double-blind study (*Westhovens et al 2014*). Serious AEs reported in both the double-blind and long-term follow-up studies were the following: serious infections (17.6 events per 100 patient-years), malignancies (3.2 events per 100 patient-years), and autoimmune events (1.2 events per 100 patient-years). In a 5-year extension trial, rates of serious infections, malignancies, and autoimmune events were 2.8, 1.5, and 0.99 events per 100 patient-years exposure, respectively. Efficacy was demonstrated by ACR 20 with response rates of 82.3% and 83.6% of patients at year 1 and year 5, respectively.
- Data from 5 RCTs of Actemra (tocilizumab), their open-label extension trials, and a drug interaction study were analyzed for measures of safety. A total of 4,009 patients with moderate to severe RA received at least 1 dose of tocilizumab. Mean duration of tocilizumab treatment was 3.07 years (up to 4.6 years); total duration of observation was 12,293 patient-years (PY). The most common AEs and serious AEs were infections. A longer-term safety profile from this analysis matches previous observations. No new safety signals were identified (*Genovese et al 2013*).
- A Cochrane review showed no evidence of a statistically significant difference in the rate of withdrawal because of AEs in the Enbrel (etanercept) plus DMARD group and the DMARD alone group at 6 months, 12 months, and 2 years. At 3 years, withdrawals were significantly reduced in the etanercept 25 mg plus DMARD group compared with the DMARD alone group (RR, 0.7; 95% CI, 0.5 to 1). There was no evidence of statistically significant differences in the rates of breast cancer at 12 months, fever at 6 months, flu-like syndrome at 6 months and 2 years, infection at 6 months and 2 years, malignancy at 12 months and 2 years, pneumonia at 12 months, and serious infection at 12 months and 2 years between the etanercept plus DMARD group and the DMARD group (*Lethaby et al 2013*).
- A systematic review analyzed 66 randomized controlled trials and 22 long-term extension studies evaluating biologics and tofacitinib for the rate of serious infections in patients with moderate to severe active RA (*Strand et al 2015b*). The estimated incidence rates (unique patients with events/100 patient-years) of serious infections were 3.04 (95% CI, 2.49 to 3.72) for abatacept, 3.72 (95% CI, 2.99 to 4.62) for rituximab, 5.45 (95% CI, 4.26 to 6.96) for tocilizumab, 4.90 (95% CI, 4.41 to 5.44) for TNF inhibitors, and 3.02 (95% CI, 2.25 to 4.05) for tofacitinib 5 mg and 3.00 (95% CI, 2.24 to 4.02) for tofacitinib 10 mg. Authors concluded that the rates of serious infections with tofacitinib in RA patients are within the range of those reported for biologic DMARDs.
- A meta-analysis analyzed 50 randomized controlled trials and long-term extension studies evaluating biologic DMARDs and tofacitinib to compare the risks of malignancies in patients with RA (*Maneiro et al 2017*). The overall risk of malignancies was 1.01 (95% CI, 0.72 to 1.42) for all TNF antagonists, 1.12 (95% CI, 0.33 to 3.81) for abatacept, 0.54 (95% CI, 0.20 to 1.50) for rituximab, 0.70 (95% CI, 0.20 to 2.41) for tocilizumab, and 2.39 (95% CI, 0.50 to 11.5) for tofacitinib. The authors concluded that treatment with biologic DMARDs or tofacitinib does not increase the risk of malignancies.

o PsO

- A total of 3,117 patients treated with at least 1 dose of Stelara (ustekinumab) for moderate to severe PsO were evaluated for long-term safety. At least 4 years of ustekinumab exposure was seen in 1,482 patients (including 838 patients with ≥ 5 years of exposure). The most commonly reported AEs were nasopharyngitis, upper respiratory tract infection, headache and arthralgia. Infections, malignancies and cardiac disorders were the most commonly reported serious AEs. Twenty deaths were reported through year 5. The causes of death were considered related to cardiovascular events (n = 5), malignancy (n = 5), infection (n = 3) and other causes (n = 7). The observed mortality rate among ustekinumab-treated patients was consistent with that expected in the general U.S. population (SMR = 0.36; 95% CI, 0.22 to 0.55). From year 1 to year 5, rates of overall AEs, and AEs leading to discontinuation generally decreased. Serious AE rates demonstrated year-to-year variability with no increasing trend. The results of this long-term study of AEs are similar to reports of shorter-term studies (*Papp et al 2013*).
- In a 5-year extension study, a total of 2510 patients on etanercept for the treatment of PsO were evaluated for long-term safety and efficacy (*Kimball et al 2015*). Serious AEs were reported as a cumulative incidence of the entire 5-year observation period. The following incidences were reported: serious infections (6.5%, 95% CI, 5.4 to 7.7%); malignancies excluding nonmelanoma skin cancer (3.2%, 95% CI, 2.3 to 4.1%); nonmelanoma skin cancer (3.6%, 95% CI, 2.7 to 4.1%); coronary artery

disease (2.8%, 95% CI, 2 to 3.6%); PsO worsening (0.7%, 95% CI, 0.3 to 1.2%); CNS demyelinating disorder (0.2%, 95%CI, 0 to 0.4%); lymphoma and tuberculosis each (0.1%, 95% CI, 0 to 0.3%); and opportunistic infection and lupus each (0.1%, 95%CI, 0 to 0.2%). A total of 51% of patients reported clear/almost clear rating at month 6 and remained stable through 5 years.

- In a ≥ 156-week extension study, a total of 1,184 patients treated with apremilast in ESTEEM 1 and 2 were evaluated for long-term safety and tolerability (*Crowley et al 2017*). Serious AEs (≥ 2 patients) were coronary artery disease (n = 6), acute myocardial infarction (n = 4), osteoarthritis (n = 4), and nephrolithiasis (n = 4). The exposure-adjusted incidence rate for major cardiac events was 0.5/100 patients years, for malignancies was 1.2/100 patient years, for serious infections was 0.9/100 patient-years, and for suicide attempts was 0.1/100 patient-years.
- A multicenter registry called Psoriasis Longitudinal Assessment and Registry (PSOLAR) evaluated the risk of serious infections in patients with PsO (*Kalb et al 2015*). Patients were followed for up to 8 years with a total of 11,466 patients with PsO enrolled, 74.3% of whom were from the U.S. A total of 22,311 patient-years of data were collected. Ustekinumab, infliximab, adalimumab, and etanercept as well as traditional DMARDs were included in the data analysis. During the follow-up period, 323 serious infections were reported. The rates of serious infections per 100 patient-years were 0.83 (secukinumab), 1.47 (etanercept), 1.97 (adalimumab), and 2.49 (infliximab). The most commonly reported serious infection was cellulitis. Risk factors for serious infections were increasing age, diabetes mellitus, smoking, and history of significant infections prior to registry entry. Exposure to infliximab (hazard ratio, 2.51; 95% CI, 1.45 to 4.33; p < 0.001) and adalimumab (hazard ratio, 2.13; 95% CI, 1.33 to 3.41; p = 0.002) during the registry were independently associated with the risk of serious infections whereas use of ustekinumab or etanercept were not.

o PsA
- Subcutaneous golimumab for patients with active PsA demonstrated safety and efficacy over 5 years in the long-term extension of the randomized, placebo-controlled GO-REVEAL study (*Kavanaugh et al 2014b*). Approximately one-half of patients also took MTX concurrently. No new safety signals were observed.

o Multiple indications
- One study looked at 23,458 patients who were treated with Humira (adalimumab) for RA, JIA, AS, PsA, PsO and CD. Patients received adalimumab for up to 12 years. No new safety signals were observed from this analysis. Rates of malignancies and infections were similar to the general population and also similar to rates reported in other shorter-term trials for anti-TNF therapies (*Burmester et al 2013b*).
- Pooled data from 5 Phase 3 trials of SQ golimumab over at least 3 years demonstrated a safety profile consistent with other TNF inhibitors (*Kay et al 2015*). A total of 1,179 patients with RA, PsA or AS were treated for at least 156 weeks. Rates of AEs up to week 160 for placebo, golimumab 50 mg and golimumab 100 mg, respectively, were as follows: 0.28, 0.30, 0.41 for death; 5.31, 3.03, 5.09 for serious infection; 0, 0.17, 0.35 for tuberculosis; 0, 0.13, 0.24 for opportunistic infection; 0, 0, 0.12 for demyelination; and 0, 0.04, 0.18 for lymphoma.
- A total of 18 multicenter, placebo-controlled, randomized controlled trials evaluated the safety profile of certolizumab pegol monotherapy or in combination with DMARDs in RA, CD, AS, PsA and PsO (*Capogrosso Sansone et al 2015).* All but 1 trial was conducted in a double-blind manner. The overall pooled risk ratios for all doses of certolizumab pegol were reported as follows: AEs (defined as AE reported but not evaluated for causality) 1.09 (95% CI, 1.04 to 1.14), serious AEs 1.50 (95% CI, 1.21 to 1.86), ADRs (defined as an AE possibly related to drug treatment by investigators) 1.20 (95% CI, 1.13 to 1.45), infectious AEs 1.28 (95% CI, 1.13 to 1.45), infectious serious AEs 2.17 (95% CI, 1.36 to 3.47), upper respiratory tract infections 1.34 (95% CI, 1.15 to 1.57), neoplasms 1.04 (95% CI, 0.49 to 2.22), and tuberculosis 2.47 (95% CI, 0.64 to 9.56). Rare AEs may not have been captured by the studies due to limiting the reporting of most AEs to those occurring in > 3 to 5%.
- Several recent meta-analyses evaluated the safety of TNF inhibitors.
  - An analysis of TNF inhibitors in RA, PsA, and AS included data from 71 randomized trials (follow-up 1 to 36 months) and 7 open-label extension studies (follow-up 6 to 48 months) (*Minozzi et al 2016*). The data demonstrated that use of TNF inhibitors increases the risk of infectious AEs. Overall, there was a 20% increase of any infections, a 40% increase of serious infections, and a 250% increase of tuberculosis. The tuberculosis incidence rate was higher with infliximab and adalimumab compared to etanercept. There was little data on the incidence of opportunistic infections.

- An analysis of TNF inhibitors in RA, PsA, and AS included data from 32 randomized trials (follow-up 2 to 36 months) and 6 open-label extension trials (follow-up 6 to 48 months) (*Bonovas et al 2016*). Synthesis of the data did not demonstrate that the use of TNF inhibitors significantly affects cancer risk during this length of treatment. However, few malignancy events were observed and evidence may be insufficient to make definitive conclusions, particularly regarding longer-term risks.

- Drug interactions
  - Do not give with live (including attenuated) vaccines; additionally, non-live vaccines may not elicit a sufficient immune response.
  - Do not give 2 immunomodulators together.
  - For Xeljanz / Xeljanz XR (tofacitinib), adjust dose with potent inhibitors of cytochrome P450 (CYP) 3A4 and medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19. Coadministration with potent CYP3A4 inducers and potent immunosuppressive drugs is not recommended.
- Risk Evaluation and Mitigation Strategy (REMS)
  - Siliq (brodalumab) is available only through the Siliq REMS program. The goal of the program is to mitigate the risk of suicidal ideation and behavior, including completed suicides, which occurred in clinical trials. Key requirements of the REMS program include:
    - Prescribers must be certified with the program.
    - Patients must sign a patient-prescriber agreement form.
    - Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive the product.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Actemra (tocilizumab)	Vials: 80 mg/4 mL; 200 mg/10 mL; 400 mg/20 mL Prefilled syringe: 162 mg/0.9 mL	**RA:** IV: 4 mg/kg IV every 4 weeks. May increase to 8 mg/kg IV every 4 weeks. Maximum dose = 800 mg. SQ: <100 kg, administer 162 mg SQ every other week, followed by an increase to every week based on clinical response; >100 kg, 162 mg administered SQ every week. **PJIA:** <30 kg, 10 mg/kg IV every 4 weeks; ≥30 kg, 8 mg/kg IV every 4 weeks. **SJIA:** <30 kg, 12 mg/kg IV every 2 weeks; ≥30 kg, 8 mg/kg IV every 2 weeks. **GCA:** 162 mg SQ every week with tapering glucocorticoids. May give every other week depending on clinical considerations. **CRS:** <30 kg, 12 mg/kg IV; ≥30 kg, 8 mg/kg IV; maximum, 800 mg per infusion.	**RA:** Can give with MTX or other DMARDs. **PJIA and SJIA:** Can give with MTX. **GCA:** Can use alone after discontinuation of glucocorticoids. **CRS:** Can give with corticosteroids. May repeat up to 3 additional doses if no clinical improvement, with at least 8 hours between doses. **RA, PJIA, and SJIA, and GCA**: Adjust dose for liver enzyme abnormalities, low platelet count and low ANC.	Give as a single 60-minute intravenous infusion. <30 kg, use a 50 mL infusion bag. ≥30 kg, use a 100 mL infusion bag. Before infusion, allow bag to come to room temperature. Do not administer with other drugs. Patients can self-inject with the prefilled syringe. Rotate injection sites.
Cimzia (certolizumab)	Powder for reconstitution: 200 mg Prefilled syringe: 200 mg/mL	**CD:** 400 mg SQ initially and at weeks 2 and 4. Maintenance dose is 400 mg every 4 weeks. **RA, PsO:** 400 mg SQ initially and at weeks 2 and 4. Then 200 mg every 2 weeks. Can consider a maintenance dose of 400 mg every 4 weeks. **AS:** 400 mg SQ initially and at weeks 2 and 4. Maintenance dose is 200 mg every 2 weeks or 400 mg every 4 weeks.	Patients can self-inject with the prefilled syringe.	When a 400 mg dose is required, give as 2 200 mg SQ injections in separate sites in the thigh or abdomen.
Cosentyx (secukinumab)	Sensoready pen: 150 mg/1 mL	**PsO:** 300 mg by SQ injection at weeks 0, 1,	**PsO:** For some patients, a dose of	Each 300 mg dose is given as 2

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	Prefilled syringe: 150 mg/1 mL Vial: 150 mg lyophilized powder	2, 3 and 4, followed by 300 mg every 4 weeks **PsA, AS:** With a loading dose (not required): 150 mg at weeks 0, 1, 2, 3, and 4, followed by 150 mg every 4 weeks; without loading dose: 150 mg every 4 weeks	150 mg may be acceptable. **PsA:** For PsA patients with coexistent moderate to severe PsO, dosing for PsO should be followed. If active PsA continues, consider 300 mg dose.	subcutaneous injections of 150 mg. Patients may self-administer with the pen or prefilled syringe. The vial is for healthcare professional use only.
Enbrel (etanercept)	Prefilled syringe: 25 mg and 50 mg Prefilled SureClick autoinjector: 50 mg Multiple-use vial: 25 mg lyophilized powder Solution Cartridge: 50 mg	**RA, AS, PsA:** 50 mg SQ weekly **PsO (adults):** 50 mg SQ twice weekly for 3 months, then 50 mg weekly **PJIA and PsO (pediatrics):** ≥63 kg, 50 mg SQ weekly; <63 kg, 0.8 mg/kg SQ weekly	**RA, AS, PsA:** MTX, NSAIDs, glucocorticoids, salicylates, or analgesics may be continued **JIA:** NSAIDs glucocorticoids, or analgesics may be continued	Patients may be taught to self-inject. May bring to room temperature prior to injecting.
Entyvio (vedolizumab)	Lyophilized cake for injection in 300 mg single-dose vial	**CD and UC:** 300 mg administered by intravenous infusion at time 0, 2, and 6 weeks, and then every 8weeks thereafter. Discontinue therapy if there is no evidence of therapeutic benefit by week 14.	All immunizations should be to date according to current guidelines prior to initial dose.	Entyvio should be reconstituted at room temperature and prepared by a trained medical professional. It should be used as soon as possible after reconstitution and dilution.
Humira (adalimumab)	Prefilled syringe: 10 mg/0.1 mL 10 mg/0.2 mL 20 mg/0.2 mL 20 mg/0.4 mL 40 mg/0.4 mL 40 mg/0.8 mL 80 mg/0.8 mL Single-use pen: 80 mg/0.8 mL 40 mg/0.8 mL 40 mg/0.4 mL Single-use vial: 40 mg/0.8 mL	**RA, AS, PsA**: 40 mg SQ every other week. For RA, may increase to 40 mg every week if not on MTX. **PJIA:** 10 kg to <15 kg: 10 mg SQ every other week; 15 kg to <30 kg: 20 mg SQ every other week; ≥30 kg, 40 mg SQ every other week **CD, HS and UC:** 160 mg SQ on Day 1 (given in 1 day or split over 2 consecutive days), followed by 80 mg SQ 2	**RA, AS, PsA:** MTX, other non-biologic DMARDS, glucocorticoids, NSAIDs, and/or analgesics may be continued. **JIA:** NSAIDs, MTX, analgesics, and/or glucocorticoids, may be continued. **CD and UC:** aminosalicylates and/or	Patients may be taught to self-inject. Injections should occur at separate sites in the thigh or abdomen. Rotate injection sites. May bring to room temperature prior to injecting.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose of 40 mg SQ every other week. **PsO and UV:** initial dose of 80 mg SQ, followed by 40 mg SQ every other week starting 1 week after the initial dose. **CD in pediatric patients ≥ 6 years and older:** 17 kg to < 40 kg: 80 mg on day 1 (given as two 40 mg injections) and 40 mg 2 weeks later (on day 15); maintenance dose is 20 mg every other week starting at week 4. ≥40 kg: 160 mg on day (given in 1 day or split over 2 consecutive days) and 80 mg 2 weeks later (on day 15); maintenance dose is 40 mg every other week starting at week 4.	corticosteroids may be continued. Azathioprine, 6-MP or MTX may be continued if necessary. Needle cover of the syringe contains dry rubber (latex).	
Ilaris (canakinumab)	Vial: 150 mg (lyophilized powder and injection solution formulations)	**SJIA:** ≥7.5 kg, 4 mg/kg SQ every 4 weeks (maximum dose of 300 mg). **CAPS**: ≥15 to ≤40 kg, 2 mg/kg SQ; >40 kg, 150 mg SQ; frequency every 8 weeks **TRAPS, HIDS/MKD, and FMF**: ≤40 kg, 2 mg/kg SQ; >40 kg, 150 mg SQ; frequency every 4 weeks	For CAPS: children 15 to 40 kg with an inadequate response can be increased to 3 mg/kg For TRAPS, HIDS/MKD, and FMF: If the clinical response is inadequate, the dose may be increased to 4 mg/kg (weight ≤40 kg) or 300 mg (weight >40 kg)	Do not inject into scar tissue.
Inflectra (infliximab-dyyb)	Vial: 100 mg	**CD (≥6 years old), PsA, PsO and UC**: 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8	**RA:** give with MTX **CD:** If no response by week	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		weeks. In adults with CD who lose response, can increase dose to 10 mg/kg. **RA:** 3 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg or give every 4 weeks. **AS:** 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks.	14, consider discontinuation.	corticosteroids. Use 250 mL 0.9% sodium chloride for infusion. Infuse over 2 hours. Do not administer with other drugs.
Kevzara (sarilumab)	Prefilled syringe: 150 mg/1.14 mL 200 mg/1.14 mL	**RA:** 200 mg SQ every 2 weeks.	**RA:** give with or without MTX or other conventional DMARDs Reduce dose for neutropenia, thrombocytopenia, and elevated liver enzymes.	Patients may be taught to self-inject. Bring to room temperature (30 minutes) prior to injecting. Rotate injection sites.
Kineret (anakinra)	Prefilled syringe: 100 mg/0.67 mL	**RA:** 100 mg SQ once daily. **CAPS (NOMID):** 1 to 2 mg/kg SQ once daily. Maximum dose is 8 mg/kg/day.	**NOMID**: dose can be given once or twice daily.	Patients may be taught to self-inject. A new syringe must be used for each dose.
Orencia (abatacept)	Vial: 250 mg Prefilled syringe: 50 mg/0.4 mL 87.5 mg/0.7 mL 125 mg/1 mL ClickJect autoinjector: 125 mg/mL	**RA:** IV: <60kg, 500 mg IV; 60 to 100 kg, 750 mg IV; >100 kg, 1,000 mg IV initially, then 2 and 4 weeks after the first infusion and every 4 weeks thereafter SQ: 125 mg SQ once weekly initiated with or without an IV loading dose. With IV loading dose, use single IV infusion as per body weight listed above, followed by the first 125 mg SQ injection within a day of the IV infusion and then once weekly. **PJIA:**		IV infusion should be over 30 minutes. Use 100 mL bag for IV infusion. Do not administer with other drugs. Patients may be taught to self-inject the SQ dose. For SQ, injection sites should be rotated.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		IV: 6 to 17 years and <75 kg: 10 mg/kg IV initially, then 2 and 4 weeks after the first infusion and every 4 weeks thereafter. >75 kg, follow adult RA IV schedule; maximum dose = 1,000 kg. SQ: 2 to 17 years, 10 to <25 kg, 50 mg once weekly; 25 to < 50 kg, 87.5 mg once weekly, ≥ 50 kg, 125 mg once weekly. **PsA:** IV: follow adult RA IV schedule. SQ: 125 mg once weekly without IV dose.		
Otezla (apremilast)	Tablet: 10 mg, 20 mg, and 30 mg	**PsA, PsO:** Day 1: 10 mg in the morning Day 2: 10 mg in the morning and in the evening Day 3: 10 mg in the morning and 20 mg in evening Day 4: 20 mg in the morning and evening Day 5: 20 mg in the morning and 30 mg in the evening Day 6 and thereafter: 30 mg twice daily	Titrate according to the labeling when initiating therapy to reduce gastrointestinal symptoms. Dosage should be reduced to 30 mg once daily in patients with severe renal impairment (CrCl <30 mL/min as estimated by the Cockcroft-Gault equation). For initial dosing in these patients, use only the morning titration schedule listed above (evening doses should be excluded).	May be taken with or without food. Do not crush, split, or chew the tablets.
Remicade (infliximab)	Vial: 100 mg	**CD (≥6 years old), PsA, PsO and UC (≥6 years old)**: 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. In adults with CD who lose response,	**RA:** give with MTX **CD:** If no response by week 14, consider discontinuation.	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or corticosteroids.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		can increase dose to 10 mg/kg. **RA:** 3 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg or give every 4 weeks. **AS:** 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks.		Use 250 mL 0.9% sodium chloride for infusion. Infuse over 2 hours. Do not administer with other drugs.
Renflexis	Vial: 100 mg	**CD (≥6 years old), PsA, PsO and UC**: 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. In adults with CD who lose response, can increase dose to 10 mg/kg. **RA:** 3 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg or give every 4 weeks. **AS:** 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks.	**RA:** give with MTX **CD:** If no response by week 14, consider discontinuation.	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion. Infuse over 2 hours. Do not administer with other drugs.
Rituxan (rituximab)	Vial: 100 mg 500 mg	**RA:** 1,000 mg IV every 2 weeks times 2 doses. Additional doses should be given every 24 weeks or based on clinical evaluation but no sooner than 16 weeks.	Give with MTX.	Give methyl-prednisolone 100 mg IV 30 minutes prior to each infusion to reduce the incidence and severity of infusion reactions.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Siliq (brodalumab)	Prefilled syringe: 210 mg/1.5 mL	**PsO:** 210 mg SQ at weeks 0, 1, and 2 followed by every 2 weeks	**PsO**: If an adequate response has not been achieved after 12 to 16 weeks, consider discontinuation	Patients may self-inject when appropriate and after proper training. The syringe should be allowed to reach room temperature before injecting.
Simponi/ Simponi Aria (golimumab)	SmartJect® autoinjector: 50 mg and 100 mg Prefilled syringe: 50 mg and 100 mg Aria, Vial: 50 mg/4 mL	**RA, PsA, and AS**: 50 mg SQ once monthly **UC:** 200 mg SQ at week 0; then 100 mg at week 2; then 100 mg every 4 weeks. **Aria (RA, PsA, and AS)**: 2 mg/kg IV at weeks 0 and 4, then every 8 weeks.	**RA:** give with MTX **PsA and AS**: may give with or without MTX or other DMARDs. Needle cover of the syringe contains dry rubber (latex). **Aria (RA)**: give with MTX (**PsA, AS)**: give with or without MTX or other non-biologic DMARDs. Corticosteroids, NSAIDs, and/or analgesics may be continued. Efficacy and safety of switching between IV and SQ formulations have not been established.	Patients may be taught to self-inject the SQ dose. For SQ, injection sites should be rotated. For SQ, bring to room temperature for 30 minutes prior to injecting. **Aria**: IV infusion should be over 30 minutes. Dilute with 0.9% sodium chloride or 0.45% sodium chloride for a final volume of 100 mL. Do not administer with other drugs.
Stelara (ustekinumab)	Prefilled syringe: 45 mg and 90 mg Vial: 130 mg	**PsO, PsA**: ≤100 kg, 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. >100 kg, 90 mg SQ initially and 4 weeks later, followed by 90 mg every 12 weeks. **PsO (adolescents):** <60 kg, 0.75 mg/kg (injection volume based on weight) 60 to 100 kg, 45 mg >100 kg, 90 mg **CD**: Initial single IV dose: ≤55 kg, 260 mg;	Needle cover of the syringe contains dry rubber (latex).	Patients may be taught to self-inject using the prefilled syringes. Stelara for IV infusion must be diluted, prepared and infused by a healthcare professional; it is diluted in 0.9% sodium chloride and infused over at least 1 hour. Rotate injection sites.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		>55 kg to ≤85 kg, 390 mg; >85 kg, 520 mg; followed by 90 mg SQ every 8 weeks (irrespective of body weight)		
Tremfya (guselkumab)	Prefilled syringe: 100 mg	**PsO:** 100 mg by SQ injection at week 0, week 4, and then every 8 weeks		Patients may be taught to self-inject. Bring to room temperature (30 minutes) prior to injecting.
Taltz (ixekizumab)	Prefilled syringe: 80 mg Autoinjector: 80 mg	**PsO:** 160 mg by SQ injection at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks **PsA:** 160 mg by SQ injection at week 0, followed by 80 mg every 4 weeks NOTE: For patients with PsA with coexistent moderate-to-severe PsO, use dosing regimen for PsO.		Patients may be taught to self-inject with either the prefilled syringe or the autoinjector. Bring to room temperature prior to injecting. Rotate injection sites.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Xeljanz / Xeljanz XR (tofacitinib)	Tablet: 5 mg Extended release Tablet: 11 mg	**RA:** 5 mg PO twice daily or 11 mg PO once daily **PsA:** 5 mg PO twice daily, used in combination with non-biologic DMARDs; 11 mg once daily used in combination with nonbiologic DMARDs	Patients may switch from Xeljanz 5 mg twice daily to Xeljanz XR 11 mg once daily the day following the last dose of Xeljanz 5 mg. Use as monotherapy or in combination with MTX or other nonbiologic DMARDs. Use of Xeljanz in combination DMARDs or with potent immunosuppres-sants such as azathioprine and cyclosporine is not recommended. Dose interruption is recommended for management of lymphopenia (< 500 cells/mm^3), neutropenia (ANC < 500 cells/mm^3) and anemia. Dose adjustment needed for hepatic and renal impairment and patients taking CYP450 inhibitors.	May take with or without food. Swallow Xeljanz XR tablets whole; do not crush, split, or chew.

ANC=absolute neutrophil count; AS=ankylosing spondylitis; CRS=cytokine release syndrome; DMARD=disease-modifying anti-rheumatic drug; GCA=giant cell arteritis; HS=hidradenitis suppurative; IV=intravenous infusion; JIA=juvenile idiopathic arthritis; MTX=methotrexate; NOMID=neonatal-onset multisystem inflammatory disease; NSAID=non-steroidal anti-inflammatory drug; PJIA=polyarticular juvenile idiopathic arthritis; PO=orally; PsA=psoriatic arthritis; PsO=plaque psoriasis; RA=rheumatoid arthritis; SJIA=systemic juvenile idiopathic arthritis; SQ=subcutaneously; UC=ulcerative colitis.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Actemra (tocilizumab)	Frequency of serious infection greater in ≥65 years. Use caution.	Not studied in children <2 years. Safety and efficacy only established in SJIA, PJIA, and CRS.	No dose adjustment in mild or moderate impairment. Not studied in severe impair-ment.	Not studied in patients with impairment.	Unclassified† Limited data in pregnant women not sufficient to determine risks. Unknown whether excreted in breast milk; risks and benefits should be considered.
Cimzia (certolizumab)	The number of subjects ≥65 years in clinical trials was not sufficient to determine whether they responded differently from younger subjects. Use caution.	Safety and effectiveness have not been established.	No data	No data	Unclassified† Limited data from ongoing pregnancy registry not sufficient to inform risks. Unknown whether excreted in breast milk, but data suggest systemic exposure to a breastfed infant is expected to be low; risks and benefits should be considered.
Cosentyx (secukinumab)	The number of subjects ≥65 years in clinical trials was not sufficient to determine whether they responded differently from younger subjects.	Safety and efficacy have not been established.	No data	No data	Unclassified† Data on use in pregnant women insufficient to inform risks. Unknown whether excreted in breast milk; use with caution.
Entyvio (vedolizumab)	The number of patients ≥65 years in clinical trials was insufficient to determine differences.	Safety and efficacy have not been established.	Safety and efficacy have not been established.	Safety and efficacy have not been established.	Pregnancy category B* Unknown whether excreted in breast milk; use with caution.
Enbrel (etanercept)	Use caution.	Not studied in children <2 years with PJIA or <4 years with PsO.	No data	No data	Unclassified† Available studies do not reliably support

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
					association with major birth defects. Present in low levels in breast milk; consider risks and benefits.
Humira (adalimumab)	Frequency of serious infection and malignancies is greater in ≥65 years. Use caution.	Only studied in PJIA (ages 2 years and older) and CD (6 years and older).	No data	No data	Unclassified† Present in low levels in breast milk; consider risks and benefits.
Ilaris (canakinumab)	The number of patients ≥65 years in clinical trials was insufficient to determine differences.	Not studied in children <2 years (SJIA, TRAPS, HIDS/ MKD, and FMF) or <4 years (CAPS).	No data	No data	Unclassified† Limited data from postmarketing reports not sufficient to inform risks. Unknown whether excreted in breast milk; consider risks and benefits.
Inflectra (infliximab-dyyb)	Frequency of serious infection is greater in ≥65 years. Use caution.	Not recom-mended in <6 years in children with CD.	No data	No data	Pregnancy category B* Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug.
Kevzara (sarilumab)	Frequency of serious infection is greater in ≥ 65 years. Use caution.	Safety and efficacy not established.	Dosage adjustment not required in mild to moderate renal impairment. Kevzara has not been studied in severe renal impairment.	No data.	Unclassified† Data on use in pregnant women insufficient to inform risks. Unknown whether excreted in breast milk; consider risks and benefits.
Kineret (anakinra)	Use caution.	For NOMID, has been used in all ages. Not possible to give a dose <20 mg.	CrCl<30 mL/min: give dose every other day	No data	Pregnancy category B* Unknown whether excreted in breast milk; use caution.
Orencia (abatacept)	Frequency of serious infection and malignancies is greater in ≥65	Not recom-mended in <2 years.	No data	No data	Unclassified† Data on use in pregnant women

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	years. Use caution.	IV dosing has not been studied in patients < 6 years old. ClickJect autoinjector subcutaneous injection has not been studied in patients < 18 years.			insufficient to inform risks. Unknown whether excreted in breast milk.
Otezla (apremilast)	No overall differences were observed in the safety profile of elderly patients.	Safety and efficacy have not been established.	The dose of Otezla should be reduced to 30 mg once daily in patients with severe renal impairment (CrCl<30 mL/min).	No dosage adjustment necessary.	Pregnancy category C* Unknown whether excreted in breast milk; use caution.
Remicade (infliximab)	Frequency of serious infection is greater in ≥65 years. Use caution.	Not recom-mended in <6 years in children with CD or UC.	No data	No data	Pregnancy category B* Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug.
Renflexis (infliximab-abda)	Frequency of serious infection is greater in ≥ 65 years. Use caution.	Not recom-mended in < 6 years in children with CD.	No data	No data	Unclassified† Available data do not report clear association with adverse outcomes. Unknown whether excreted in breast milk; consider risks and benefits.
Rituxan (rituximab)	Rates of serious infections, malignancies, and cardiovascular events were higher in older patients.	Safety and effectiveness have not been established.	No data	No data	Pregnancy category C* Unknown whether excreted in breast milk; risks and benefits should be weighed before use.
Siliq (brodalumab)	No differences in safety or efficacy were observed between older and	Safety and effectiveness in <18 years have	No data	No data	Unclassified† There are no human data in pregnant

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	younger patients, but the number of patients ≥65 years was insufficient to determine any differences in response.	not been established.			women to inform risks. Unknown whether excreted in breast milk; risks and benefits should be weighed before use.
Simponi/ Simponi Aria (golimumab)	SQ: No differences in AEs observed between older and younger patients. Use caution. IV Aria: Use caution.	Effectiveness in <18 years has not been established (Simponi). Safety and effectiveness in < 18 years have not been established (Aria).	No data	No data	Pregnancy category B* (Aria) Unclassified† No adequate and well-controlled trials in pregnant women. (Simponi). Unknown whether excreted in breast milk. Discontinue nursing or discontinue the drug (Aria). Consider risks and benefits (Simponi).
Stelara (ustekinumab)	No differences observed between older and younger patients. Use caution.	Safety and effectiveness have not been established.	No data	No data	Unclassified† Limited data in pregnant women are insufficient to inform risks. Unknown whether excreted in breast milk; systemic exposure to breasted infant expected to be low; consider risks and benefits.
Taltz (ixekizumab)	No differences observed between older and younger patients; however, the number of patients ≥65 years was not sufficient to determine differences.	Safety and effectiveness have not been established.	No data	No data	Unclassified† There are no available data in pregnant women to inform risks. Unknown whether excreted in breast milk; consider risks and benefits.
Tremfya (guselkumab)	No differences observed between older and younger	Safety and efficacy have	No data	No data	Unclassified†

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	patients; however, the number of patients ≥ 65 years was not sufficient to determine differences.	not been established.			No available data in pregnant women to inform risks. Unknown whether excreted in breast milk; consider risks and benefits.
Xeljanz / Xeljanz XR (tofacitinib)	Frequency of serious infection is greater in ≥65 years. Use caution.	Safety and effectiveness have not been established.	Reduce dose to 5 mg daily in moderate to severe impairment.	Reduce dose to 5 mg daily in moderate hepatic impairment. Not recom-mended in severe hepatic impairment.	Unclassified† No adequate and well-controlled studies in pregnancy are available. Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug.

CrCl=creatinine clearance; CRS=cytokine release syndrome; NOMID= Neonatal-Onset Multisystem Inflammatory Disease; PJIA=polyarticular juvenile idiopathic arthritis; SJIA=systemic juvenile idiopathic arthritis
*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

CONCLUSION

- Immunomodulators for a variety of conditions associated with inflammation are available. Mechanisms of action and indications vary among the products. Products in this class have clinical trial data supporting efficacy for their FDA-approved indications.
- Limited head-to-head clinical trials between the agents have been completed.
    - In patients with RA, abatacept and infliximab showed comparable efficacy at 6 months, but abatacept demonstrated greater efficacy after 1 year on some endpoints such as DAS28-ESR, EULAR response, LDAS, and ACR 20 responses (*Schiff et al 2008*).
    - In patients with RA, abatacept and adalimumab were comparable for ACR 20 and ACR 50 responses over 2 years in a single-blind study (*Schiff et al 2014*).
    - In patients with RA and an inadequate response or intolerance to MTX, sarilumab significantly improved change from baseline in DAS28-ESR over adalimumab (*Burmester et al 2017*). DAS28-ESR remission, ACR 20/50/70 response rates, and improvements in HAQ-DI scores were also more likely with sarilumab.
    - Patients with severe arthritis who could not take MTX were randomized to monotherapy with tocilizumab or adalimumab for 24 weeks in a randomized, double-blind study (*Gabay et al 2013*). The patients in the tocilizumab group had a significantly greater improvement in DAS28 at week 24 than patients in the adalimumab group.
    - In biologic-naïve patients with RA and an inadequate response to DMARDs, initial treatment with rituximab was demonstrated to have non-inferior efficacy to initial TNF inhibitor treatment (*Porter et al 2016*).
    - A randomized, open-label trial evaluated biologic treatments in patients with RA who had had an inadequate response to a TNF inhibitor. In this population, a non-TNF biologic (tocilizumab, rituximab, or abatacept) was more effective in achieving a good or moderate disease activity response at 24 weeks than use of a second TNF inhibitor. However, a second TNF inhibitor was also often effective in producing clinical improvement (*Gottenberg et al 2016*). Another recent randomized trial did not demonstrate clinical efficacy differences

between abatacept, rituximab, and use of a second TNF inhibitor in this patient population *(Manders et al 2015*).
    - Secukinumab and ustekinumab were compared for safety and efficacy in the CLEAR study, a double-blind, randomized controlled trial in 676 patients with moderate to severe PsO (*Thaçi et al 2015*). The proportion of patients achieving PASI 90 at week 16 was significantly higher with secukinumab compared to ustekinumab (79% vs 57.6%; p < 0.0001).
    - In the IXORA-S study, the proportion of patients achieving PASI 90 at week 12 was significantly higher with ixekizumab compared to ustekinumab (72.8% vs 42.2%, respectively; p < 0.001) (*Reich et al 2017 [b]).*
    - A greater proportion of PsO patients achieved the primary outcome, PASI 75 at week 12, with ustekinumab 45 mg (67.5%) and 90 mg (73.8%) compared to etanercept 50 mg (56.8%; p = 0.01 vs ustekinumab 45 mg; p < 0.001 vs ustekinumab 90 mg). In this trial, etanercept therapy was associated with a greater risk of injection site erythema than ustekinumab (14.7% vs 0.7%) (*Griffiths et al 2010*).
    - In the FIXTURE study in patient with moderate to severe PsO, 77.1%, 67%, 44%, and 4.9% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, etanercept at FDA-recommended dosing, and placebo, respectively (*Langley et al 2014*).
    - In the UNCOVER-2 and UNCOVER-3 studies, the proportions of patients achieving PASI 75 and achieving PGA 0 or 1 were higher in patients treated with ixekizumab compared to those treated with etanercept.
    - In the AMAGINE-2 and AMAGINE-3 studies, the proportions of patients achieving PASI 100 were higher in patients treated with brodalumab compared to those treated with ustekinumab (*Lebwohl et al 2015*).
    - In the VOYAGE 1 and VOYAGE 2 studies, the proportions of patients with moderate to severe PsO achieving IGA 0 or 1 and PASI 90 were higher with guselkumab compared to those treated with adalimumab *(Blauvelt et al 2017, Reich et al 2017[a]*).
    - No meaningful differences were shown in the treatment of RA and PsA in comparisons of infliximab and infliximab-dyyb conducted to establish biosimilarity between these agents (*Park et al 2013, Park et al 2016, Park et al 2017, Yoo et al 2013, Yoo et al 2016, Yoo et al 2017*). Similarly, no meaningful differences between infliximab and infliximab-abda were found in treatment of RA in clinical studies to establish biosimilarity (*Choe et al 2017, Shin et al 2015*).
    - In patients with CD, UC, RA, PsA, spondyloarthritis, and PsO who were treated with the originator infliximab for ≥ 6 months, infliximab-dyyb was noninferior to infliximab originator group for disease worsening (*Jørgensen et al 2017*).
    - More comparative studies are needed.
- For RA, patients not responding to initial DMARD treatment may be treated with combination DMARDs, TNF inhibitors, non-TNF inhibitor biologics, and/or tofacitinib (*Singh et al 2016c; Smolen et al 2017*). EULAR has released guidelines for use of antirheumatic drugs in pregnancy, which state that the TNF inhibitors etanercept and certolizumab are among possible treatment options for patients requiring therapy (*Götestam Skorpen et al 2016*).
- For the management of PsO, biologic agents are routinely used when ≥ 1 traditional systemic agents are not tolerated, fail to product an adequate response, or are unable to be used due to patient comorbidities (*Gottleib et al 2008, Menter et al 2008, Menter et al 2009a, Menter et al 2009b, Menter et al 2010, Menter et al 2011, Nast et al 2015b*). EULAR 2015 PsA guidelines recommend TNF inhibitors in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, such as MTX (*Gossec et al 2016, Ramiro et al 2016*). For patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, in whom a TNF inhibitor is not appropriate, biologics targeting IL-12/23 or IL-17 pathways may be considered. Apremilast is considered a treatment option in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, in whom biologics are not appropriate. Guidelines from GRAPPA recommend various biologics for the treatment of PsO and PsA based on patient-specific factors, including TNF inhibitors, IL-17 and IL-12/23 inhibitors, and PDE-4 inhibitors (*Coates et al 2016*).
- In patients with JIA and involvement of ≥ 5 joints, the ACR recommends the use of a TNF inhibitor after an adequate trial of a conventional DMARD (*Beukelman et al 2011*). The ACR updated guideline for SJIA notes that IL-1 and IL-6 play a central role in the inflammatory process for this condition, and recommend agents such as anakinra, canakinumab, tocilizumab, abatacept, and TNF inhibitors among either first- or second-line treatments (*Ringold et al 2013*).
- According to the ACG, for the treatment of UC, infliximab should be considered after failure of first-line non-biologic agents (*Kornbluth et al 2010*). Other immunomodulators were not indicated for UC when these guidelines were written.
- Based on ACG guidelines, the anti-TNF monoclonal antibodies adalimumab, certolizumab, and infliximab are effective in the treatment of moderate to severely active CD in patients who have not responded despite complete and adequate therapy with a corticosteroid or an immunosuppressive agent. These TNF inhibitors may also be used as

alternatives to steroid therapy in selected patients in whom corticosteroids are contraindicated or not desired (*Lichtenstein et al 2009*). The AGA recommends using anti-TNF drugs to induce remission in patients with moderately severe CD (*Terdiman et al 2013*). ECCO recommends TNF inhibitors for patients with CD who have relapsed or are refractory to corticosteroids, depending on disease location and severity, and states that early TNF inhibitor therapy should be initiated in patients with high disease activity and features indicating a poor prognosis; vedolizumab is an alternative for some patients (*Gomollón et al 2017*).

- Consensus statements for the management of inflammatory bowel disease in pregnancy, coordinated by the Canadian Association of Gastroenterology, state that TNF inhibitor treatment does not appear to be associated with unfavorable pregnancy outcomes and should generally be continued during pregnancy (*Nguyen et al 2016b*).
- Based upon guidelines from the European Dermatology Forum, adalimumab is recommended among first-line therapies for HS, with infliximab a potential second-line option (*Gulliver et al 2016, Zouboulis et al 2015*).
- Joint guidelines from ASAS and EULAR state that biologic DMARDs should be considered in patients with AS and persistently high disease activity despite conventional treatments (*van der Heijde et al 2017*). The 2015 ACR, Spondylitis Association of America, and Spondyloarthritis Research and Treatment Network guidelines strongly recommend TNF inhibitors for patients who have active disease despite NSAIDs; no TNF inhibitor is preferred over another for AS for most patients (*Ward et al 2016*).
- Infliximab and adalimumab are recommended over etanercept for various ocular inflammatory disorders (*Levy-Clarke et al 2016*).
- Caution is warranted with these biologic agents due to severe infections and malignancies that can occur with their use. Tocilizumab, TNF inhibitors, and tofacitinib have boxed warnings regarding a risk of serious infections. TNF inhibitors and tofacitinib also have boxed warnings regarding an increased risk of malignancies. Brodalumab has a boxed warning regarding the risk of suicidal ideation and behavior.
- Warnings, precautions, and AE profiles vary in this class.
- All of the biologic agents with the exception of apremilast and tofacitinib are given by subcutaneous injection and/or intravenous infusion. Administration schedule varies among the injectable agents in the class. Apremilast and tofacitinib are given orally.
- Selection of an agent for a patient is determined by approved indications, response, administration method, tolerability, AE profile, and cost of the agent.

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Publication Date: March 26, 2018

Therapeutic Class Overview
Beta-adrenergic Blocking Agents

INTRODUCTION

- Approximately 92.1 million American adults have at least 1 type of cardiovascular disease according to the American Heart Association (AHA) Heart Disease and Stroke Statistics 2018 update. From 2003 to 2015, mortality associated with cardiovascular disease declined 25.5% *(Benjamin et al 2018)*.
- Beta-adrenergic blocking agents (beta-blockers) are a group of drugs that block the sympathomimetic effects of catecholamines on beta receptors. This results in negative inotropic and chronotropic effects and relaxation of smooth muscle.
- Beta-blockers have varied pharmacologic properties.
  - Cardioselective beta-blockers preferentially interact with $beta_1$-receptors, which are predominantly found in the heart. Non-cardioselective beta-blockers also interact with $beta_2$-receptors found on smooth muscle in the lungs, blood vessels, and other tissues. The cardioselectivity of beta-blockers is dose dependent; therefore, $beta_2$ blockade can occur at higher doses with certain cardioselective agents.
  - Some beta-blockers (acebutolol and pindolol) have intrinsic sympathomimetic activity (ISA), which may result in a lower incidence of bradycardia and bronchoconstriction *(Facts and Comparisons 2018)*. In addition, some beta-blockers (nebivolol and propranolol) have higher lipophilicity, which may increase the risk for central nervous system-related adverse events *(Facts and Comparisons 2018)*.
  - Carvedilol and labetalol also block alpha-adrenergic receptors and may reduce peripheral resistance more than other beta-blockers *(Clinical Pharmacology 2018)*.
- Specific indications for the beta-blockers vary by product. Most beta-blockers (all except sotalol) are approved to treat hypertension (HTN). The 2017 American College of Cardiology (ACC)/AHA clinical practice guideline defines HTN as blood pressure (BP) ≥ 130/80 mm Hg (*Whelton et al 2017).* Nearly half of American adults (46%) have HTN based on this definition. Other indications for 1 or more beta-blockers include, but are not limited to: angina pectoris, arrhythmias, myocardial infarction (MI), heart failure, left ventricular dysfunction following MI, treatment of essential tremor, and migraine prophylaxis.
- Most of the beta-blockers are available generically. There are no generics available for Bystolic (nebivolol) and branded Levatol (penbutolol), which was discontinued in 2014, has no generics currently on the market. Brand Hemangeol is an oral solution in strengths of 4.28 mg/mL (equivalent to 3.75 mg); however generic propranolol is available in strengths of 4 and 8 mg/mL oral solutions.
- There has been extensive experience with beta-blockers in clinical practice, and clinical trials do not consistently demonstrate a clinical advantage of one agent over another for most Food and Drug Administration (FDA)-approved indications. In general, treatment guidelines do not recommend the use of one beta-blocker over the other, as recommendations regarding the use of these agents are made for the class as a whole. There are some exceptions, however. Guidelines do recognize the role of 3 beta-blockers (carvedilol, bisoprolol, and extended release metoprolol) for the reduction of mortality and hospitalization in patients with heart failure *(Ponikowski et al 2016, Yancy et al 2013, Yancy et al 2017)*. Also, sotalol has some unique properties and is considered separately from the other beta-blockers, as this agent is not indicated to treat hypertension and is instead used to treat certain ventricular arrhythmias or for the maintenance of normal sinus rhythm in patients with symptomatic atrial fibrillation/atrial flutter.
- Although some single-ingredient beta-blockers have several indications, the beta blocker/diuretic combination products are FDA-approved only for the treatment of hypertension. Patients with hypertension frequently require the use of 2 or more agents from different therapeutic classes in order to adequately reduce BP, and the dose of each product should be titrated to its desired effect. Thus, the place in therapy for the beta blocker/diuretic combinations is for patients who require both agents at doses for which a combination product is available. Several of the combination products (all except for Dutoprol and Ziac) contain specific wording in their prescribing information stating that the product is not approved for initial therapy *(Gradman 2012)*.
- Both beta-blockers and diuretics are well established in the management of hypertension. The choice of antihypertensive agent(s) for a particular patient will depend on the patient's comorbidities.

- All of the beta-blockers contained within the combination products are also available generically as single-entity agents. The diuretics hydrochlorothiazide (HCTZ) and chlorthalidone are available generically as single-entity agents; however, bendroflumethiazide is not available as a single agent. All of the combination products except for Dutoprol (metoprolol succinate extended release/HCTZ are available generically. Dutoprol is not available as a generic but its individual components are.
- Little guidance on the use of fixed-dose combination products is available within treatment guidelines; however, they are recognized as having the ability to simplify treatment regimens and to improve adherence to therapy *(Mancia et al 2013)*.
- This class includes the orally-administered beta-blockers, as well as the orally-administered alpha/beta-blocking agents, carvedilol and labetalol, and the beta blocker/diuretic combination products. Several beta-blockers are also available in intravenous (IV) forms for in-hospital use; however, the IV formulations are not included within the scope of this review.
- Medispan drug class: Beta Blockers - Beta Blockers Non-Selective; Beta Blockers Cardio-Selective; Alpha-Beta Blockers; Antihypertensive Combinations - Beta Blocker & Diuretic Combinations

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single-Entity Beta-blockers	
acebutolol*	✔
Betapace, Betapace AF, Sorine, Sotylize (sotalol)	✔ ‖
betaxolol*	✔
bisoprolol*	✔
Bystolic (nebivolol)	-
Coreg, Coreg CR (carvedilol)	✔
Corgard (nadolol)	✔
Hemangeol, Inderal LA, Inderal XL, Innopran XL (propranolol)*	✔ ‡
labetalol*	✔
Lopressor (metoprolol tartrate)	✔
pindolol*	✔
Tenormin (atenolol)	✔
timolol*	✔
Toprol XL (metoprolol succinate extended release)	✔
Beta-blocker/Diuretic Combinations	
Corzide (nadolol/bendroflumethiazide)	✔
Dutoprol (metoprolol succinate extended release/HCTZ)	-
Lopressor HCT (metoprolol tartrate/HCTZ)	✔
propranolol/HCTZ*	✔
Tenoretic (atenolol/chlorthalidone)	✔
Ziac (bisoprolol/HCTZ)	✔

*Branded Sectral (acebutolol), Kerlone (betaxolol), Zebeta (bisoprolol), Trandate (labetalol), Visken (pindolol), Blocadren (timolol), Inderal (propranolol), and Inderide (propranolol/HCTZ) are no longer marketed.
‡ Hemangeol (propranolol oral solution) , Inderal XL, and Innopran XL are brand-name only.
‖ Sotylize (sotalol oral solution) is brand-name only.

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. FDA-Approved Indications for Single-Entity Beta-blockers

Generic Name	Hypertension	Angina Pectoris	Cardiac Arrhythmias*	MI	Heart Failure	Pheochromocytoma	Migraine Prophylaxis	Hypertrophic Subaortic Stenosis	Proliferating Infantile Hemangioma requiring systemic therapy	Essential Tremor	Left Ventricular Dysfunction Following MI
Acebutolol	✔ †		✔								
Atenolol	✔ †	✔ ‡		✔ §							
Betaxolol	✔ †										
Bisoprolol	✔ ‖										
Carvedilol	✔ †¶				✔ #						✔ **
Labetalol	✔ ††										
Metoprolol	✔ §§	✔ ‖‖		✔ ¶¶	✔ ##						
Nadolol	✔ †	✔ ***									
Nebivolol	✔ ‖										
Pindolol	✔ †										
Propranolol	✔ †,†††	✔ ‡‡‡	✔	✔ §§§		✔ ‖‖‖	✔	✔ ¶¶¶	✔ ††††	✔ ###	
Sotalol			✔								
Timolol	✔ †			✔ ****			✔				

* See Table 3 for the specific cardiac arrhythmias for which these agents are indicated.
† May be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.
‡ Indicated for the long term management of patients with angina pectoris due to coronary atherosclerosis.
§ Indicated for the management of hemodynamically stable patients with definite or suspected acute MI to reduce cardiovascular mortality.
‖ May be used alone or in combination with other antihypertensive agents.
¶ Indicated for the management of essential hypertension.
# Indicated for the treatment of mild to severe chronic heart failure of ischemic or cardiomyopathic origin, usually in addition to diuretics, angiotensin converting enzyme inhibitors and digitalis to increase survival, and also to reduce the risk of hospitalization.
** Indicated to reduce cardiovascular mortality in clinically stable patients who survived the acute phase of an MI and have a left ventricular ejection fraction ≤ 40% (with or without symptomatic heart failure).
†† Labetalol tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.
§§ Metoprolol succinate extended-release tablets and capsules and metoprolol tartrate tablets may be used alone or in combination with other antihypertensive agents.
‖‖ Metoprolol succinate extended-release tablets and capsules and metoprolol tartrate tablets are indicated in the long term treatment of angina pectoris.
¶¶ Metoprolol tartrate tablets are indicated in the treatment of hemodynamically stable patients with definite or suspected acute MI to reduce cardiovascular mortality when used alone or in conjunction with IV metoprolol tartrate. Oral therapy can be initiated after IV therapy or, alternatively, oral treatment can begin within 3 to 10 days of the acute event.
Metoprolol succinate extended-release tablets are indicated for the treatment of stable, symptomatic (New York Heart Association Class II or III) heart failure of ischemic, hypertensive or cardiomyopathic origin. Metoprolol succinate extended release capsules are indicated for the treatment of patients with heart failure to reduce the risk of cardiovascular mortality and heart failure-related hospitalization.
*** Indicated for the long term management of patients with angina pectoris.
††† Inderal XL and Innopran XL are indicated for the treatment of hypertension only.
‡‡‡ Indicated to decrease angina frequency and increase exercise tolerance in patients with angina pectoris due to coronary atherosclerosis.
§§§ Propranolol tablets and oral solution are indicated to reduce cardiovascular mortality in patients who have survived the acute phase of an MI and are clinically stable.
‖‖‖ Propranolol tablets and oral solution are indicated as an adjunct to alpha-adrenergic blockade to control BP and reduce symptoms of catecholamine-secreting tumors.
¶¶¶ Improves New York Heart Association functional class in symptomatic patients with hypertrophic subaortic stenosis.

Propranolol tablets and oral solution are indicated for the management of familial or hereditary essential tremor.
**** Indicated in patients who have survived the acute phase of an MI, and are clinically stable, to reduce cardiovascular mortality and the risk of reinfarction.
†††† Only approved for Hemangeol oral solution. Hemangeol is not FDA-approved for any other indication.

(Prescribing information: acebutolol 2017, betaxolol 2017, bisoprolol 2016, Betapace and Betapace AF 2016, Bystolic 2017, Coreg 2017, Coreg CR 2017, Corgard 2015, Hemangeol 2015, Inderal LA 2016, Inderal XL 2017, Innopran XL 2017, labetalol 2017, Lopressor 2017, metoprolol succinate extended release capsules 2018, pindolol 2016, propranolol solution 2017, propranolol tablets 2016, Sorine 2017, Sotylize 2015, Tenormin 2017, timolol 2006, Toprol XL 2016)

Table 3. FDA-Approved Cardiac Arrhythmia Indications

Indication	Acebutolol	Propranolol	Sotalol
Control ventricular rate in patients with atrial fibrillation and a rapid ventricular response		✔ (oral solution, tablet)	
Maintenance of normal sinus rhythm (delay in time to recurrence of atrial fibrillation/atrial flutter [AFIB/AFL] in patients with symptomatic AFIB/AFL who are currently in sinus rhythm*			✔
Management of ventricular premature beats	✔		
Treatment of documented life-threatening ventricular arrhythmias, such as sustained ventricular tachycardia**			✔

* Limitations of use: Because sotalol can cause life-threatening ventricular arrhythmias, reserve it for patients in whom AFIB/AFL is highly symptomatic. Patients with paroxysmal AFIB whose AFIB/AFL that is easily reversed (by Valsalva maneuver, for example) should usually not be given sotalol.
** Limitations of use: Sotalol may not enhance survival in patients with ventricular arrhythmias. Because of the proarrhythmic effects of Betapace/Betapace AF, including a 1.5 to 2% rate of Torsade de Pointes (TdP) or new ventricular tachycardia/fibrillation (VT/VF) in patients with either non-sustained ventricular tachycardia (NSVT) or supraventricular arrhythmias (SVT), its use in patients with less severe arrhythmias, even if the patients are symptomatic, is generally not recommended. Avoid treatment of patients with asymptomatic ventricular premature contractions.

(Prescribing information: acebutolol 2017, propranolol solution 2017, propranolol tablets 2016, Betapace and Betapace AF 2016, Sorine 2017, Sotylize 2015)

Table 4. FDA-Approved Indications for Beta-blocker/Diuretic Combinations

Drug	Hypertension
Corzide (nadolol/bendroflumethiazide)	✔ *
Dutoprol (metoprolol succinate extended release/HCTZ)	✔
Lopressor HCT (metoprolol tartrate/HCTZ)	✔ *
propranolol/HCTZ	✔ *
Tenoretic (atenolol/chlorthalidone)	✔ *
Ziac (bisoprolol/HCTZ)	✔

*The fixed-dose combination product is not indicated for initial therapy of hypertension. If the fixed combination represents the dose titrated to the individual patient's needs, it may be more convenient than the separate components.

(Prescribing information: Corzide 2016, Dutoprol 2017, Lopressor HCT 2012, propranolol and HCTZ 2015, Tenoretic 2016, Ziac 2018)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Clinical trials demonstrating the safety and efficacy of beta-blockers for their FDA approved indications have demonstrated that beta-blockers are superior to placebo and efficacious compared to active comparators for these varied indications, including:

- Hypertension *(Dahlöf et al 1991, Davidov et al 1988, Dhakam et al 2008, Dietz et al 2008, Fogari et al 1997, Giles et al 2014, Greathouse 2010, Materson et al 1990, Neutel et al 2010, Stoschitzky et al 2006, Van Bortel et al 2005, Veterans Administration Cooperative Study Group on Antihypertensive Agents 1977, Wald et al 2008)*
- Angina *(Pandhi et al 1985, van der Does et al 1999, Weiss et al 1998)*
- Arrhythmia *(Lui et al 1983, Seidl et al 1998)*
- Heart failure *(Bristow et al 1996, CIBIS Investigators and Committees 1994, CIBIS-II Investigators and Committees 1999, Dargie et al 2001, Di Lenarda et al 1999, Flather et al 2005, Goldstein et al 2001, Krum et al 1995, MERIT-HF Study Group 1999, Metra et al 2000, Packer et al 1996, Packer et al 2001[b], Packer et al 2002, Poole-Wilson et al 2003, Ruwald et al 2013, Waagstein et al 1993)*
- Infantile hemangiomas *(Bauman et al 2014)*
- Essential tremor *(Calzetti et al 1981, Gironell et al 1999, Yetimalar et al 2005)*
- Migraine prophylaxis *(Ashtari et al 2008, Domingues et al 2009, Rao et al 2000, Schellenberg et al 2008, Tfelt-Hansen et al 1984)*

- Head-to-head trials have demonstrated that no one beta-blocker is consistently superior compared to the others for the treatment of hypertension *(Czuriga et al 2003, Davidov et al 1988, Dhakam et al 2008, Fogari et al 1997)*.
- Trials have demonstrated cardiovascular advantages with beta-blocker use in patients with prior MI; however, recent post-hoc analyses examining the use of beta-blockers have been mixed *(Bangalore et al 2014, Freemantle et al 1999, Gottlieb et al 2001, Jonsson et al 2005, Olsson et al 1992)*.
- For the treatment of heart failure, a survival benefit has been demonstrated with bisoprolol, carvedilol, and sustained-release metoprolol succinate; however, only carvedilol and metoprolol succinate are FDA-approved for the treatment of heart failure. Carvedilol has demonstrated superiority to other beta-blockers in certain populations. Beta-blockers that have been shown to reduce mortality in patients with systolic dysfunction include carvedilol, bisoprolol, and long-acting metoprolol *(Bristow et al 1996, CIBIS-II Investigators and Committees 1999, Dargie 2001, Di Lenarda et al 1999, Goldstein et al 2001, Hamaad et al 2007, Maack et al 2001, MERIT-HF Study Group 1999, Metra et al 2000, Packer et al 1996, Packer et al 2001[b], Packer et al 2002, Poole-Wilson et al 2003, Ruwald et al 2013, Sanderson et al 1999)*. In elderly patients with heart failure, nebivolol demonstrated a significant improvement in a composite measure of death or cardiovascular hospitalization; however, differences for the individual components of the composite measure did not reach statistical significance *(Flather et al 2005)*.
  - Head-to-head trials have compared metoprolol to carvedilol in patients with heart failure; however, available trials used the immediate-release formulation of metoprolol rather than the extended release formulation that has FDA approval for this indication *(Di Lenarda et al 1999, Maack et al 2001, Metra et al 2000, Poole-Wilson et al 2003, Sanderson et al 1999)*. Most of the comparative trials have been small and have evaluated outcomes other than mortality *(Di Lenarda et al 1999, Maack et al 2001, Metra et al 2000, Sanderson et al 1999)*. One larger trial, COMET (N = 3029), demonstrated that all-cause mortality was significantly lower in patients treated with carvedilol compared to patients treated with metoprolol tartrate (hazard ratio [HR], 0.83; 95% confidence interval [CI]: 0.74 to 0.93; p = 0.0017). However, questions have been raised about the choice of metoprolol formulation and its dosing for this trial, so definitive conclusions could not be made *(Kveiborg et al 2007)*.
  - A meta-analysis that included trials that evaluated immediate- and sustained-release metoprolol revealed that treatment with carvedilol improved mean left ventricular ejection fraction significantly more than treatment with metoprolol *(Packer et al 2001[a])*.
  - Another meta-analysis found that carvedilol significantly reduced the incidence of post-operative atrial fibrillation when compared to metoprolol in patients following a coronary artery bypass grafting (CABG) procedure *(DiNicolantonio et al 2014)*.
- Several meta-analyses have confirmed the mortality benefit of beta-blockers for the treatment of heart failure *(Brophy et al 2001, Chatterjee et al 2013, Lechat et al 1998, Whorlow et al 2000)*.

Combination products

- Most trials compared the combination product to placebo or to 1 or both of the individual product components. Results demonstrate that:
  - The combination products are superior to placebo *(de Leeuw et al 1997, Lewin et al 1993, Nissinen et al 1980)*.
  - Additional BP lowering is achieved when the combination therapy is compared to 1 or both of the individual drug components administered as monotherapy *(Dafgard et al 1981, Fogari et al 1984, Frishman et al 1994, Frishman et al*

1995, Hansson et al 1999, Leonetti et al 1986, Liedholm et al 1981, Smilde et al 1983, Stevens et al 1982, Veterans Administration Cooperative Study Group on Antihypertensive Agents 1983).

- The CAPPP study compared an angiotensin converting enzyme (ACE) inhibitor to treatment with a diuretic and/or beta-blockers. For both diabetic and non-diabetic patients, both regimens were equally effective in preventing the composite of fatal and non-fatal MI, stroke, and cardiovascular deaths *(Hansson et al 1999)*. A sub-analysis of diabetic patients within the CAPPP trial found that in hypertensive diabetic patients, captopril (ACE inhibitor) was superior to a diuretic and/or beta-blocker antihypertensive treatment regimen in preventing cardiovascular events, especially in those with metabolic decompensation *(Niskanen et al 2001)*. Further studies should be performed to validate beta-blockers in combination with a diuretic and their place in therapy with diabetic patients.

CLINICAL GUIDELINES

- Hypertension:
  - The 2017 ACC/AHA guideline for the prevention, detection, evaluation, and management of high BP in adults *(Whelton et al 2017)* offers updated classifications of HTN and goals of treatment (see Table 5).

Table 5. Classification of BP measurements

BP Category	BP	Treatment or follow up
Normal	SBP < 120 mm Hg *and* DBP < 80 mm Hg	▪ Evaluate yearly; lifestyle changes are recommended
Elevated	SBP 120 - 129 mm Hg *and* DBP < 80 mm Hg	▪ Evaluate in 3 to 6 months; lifestyle changes are recommended
HTN stage 1	SBP 130 - 139 mm Hg *or* DBP 80 - 89 mm Hg	▪ Assess the 10-year risk for heart disease and stroke using the ASCVD risk calculator. ▪ If ASCVD risk is < 10%, lifestyle changes are recommended. A BP target of < 130/80 mm Hg may be reasonable. ▪ If ASCVD risk is > 10%, or the patient has known CVD, DM, or CKD, lifestyle changes and 1 BP-lowering medication are recommended. A target BP of < 130/80 mm Hg is recommended.
HTN stage 2	SBP ≥ 140 mm Hg *or* DBP ≥ 90 mm Hg	▪ Lifestyle changes and BP-lowering medication from 2 different classes are recommended.

Abbrv: ASCVD= atherosclerotic cardiovascular disease, BP = blood pressure, CKD= chronic kidney disease, CVD= cardiovascular disease, DBP= diastolic blood pressure, DM=diabetes mellitus, HTN= hypertension, SBP= systolic blood pressure

- In patients with stage 1 HTN, it is reasonable to initiate therapy with a single antihypertensive agent. In patients with stage 2 HTN and BP more than 20/10 mm Hg higher than their target, 2 first-line agents of different classes should be initiated.
  - First-line antihypertensive agents include: thiazide diuretics, calcium channel blockers (CCBs), and ACE inhibitors or angiotensin II receptor blockers (ARBs).
  - Diuretics, ACE inhibitors, ARBs, CCBs, and beta-blockers have been shown to prevent CVD compared with placebo.
    - Beta blockers are not recommended as first-line agents unless the patient has ischemic heart disease (IHD) or heart failure.
    - Cardioselective beta-blockers (atenolol, betaxolol, bisoprolol, metoprolol tartrate and succinate) are preferred in patients with bronchospastic airway disease requiring a beta-blocker.
    - Non-cardioselective beta-blockers (ie, nadolol, propranolol) should be avoided in patients with reactive airways disease.

- Bisoprolol, carvedilol, and metoprolol succinate are preferred in patients with heart failure with reduced ejection fraction (HFrEF).
- In general, beta-blockers with ISA (ie, acebutolol, carteolol, penbutolol, pindolol) should be avoided, especially in patients with IHD or HF.

  - Most hypertension guidelines recommend a thiazide-type diuretic, an ACE inhibitor, an ARB, or a CCB as first line therapy *(Go et al 2014, James et al 2014, Mancia et al 2013, Weber et al 2014, Whelton et al 2017)*. However, the 2013 European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines also recommend beta-blockers as a first line therapy option *(Mancia et al 2013)*.
  - In the treatment of severe hypertension in pregnancy, labetalol is outlined as an option with consideration of maternal and fetal side effects *(Bushnell et al 2014, de Boer et al 2017, Weber et al 2014)*.
  - Beta blockers have strong clinical outcome benefits in hypertensive patients with a history of MI, heart failure, acute coronary syndrome, and in the management of angina pectoris *(Go et al 2014, Mancia et al 2013, Rosendorff et al 2015, Weber et al 2014)*.
- The beta-blockers are also a mainstay of heart failure treatment, as evidenced by recommendations within treatment guidelines *(Ponikowski et al 2016, Yancy et al 2013, Yancy et al 2017)*. Of note, carvedilol and metoprolol succinate are the only 2 beta-blockers FDA-approved for the treatment of heart failure, but a mortality benefit has also been shown for bisoprolol in clinical trials, and all 3 are recognized as appropriate options in clinical guidelines *(CIBIS Investigators and Committees 1994, CIBIS-II Investigators and Committees 1999, MERIT-HF Study Group 1999, Ponikowski et al 2016, Waagstein et al 1993, Yancy et al 2013, Yancy et al 2017)*.
  - Conclusive data on the medical management of heart failure in patients with a systemic right ventricle (RV) are lacking, despite the high incidence of late clinical heart failure and sudden death in this population. Use of conventional heart failure medications may be problematic because of preexisting sinus node dysfunction, heart block, baffle stenosis, nondistensible atria, and restrictive RV physiology. Beta-blockade may exacerbate bradyarrhythmias, whereas vasodilation could be counterproductive in patients with nondistensible atria or restrictive physiology *(Stout et al 2016)*.
- Guidelines also support the use of beta-blockers for additional cardiovascular diseases including stable ischemic heart disease, unstable angina, MI (acute and long-term after MI), rate control in atrial fibrillation and atrial flutter, maintenance of normal sinus rhythm in atrial fibrillation (sotalol), non-ST-segment elevation acute coronary syndromes, select ventricular and supraventricular arrhythmias, complications following coronary artery bypass grafting (CABG), valvular heart disease, and hypertrophic cardiomyopathy *(Amsterdam et al 2014[a,b], Fihn et al 2012, Fihn et al 2014, Gersh et al 2011,Ibanez et al 2018, January et al 2014[a,b], Jneid et al 2012, Montalescot et al 2013, Nishimura et al 2014[a,b], Nishimura et al 2017, O'Gara et al 2013, Page et al 2016, Priori et al 2015, Roffi et al 2016, Rosendorff et al 2015, Windecker et al 2014)*.
- Metoprolol, propranolol, and timolol are established as effective for migraine prevention *(Silberstein et al 2012, Snow et al 2002)*.
- Propranolol is the only beta-blocker FDA-approved for the treatment of essential tremor. Guidelines recommend propranolol, long-acting propranolol, or primidone for limb tremor in essential tremor, depending on concurrent medical conditions and potential side effects *(Zesiewicz et al 2011)*.
- Treatment guidelines for infantile hemangioma are not available; however, consensus recommendations state that therapy must be individualized. Oral propranolol may be considered in patients with ulcerative hemangiomas, impairment of a vital function (ocular compromise or airway obstruction), or in cases with a risk of permanent disfigurement. Monitoring of infants for adverse events is required *(Drolet et al 2013)*.

SAFETY SUMMARY

- Beta-blockers have a number of contraindications related to their pharmacologic properties. They should be avoided in patients with sinus bradycardia and second- or third-degree heart block. They also should not be initiated in patients with uncontrolled heart failure or cardiogenic shock. Based on their ability to block $beta_2$ receptors in the lung, beta-blockers should generally not be used (or used with caution) in patients with asthma and/or chronic obstructive pulmonary disease. This is particularly a concern with non-selective beta-blockers. Other contraindications vary based on the specific drug and the clinical use.
- A boxed warning exists for atenolol, metoprolol (non-boxed warning for metoprolol succinate extended release capsules), nadolol, propranolol, and timolol, noting that severe exacerbation of angina and the occurrence of MI and

ventricular arrhythmias have been reported in patients with angina following the abrupt discontinuation of therapy with beta-blockers. When discontinuing a chronically administered beta-blocker, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1 to 2 weeks, and the patient should be carefully monitored. Sotalol also carries a boxed warning, noting that patients initiated or reinitiated on sotalol or sotalol AF should be placed for a minimum of 3 days (on their maintenance dose) in a facility that can provide cardiac resuscitation and continuous electrocardiographic monitoring. Creatinine clearance should be calculated prior to dosing.

- Hemangeol has specific contraindications for use in premature infants with corrected age < 5 weeks, infants weighing < 2 kg, BP < 50/30 mm Hg, and pheochromocytoma.
- Key additional warnings and precautions include:
  - Beta blockers can precipitate or aggravate symptoms of arterial insufficiency in peripheral vascular disease.
  - Patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge when taking a beta-blocker. Such patients may also be unresponsive to the usual doses of epinephrine used to treat allergic reactions.
  - Beta-blocker therapy should not be routinely withdrawn prior to major surgery; however, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.
  - Some beta-blockers may potentiate insulin-induced hypoglycemia and mask some of its manifestations (eg, tachycardia).
  - Beta-blockers should not be given to patients with untreated pheochromocytoma. In patients with this condition, a beta-blocker should be given only after an alpha-blocker has been initiated.
  - Bradycardia and/or hypotension may occur.
  - Sotalol can provoke new or worsened ventricular arrhythmias in some patients. This may include Torsades de Pointes, the risk of which increases with increasing prolongation of the QT interval. Use with particular caution if the QTc is > 500 milliseconds.
  - The value of using betaxolol in psoriatic patients should be carefully weighed since it has been reported to cause an aggravation in psoriasis.
  - Hemangeol has demonstrated an increased risk of stroke in PHACE syndrome patients with severe cerebrovascular anomalies. Infants with large facial infantile hemangioma should be investigated for potential arteriopathy associated with PHACE syndrome prior to therapy.
- Common adverse reactions (occurring in > 10% of patients for at least 1 medication) include: bradycardia, chest pain, hypotension, palpitations, dizziness, drowsiness, fatigue, headache, insomnia, lightheadedness, hyperglycemia, diarrhea, nausea, weight gain, decreased sexual ability, weakness, and dyspnea.

Combination products

- Based on the beta-blocker component, the beta-blocker/diuretic combinations are contraindicated in patients with sinus bradycardia, second-or third-degree heart block, cardiogenic shock, and overt cardiac failure.
- Based on the diuretic component, the beta-blocker/diuretic combinations are contraindicated in patients with anuria, hypersensitivity to the ingredients, or hypersensitivity to sulfonamide-derived drugs.
  - Lopressor HCT and Dutoprol are contraindicated in patients with sick sinus syndrome, which include patients with sinus bradycardia and patients with sinus pauses or arrest.
  - Lopressor HCT is contraindicated in those with severe peripheral arterial circulatory disorders.
  - Corzide and propranolol/HCTZ are contraindicated in patients with bronchial asthma.
- Boxed warning for Corzide, Dutoprol, Lopressor HCT, and propranolol/HCTZ: Do not discontinue abruptly; withdraw gradually with appropriate monitoring to avoid potential exacerbation of ischemic heart disease. This is also a warning for Tenoretic and Ziac (although not boxed).
- Avoid in overt heart failure; use with caution in patients with controlled heart failure.
- Avoid in patients with bronchospastic disease. Low doses of $beta_1$ selective agents may be used in patients with bronchospastic disease when no acceptable alternative exists.
- Dutoprol has a warning for bradycardia, particularly in patients with first-degree atrioventricular block, sinus node dysfunction, or conduction disorders. Concomitant use of beta adrenergic blockers, non-dihydropyridine calcium channel blockers, digoxin, or clonidine increases the risk. The drug also has additional warnings for acute renal failure in patients with chronic kidney disease, severe heart failure, or volume depletion when also taking HCTZ-containing drugs; and reduced effectiveness of epinephrine when treating anaphylaxis.

- Some beta-blockers may cause hypoglycemia or potentiate insulin-induced hypoglycemia and mask some of its manifestations (eg, tachycardia).
- Thyrotoxicosis: Beta blockade may mask certain clinical signs of thyrotoxicosis (eg, tachycardia). Abrupt withdrawal of beta blockade may precipitate a thyroid storm.
- Thiazides should be used with caution in severe renal disease, as they may precipitate azotemia in this setting.
- Thiazides should be used with caution in patients with impaired hepatic function because minor alterations of fluid/electrolyte balance may precipitate hepatic coma.
- Adverse reactions reported in > 5% of patients in clinical trials for Dutoprol and Lopressor HCT include bradycardia, dizziness/vertigo, drowsiness/somnolence, fatigue/lethargy, and headache.
- Adverse reaction rates for the other fixed-dose combination products (Corzide, propranolol/HCTZ, and Tenoretic) are not specifically listed in the prescribing information; however, adverse reactions are known based on experience with their components. Notable adverse reactions include heart failure, intensification of atrioventricular block, bradycardia, peripheral vascular insufficiency, heart rhythm/conduction disturbance, depression, nausea, vomiting, diarrhea, constipation, orthostatic hypotension, dizziness, fatigue, vertigo, headache, hypersensitivity, hyperglycemia, hyperuricemia, and bronchospasm.

DOSING AND ADMINISTRATION

Table 6. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single-Entity Beta-blockers				
Acebutolol	Capsules	Oral	Cardiac arrhythmias (ventricular): Twice daily Hypertension: Once to twice daily	Dosage adjustment in renal impairment is required. Older patients have an approximately 2-fold increase in bioavailability and may require lower maintenance doses; avoid doses above 800 mg.
Atenolol	Tablets	Oral	Angina pectoris: Once daily Hypertension: Once daily Acute MI: After initial IV dosing in the acute setting, 50 mg should be initiated 10 minutes after the last IV dose followed by another 50 mg oral dose 12 hours later. Thereafter, once or twice daily for a further 6 to 9 days or until discharge from the hospital.	Dosage adjustment in renal impairment is required. Atenolol can cause fetal harm when used in pregnancy. Low birth weights have been reported with use; drug is excreted in breast milk; use with caution. Neonates may be at risk for hypoglycemia and bradycardia.
Betaxolol	Tablets	Oral	Hypertension: Once daily	Dosage adjustment in renal impairment is required. Consideration should be given to reduction in the starting

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				dose to 5 mg in elderly patients.
Bisoprolol	Tablets	Oral	Hypertension: Once daily	Dosage adjustment in renal and hepatic impairment is required.
Carvedilol	ER capsules, tablets	Oral	Heart failure: ER capsule: Once daily Tablet: Twice daily Hypertension: ER capsule: Once daily Tablet: Twice daily Left ventricular dysfunction following MI: ER capsule: Once daily Tablet: Twice daily	Patients controlled with immediate release (IR) tablets may be switched to ER capsules (see prescribing information for details). When switching from the higher doses of IR carvedilol to ER, a lower starting dose is recommended for the elderly. Contraindicated in severe hepatic dysfunction. ER capsule: Take once daily in the morning with food. Should be swallowed as a whole capsule or may alternatively be opened, and the beads sprinkled over a spoonful of applesauce. Tablet: Take with food.
Labetalol	Tablets	Oral	Hypertension: Twice daily	Dose adjustment is required in the elderly. Use with caution in hepatic dysfunction; metabolism of the drug may be diminished.
Metoprolol	ER tablets (succinate), ER capsules (succinate)§, tablets (tartrate)	Oral	Angina pectoris: ER tablet or ER capsule: Once daily Tablet: Daily in 2 divided doses Heart failure: ER tablet (NYHA Class II): Once daily [start with 25 mg/day] ER tablet (severe heart failure): Once daily [start with 12.5 mg/day]	A hepatic dosage adjustment may be necessary; initiate at low doses with cautious gradual titration. ER tablet or ER capsule: Dosing recommendations are available for pediatric hypertensive patients ≥ 6 years of age; product is not recommended in patients < 6 years. ER tablet: Take with or immediately after meals. ER

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			ER capsule: once daily [start with 25 mg/day] Hypertension: ER tablet or ER capsule: Once daily Tablet: Daily in single or divided doses MI: Tablet: After initial IV dosing in the acute setting, initiate tablets at 50 mg every 6 hours 15 minutes after the last IV dose and continue for 48 hours; thereafter, the maintenance dose is 100 mg twice daily	tablets are scored and can be divided, but not crushed or chewed. ER capsule: swallow whole or sprinkle capsule contents over soft food; mix contents with water for nasogastric tube administration ER capsule: 1 to 1 dose conversion with ER tablet Tablet: Take with or immediately after meals. Do not chew.
Nadolol	Tablets	Oral	Angina pectoris: Once daily Hypertension: Once daily	Dosage adjustment in renal impairment is required.
Nebivolol	Tablets	Oral	Hypertension: Once daily	Dosage adjustment in renal and hepatic impairment is required.
Pindolol	Tablets	Oral	Hypertension: Twice daily	Poor hepatic function may cause blood levels to increase substantially; use with caution.
Propranolol	ER capsules (Inderal LA), ER beads capsules (Inderal XL, Innopran XL), oral solution (Hemangeol), oral solution (generic), tablets (generic)	Oral	Angina pectoris: ER capsule (Inderal LA): Once daily Oral solution, tablet: Daily in 2, 3 or 4 divided doses Cardiac arrhythmias (atrial fibrillation): Oral solution, tablet: Three to 4 times daily before meals and at bedtime Essential tremor: Oral solution, tablet: Twice daily Hypertension:	Propranolol is not indicated for the treatment of hypertensive emergencies. With propranolol, hepatic insufficiency increases plasma concentration and prolongs the half-life; use with caution. Hemangeol is not intended for pregnant or nursing women. Hemangeol should be initiated at ages 5 weeks to 5 months. Administer doses at least 9 hours apart and during or after feeding. Monitor heart rate and BP for 2 hours after first dose or increasing dose. Of 460 infants (aged 5 weeks to 5

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			ER capsules (all): Once daily Oral solution, tablet: Twice daily; if control is not adequate, a larger dose, or 3 times daily therapy may achieve better control Hypertrophic subaortic stenosis: Oral solution, tablet: Three to 4 times daily before meals and at bedtime ER capsule (Inderal LA): Once daily Infantile hemangioma: Oral solution (Hemangeol): Twice daily Migraine prophylaxis: Oral solution, tablet: Daily in divided doses ER capsule (Inderal LA): Once daily MI: Oral solution, tablet: Twice or 3 times daily Pheochromocytoma: Oral solution, tablet (operable tumors): Daily in divided doses for 3 days preoperatively as adjunct to alpha-adrenergic blockade Oral solution, tablet (inoperable tumors): Daily in divided doses as adjunct to alpha-adrenergic blockade	months), 60% had complete or near complete resolution of hemangioma at week 24. Inderal XL and Innopran XL should be administered once daily at bedtime and should be taken consistently either on an empty stomach or with food.
Sotalol	Tablets (Betapace, Betapace AF, Sorine), Oral solution (Sotylize)	Oral	Cardiac arrhythmias (maintenance of normal sinus rhythm in patients	Pediatric dosing is available for the treatment of cardiac arrhythmias (ventricular and

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			with symptomatic atrial fibrillation/atrial flutter): Tablet (Betapace, Betapace AF, Sorine): Twice daily Oral solution (Sotylize): Once or twice daily based on renal function Cardiac arrhythmias (ventricular): Tablet (Betapace, Betapace AF, Sorine): Twice daily Oral solution (Sotylize): Once or twice daily based on renal function	symptomatic atrial fibrillation/ atrial flutter). Dosage adjustment in renal impairment is required. For treatment of atrial fibrillation or flutter, use is contraindicated if creatinine clearance is < 40 mL/min. See the Betapace prescribing information for instructions on compounding an oral solution from the tablets.
Timolol	Tablets	Oral	Hypertension: Twice daily Migraine prophylaxis: Twice daily MI: Twice daily	During maintenance therapy for migraine prophylaxis, doses of 10 mg or 20 mg may be given once daily. Dosage reductions may be necessary in kidney and hepatic dysfunction as timolol is substantially excreted by the kidney (ie, risk of toxic reactions may be increased) and is partially metabolized in the liver.
Beta-blocker/Diuretic Combinations				
Corzide (nadolol/ bendroflumethiazide)	Tablets	Oral	Once daily	Dosage adjustment in renal impairment is required.
Dutoprol (metoprolol succinate extended release/ HCTZ)	Tablets	Oral	Once daily	Safety and effectiveness in severe renal impairment (creatinine clearance < 30 mL/min) have not been established; no dose adjustment necessary in patients with moderate renal impairment. Minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Lopressor HCT (metoprolol tartrate/ HCTZ)	Tablets	Oral	Daily in single or divided doses	While once-daily dosing is effective and can maintain a reduction in BP throughout the day, lower doses may not maintain a full effect at the end of the 24-hour period; larger or more frequent doses may be required. Should be taken with or immediately following meals.
propranolol/ HCTZ	Tablets	Oral	Twice daily	Use with caution in severe renal disease.
Tenoretic (atenolol/ chlorthalidone)	Tablets	Oral	Once daily	Dosage adjustment in renal impairment is required. Atenolol can cause fetal harm when used in pregnancy and thiazide diuretics have caused adverse reactions for the fetus in pregnancy; use in pregnancy only if clearly needed. Excreted in breast milk; use with caution. Clinically significant bradycardia and hypoglycemia in nursing infants has been reported.
Ziac (bisoprolol/ HCTZ)	Tablets	Oral	Once daily	Use with caution when dosing/titrating patients with renal and hepatic impairment; discontinue use with progressive renal impairment.

§Not yet launched.
NYHA = New York Heart Association

See the current prescribing information for full details

CONCLUSION

- Beta-blockers are a group of drugs that block the effects of catecholamines on beta receptors.
- Beta-blockers have a range of FDA-approved indications as the agents within the class differ in pharmacologic and pharmacokinetic properties. Such differences may include adrenergic-receptor blocking activity, ISA, and lipophilicity.
- There are several national and international evidence-based antihypertensive guidelines that provide recommendations regarding the use of beta-blockers. All of the agents within the class, with the exception of sotalol, are FDA-approved for the treatment of hypertension. Most guidelines recommend that the selection of an antihypertensive agent be based on compelling indications for use; the 2017 ACC/AHA guideline for the prevention, detection, evaluation, and management of high BP in adults recommends the use of beta-blockers as secondary agents after thiazide diuretics, ACE inhibitors, ARBs, and CCBs *(Whelton et al 2017)*.

- The choice of a beta-blocker for a specific patient will depend on several factors. In addition to considering the clinical trial data and FDA-approved indications, patient diagnoses and comorbidities should be considered when selecting a product; for example:
  - Beta-blockers are best avoided in patients with asthma and chronic obstructive pulmonary disease; however if no suitable alternatives exist, a beta$_1$-selective agent is preferred.
  - For patients with heart failure, bisoprolol, carvedilol, or sustained release metoprolol should be considered as these have demonstrated a reduction in mortality; although some guidelines recommend nebivolol as an option in certain heart failure patients *(Ponikowski et al 2016, Rosendorff et al 2015)*.
  - For patients with hepatic or renal disease, drugs that are not hepatically or renally eliminated, respectively, are preferred.
  - For patients receiving concomitant therapy with a CYP2D6 inhibitor, beta-blockers that are not CYP2D6 substrates are preferred *(Clinical Pharmacology 2018)*.
  - For patients with hypertension and acute coronary syndrome, initial therapy should include a short-acting beta$_1$-selective beta blocker without ISA (metoprolol tartrate or bisoprolol) *(Rosendorff et al 2015)*.
- Most beta-blockers are available generically, including those that are recognized as effective for providing a mortality benefit in patients with heart failure *(Drugs@FDA 2018, Yancy et al 2013, Yancy et al 2017)*. Available generic products will provide ample options for the majority of patients and clinical situations.
- The beta blocker/diuretic combination products are FDA-approved for the treatment of hypertension and are well-established for this indication.
- The beta blocker/diuretic combinations are more effective compared to placebo and compared to the individual components given alone. There are currently no head-to-head trials comparing the various combination products to one another or any trials to demonstrate differences in clinical outcomes when the drug components are administered as separate agents concurrently versus the fixed-dose combination products.
- Many patients with hypertension require more than 1 antihypertensive medication to achieve BP goals. Little guidance on the use of fixed-dose combination products is available within treatment guidelines; however, they are recognized as having the ability to simplify treatment regimens and to improve adherence *(Mancia et al 2013)*.
- Hypertension guidelines recommend combination therapy as a treatment option in patients who have BP that is not at goal *(James et al 2014, Mancia et al 2013, Weber et al 2014)*.
- Most guidelines agree that beta-blockers are of particular value for hypertensive patients with certain co-morbid diseases, such as heart failure, post-MI, angina pectoris, coronary artery disease, and ventricular dysfunction *(Go et al 2014, Mancia et al 2013, Rosendorff et al 2015, Weber et al 2014)*. Other guidelines recommend beta-blockers for atrial fibrillation and diabetes *(Go et al 2014, Mancia et al 2013)*. Diuretics also offer benefits in terms of diseases associated with edema, such as heart failure *(Go et al 2014, Mancia et al 2013, Weber et al 2014)*. However, caution should be exercised as some guidelines do not recommend the use of beta-blockers in combination with a diuretic in patients at risk for diabetes as they have adverse effects associated with glucose metabolism *(Weber et al 2014)*.

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Publication Date: June 4, 2018

Therapeutic Class Overview
Statins (HMG-CoA Reductase Inhibitors)

INTRODUCTION

- The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (also known as statins) include single entity agents (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin), as well as fixed-dose combination products (amlodipine/atorvastatin, ezetimibe/atorvastatin, and ezetimibe/simvastatin). The statins work by inhibiting HMG-CoA reductase, which is the rate-limiting enzyme involved in hepatic cholesterol synthesis. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is a cholesterol precursor. Inhibition of HMG-CoA reductase decreases hepatic cholesterol synthesis, causing up-regulation of low-density lipoprotein cholesterol (LDL-C) receptors. Statins also decrease the release of lipoproteins from the liver.
- The statins are the most effective class of oral drugs to lower LDL-C. Depending on the agent selected, moderate-intensity statins can decrease LDL-C by 30 to 49% and high-intensity statins can decrease LDL-C levels ≥ 50%. The effects on LDL-C are dose-dependent and log-linear. Statins also decrease triglycerides (TG) and increase high-density lipoprotein cholesterol (HDL-C) by varying levels (Stone et al, 2014).
- Ezetimibe inhibits the intestinal absorption of cholesterol, which decreases the delivery of cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood.
- Amlodipine is a calcium channel blocker that is approved for the treatment of hypertension (HTN), chronic stable angina and vasospastic angina, as well as to reduce the risks of hospitalization or revascularization in patients with angiographically confirmed coronary artery disease (CAD).
- Statins that are included in this review are listed in Table 1. All products are now available in a generic formulation except for ALTOPREV® (lovastatin extended-release tablet), FLOLIPID (simvastatin oral suspension), LIVALO (pitavastatin tablet), and ZYPITAMAG (pravastatin tablet) (Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2018).
- The combinations niacin/lovastatin (ADVICOR®) and niacin/simvastatin (SIMCOR®) were removed from the market because the Food and Drug Administration (FDA) determined that a reduction in TG and increase in HDL-C do not contribute to decreased cardiovascular events according to the newest evidence (AbbVie, 2016).
- The agents included in this review are listed in Table 1 by brand name. Since there are some branded agents that contain the same generic component, the remaining tables in the review are organized by generic name.

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
ALTOPREV (lovastatin extended-release)	Covis Pharma	06/26/2002	-
CRESTOR (rosuvastatin)	AstraZeneca Pharmaceuticals	08/12/2003	✔
FLOLIPID (simvastatin oral suspension)	Salerno Pharmaceuticals LP	04/21/2016	-
LESCOL (fluvastatin)*	Novartis	12/31/1993	✔
LESCOL XL (fluvastatin extended-release)	Novartis	10/06/2000	✔
LIPITOR (atorvastatin)	Pfizer	12/17/1996	✔
LIVALO, ZYPITAMAG (pitavastatin)€	Kowa Company (LIVALO) Medicure (ZYPITAMAG)	08/03/2009	-
MEVACOR (lovastatin)*	Merck & Co., Inc	08/31/1987	✔

Drug	Manufacturer	FDA Approval Date	Generic Availability
PRAVACHOL (pravastatin)	Bristol Myers Squibb Company	10/31/1991	✔
ZOCOR (simvastatin)	Merck & Co., Inc.	12/31/1991	✔
CADUET (amlodipine/ atorvastatin)	Pfizer	01/30/2004	✔
LIPTRUZET† (ezetimibe/atorvastatin)	Watson Labs Teva	04/26/2017	✔
VYTORIN® (ezetimibe/simvastatin)	Merck & Co., Inc.	07/23/2004	✔

*The brands, LESCOL and MEVACOR, have been discontinued, but the generic formulations are available.
€The brand NIKITA was discontinued.
†The brand, LIPTRUZET, by Merck was discontinued in 2015. A generic formulation by Watson Labs Teva was recently approved by the FDA, however, current market availability is unknown.

(Drugs@FDA, 2018; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2018)

INDICATIONS

Table 2. FDA-approved indications

Indications	Single-Entity Agents							Combination Products		
	atorvastatin	fluvastatin	lovastatin	pitavastatin	pravastatin	rosuvastatin	simvastatin	amlodipine/ atorvastatin	ezetimibe/ atorvastatin	ezetimibe/ simvastatin
Hypertriglyceridemia										
Reduce elevated TG in patients with hypertriglyceridemia							✔			
Treatment of adult patients with hypertriglyceridemia in combination with diet	✔				✔	✔		✔ (atorvastatin)		
Primary Hypercholesterolemia and Mixed Dyslipidemia										
Reduce elevated total cholesterol (TC), LDL-C, apolipoprotein B (apo B), and TG and to increase HDL-C in patients with primary hyperlipidemia or hypercholesterolemia and mixed dyslipidemia	✔	✔	✔ § (ER)	✔	✔	✔	✔	✔ (atorvastatin)	✔	✔
Reduce TC, LDL-C, and apo B levels in children with heterozygous familial hypercholesterolemia (HeFH) if after an adequate trial of diet therapy the following findings are present: LDL-C remains ≥189 (lovastatin only) or 190 mg/dL OR LDL-C remains ≥160 mg/dL and there is a positive family history of premature cardiovascular disease (CVD) or two or more other cardiovascular risk factors are present in the pediatric patient	✔ ¶	✔ #	✔ ** (IR)		✔ ††	✔ ††	✔ **	✔ (atorvastatin)		
Reduce elevated TG and very high LDL-C in patients with primary dysbetalipoproteinemia							✔			
Reduce TC and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH) as an adjunct to other lipid-lowering treatments or if such treatments are unavailable	✔						✔	✔ (atorvastatin)	✔	✔
Reduce TC, LDL-C, and apo B in adults with HoFH						✔				
Reduce LDL-C, TC, non HDL-C and apo B in children and adolescents with HoFH, as monotherapy or with other lipid-lowering therapies						✔ ~~A~~				
Reduction of elevated TC and LDL-C levels in patients with primary hypercholesterolemia			✔ § (IR)							

Treatment of patients with primary dysbetalipoproteinemia who do not respond adequately to diet	✔				✔	✔		✔ (atorvastatin)		
Prevention of CVD										
Adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower TC and LDL-C to target levels						✔				
Reduce the risk of myocardial infarction (MI) and stroke in patients with type 2 diabetes, and without clinically evident coronary heart disease (CHD), but with multiple risk factors for CHD such as retinopathy, albuminuria, smoking, or HTN	✔							✔ (atorvastatin)		
Reduce the risk of MI, stroke, revascularization procedures, and angina in adult patients without clinically evident CHD, but with multiple risk factors for CHD such as age, smoking, HTN, low HDL-C, or a family history of early CHD	✔							✔ (atorvastatin)		
Reduce the risk of MI, undergoing myocardial revascularization procedures, and cardiovascular mortality with no increase in death from noncardiovascular causes in patients with hypercholesterolemia without clinically evident CHD					✔					
Reduce the risk of MI, unstable angina, and coronary revascularization procedures in patients without symptomatic CVD			✔ ɣ							
Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for congestive heart failure, and angina in patients with clinically evident CHD	✔							✔ (atorvastatin)		
Reduce the risk of stroke, MI, and arterial revascularization procedures in patients without clinically evident CHD but with an increased risk of CVD based on age ≥50 years old in men and ≥60 years old in women, high sensitivity C-reactive protein ≥2 mg/L, and the presence of at least one additional CVD risk factor such as HTN, low HDL-C, smoking, or a family history of premature CHD						✔				
Reduce the risk of total mortality by reducing coronary death, MI, undergoing myocardial revascularization procedures, stroke and stroke/transient ischemic attack, and to slow the progression of coronary atherosclerosis in patients with clinically evident CHD					✔					
Reduce the risk of total mortality by reducing CHD deaths, non-fatal MI and stroke, and need for coronary and non-coronary							✔			

revascularization procedures in patients at high risk of coronary events because of existing CHD, diabetes, peripheral vascular disease, history of stroke or other cerebrovascular disease										
Reduce the risk of undergoing coronary revascularization procedures and slow the progression of coronary atherosclerosis in patients with clinically evident CHD		✔								
Slow the progression of coronary atherosclerosis in patients with CHD as part of a treatment strategy to lower TC and LDL-C to target levels			✔							
Other										
Reduce the risk of hospitalization for angina and to reduce the risk of a coronary revascularization procedure in patients with recently documented CAD by angiography and without heart failure or an ejection fraction <40%								✔ (amlodipine)		
Symptomatic treatment of chronic stable angina								✔ (amlodipine)		
Treatment of confirmed or suspected vasospastic angina								✔ (amlodipine)		
Treatment of HTN, to lower blood pressure								✔ (amlodipine)		

Abbrv: CAD=coronary artery disease, CHD=coronary heart disease, ER=extended-release, IR=immediate-release, HTN=hypertension, MI=myocardial infarction.
§When the response to diet restricted in saturated fat and cholesterol and to other nonpharmacological measures alone has been inadequate.
¶In boys and postmenarchal girls 10 to 17 years of age.
#In adolescent boys and adolescents girls who are at least one year post-menarche, 10 to 16 years of age.
**In adolescent boys and girls who are at least one year post-menarche, 10 to 17 years of age.
††In children and adolescent patients eight to 17 years of age
ǂIn children and adolescents ages seven to 17 years of age
ɣFor ER lovastatin, for patients at high risk; for IR lovastatin, for patients with average to moderately elevated TC and LDL-C and below average HDL-C

(Prescribing information: ALTOPREV®, 2018; CADUET®, 2017; CRESTOR®, 2017; FLOLIPID, 2017; Fluvastatin, 2017; LESCOL XL®, 2017; LIPITOR®, 2017; LIVALO®, 2016 Lovastatin 2017; PRAVACHOL®, 2017; VYTORIN®, 2018; ZOCOR®, 2018, ZYPITAMAG, 2018)
Clinical Pharmacology, 2018

Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Numerous clinical trials have demonstrated that the statins (single-entity and combination products) can effectively lower LDL-C, non-HDL-C, total cholesterol (TC), and TG, as well as positively impact other lipid/lipoprotein parameters. Additionally, many studies have compared active treatment to placebo or compared combination therapy to monotherapy. In these studies, the more aggressive treatment regimens often improved lipid parameters to a greater extent than the less-intensive treatment regimens (Ai et al, 2008; Alvarez-Sala et al, 2008; Arca et al, 2007; Avis et al, 2007; Avis et al, 2010; Ballantyne et al, 2003; Ballantyne et al, 2004; Ballantyne et al, 2005; Ballantyne et al, 2006; Ballantyne et al, 2007; Ballantyne et al, 2008; Bardini et al, 2010; Bays et al, 2004; Bays et al, 2010; Bays et al, 2013; Bays et al, 2008a; Bays et al, 2008b; Becker et al, 2008; Betteridge et al, 2007a; Betteridge et al, 2007b; Braamskamp et al, 2015; Brown et al, 1990; Bullano et al, 2006; Bullano et al, 2007; Calza et al, 2008; Catapano et al, 2006; Charland et al, 2010; Chenot et al, 2007; Clearfield et al, 2006; Coll et al, 2006; Conard et al, 2008; Constance et al, 2007; Davidson et al, 2002; Deedwania et al, 2007a; Derosa et al, 2009; Erdine et al, 2009; Eriksson et al, 1998; Eriksson et al, 2011; Faergeman et al, 2008; Farnier et al, 2007; Farnier et al, 2008; Farnier et al, 2009; Feldman et al, 2004; Feldman et al, 2006; Ferdinand et al, 2006; Ferdinand et al, 2012; Flack et al, 2008; Florentin et al, 2011; Foody et al, 2010; Fox et al, 2007a; Fox et al, 2007b; Gagné et al, 2002; Gaudiani et al, 2005; Goldberg et al, 2004; Goldberg et al, 2006; Goldberg et al, 2009; Grimm et al, 2010; Gumprecht et al, 2011; Hall et al, 2009; Harley et al, 2007; Hing Ling et al, 2012; Hobbs et al, 2009; Hogue et al, 2008; Hunninghake et al, 2001; Illingworth et al,1994; Insull et al, 2007; Jones et al, 2003; Jones et al, 2009a; Jones et al, 2009b; Kerzner et al, 2003; Kipnes et al, 2010; Knapp et al, 2001; Koshiyama et al, 2008; Kumar et al, 2009; Lee et al, 2007; Leiter et al, 2007; Leiter et al, 2008; Lewis et al, 2007; Lloret et al, 2006; Marais et al, 2008; May et al, 2008; Mazza et al, 2008; Melani et al, 2003; Meredith et al, 2007; Messerli et al, 2006; Milionis et al, 2006; Mohiuddin et al, 2009; Motomura et al, 2009; Neutel et al, 2009; Nicholls et al, 2010; Ose et al, 2007; Ose et al, 2009; Ose et al, 2010; Park et al, 2005; Park et al, 2010; Pearson et al, 2007; Piorkowski et al, 2007; Polis et al, 2009; Preston et al, 2007; Reckless et al, 2008; Robinson et al, 2009; Rodenburg et al, 2007; Roeters van Lennep et al, 2008; Rogers et al, 2007; Rosenson et al, 2009; Rotella et al, 2010; Roth et al, 2010; Saito et al, 2002; Sansanayudh et al, 2010; Sasaki et al, 2008; Shafiq et al, 2007; Stalenhoef et al, 2005; Stein et al, 2003; Stein et al, 2004; Stein et al, 2007; Stein et al, 2008; Viigimaa et al, 2010; Vuorio et al, 2014; Winkler et al, 2007; Winkler et al, 2009; Wlodarczyk et al, 2008; Wolffenbuttel et al, 2005; Yoshitomi et al, 2006; Zieve et al, 2010).
- All of the statins, with the exception of pitavastatin, have been shown to have beneficial effects on CHD outcomes, and the majority of them (atorvastatin, pravastatin, rosuvastatin, and simvastatin) have also been shown to decrease the risk of stroke (Afilalo et al, 2007; Afilalo et al, 2008; Ahmed et al, 2006; Amarenco et al, 2009a; Amarenco et al, 2009b; Asselbergs et al, 2004; Athyros et al, 2002; Athyros et al, 2007; Baigent et al, 2005; Barter et al, 2007; Briel et al, 2006; Bushnell et al, 2006; Byington et al; 1995; Cannon et al, 2004; Cannon et al, 2006; Cannon et al, 2015; Chan et al, 2010; Cholesterol Treatment Trialists' (CTT) Collaborators, 2008; Chonchol et al, 2007; Colhoun et al, 2004; Collins et al, 2003; Crouse et al, 2007; de Lemos et al, 2004; Deedwania et al, 2006; Deedwania et al, 2007b; Downs et al, 1998; Everett et al, 2010; Ford et al, 2007; Furberg et al, 1994; Hitman et al, 2007; Hulten et al, 2006; Khush et al, 2007; Knopp et al, 2006; Koenig et al, 2001; Koga et al, 2018; LaRosa et al, 2005; LaRosa et al, 2007; Liem et al, 2002; Meaney et al, 2009; Mood et al, 2007; Mora et al, 2010; Murphy et al, 2007; Nakamura et al, 2006; Neil et al, 2006; Nicholls et al, 2006; Nissen et al, 2004; Nissen et al, 2005; Nissen et al, 2006; No authors listed, 1994; No authors listed, 2002; No authors listed, 2007; Olsson et al, 2007; O'Regan et al, 2008; Pedersen et al, 2005; Pitt et al, 1999; Pitt et al, 2012; Ray et al, 2005; Ray et al, 2006; Ridker et al, 2008; Ridker et al, 2009; Ridker et al, 2010; Rossebø et al, 2008; Sacks et al,1996; Sakamoto et al, 2007; Sato et al, 2008; Schmermund et al, 2006; Schoenhagen et al, 2006; Schouten et al, 2009; Schwartz et al, 2005; Scirica et al, 2006; Serruys et al, 2002; Sever et al, 2003; Sever et al, 2005; Shah et al, 2008; Shepherd et al, 1995; Shepherd et al, 2007; Shepherd et al, 2006; Shepherd J et al, 2002; Strandberg et al, 2009; Tavazzi L et al, 2008; Taylor et al, 2013; The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002; The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group, 1998; The Pravastatin Multinational Study Group for Cardiac Risk Patients (PMS-CRP), 1993; Thompson et al, 2004; Tikkanen et al, 2009; Waters et al, 2006; Wenger et al, 2007; Yu et al, 2007).
- Two early primary prevention trials (West of Scotland Coronary Prevention Study [WOSCOPS] and Air Force/Texas Coronary Atherosclerosis Prevention Study [AFCAPS/TexCAPS) demonstrated that the use of statins significantly reduced the risk for major coronary events (Downs et al, 1998; Shepard et al, 1995).
- Specifically, the WOSCOPS trial (N=6959) demonstrated that compared to placebo, pravastatin (40 mg/day) was associated with a significant 31% reduction in the risk of the combined endpoint of CHD death and nonfatal MI (P<0.001). A reduction in the secondary endpoint of cardiovascular death was also significant in favor of pravastatin

(32%; P=0.033) (Shepard et al, 1995). Results of a 20-year observational follow-up of this trial continued to show beneficial effects of pravastatin on reduction of CHD. Among those with and without LDL-C ≥190 mg/dL (N=5529), pravastatin reduced the risk of CHD by 27% (*P*=0.002) and MACE by 25% (*P*=0.004). Among individuals with LDL-C ≥190 mg/dL (N=2560), pravastatin reduced the risk of CHD-related death, cardiovascular death, and all-cause mortality by 28% (*P*=0.020), 25% (*P*=0.009), and 18% (*P*=0.004), respectively (Vallejo-Vaz et al, 2017).

- The AFCAPS/TexCAPs trial (N=6,605) demonstrated similar benefits but with lovastatin (20 to 40 mg/day). In this trial, lovastatin was associated with a significant 37% reduction in the risk of the combined endpoint of fatal or nonfatal MI, unstable angina or sudden cardiac death (P<0.001). The AFCAPS/TexCAPs trial contained too few events to perform survival analysis on cardiovascular and CHD mortality (Downs et al, 1998).
- The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT, N=10,305) was terminated early (median duration, 3.3 years) due to the significant benefits observed with atorvastatin. In this trial, patients had average cholesterol concentrations but were at an increased risk for CHD due to the presence of HTN and three additional CHD risk factors. Compared to placebo, atorvastatin significantly reduced the risk of the combined endpoint of CHD death and nonfatal MI by 35% (P=0.0005) (Sever et al, 2003).
- Despite not demonstrating any benefit on all-cause mortality within the ASCOT trial (P=0.1649), atorvastatin has been associated with significant reductions in all-cause mortality in other primary prevention trials (Colhoun et al, 2004; Sever et al, 2003; Sever et al, 2005).
- A benefit in all-cause mortality, as well as other cardiovascular outcomes, with rosuvastatin in primary prevention was demonstrated in the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial (N=17,802). This trial sought to evaluate the efficacy of rosuvastatin in reducing cardiac events in patients with elevated high sensitivity C-reactive protein levels, which they note as being a predictor for cardiac events. This trial was terminated early (median duration 1.9 years) due to the significant benefits observed with rosuvastatin. Compared to placebo, rosuvastatin significantly reduced the risk of a first major cardiovascular event (nonfatal MI, nonfatal stroke, hospitalization for unstable angina, revascularization procedure or cardiovascular death) by 44% (P<0.0001). When analyzed individually, rosuvastatin was associated with a significant benefit for all primary outcomes, as well as all-cause mortality (P=0.02) (Ridker et al, 2008).
- Meta-analyses support the findings observed in the individual primary prevention trials (Adams et al, 2018; Baigent et al, 2005; CTT Collaborators et al, 2008; Mora et al, 2010; O'Regan et al, 2008; Taylor et al, 2011, Nunes et al, 2017).
- The Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL) trial (N=8,888) compared intensive lipid lowering therapy with atorvastatin 80 mg/day to moderate therapy with simvastatin 20 mg/day (with the potential to increase to 40 mg/day based on improvements in lipid profile). In this trial, atorvastatin did not significantly reduce the risk of the primary composite endpoint of CHD death, nonfatal MI, or cardiac arrest with resuscitation (hazard ratio [HR], 0.89; 95% confidence interval [CI], 0.78 to 1.01; P=0.07). Atorvastatin was associated with a significant reduction in the risk of major cardiovascular events compared to simvastatin (12.0 vs 13.7%; HR, 0.87; P=0.02). Atorvastatin was associated with a significant reduction in the risk of any CHD event compared to simvastatin (20.2 vs 23.8%; HR, 0.84; P<0.001) and for the risk of any cardiovascular events compared to simvastatin (26.5 vs 30.8%; HR, 0.84; P<0.001). For the individual events, atorvastatin had a lower rate of nonfatal acute MI than simvastatin (7.2% vs. 6.0%; HR, 0.83; 95% CI, 0.71 to 0.98; P=0.02), but the treatments were no different in terms of all-cause (P=0.81) or noncardiovascular (P=0.47) mortality. In addition, intensive therapy with atorvastatin 80 mg/day was associated with a significantly higher incidence of discontinuations due to adverse events (P<0.001) (Pedersen et al, 2005). A total of 94 patients (2.2%) receiving atorvastatin and 135 patients (3.2%) receiving simvastatin developed peripheral arterial disease (HR, 0.7; 95% CI, 0.53 to 0.91; P=0.007) (Stoekenbroek et al, 2015).
- Several trials have demonstrated that statins are effective in delaying the progression of atherosclerotic disease in patients with CHD. Included in these is the head-to-head REVERSAL trial that demonstrated that intensive lipid lowering with atorvastatin 80 mg/day was associated with a significantly lower median percentage change in atheroma volume compared to moderate lipid lowering with pravastatin 40 mg/day after 18 months (P=0.02) (Byington et al, 1995; Chan et al, 2010; Crouse et al, 2007; Furberg et al, 1994; Karlson et al, 2018; Nicholls et al, 2006; Nissen et al, 2004; Nissen et al, 2005; Nissen et al, 2006; Schmermund et al, 2006; Schoenhagen et al, 2006). A meta-analysis comparing the efficacy and safety of atorvastatin and pitavastatin on the regression of atherosclerosis did not find a statistically significant difference between these agents when evaluating changes in plaque volume, lumen volume, and external elastic membrane. However, atorvastatin was potentially more effective than pitavastatin at reducing LDL-C and improving HDL-C (Liu et al, 2018).

- The majority of secondary prevention trials have evaluated the use of statins initiated three to six months after an acute cardiac event; however, evidence supports the use of these agents initiated right after an acute event (Briel et al, 2006; Cannon et al, 2004; de Lemos et al, 2004; Liem et al, 2002).
- The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial (N=3,086), a placebo-controlled trial with atorvastatin, is noteworthy as it demonstrated that when initiated in the hospital following an acute coronary syndrome (ACS), atorvastatin was safe and associated with a 16% reduction in the composite of death, nonfatal acute MI, resuscitated cardiac arrest, or recurrent symptomatic myocardial ischemia after 16 weeks (P=0.048) (Schwartz et al, 2005). However, a 2018 RCT that included 4191 patients with ACS and planned PCI found that 2 loading doses of atorvastatin 80 mg before and 24-hours after surgery did not reduce the rate of MACE at 30 days when compared to placebo (absolute difference, 0.85%; 95% CI, -0.70% to 2.41%; hazard ratio, 0.88; 95% CI, 0.69-1.11; P=0.27) (Berwanger et al, 2018).
- The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) investigated the efficacy of the addition of ezetimibe to simvastatin for the prevention of stroke and other adverse cardiovascular events in 18,144 patients. After 7 years, the combination of ezetimibe and simvastatin significantly reduced the risk of stroke of any etiology (HR, 0.83; 95% CI, 0.70-0.98; P=0.029) and ischemic stroke (HR, 0.76; 95% CI, 0.63-0.91; P=0.003) when compared to simvastatin monotherapy. Significant benefits were also observed in the subgroup of patients with prior stroke (Bohula et al, 2017).
- Of the head-to-head trials, the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial (N=4,162) again compared intensive lipid therapy with atorvastatin 80 mg/day to standard therapy with pravastatin 40 mg/day (with a potential to increase to 80 mg/day based on improvements in lipid profile). Patients who were hospitalized with an ACS within the preceding 10 days were enrolled. After two years, atorvastatin significantly reduced the combined endpoint of all-cause mortality, MI, unstable angina requiring hospitalization, coronary revascularization performed >30 days after randomization, and stroke by 16% compared to pravastatin (P=0.005). Among the individual endpoints, atorvastatin was significant for reducing the risk of revascularization (P=0.04) and unstable angina (P=0.02). In this trial, discontinuations due to adverse events were similar between the two treatments (P=0.11) (Cannon et al, 2004).
- A meta-analysis which assessed the efficacy of high dose atorvastatin in patients who underwent percutaneous coronary intervention (PCI) (N=2,850) found that atorvastatin significantly reduced the risk of MI in patients with PCI compared to placebo (RR, 0.62; 95% CI, 0.49 to 0.78) (Lu et al, 2017).
- A meta-analysis evaluated the efficacy and safety of dosing statins on alternative days (N=505) compared to daily dosing (N=518). Although there was no differences on TG, the reduction in TC (P<0.00001) and LDL-C (P=0.003) was significantly greater in the daily dosing group (Awad et al, 2017).
- A Cochrane review assessed the effectiveness of statins in children aged 4 to 18 years with HeFH and found that statin treatment is effective. Statin therapy was found to be safe with no significant safety issues in the short-term (Vuorio et al, 2017).

SAFETY SUMMARY

- Statins are contraindicated in documented hypersensitivity to the agent, unexplained elevations in serum transaminases, active liver disease, and patients who are pregnant or nursing.
- The statins are generally well-tolerated, and the most common side effects are gastrointestinal disturbances, headache, insomnia, myalgia, and rash. Muscle aches and weakness are reported by 1 to 2% of patients taking statins. The symptoms are usually mild and generally do not lead to discontinuation, however, myopathy can sometimes take the form of rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria. Rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. All statins can increase hepatic transaminase levels and creatinine kinase.
- Increases in hemoglobin A1c (HbA1c) and fasting serum glucose have been reported with statins. New-onset diabetes is increased in patients treated with statins; however, it is dose-related, occurs primarily in patients on metformin and a sulfonylurea, appears to be less common with pravastatin and possibly pitavastatin, and occurs overall to a lesser extent than the associated decrease in atherosclerotic cardiovascular disease (ASCVD) (Jellinger et al, 2017).
- Pravastatin is the only statin that does not undergo cytochrome (CYP) 450 metabolism, and is therefore associated with a lower risk for drug interactions. Atorvastatin (to a lesser extent), lovastatin, and simvastatin are primarily metabolized by the CYP3A4 isoenzyme, while fluvastatin, pitavastatin, and rosuvastatin are metabolized by the CYP2C9 isoenzyme, which may result in differences in their drug interaction profiles (Wiggins et al, 2016).

- The 2016 scientific statement written by the American Heart Association (AHA) stated that the risk for interactions between statins and other cardiovascular drugs may be unavoidable for heart patients, but it can be reduced with proper clinical management. A review of all of the medications that statin-treated patients are taking should be done at each patient visit, so that potential drug interactions can be identified early. Some key recommendations include:
    - Concomitant use of lovastatin, pravastatin, or simvastatin with gemfibrozil should be avoided. When gemfibrozil is used with other statins, a lower statin dose should be utilized.
    - A non-CYP3A4-metabolized statin should be used in combination with verapamil and diltiazem (calcium channel blockers). The dose of lovastatin or simvastatin should be limited to 20 mg daily or less when given with the calcium channel blocker amlodipine.
    - The concomitant use of cyclosporine, everolimus, sirolimus, or tacrolimus should be avoided with lovastatin, simvastatin, and pitavastatin, as the combination could be potentially harmful.
    - Numerous other drug interactions are listed, many of which require dose adjustment of statin therapy or drug level monitoring (e.g. digoxin) (Wiggins et al, 2016).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Single-Entity Agents				
atorvastatin	Tablet: 10 mg 20 mg 40 mg 80 mg	Hyperlipidemia: Tablet: initial, 10 to 40 mg once daily; maintenance, 10 to 80 mg/day Adjunct to diet for the treatment of patients with elevated serum TG levels, reduce TC and LDL-C in patients with HoFH as an adjunct to other lipid lowering treatments or if such treatments are unavailable, treatment of patients with primary dysbetalipoproteinemia: Tablet: 10 to 80 mg/day HeFH in pediatric patients 10 to 17 years old: Tablet: initial dose 10 mg/day, maximum dose 20 mg/day	After initiation and/or upon titration, lipid levels should be analyzed within two to four weeks and dosage adjusted accordingly.	May be administered with or without food. Tablets may be taken at any time during the day.
fluvastatin	Capsule: 20 mg 40 mg Extended-release tablet: 80 mg	Hypercholesterolemia (including HeFH and nonfamilial) and mixed dyslipidemia in adults: Capsule: 40 mg once daily or 40 mg twice daily Patients requiring LDL-C reductions ≥25% should initiate fluvastatin therapy at 40 mg once daily or 80 mg in divided doses of the 40 mg capsule given twice daily. Patients requiring LDL-C reductions < 25% should initiate a starting dose of 20 mg.	After initiation and/or upon titration, lipid levels should be analyzed after four weeks and dosage adjusted accordingly. Max dose is 20 mg twice daily when used with cyclosporine or fluconazole.	Capsules should be taken in the evening if dosed once daily. If 80 mg/day is used, it should be administered in two divided doses (immediate-release capsule). May be administered with or without food. Tablets may be taken at any time

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		Extended-release tablet: 80 mg once daily HeFH in pediatric patients: Capsule: 20 mg daily, maximum dose 40 mg twice daily Extended-release tablet: 80 mg once daily		during the day (extended-release tablet). Tablets should be swallowed whole. (extended-release tablet).
lovastatin	Extended-release tablet: 20 mg 40 mg 60 mg Tablet: 10 mg 20 mg 40 mg	Hyperlipidemia: Extended-release tablet: initial, 20 to 60 mg once daily; maintenance, 20 to 60 mg/day Tablet: initial, 20 mg once daily; maintenance, 10 to 80 mg/day in single or two divided doses; maximum, 80 mg/day Prevention of CVD: Extended-release tablet: initial, 20 to 60 mg once daily; maintenance, 20 to 60 mg/day Tablet: initial, 20 mg once daily; maintenance, 10 to 80 mg/day in single or two divided doses; maximum, 80 mg/day	Prior to initiation and periodically during therapy, lipid levels should be analyzed and dosage adjusted accordingly.	Extended-release tablet should be taken at bedtime. Extended-release tablets should be swallowed whole. Immediate-release tablet should be taken with an evening meal.
pitavastatin	Tablet: 1 mg 2 mg 4 mg	Hyperlipidemia: Tablet: initial, 2 mg once daily; maintenance, 1 to 4 mg/day; maximum, 4 mg/day	After initiation and/or upon titration, lipid levels should be analyzed after four weeks and dosage adjusted accordingly. Do not exceed 4 mg once daily dosing due to increased risk of severe myopathy Max dose is 1 mg mg/day when used with erythromycin.	May be administered with or without food. Tablets may be taken at any time during the day.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			Max dose is 2 mg mg/day when used with rifampin. Use caution in patients receiving ≥ 1 gram daily of niacin-containing products.	
pravastatin	Tablet: 10 mg* 20 mg 40 mg 80 mg	Hyperlipidemia: Tablet: initial, 40 mg once daily; maintenance, 40 to 80 mg once daily Prevention of CVD: Tablet: initial, 40 mg once daily; maintenance, 40 to 80 mg once daily Pediatric patients: Ages eight to 13 years old: 20 mg once daily Ages 14 to 18 years old: 40 mg once daily	After initiation and/or upon titration, lipid levels should be analyzed after four weeks and dosage adjusted accordingly. Max dose in patients taking cyclosporine is 20 mg/day. Max dose in patients taking clarithromycin is 40 mg/day.	May be administered with or without food. Tablets may be taken at any time during the day.
rosuvastatin	Tablet: 5 mg 10 mg 20 mg 40 mg	Hyperlipidemia: Tablet: initial, 10 to 20 mg once daily; maintenance, 5 to 40 mg/day Reduce TC, LDL-C and apo B in patients with HoFH: Tablet: initial, 20 mg once daily; Ages seven to 17 years: Tablet: 20 mg once daily Reduce TC, LDL-C and apo B in pediatric patients with HeFH: Aged eight to less than 10 years: Tablet: maintenance, 5 to 10 mg/day Aged 10 to 17 years: Tablet: maintenance, 5 to 20 mg/day	After initiation and/or upon titration, lipid levels should be analyzed within two to four weeks and dosage adjusted accordingly. Dosing in Asian patients: initial, 5 mg once daily Max dose is 5 mg once daily when used with cyclosporine and 10 mg once daily when used with gemfibrozil, atazanavir/	May be administered with or without food. Tablets may be taken at any time during the day.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			ritonavir, lopinavir/ritonavir, or simeprevir.	
simvastatin	Tablet: 5 mg 10 mg 20 mg 40 mg 80 mg Oral suspension: 20 mg/5 mL 40 mg/5 mL	Hyperlipidemia: Tablet: initial, 10 or 20 mg once daily; maintenance, 5 to 40 mg/day Reduce TC and LDL-C in patients with HoFH as an adjunct to other lipid lowering treatments or if such treatments are unavailable: Tablet: 40 mg once daily Prevention of CVD: Tablet: initial, 10 or 20 mg once daily; maintenance, 5 to 40 mg/day Reduce TC, LDL-C and apo B in pediatric patients with HeFH: Aged 10 to 17 years: Tablet: initial, 10 mg/day; maintenance, 10 to 40 mg/day; maximum dose is 40 mg/day	After initiation and/or upon titration, lipid levels should be analyzed after four weeks and dosage adjusted accordingly. Dose should be decreased by 50% if initiating lomitapide. Simvastatin dosage should not exceed 20 mg/day (or 40 mg/day for patients who have previously taken simvastatin 80 mg/day chronically (e.g. for 12 months or more) without evidence of muscle toxicity) while taking lomitapide. Use caution in Chinese patients receiving doses >20 mg with niacin-containing products. Max dose is 10 mg/day when used with verapamil, diltiazem, or dronedarone. Max dose is 20 mg/day when	Tablets should be taken in the evening. The oral suspension should be taken on an empty stomach. Shake oral suspension bottle for at least 20 seconds. Use accurate measuring device. Due to the increased risk of myopathy, including rhabdomyolysis, particularly during the first year of treatment, use of the 80 mg dose should be restricted to patients who have been taking the 80 mg dose chronically without evidence of muscle toxicity.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			used with amiodarone, amlodipine, or ranolazine. Simvastatin is contraindicated for use with strong CYP3A4 inhibitors. For patients at high risk for a CHD event due to existing CHD, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, the recommended starting dose is 40 mg/day. Use caution in patients receiving ≥ 1 gram daily of niacin-containing products.	
Combination Products				
amlodipine/ atorvastatin	Tablet: 2.5/10 mg 2.5/20 mg 2.5/40 mg 5/10 mg 5/20 mg 5/40 mg 5/80 mg 10/10 mg 10/20 mg 10/40 mg 10/80 mg	Dosage of amlodipine/atorvastatin must be individualized on the basis of both effectiveness and tolerance for each individual component in the treatment of hypertension/angina and hyperlipidemia. Select doses of amlodipine and atorvastatin independently. The usual starting dose for amlodipine is 5 mg daily and for atorvastatin 10 to 20 mg daily. The maximum dose is amlodipine 10 mg daily and atorvastatin 80 mg daily. Patients requiring large LDL-C reductions (>45%) should initiate	After initiation and/or upon titration, lipid levels should be analyzed within two to four weeks and dosage adjusted accordingly. Dosage should be adjusted to achieve blood pressure goals. In general, wait seven to 14 days between titration steps.	May be administered with or without food. Tablets may be taken at any time during the day.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		atorvastatin therapy at 40 mg once daily. HeFH in pediatric patients 10 to 17 years old: *Atorvastatin* Tablet: initial dose 10 mg/day, maximum dose 20 mg/day *Amlodipine [age 6 to 17 years old]* Tablet: initial dose 2.5 to 5 mg maximum dose 5 mg	Titration may proceed more rapidly if clinically warranted, provided the patient is assessed frequently.	
ezetimibe/ atorvastatin	Tablet: 10/10 mg 10/20 mg 10/40 mg 10/80 mg	Usual starting dose: 10/10 mg or 10/20 mg once daily. Usual dose range is 10/10 mg to 10/80 mg once daily. May initiate at 10/40 mg once daily for patients requiring a larger LDL-C reduction (> 55%). HoFH: 10/40 mg or 10/80 mg once daily.	After initiation or titration of doses, lipid levels may be analyzed after two or more weeks. For patients taking clarithromycin, itraconazole, saquinavir + ritonavir, darunavir + ritonavir, or fosamprenair alone or with ritonavir: Do not exceed 10/20 mg once daily. For patients taking nelfinavir: Do not exceed 10/40 mg once daily.	Tablets may be taken at any time of the day. May be administered with or without food.
ezetimibe/ simvastatin	Tablet: 10/10 mg 10/20 mg 10/40 mg 10/80 mg	Hyperlipidemia: Adjunct to diet to reduce elevated TC, LDL-C, apo B and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia, reduce TC and LDL-C in patients with HoFH as an adjunct to other lipid lowering treatments or if such treatments are unavailable: Tablet: initial, 10/10 or 10/20 mg once daily; maintenance, 10/10 to 10/40 mg/day	After initiation and/or upon titration, lipid levels should be analyzed within two or more weeks and dosage adjusted accordingly. Decrease dose of VYTORIN by 50% if initiating lomitapide.	May be administered with or without food. Tablets should be taken in the evening. Due to the increased risk of myopathy, particularly during the first year of treatment, use of

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			VYTORIN dosage should not exceed 10/20 mg once day (or 10/40 mg once daily for patients who have previously taken simvastatin 80 mg once day chronically, e.g., for 12 months or more, without evidence of muscle toxicity) while taking lomitapide. Max dose is 10/10 mg/day when used with verapamil, diltiazem, or dronedarone. Max dose is 10/20 mg/day when used with amiodarone, amlodipine, or ranolazine. VYTORIN is contraindicated for use with strong CYP3A4 inhibitors. Use caution in patients receiving ≥ 1 gram daily of niacin-containing products.	the 10/80 mg dose should be restricted to patients who have been taking the 10/80 mg dose chronically.

*Pravachol 10 mg is no longer available, however, generic pravastatin 10 mg remains available.

Clinical Pharmacology, 2018.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
atorvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Approved for use in children 10 to 17 years of age for the treatment of HeFH. Doses of >20 mg have not been studied in this population. Safety and efficacy in children <10 years of age have not been established.	No dosage adjustment required.	Contraindicated in active liver disease or in patients with unexplained persistent elevations or serum transaminases.	Unclassified† Contraindicated in pregnant women. Contraindicated during breastfeeding.
fluvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Approved for use in children 9 to 16 years of age for the treatment of HeFH. Safety and efficacy in children for other approved indications have not been established.	No dosage adjustment required in mild to moderate renal dysfunction. Use with caution in severe renal dysfunction; doses above 40 mg per day have not been studied.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Pregnancy Category X Potential excretion into breast milk; contraindicated during breastfeeding
lovastatin	No dosage adjustment required in the elderly. The initial starting dose of lovastatin extended-release should not exceed 20 mg/day (ALTOPREV).	Approved for use in children 10 to 17 years of age for the treatment of HeFH (MEVACOR); maximum dose of 40 mg/day. Safety and efficacy in children <10 years of age have not been established (MEVACOR). Safety and efficacy in children have not been	Renal dosage adjustment is required; for creatinine clearances <30 mL/minute, use with caution and carefully consider doses >20 mg/day.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Pregnancy Category X (MEVACOR) No data on excretion in breast milk; not recommended (MEVACOR) Unclassified† (ALTOPREV) Contraindicated in pregnant women (ALTOPREV). Contraindicated during

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
		established (ALTOPREV).			breastfeeding (ALTOPREV).
pitavastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Safety and efficacy in children have not been established.	Renal dosage adjustment is required; for creatinine clearances 15 to 59 mL/ minute or end-stage renal disease receiving hemodialysis, an initial dose of 1 mg once daily and a maximum dose of 2 mg/day is re-commended.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Unclassified† Contraindicated in pregnant women. Contraindicated during breastfeeding.
pravastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Approved for use in children eight to 18 years of age for the treatment of HeFH. Safety and efficacy in children <8 years of age have not been established.	Renal dosage adjustment is required in severe renal impairment; an initial dose of 10 mg/day is recommended.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Unclassified† Contraindicated in pregnant women. Pravastatin is present in breast milk; contraindicated during breastfeeding.
rosuvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Approved for use in children 8 to 17 years of age for the treatment of HeFH and 7 to 17 years of age for the treatment of HoFH. Safety and efficacy in children <7 years of age have not been established.	No dosage adjustment required in mild to moderate renal dysfunction. Renal dosage adjustment required; for creatinine clearances <30 mL/minute, an initial dose of 5 mg/day and a maximum dose of 10 mg/day are recommended.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Unclassified† Contraindicated in pregnant women. Limited data indicate that the drug is in breast milk; contraindicated during breastfeeding.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
simvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Approved for use in children 10 to 17 years of age for the treatment of HeFH. Doses greater than 40 mg have not been studied in this population. Safety and efficacy in children <10 years of age have not been established.	No dosage adjustment required in mild to moderate renal dysfunction. Renal dosage adjustment required for severe renal impairment: an initial dose of 5 mg/day with close monitoring is recommended.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Pregnancy Category X Unknown whether excreted in breast milk; contraindicated during breastfeeding.
Combination Products					
amlodipine/ atorvastatin	Safety and efficacy in elderly patients have not been established. Elderly patients have decreased clearance of amlodipine; lower initial doses of amlodipine may be required.	Safety and efficacy in children have not been established. Safety and efficacy of atorvastatin in children <10 years and amlodipine in children <6 years of age have not been established	No dosage adjustment required.	Contraindicated in active liver disease.	Unclassified† Contraindicated for use during pregnancy and in women who may become pregnant. Contraindicated for use during breastfeeding.
ezetimibe/ atorvastatin	The maximum dosage limit is 10/80 mg once daily for most patients.	Safety and efficacy have not been established.	No dosage adjustment is needed.	Contraindicated in patients with active hepatic disease or unexplained transaminase elevations.	Unclassified† Contraindicated for use during pregnancy and in women who may become pregnant. Contraindicated for use during breastfeeding.
ezetimibe/ simvastatin	No evidence of overall differences in safety or efficacy observed between elderly	Safety and efficacy in children < 10 years old have not been established.	Use with caution doses exceeding 10/20 mg in patients with moderate to	Contraindicated in active liver disease or unexplained persistent elevations in	Unclassified† Contraindicated for use during pregnancy and in women who may

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
	and younger adult patients; prescribe with caution.		severe renal dysfunction.	serum transaminases.	become pregnant. Contraindicated for use during breastfeeding.

* Pregnancy Category X = Contraindicated in pregnant women due to evidence of fetal abnormalities from adverse effects data from investigational or marketing experience. Risks of use of the drug in pregnant women clearly outweigh potential benefits.

†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

Clinical Pharmacology, 2018

CONCLUSION

- Statins are approved for the treatment of a variety of lipid disorders, including primary hypercholesterolemia, mixed dyslipidemia, and hypertriglyceridemia.
- The fixed-dose combination products (CADUET [amlodipine/atorvastatin], ezetimibe/atorvastatin, and VYTORIN [ezetimibe/simvastatin]) are indicated for use when dual therapy is appropriate.
- Statins decrease LDL-C according to the intensity of statin used and TG by 7% to 30%, as well as increase HDL-C by 5% to 15% when administered as monotherapy. The effects on LDL-C are dose-dependent and log-linear. Statins also decrease TG and increase HDL-C by varying levels.
- All products in this review are now available in a generic formulation except for ALTOPREV® (lovastatin extended-release), FLOLIPID (simvastatin oral suspension), LIVALO (pitavastatin), and Zypitamag (pitavastatin) (Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2018).
- In general, therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia. When LDL-C lowering is required, initial treatment with a statin is recommended.
- In 2004, the National Cholesterol Education Program (NCEP) published guidelines on the Implications of Recent Clinical Trials for the NCEP Adult Treatment Panel III, which stated the following:
    - When LDL-C lowering drug therapy is employed in high-risk or moderately-high risk patients, it is advised that intensity of therapy be sufficient to achieve ≥30 to 40% reduction in LDL-C levels.
    - Standard statin doses are defined as those that lower LDL-C levels by 30 to 40%. The same effect may be achieved by combining lower doses of statins with other drugs or products such as bile acid sequestrants, ezetimibe, nicotinic acid, or plant stanols/sterols.
    - When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the statin dose may need to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals.
    - Fibrates may have an adjunctive role in the treatment of patients with high TG and low HDL-C, especially in combination with statins.
    - In high risk patients with high TG or low HDL-C levels, consideration can be given to combination therapy with fibrates or nicotinic acid and a LDL lowering agent.
    - For the treatment of HeFH, LDL-C lowering drugs should be initiated in young adulthood. Statins are considered first-line therapy. Two-drug and sometimes three-drug therapy may be needed (Grundy et al, 2004).
- The 2013 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines on Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults focus on primary and secondary atherosclerotic cardiovascular disease (ASCVD) risk reduction in adults (Stone et al, 2014).
    - These guidelines established four statin benefit groups: (1) individuals with clinical ASCVD (2) individuals with primary elevations of LDL–C >190 mg/dL (3) individuals with diabetes aged 40 to 75 years with LDL–C 70 to 189 mg/dL and without clinical ASCVD, and (4) individuals aged 40 to 75 years without clinical ASCVD or diabetes with LDL–C 70 to 189 mg/dL and estimated 10-year ASCVD risk >7.5%

  - Intensity of statin therapy (high, moderate, and low) is the new goal of treatment in the benefit groups for use in primary and secondary prevention of ASCVD.
  - A new cardiovascular risk tool, based on pooled cohort equations, has been created to estimate absolute 10-year ASCVD risk (defined as first occurrence nonfatal and fatal MI, and nonfatal and fatal stroke). The Pooled Cohort Equations should be used to estimate 10-year ASCVD risk for individuals without clinical ASCVD or diabetes and LDL–C 70 to189 mg/dL to guide the initiation of statin therapy. For the primary prevention of ASCVD in individuals with diabetes (diabetes mellitus type-1 and type-2), estimated 10-year ASCVD risk can also be used to guide the intensity of statin therapy. For those with clinical ASCVD or with LDL–C ≥190 mg/dL who are already in a statin benefit group, it is not necessary to estimate 10-year ASCVD risk (Stone et al, 2014).
  - Statins are the primary medications to utilize for ASCVD risk reduction according to the 2013 guidelines, which focus on treatments proven to reduce ASCVD and not comprehensive lipid management.
- The 2015 AHA Scientific Statement on Familial Hypercholesterolemia (FH) recommends aggressive pharmacological treatment for patients with HeFH beginning at age eight to 10 years. Pharmacological treatment may also be considered in younger patients (less than eight years of age) with extreme elevation of LDL-C or those with other major risk factors suggesting very premature CVD. In HeFH pediatric patients, LDL-C goals are not well defined; however, treatment is recommended based on LDL-C levels and not based on genetic abnormalities or other clinical features. In adult patients with HeFH, the initial goal is to reduce LDL-C by 50% and treatment with a high-intensity statin (rosuvastatin or atorvastatin) is recommended. If LDL-C levels remain above goal after three months, then ezetimibe may be added. If LDL-C continues to be above goal after three months of two-drug therapy, then the addition of a PCSK9 inhibitor, bile acid sequestrant, or niacin can be considered. In patients with HoFH, lipid-lowering therapy should be initiated as soon as possible, with statins providing a 10 to 25% reduction in LDL-C (Gidding et al, 2015).
- The 2016 United States Preventive Services Task Force (USPSTF) recommendations for statin use for the primary prevention of cardiovascular disease in adults note the following:
  - Adults without a history of CVD should use a low- to moderate-dose statin for the prevention of CVD events and mortality when the following criteria are met: (1) they are aged 40 to 75 (2) they have one or more CVD risk factor such as dyslipidemia, diabetes, hypertension, or smoking (3) they have a calculated 10-year risk of a cardiovascular risk of 10% or more.
  - Although statin use may be beneficial for the primary prevention of CVD in some adults with a 10-year cardiovascular risk of <10%, the benefits are likely smaller. A low- to moderate-dose statin may be offered to certain adults without a history of CVD when all of the following criteria are met: (1) they are aged 40 to 75 years (2) they have one or more CVD risk factor (3) they have a calculated 10-year risk of a cardiovascular event of 7.5 to 10%.
  - There is insufficient evidence to assess the balance of benefits to risks of initiating a statin for the primary prevention of CVD and mortality in patients ≥76 years without a history of MI or stroke (US Preventative Task Force, 2016).
- In 2017, the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) recommended the addition of another agent when statin therapy alone does not achieve therapeutic goals; their guidance offers cholesterol absorption inhibitors, bile acid sequestrants, and proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors as options (Jellinger et al, 2017). The recommendations for statin therapy for managing dyslipidemia and prevention of cardiovascular disease are stated as the following:
  - Statin therapy is recommended as the primary pharmacologic agent to achieve target LDL-C goals on the bases of morbidity and mortality outcome trials.
  - For clinical decision making, mild elevations in blood glucose levels and/or an increased risk of new-onset type 2 diabetes mellitus associated with intensive statin therapy do not outweigh the benefits of statin therapy for ASCVD risk reduction.
  - In individuals within high-risk and very high-risk categories, further lowering of LDL-C beyond established targets with statins results in additional ASCVD event reduction and may be considered.
  - Very high-risk individuals with established coronary, carotid, and peripheral vascular disease, or diabetes who also have at least 1 additional risk factor should be treated with statins to target a reduced LDL-C treatment goal of <70 mg/dL.
  - Extreme-risk individuals should be treated with statins to target an even lower LDL-C treatment goal <55 mg/dL.

- Numerous clinical trials have demonstrated that the statins (single entity and combination products) can effectively lower LDL-C, non-HDL-C, TC, and TG, as well as positively impact other lipid/lipoprotein parameters. Many studies have compared active treatment to placebo or compared combination therapy to monotherapy. In these studies, the more aggressive treatment regimens often improved lipid parameters to a greater extent than the less-intensive treatment regimens.
- All of the statins, with the exception of pitavastatin, have been shown to have beneficial effects on CHD outcomes, while the majority of them (atorvastatin, pravastatin, rosuvastatin, and simvastatin) have also been shown to decrease the risk of stroke.
- Atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin have been shown to reduce cardiovascular events in patients with clinically evident CHD (secondary prevention). In addition, fluvastatin, lovastatin, pravastatin, and rosuvastatin have been shown to slow progression of coronary atherosclerosis in patients with CHD.
- No incremental benefit of the combination statin products on cardiovascular morbidity and mortality has been established over and above that demonstrated for the single entity statin products.
- The statins are generally well-tolerated, and the most common side effects are gastrointestinal disturbances, headache, insomnia, myalgia, and rash. Muscle aches and weakness are reported by one to two percent of patients taking statins. The symptoms are usually mild and generally do not lead to discontinuation. All statins can increase hepatic transaminase levels and creatinine kinase.
- Pravastatin is the only statin that does not undergo cytochrome (CYP) 450 metabolism, and is therefore associated with a lower risk for drug interactions. Atorvastatin (to a lesser extent), lovastatin, and simvastatin are primarily metabolized by the CYP3A4 isoenzyme, while fluvastatin, pitavastatin, and rosuvastatin are metabolized by the CYP2C9 isoenzyme, which may result in differences in their drug interaction profiles.
- There is insufficient evidence to support that one statin is safer or more efficacious than another statin.

Table 5. Advantages and Disadvantages of Statins

Drug	Advantages	Disadvantages
Atorvastatin	• Available generically both alone and in combination with ezetimibe • Has been documented to have more potency in cholesterol-lowering than certain other statins • Cardiovascular outcomes studies support the use of the 80 mg strength in certain populations (e.g., as secondary prophylaxis following ST elevation MI)	• Associated with drug-drug interactions through the CYP3A4 isoenzyme system
Fluvastatin	• Available generically • Available in an extended-release formulation • Not associated with drug-drug interactions through the CYP3A4 isoenzyme system	• Associated with drug-drug interactions through the CYP2C9 isoenzyme system
Lovastatin	• Available generically (immediate release formulation) • Available in an extended-release formulation	• Associated with drug-drug interactions through the CYP3A4 isoenzyme system
Pitavastatin	• Not associated with drug-drug interactions through the CYP isoenzyme system	• Effect on cardiovascular morbidity and mortality has not been determined
Pravastatin	• Available generically • Not associated with drug-drug interactions through the CYP isoenzyme system	
Rosuvastatin	• Available generically	

Drug	Advantages	Disadvantages
	• Has been documented to have more potency in cholesterol-lowering than certain other statins	
Simvastatin	• Available as an oral suspension • Tablet form is available generically • Available both alone and in combination with ezetimibe	• Associated with drug-drug interactions through the CYP3A4 isoenzyme system

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Publication Date: July 2, 2018

Therapeutic Class Overview
Erythropoiesis Stimulating Agents

INTRODUCTION

- Iron deficiency anemia is the most common form of anemia. Anemia is also associated with a variety of conditions including cancer, chronic kidney disease (CKD), rheumatoid arthritis, human immunodeficiency virus (HIV), chronic heart failure, and chronic disease (*Schrier 2017*).
- Management of anemia of chronic disease is often more complex, and administration of erythropoiesis-stimulating agents (ESAs) or red blood cell (RBC) transfusions may be necessary for patients with severe, symptomatic anemia (eg, hemoglobin [Hb] <10 g/dL) (*Schrier and Camaschella 2017*).
- Although allogeneic RBC transfusions provide rapid correction of Hb stores, they are also accompanied by significant risks, which include transmission of communicable diseases, antibody formation against blood cell antigens, sensitization to transplant antigens, volume overload, hyperkalemia, and iron overload (*Carson and Kleinman 2017*).
- Erythropoietin is a naturally occurring glycoprotein hormone that stimulates the production and maturation of erythrocytes in the bone marrow. Erythrocytes, or RBCs, are responsible for transporting oxygen from the lungs to the peripheral tissues. Erythropoietin is primarily produced and released into the bloodstream by the kidneys. Renal production of erythropoietin is stimulated when the renal oxygen sensor is triggered by hypoxia or low tissue oxygen (*Hörl 2013*).
- In order to mitigate the risks associated with RBC transfusions, ESAs were introduced in the early 1990's and provided a treatment option to patients with CKD or with malignancies who were unable to maintain their Hb within the acceptable ranges (*Schrier et al 2017*).
- Although ESAs may decrease the need for RBC transfusions, multiple meta-analyses of randomized controlled trials (RCTs) have demonstrated an increase in mortality, cardiovascular events, and cancer progression without significant improvements in morbidity or quality of life (QoL) for patients receiving therapy (*Collister et al 2016, Grant et al 2013, Palmer et al 2014a, Tonia et al 2012*).
- The ESAs approved by the Food and Drug Administration (FDA) in the United States include Epogen (epoetin alfa), Procrit (epoetin alfa), Aranesp (darbepoetin alfa), and Mircera (methoxy polyethylene glycol-epoetin beta).
- Both epoetin alfa and darbepoetin alfa also carry boxed warnings regarding shortened survival and increased risk of tumor progression or recurrence in patients with breast, non-small cell lung, head and neck, lymphoid and cervical cancers. Furthermore, the warnings emphasize to use ESAs only for the treatment of anemia due to concomitant myelosuppressive chemotherapy and to discontinue ESAs following completion of a chemotherapy course. ESAs should not be initiated in cancer patients receiving myelosuppressive therapy when the anticipated outcome is cure.
- Medispan Therapeutic Class: Erythropoietins

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
Aranesp (darbepoetin alfa)	Amgen	09/17/2001	-
Epogen, Procrit (epoetin alfa)	Amgen	06/01/1989	-
Mircera (methoxy polyethylene glycol-epoetin beta)	Galenica	11/14/2007	-

(*DRUGS@FDA 2018; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018)*

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Aranesp (darbepoetin alfa)	Epogen, Procrit (epoetin alfa)	Mircera (methoxy polyethylene-epoetin beta)
Treatment of anemia associated with chronic kidney disease, including patients on dialysis and patients not on dialysis	✔	✔ *	✔
Treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy	✔	✔	
Treatment of anemia due to zidovudine administered at ≤ 4200 mg/week in human immunodeficiency virus (HIV)-infected patients with endogenous serum erythropoietin levels of ≤ 500 mUnits/mL		✔	
Reduce the need for allogeneic red blood cell transfusions among patients with perioperative Hb > 10 to ≤ 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery		✔	

*To decrease the need for transfusions in these patients.

- **Limitations of indications:**
  - All ESAs have not been shown to improve QoL, fatigue, or patient well-being.
  - ESAs are not indicated as a substitute for RBC transfusions in patients who require immediate correction of anemia.
- Aranesp, Epogen, and Procrit are not indicated for use:
  - In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy.
  - In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
  - In patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion.
- Epogen and Procrit are not indicated for use:
  - In patients scheduled for surgery who are willing to donate autologous blood.
  - In patients undergoing cardiac or vascular surgery.
- Mircera is not indicated for use:
  - In the treatment of anemia due to cancer chemotherapy.

(*Prescribing information: Aranesp 2017, Epogen 2017, Mircera 2016, Procrit, 2017*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Only a few clinical studies have compared the efficacy and safety of epoetin alfa to darbepoetin alfa for the treatment of anemia due to CKD or myelosuppressive chemotherapy. None of these agents have been shown to improve QoL, fatigue, or patient well-being. Since initial FDA-approval, the ESAs have been shown to increase the risk of death,

myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access, and tumor progression or recurrence. Earlier studies utilized ESA to maintain higher Hb targets than the targets recommended currently. Numerous observational, non-interventional, retrospective, and single-center studies have evaluated these agents in the correction of anemia due to CKD or myelosuppressive chemotherapy. However, these studies are not included in this review.

Anemia in CKD

- ESAs provided an attractive solution to decreasing the number of allogeneic blood transfusions; however, multiple meta-analyses of RCTs have demonstrated an increase in mortality, cardiovascular events, and cancer progression without improvement in morbidity or QoL for patients receiving therapy (*Collister et al 2016, Grant et al 2013, Palmer et al 2014a*).
- According to a Cochrane review, use of ESAs in predialysis patients corrected anemia and avoided blood transfusions compared to placebo or no treatment (*Cody et al 2016*). A total of 19 studies (N = 993) evaluated ESAs, with the majority of the studies being published prior to 2000. ESAs improved Hb (mean difference [MD] 1.90 g/dL, 95% CI, -2.34 to -1.47) and decreased the number of patients with blood transfusions (risk ratio [RR] 0.32, 95% confidence interval [CI], 0.12 to 0.83). No differences with the measure of kidney disease progression were observed. Endpoints of QoL and change in exercise capacity were not measured in a manner which was suitable for analysis.
- The harms of high Hb targets compared to lower Hb targets were evaluated. The Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease (CHOIR) trial was a notable trial that found that patients with CKD with a higher target Hb had higher risk for the composite outcome of death, nonfatal myocardial infarction, stroke, and hospitalization for congestive heart failure (CHF) than patients with a lower Hb target (17.5 vs 13.5%; hazard ratio [HR], 1.34; 95% CI, 1.03 to 1.74; p = 0.03) (*Singh et al 2006*). Analysis of study data in the intent-to-treat (ITT) population and including all events from randomization until study termination or 30 days after the last dose showed a higher incidence of events in the high-Hb group (HR, 1.3; 95% CI, 1.01 to 1.62; p = 0.04). Even though the trial was halted early, evidence suggested that higher Hb levels led to an increased rate of adverse events. The prescribing information and warnings for all drugs of this class were updated to reflect these findings. Findings were similar to the Normal Hematocrit Study performed in patients with CKD on dialysis with CHF or ischemic heart disease (*Besarab et al 1998*).
- A systematic review evaluated nine trials comparing epoetin alfa and darbepoetin alfa for all-cause mortality in patients with anemia in adults with CKD including those on dialysis (N = 2024). Duration of the trials was 20 to 52 weeks. No significant difference in mortality between epoetin and darbepoetin was detected (odds ratio [OR] 1.33; 95% CI, 0.88 to 2.01) (*Wilhelm-Leen et al 2015*).
- Numerous trials have evaluated extended dosing intervals of epoetin for patients with CKD. In general, larger doses given less frequently demonstrated similar outcomes with epoetin alfa and darbepoetin (*Benz et al 2007, Patel et al 2012, Pergola et al 2009, Pergola et al 2010, Provenzano et al 2004, Provenzano et al 2005, Spinowitz et al 2008a, Warady et al 2018*). A systematic review confirmed that various dosing frequencies of darbepoetin and epoetin result in similar mean final Hb values in patients receiving hemodialysis (*Hahn et al 2014*). Many of these dosing regimen studies were completed in small patient populations and open-label design. The FDA-approved dosing regimen for epoetin alfa is three times weekly for patients with CKD.
- Patients with CKD on dialysis should receive intravenous (IV) darbepoetin and epoetin alfa. Cases of pure red cell aplasia and severe anemia have been reported more frequently with the subcutaneous (SC) administration of ESAs in patients with CKD. Comparisons of the method of administration (IV vs SC) have been completed with epoetin and darbepoetin. In an open-label, German study, switching patients on dialysis from SC darbepoetin to IV administration led to stable mean Hb levels and mean weekly darbepoetin doses (*Bommer et al 2008*). Another open-label study showed that switching patients on dialysis from SC epoetin to IV darbepoetin resulted in stable mean Hb levels at stable darbepoetin doses after three months (*Chazot et al 2009*). Mircera is indicated for IV or SC administration.
- In a double-blind, multicenter, placebo-controlled, randomized clinical trial, the safety of darbepoetin in patients with type 2 diabetes mellitus, CKD, and anemia were evaluated (*Pfeffer et al 2009*). The patients had a baseline Hb level of ≤11 g/dL. The primary endpoint of the TREAT study was the composite of death or a non-fatal cardiovascular event (nonfatal myocardial infarction, congestive heart failure, stroke or hospitalization for myocardial ischemia) and death or end-stage renal disease. The primary cardiovascular composite outcome of death or nonfatal cardiovascular event occurred in 632 patients (31.4%) of the darbepoetin group and 602 patients (29.7%) treated with placebo (HR for darbepoetin vs placebo, 1.05; 95% CI, 0.94 to 1.17; p = 0.41). For the individual endpoints contributing to the composite, there were no

statistically significant differences between the groups for any parameter except for fatal and non-fatal stroke which occurred more frequently with darbepoetin (5% vs 2.6%; HR, 1.92; 95% CI, 1.38 to 2.68; p < 0.001). For the composite endpoint of death or end-stage renal disease, no significant difference was detected (darbepoetin 32.4% vs 30.5% placebo; HR, 1.06; 95% CI, 0.95 to 1.19; p = 0.29). The study was performed from 2004 to 2007, when the standard of care target Hb level was 13 g/dL. Additional notification was sent to investigators and participants of the adverse outcomes with higher Hb targets; however, the study protocol was not modified. A third party vendor assayed Hb levels and reported the dosage adjustment necessary for patients receiving darbepoetin. At baseline, the darbepoetin group had a lower proportion of patients with a history of CHF (31.5 vs 35.2%; unadjusted p = 0.01). In summary, darbepoetin in patients with anemia, diabetes and chronic renal disease did not increase the risk of the composite outcome of death or cardiovascular outcome and death or end-stage renal disease. It was noted that stroke, fatal or non-fatal, occurred more frequently in patients who received darbepoetin compared to placebo.

- A systematic review evaluated darbepoetin and the other ESAs in 21 studies in patients with CKD for the effect on blood transfusion (*Palmer et al 2014b*). Darbepoetin reduced the need for blood transfusions compared to placebo or no treatment; however, in three studies comparing darbepoetin to epoetin, darbepoetin had uncertain effects on RBC transfusions and all-cause mortality compared to epoetin. Darbepoetin and methoxy polyethylene glycol-epoetin beta were similar for risk of RBC transfusions.
- A Cochrane review compared the efficacy and safety of the ESAs (Mircera, epoetin alfa, epoetin beta, darbepoetin alfa, and biosimilar ESAs) in adults with CKD. A total of 56 studies (N = 15,596) were included in the analysis. In network analyses, there was moderate to low confidence that the ESAs prevented blood transfusions compared to placebo. The authors concluded that there was insufficient evidence to suggest superiority of any ESA formulation based on available safety and efficacy data (*Palmer et al 2014a*).
- A recent systematic review evaluated 17 studies (N = 10,049) with ESAs for effects on health-related quality of life (HRQoL) in CKD patients (*Collister et al 2016*). Higher Hb target levels (range: 10.2 to 13.6 g/dL) resulted in no statistically significant improvements in Short-Form 36 (SF-36) domains or for the Kidney Disease Questionnaire (KDQ) compared to patients on placebo or lower Hb target levels (range: 7.4 to 12 g/dL). For the KDQ, patients with higher Hb targets had an improvement of 0.5 (95% CI, -2.2 to 1.2) points in the physical symptom domain, 0.5 point improvement in the fatigue domain (95% CI, -1.6 to 0.5), and 0.2 point improvement in the depression domain (95% CI, -1.1 to 0.8). A clinically meaningful benefit is considered a minimum of 0.5 point improvement on the KDQ. The systematic review is consistent with the prescribing information and previously published reports.
- Very few randomized controlled studies comparing darbepoetin and epoetin alfa have been published. Two non-inferiority studies comparing epoetin alfa to darbepoetin alfa in the treatment of anemia of CKD demonstrated no difference in efficacy between the two agents. In a study of adult patients with CKD by *Nissenson et al*, the mean changes in Hb levels from baseline to the evaluation period were similar between the darbepoetin alfa (0.16 to 0.09 g/dL) and epoetin alfa (0 to 0.06 g/dL) groups (difference, 0.16 g/dL; 95% CI, -0.06 to 0.38; p value not reported). In a second study by *Vanrenterghem et al* (N = 522) of patients with CKD on dialysis, the mean change in Hb was 0.05 g/dL in the darbepoetin alfa group compared to 0 g/dL in the epoetin alfa treatment (difference, 0.05 g/dL; 95% CI, -0.14 to 0.24; p values not reported). No statistically significant differences in the mean change in Hb levels from baseline, the primary endpoint were reported. In addition, in both studies there were no differences in safety profiles, and no antibodies detected to either treatment (*Nissenson et al 2002, Vanrenterghem et al 2002*). An open-label trial comparing darbepoetin SC 0.45 mcg/kg once weekly and epoetin SC 50 units/kg twice weekly found similar efficacy in achieving a Hb response and similar safety profile in 166 patients with CKD not on dialysis (*Locatelli et al 2001*).
- The safety and efficacy of Mircera were established in Phase 3, multicenter, open-label, active-controlled trials that randomized patients with CKD with anemia to treatment with either Mircera or a comparator ESA.
- Four of the clinical trials assessed Mircera in the maintenance of Hb levels among patients currently treated with other ESAs for anemia of CKD (*Canaud et al 2008, Levin et al 2007, Spinowitz et al 2008b, Sulowicz et al 2007*). Patients were randomized to receive Mircera administered either once every two weeks or once every four weeks, or to continue their current ESA schedule and dose. Throughout the trials, treatment with Mircera consistently maintained Hb concentrations within the targeted range (10 to 13.5 g/dL) and demonstrated non-inferiority compared to other ESAs.
- In addition, an extension trial was conducted that demonstrated the long-term safety and efficacy of Mircera administered every four weeks in maintaining stable Hb levels in patients with CKD not on dialysis following correction with Mircera administered every two weeks (*Kessler et al 2010*).

- Other direct-comparative trials have been conducted to evaluate the safety and efficacy of Mircera to other ESAs. In the trials, mean Hb concentrations remained constant within the recommended target range in all treatment groups and further confirmed the efficacy and safety of once monthly Mircera for correction and maintenance of Hb (*Al-Ali et al 2015, Carrera et al 2010, Roger et al 2011*).
  - The PATRONUS study evaluated Mircera IV every 4 weeks to IV darbepoetin alfa every four weeks in patients on hemodialysis (N = 490) (*Carrera et al 2010*). For the primary endpoint, Hb response rate (average Hb ≥ 10.5 g/dL with a decrease from baseline of ≤ 1 g/dL) was significantly higher in patients on Mircera (64.1%) in comparison to those given IV darbepoetin alfa (40.4%) ($p < 0.0001$).
- A systematic review compared the efficacy and tolerability of Mircera with darbepoetin alfa for the treatment of anemia in non-dialysis dependent patients (N = 1155) with CKD (*Alsalimy et al 2014*), Based on the analysis, changes in Hb level from baseline demonstrated that Mircera was clinically non-inferior to darbepoetin alfa.
- Two studies evaluated Mircera in the correction of Hb levels in anemic patients with CKD who were not treated with an ESA at baseline.
  - In the ARCTOS study, patients (N = 324) not currently receiving dialysis were randomized to Mircera administered every two weeks or darbepoetin alfa administered once a week for 28 weeks. Hb response rate, defined as an increase ≥1 g/dL vs baseline and a concentration ≥11 g/dL, was achieved in 97.5% of patients treated with Mircera and 96.3% of patients treated with darbepoetin alfa (*Macdougall et al 2008*).
  - In the second study, patients who were receiving either peritoneal dialysis or hemodialysis were randomized to Mircera IV every two weeks or epoetin alfa or beta IV administered three times weekly for 24 weeks. Hb response rate was achieved in 93.3% of patients treated with Mircera and 91.3% of patients treated with epoetin (*Klinger et al 2007*). Peak Hb levels were 12.28 g/dL for Mircera and 12.19 g/dL for epoetin.
- A Cochrane systematic review and meta-analysis evaluated the effect of treatment with continuous erythropoiesis receptor activator (Mircera) on health outcomes from 27 RCTs in 5410 adults with anemia and CKD, vs a different ESA (darbepoetin alfa or epoetin alfa or beta) or placebo (*Saglimbene et al 2017*).
  - The analysis demonstrated that overall, there was low certainty evidence that Mircera had little or no effects on patient-centered outcomes, including little or no effects on mortality (RR 1.07, 95% CI 0.73 to 1.57; RR 1.11, 95% CI 0.75 to 1.65), major adverse cardiovascular events (RR 5.09, 95% CI 0.25 to 105.23; RR 5.56, 95% CI 0.99 to 31.30), need for blood transfusion (RR 1.02, 95% CI 0.72 to 1.46; RR 0.94, 95% CI 0.55 to 1.61), or additional iron therapy (RR 1.03, 95% CI 0.91 to 1.15; RR 0.99, 95% CI 0.95 to 1.03) vs epoetin alfa/beta or darbepoetin alfa respectively.
  - There was insufficient evidence to compare the effect of Mircera to placebo on clinical outcomes.
  - No studies reported comparative treatment effects of different ESAs on HRQoL.

Anemia associated with chemotherapy

- In patients with anemia due to chemotherapy, ESAs should be avoided when the anticipated outcome of chemotherapy is cure. The use of ESAs for anemia from myelosuppressive chemotherapy should be at the lowest dose to avoid RBC transfusions and should be discontinued upon the completion of chemotherapy.
- The Agency for Healthcare Research and Quality (AHRQ) performed an updated meta-analysis of 59 randomized controlled studies, five of which directly compared epoetin alfa to darbepoetin alfa in patients diagnosed with malignant disease that were anemic or at risk for anemia from chemotherapy and/or radiotherapy or the underlying malignant disease. Of the endpoints evaluated, AHRQ found that the evidence did not show any clinically significant differences between epoetin alfa and darbepoetin alfa with regard to transfusion risk (pooled relative risk [RR], 1.14; 95% CI, 0.82 to 1.59; I^2=43%; 5 trials; N = 2005), on-study mortality (pooled HR, 0.9; 95% CI, 0.67 to 1.2; I^2 = 72%; 2 trials; N = 1567) and thromboembolic events (pooled RR, 0.86; 95% CI, 0.61 to 1.21; I^2 = 0%; 3 trials; N = 1873). ESA therapy was associated with higher thromboembolic event rates (pooled RR, 1.51; 95% CI, 1.3 to 1.74; I^2 = 0%; 37 trials; N = 12,570) and rates of on-study mortality (pooled HR, 1.17; 95% CI, 1.04 to 1.31; I^2 = 0%; 37 trials; N = 11,266) compared to controls. Of the other endpoints evaluated, it was determined that the evidence was not sufficient for conclusions on effects of either epoetin alfa or darbepoetin alfa compared to control on HRQoL, tumor response and progression, overall survival or adverse outcomes (*Grant et al 2013*).
- In another systematic review, ESAs were associated with a hematological response (defined as ≥2 g/dL increase in Hb or ≥6% increase in hematocrit) compared to control (risk ratio, 3.39; 95% CI, 3.1 to 3.71; 31 trials; N = 6413). However, there was significant heterogeneity between trials (I^2 = 53%). It was noted that all trials indicated a beneficial effect of

ESAs on hematological response (*Tonia et al 2012*). Other meta-analyses have reported similar findings (*Bohlius et al 2009*).

- In a patient-level meta-analysis, the effectiveness of darbepoetin in improving Hb levels and blood transfusions was evaluated in patients with chemotherapy-induced anemia with an initial Hb of ≤10 g/dL (*Pirker et al 2016*). Patient level data were obtained from four, Phase 3, randomized, double-blind, placebo-controlled trials of darbepoetin of 12 to 18 weeks in duration; for this analysis, data were extracted for patients with baseline Hb ≤10 g/dL (n = 261 for darbepoetin; n = 273 for placebo). This represented only 33% of the enrolled population. A second analysis evaluated darbepoetin only and identified 15 studies (n = 3768) without front loading and six studies with front loading (n = 901). For the endpoint of Hb increase of ≥1 g/dL or ≥2 g/dL vs placebo, darbepoetin improved Hb levels (HR 2.07, 95% CI, 1.62 to 2.63) and (HR 2.91, 95% CI, 2.09 to 4.06), respectively. Mean time to ≥1 g/dL increase in Hb was 43 days (95% CI, 37 to 50 days) for darbepoetin and not evaluable for placebo. Median time to a ≥2 g/dL increase was 78 days (95% CI, 71–not evaluable days) for darbepoetin and not evaluable for placebo. Transfusions were more commonly required between the start of week 5 and end of week 12 in patients who received placebo than in patients who received darbepoetin. Note that only Amgen sponsored studies were included in this analysis, and Amgen supported the meta-analysis.
- In an open-label, multicenter, randomized noninferiority trial, the impact on epoetin 40,000 units weekly on tumor outcomes was compared with the best supportive care for the treatment of anemia in 2098 patients receiving chemotherapy for metastatic breast cancer (*Leyland-Jones et al 2016*). The median progression-free survival (PFS) (based on investigator-determined disease progression) was 7.4 months in both groups (HR 1.089, 95% CI, 0.988 to 1.200) with the upper bound exceeding the prespecified noninferiority margin of 1.15. There was a reduction in the number of RBC transfusions in the epoetin-treated patients vs best supportive care (5.8 vs 11.4%; p < 0.001), while the rate of thrombotic vascular events was higher (2.8 vs 1.4%, respectively; p = 0.038). Overall, the noninferiority of treatment with epoetin was not established, and RBC transfusion was shown to be the best approach to manage anemia in patients with metastatic breast cancer receiving chemotherapy.
- Extended dosing intervals have been investigated. These extended dosing intervals of epoetin such as once every three weeks are not FDA-approved (*Glaspy et al 2009*).

Anemia associated with zidovudine in patients with HIV

- Early trials with epoetin in HIV were performed when zidovudine was one of only a few antiretrovirals available for treatment of HIV. Since the late 1980's and 1990's, numerous antiretroviral treatment options have become available and resulted in limited use of zidovudine. A meta-analysis of four, small, double-blind, randomized trials evaluated the efficacy and safety of epoetin compared to placebo in improving hematocrit values in patients with HIV or Acquired Immunodeficiency Syndrome (AIDS) (*Henry et al 1992*). In the 12-week trials, epoetin significantly increased hematocrit from baseline compared to placebo in patients with an endogenous erythropoietin level of ≤500 IU/L (mean change, 4.6 vs 0.5, respectively; p = 0.0002; mean difference, 3.9; 95% CI, 1.8 to 6).
- A meta-analysis of six randomized, clinical trials with 537 subjects evaluated the risk of death associated with epoetin or placebo in patients with HIV or AIDS and anemia (*Martí-Carvajal et al 2011*). None of the studies included evaluated death as a primary outcome. The risk of death was not statistically significant for epoetin versus placebo or when comparing epoetin once weekly vs three times weekly. Studies had significant attrition bias.

Reduced need for transfusions associated with surgery

- Clinical trials have evaluated the use of epoetin in reducing the need for blood transfusions in adults undergoing elective surgeries (*de Andrade et al 1996, Faris et al 1996, Goldberg et al 1996, Zhao et al 2016*). Epoetin is associated with an increased risk of deep venous thrombosis; therefore, appropriate preventative measures should be utilized.
- In a double-blind, multicenter, placebo-controlled trial, the efficacy and safety of epoetin 300 units/kg and 100 units/kg were compared to placebo in 316 adult patients scheduled for elective orthopedic surgery. The primary outcome was the rate of transfusion which was significantly lower in patients receiving epoetin 300 units/kg with a pretreatment Hb of >10 to ≤13 g/dL (epoetin 300 units/kg,16%; epoetin 100 units/kg, 23%; placebo, 45%; p = 0.024) (*de Andrade et al 1996*).
- Epoetin has been shown to reduce the need for blood transfusions in 200 patients undergoing elective orthopedic surgeries compared to placebo (*Faris et al 1996*). Epoetin 100 units/kg/day (17%) and epoetin 300 units/kg/day (25%) led to a reduction in the percentage of patients who required a blood transfusion following a major elective orthopedic surgery compared to control (54%; p ≤ 0.001 for both epoetin groups vs placebo). There was no significant difference between the two epoetin groups (p value not reported). The mean number of units transfused for each patient was significantly lower in the epoetin groups compared to the placebo group (epoetin 100 units/kg/day, 0.37±0.96; epoetin

300 units/kg/day, 0.58±1.15; placebo, 1.42±1.67; p < 0.01 for both epoetin groups compared to placebo). There was no significant difference between the epoetin groups (p > 0.05).

- A meta-analysis evaluated seven studies (N = 2439) to evaluate efficacy and safety of treatment with erythropoietin compared with controls (placebo or no intervention) in patients undergoing total hip or knee arthroplasty (*Voorn et al 2016*). Erythropoietin was shown to reduce exposure to RBC transfusion in both hip (RR 0.45, 95% CI, 0.33 to 0.61) and knee (RR 0.38, 95% CI 0.27 to 0.53) arthroplasty, without differences between indications (p = 0.44), and the mean number of transfused RBC units was decreased in erythropoietin-treated patients (mean difference -0.57, 95% CI -0.86 to -0.29) for both indications. There were no differences detected in thromboembolic and vascular adverse events (RR 1.14, 95% CI 0.71 to 1.84), nor other adverse events (RR 1.01, 95% CI 0.94 to 1.01) between erythropoietin compared with controls.
- A systematic review and meta-analysis evaluated 15 RCTs (N = 2155) to evaluate the hematopoiesis-promoting effect and potential complications, preoperative use of erythropoietin in patients scheduled for total hip or knee arthroplasty (*Zhao et al 2016*). Preoperative use of erythropoietin was associated with lower exposure to allogeneic blood transfusion (OR = 0.41) and higher hemoglobin concentration after surgery (standardized mean difference 0.86; p < 0.001). Complications were not generally reported, but there was no significant difference between the group with and without erythropoietin based on given data.

CLINICAL GUIDELINES

CKD

- The Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest that ESAs not be used to maintain Hb concentration above 11.5 g/dL in adults with CKD. In all adult patients, ESAs should not be used to increase Hb concentrations above 13 g/dL (*KDIGO 2012*). Current practice guidelines for anemia of CKD do not specify a preferred agent. The guidelines recommend that 'copy' versions of ESAs should only be those which have been designated true biosimilars (*KDIGO 2012*).
- Based on the recommendations from the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NHF – KDOQI) Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in CKD, the Hb level at which ESA therapy should be initiated as well as the Hb target during therapy should be based on the individual patient, potential benefits (including improvement in QoL and avoidance of transfusion) and potential harms of therapy (including the risk of life-threatening adverse events). Generally speaking, the guidelines recommend that patients with CKD, both dialysis and nondialysis, receiving ESA therapy have a Hb target range of 11 to 12 g/dL, and the Hb levels should not exceed 13 g/dL. This recommendation is based on clinical studies demonstrating that patients with a Hb ≥13 g/dL do not have improvements in survival, hospitalization or left ventricular hypertrophy and may in fact be more prone to excessive adverse cardiovascular events compared to individuals with lower Hb targets (*KDOQI 2006, KDOQI 2007*).
  - In June 2011, the FDA released more conservative recommendations for using the ESAs in patients with anemia of CKD resulting from data showing that using ESAs to target a Hb level of >11 g/dL increased the risk of cardiovascular events, without providing any additional benefit to patients (*FDA Drug Safety Communication 2011*). For patients with anemia of CKD who are not on dialysis, ESA treatment can be considered when the Hb level is <10 g/dL, and the dose should be reduced or interrupted when Hb exceeds 10 g/dL. For patients with anemia of CKD currently on dialysis, ESA treatment should be initiated when the Hb level is <10 g/dL, and the dose should be reduced or interrupted when Hb approaches or exceeds 11 g/dL.
  - The KDOQI US Commentary on the 2012 KDIGO guidelines state KDOQI continues to endorse the FDA-recommended upper cutoff of 11 g/dL (*Kliger et al 2013*).
- The European Renal Best Practice guidelines state Hb target range in patients with CKD should be 11 to 12 g/dL, ESAs should not be used to maintain Hb above 11.5 g/dL, and Hb should not exceed 13 g/dL (*Locatelli et al 2009, Locatelli et al 2010, Locatelli et al 2013*). Continuous erythropoiesis receptor activator (Mircera), a modified recombinant human erythropoietin, has a considerably longer half-life than other ESAs and should be dosed once every two weeks for anemic correction and once every four weeks for maintenance of Hb levels. The safety and tolerability of continuous erythropoiesis receptor activator are similar to that of other ESAs. Biosimilars of epoetin alfa can only be administered intravenously and should not be used in exchange of the original ESA or other ESAs without physician's approval. A lower Hb target range of 10 to 12 g/dL is reasonable in nondialysis patients with type 2 diabetes. In initiating and maintaining ESA therapy, the potential benefits of reducing blood transfusions and anemia-related symptoms should be

balanced against the risks of harm in individual patients (e.g. stroke, vascular access loss, or hypertension). ESAs should be used with great caution, if at all, in CKD patients with active malignancy, in particular when cure is the anticipated outcome, or with a history of stroke or malignancy. The lowest possible ESA dose should be used to reach the Hb target.

Chemotherapy Associated Anemia

- Based on the recommendations from the clinical guidelines, ESAs should be considered equivalent with respect to effectiveness and safety for the management of chemotherapy-induced anemia in patients with cancer (*Rizzo et al 2010*).

Perioperative Use of ESA

- Literature supports the use of ESAs with or without iron, as ESAs are effective in reducing the number of patients requiring allogeneic blood transfusions and reducing the volume of allogenic blood transfused (*American Society of Anesthesiologists Task Force 2015*) (Category A1-B evidence – supported by a sufficient number of randomized clinical trials to conduct a meta-analysis and supported by membership opinion).
  - Insufficient evidence exists to evaluate the efficacy of ESA with iron compared to ESA without iron.
  - ESAs with or without iron may be given, when possible, to reduce the need for allogeneic blood transfusions in selected patient populations such as renal insufficiency, anemia of chronic disease, or cases of refusal of transfusion.

SAFETY SUMMARY

- Contraindications:
  - Epoetin alfa from multiple-dose vials contains benzyl alcohol and is contraindicated for use in neonates, infants, pregnant women, and lactating women.
    - Benzyl alcohol has been associated with serious adverse events and death, particularly in pediatric patients.
    - When therapy is needed in neonates and infants, or pregnant or nursing mothers, use single-dose vials.
  - ESAs should not be used in patients with uncontrolled hypertension.
  - ESAs are contraindicated if pure red blood cell aplasia (PRCA) begins after treatment with erythropoietin agents.
- Boxed Warnings:
  - Erythropoiesis-stimulating agents (ESAs) increase the risk of death, myocardial infarction (MI), stroke, venous thromboembolism, thrombosis of vascular access, and tumor progression or recurrence.
  - In controlled trials, patients with CKD experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered ESAs to a target Hb level of > 11 g/dL. No trial has identified a Hb target level, ESA dose, or dosing strategy that does not increase these risks. Use the lowest dose of ESA sufficient to reduce the need for RBC transfusions.
  - In patients with cancer, ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in patients with breast, non-small cell lung, head and neck, lymphoid and cervical cancers. The warnings emphasize to only administer darbepoetin or epoetin for the treatment of anemia due to concomitant myelosuppressive chemotherapy and to discontinue ESAs following completion of a chemotherapy course. ESAs should not be initiated in cancer patients receiving myelosuppressive therapy when the anticipated outcome is cure.
  - Mircera is not indicated and is not recommended for the treatment of anemia due to cancer chemotherapy. A dose-ranging study of Mircera was terminated early because of more deaths among patients receiving Mircera than another ESA.
  - Perisurgery: Deep venous thrombosis prophylaxis is recommended when epoetin alfa is used preoperatively.
- Key Warnings/Precautions:
  - ESAs increase the risk of seizures in patients with CKD.
  - Epoetin alfa contains albumin, a derivative of human blood. There is an extremely remote risk for transmission of viral diseases.
  - Severe cutaneous reactions, including erythema multiforme and Stevens-Johnson Syndrome/toxic epidermal necrolysis, have been reported in patients treated with ESAs.
  - There is a risk of serious adverse reactions due to benzyl alcohol preservative in multiple-dose vials of epoetin alfa. Do not mix epoetin alfa with bacteriostatic saline (which also contains benzyl alcohol) when administering to neonates, infants, pregnant women, and lactating women.

- Serious and fatal reactions including “gasping syndrome” may occur in neonates and infants treated with benzyl alcohol-preserved drugs. The “gasping syndrome” is characterized by central nervous system depression, metabolic acidosis, and gasping respirations.
- There is a potential for similar risks to fetuses and infants exposed to benzyl alcohol in utero or in breast-fed milk, respectively.
- The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known
  - There is a risk of PRCA with darbepoetin alfa, epoetin alfa, and methoxy polyethylene glycol-epoetin beta therapy.
  - ESAs may decrease progression-free survival and overall survival in patients with breast cancer, lymphoid malignancy, cervical cancer, advanced head and neck cancer, non-small cell lung cancer or other malignancies.
- Risk Evaluation and Mitigation Strategy (REMS):
  - On April 13, 2017, the FDA removed the REMS from Aranesp, Epogen, and Procrit (*FDA REMS program 2018, Information for Epogen/Procrit 2017*). The decision was based on a survey showing that prescribers were already educated on the potential contribution of these products to the decreased survival or increased risk of tumor progression or recurrence when used for anemia due to myelosuppressive chemotherapy. Moreover, most data showed that ESAs were prescribed for FDA-approved indications. Due to removal of the REMS, health care providers and hospitals are no longer required to enroll and become certified to prescribe and dispense these agents.
- The most commonly reported adverse events with ESAs include hypertension, arthralgia, muscle spasm, and fever.
- There are no specific drug interactions reported with the use of ESAs.

Table 3. Specific Populations

Drug	Pediatrics	Pregnancy and Nursing
Aranesp (darbepoetin alfa)	Safety and efficacy of Aranesp in adults and pediatric patients were similar for the initial treatment of anemia in patients with CKD or in transition from another erythropoietin in pediatric patients with CKD. Safety and efficacy of Aranesp in pediatric patients with cancer have not been established.	Pregnancy Category C* Unknown whether excreted in breast milk; should be used with caution.
Epogen, Procrit (epoetin alfa)	Indicated in pediatric patients 1 month to 16 years of age for treatment of anemia in CKD requiring dialysis, and in patients 5 to 18 years of age for treatment of anemia due to concomitant myelosuppressive chemotherapy. Limited data are available on the use of epoetin in children with HIV receiving zidovudine. Multidose vials of Epogen/Procrit are formulated with benzyl alcohol. Do not administer to neonates or infants from multidose vials.‡	Unclassified† Data are limited: risks and benefits of single dose vials should be considered. Unknown whether excreted in breast milk; should be used with caution. The multidose vials of Epogen /Procrit are formulated with benzyl alcohol. Do not administer from multidose vials.†
Mircera (methoxy polyethylene glycol-epoetin beta)	Safety and efficacy have not been established.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.

* Pregnancy Category C = risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
†In accordance with the FDA’s Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.
‡Benzyl alcohol, found in multiple-dose preserved formulations, has been reported to be associated with an increased incidence of neurological and other complications in premature infants, which are sometimes fatal. Benzyl alcohol has also been associated with serious adverse events and death, particularly in pediatric patients.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Aranesp (darbepoetin alfa)	Single-dose vials, single-dose prefilled syringe (SingleJect®)	IV or SC injection	Anemia associated with CKD for patients on dialysis when Hb < 10 g/dL: Initial, once weekly once every two weeks; maintenance, dose should be individualized to maintain Hb levels that do not exceed 11 g/dL Anemia associated with CKD for patients not on dialysis when Hb is < 10 g/dL, and the rate of decline indicates a blood transfusion is likely and reducing RBC transfusion-related risks is a goal: Initial, once every four weeks; maintenance, dose should be individualized to maintain Hb levels that do not exceed 10 g/dL. Pediatrics with CKD: Initiate when Hb is < 10 g/dL. Hemodialysis: once weekly Non-hemodialysis: weekly or once every two weeks Anemia associated with concomitant chemotherapy in patients with non-myeloid malignancies when Hb < 10 g/dL and two or more additional months of chemotherapy are planned: Initial, once weekly or once every three weeks until completion of a chemotherapy course; maintenance, dose should be individualized to maintain desired response.	
Epogen, Procrit (epoetin alfa)	Multiple-dose vials (preserved solution), single-dose vials (preservative-free solution)	IV or SC injection	Anemia associated with CKD, including patients on dialysis and patients not on dialysis: Initial, three times weekly; maintenance, dose should be individualized to maintain Hb levels that do not exceed 11 g/dL (dialysis) or 10 g/dL (non-dialysis). For pediatric patients, three times weekly (dialysis). Anemia associated with concomitant chemotherapy in patients with non-myeloid malignancies when Hb < 10 g/dL and two or more additional months of chemotherapy are planned: Initial, three times weekly or once weekly until completion of a chemotherapy course;	Benzyl alcohol, found in multiple-dose preserved formulations, has been reported to be associated with an increased incidence of neurological and other complications, which are sometimes fatal, in premature infants. Single-dose preservative-free vials should be used in neonates and infants, as well as pregnant and nursing women.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			maintenance, dose should be individualized to maintain the lowest Hb level sufficient to avoid red blood cell transfusion. Pediatric patients (5 to 18 years of age): weekly until completion of chemotherapy course. Anemia associated with therapy of zidovudine in HIV-infected patients with endogenous serum erythropoietin levels < 500 mUnits/mL: Initial, three times weekly for eight weeks; maintenance, dose should be individualized to maintain desired response. Withhold epoetin if Hb >12 g/dL. Treatment of anemic patients (Hb > 10 to < 13 g/dL) at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions: daily dose for 10 days before surgery, on the day of surgery and for four days after surgery; alternative dosing schedule is once weekly, at 21, 14 and 7 days before surgery, with a fourth dose on the day of surgery.	
Mircera (methoxy poly-ethylene glycol-epoetin beta)	Prefilled syringes	IV or SC injection	Anemia associated with CKD, including patients on dialysis and patients not on dialysis: Initial, once every two weeks, dose should be individualized to maintain Hb levels that do not exceed 11 g/dL (dialysis) or 10 g/dL (non-dialysis). Once the Hb has been stabilized, may be administered once monthly.	When SC administered, should be injected in the abdomen, arm or thigh.

See the current prescribing information for full details.

- The iron status in all patients should be evaluated in all patients before and during treatment, and iron repletion maintained. Other causes of anemia should be corrected or excluded before initiating ESA.
- Intravenous administration of ESAs is recommended for patients receiving hemodialysis.
- For all ESAs, the dosing should be individualized and the lowest dose sufficient to reduce the need for RBC transfusions should be used.

CONCLUSION

- The FDA-approved erythropoiesis-stimulating agents (ESAs) in the United States are Aranesp (darbepoetin alfa), Epogen (epoetin alfa), Procrit (epoetin alfa), and Mircera (methoxy polyethylene-glycol epoetin beta). All agents are indicated for the treatment of anemia associated with CKD.
  - Aranesp, Epogen and Procrit are also indicated for the treatment of anemia due to the effect of concomitantly administered chemotherapy in patients with non-myeloid malignancies.

- Epogen and Procrit are also indicated for treatment of anemia related to therapy with zidovudine in HIV-infected patients as well as the treatment of anemic patients who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery.
- Clinical trials and meta-analyses comparing the efficacy of epoetin alfa and darbepoetin alfa for the treatment of anemia associated with CKD as well as anemia due to concomitant chemotherapy have demonstrated no differences between the agents (*Bohlius et al 2009, Collister et al 2016, Grant et al 2013, Nissenson et al 2002, Palmer et al 2014a, Palmer et al 2014b, Vanrenterghem et al 2002, Tonia et al 2012, Wilhelm-Leen et al 2015*).
- Numerous RCTs provide supportive evidence demonstrating the effectiveness of Mircera for the correction and maintenance of Hb in patients with anemia of CKD. Throughout the trials, treatment with Mircera corrected and maintained Hb concentrations within the targeted Hb range and demonstrated non-inferiority compared to other ESAs (*Al-Ali et al 2015, Carrera et al 2010, Canaud et al 2008, Levin et al 2007, Spinowitz et al 2008b, Sulowicz et al 2007, Roger et al 2011*). A meta-analysis demonstrated a low certainty of evidence that Mircera had little or no effects on patient-centered outcomes, including little or no effects on mortality, major adverse cardiovascular events, or need for blood transfusion vs epoetin alfa/beta or darbepoetin alfa (*Saglimbene et al 2017*).
- The ESAs are commonly used for the treatment of anemia associated with CKD to reduce the need for transfusions. The KDIGO guidelines suggest that ESAs not be used to maintain Hb concentration above 11.5 g/dL in adults with CKD. In adult patients, ESAs should not be used to increase Hb concentrations above 13 g/dL (*KDIGO 2012*). Current practice guidelines for anemia of CKD do not specify a preferred agent. The KDOQI guidelines state that each of the agents is effective at achieving and maintaining target Hb levels, and endorse the FDA-recommended upper cutoff of 11 g/dL (*KDIGO 2012, KDOQI 2006, KDOQI 2007, Kliger et al 2013*).
  - Based on the recommendations from the clinical guidelines, ESAs should be considered equivalent with respect to effectiveness and safety for the management of chemotherapy-induced anemia in patients with cancer (*Rizzo et al 2010*).
- All ESAs carry a boxed warning of increased mortality, serious cardiovascular and thromboembolic events, stroke and increased risk of tumor progression.
  - Multiple-dose vials of Epogen (epoetin alfa) and Procrit (epoetin alfa) contain benzoyl alcohol.
- Aranesp (darbepoetin alfa) is administered weekly or every two weeks, Epogen (epoetin alfa) and Procrit (epoetin alfa) are administered one to three times weekly and Mircera (methoxy polyethylene-glycol epoetin beta) is administered every two to four weeks.

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Publication Date: March 26, 2018

Therapeutic Class Overview
Alzheimer's Disease Agents

INTRODUCTION

- Alzheimer's disease (AD) is a progressive, degenerative neurological disease often presenting in later stages of life. In 2007, it was estimated that 5.1 million Americans are afflicted with AD, of which 4.9 million are aged ≥ 65 years. Before the age of 80 years, AD is more common in men and after the age of 80 years, the disease becomes more common in women (*Alzheimer's Association 2007, Letenneur et al 1999*).
- Patient presentation is diverse and includes a wide range of symptoms that manifest with cognitive and neuropsychiatric effects as a result of brain cell destruction. AD often begins with memory impairment that is followed, after several years, by a variety of other symptoms that affect motor function, planning and reasoning skills, and the ability to recognize objects and people (*American Psychiatric Association [APA] 2007, Bond et al 2012, Jones et al 2004, Wilcock et al 2003*).
- Patients often present with memory loss, aphasia, apraxia, agnosia, and loss of abstract planning skills.
  - Mild disease: Decline in ability to function at work or other usual activities, cognitive impairment, and poor judgment.
  - Moderate disease: Forgetfulness and poor understanding of safety risks that can lead to aimless wandering, mismanagement of finances, and household accidents like kitchen fires for which the individual may not understand how to manage.
  - Severe disease: Rely on others to carry out daily tasks involving grooming, feeding, and general self-care. (*APA 2007, Bond et al 2012, McKann et al 2011).*
- Various criteria have been developed in order to consistently and accurately diagnose AD, the most commonly used tools being the Mini Mental State Examination (MMSE), Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-V), Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog), and the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.
- These clinical diagnostic tools often correlate with pathological diagnosis, which is the only absolute method of diagnosis and can only be completed with an autopsy after death. During this autopsy, the examiner looks for amyloid-beta (Aβ) plaques and neurofibrillary tangles in the cerebral cortex, which confirm the diagnosis of AD (*APA 2007, Bond et al 2012, McKann et al 2011*).
- Typical management of AD includes an acetylcholinesterase (AChE) inhibitor with or without a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist depending on the severity stage diagnosis. These therapies, along with psychosocial treatment methods, have been shown to be effective in managing patient symptoms with some evidence to support their effect on the behavioral symptoms of AD (*APA 2007, Bond et al 2012, Jones et al 2004*).
- The AChE inhibitors include donepezil, rivastigmine, and galantamine. Memantine is a NMDA receptor antagonist.
- AChE inhibitors increase cholinergic function by inhibiting hydrolysis of acetylcholine. NMDA receptor antagonists prevent excess stimulation by blocking glutamate from binding (*Micromedex 2018, Wilcock et al 2003*).
- In the past, Vitamin E, NSAIDs, and estrogen supplements have been recommended for treatment of AD. This is no longer recommended due to a lack of supportive evidence regarding their efficacy as well as potential safety concerns associated with vitamin E (*APA 2007*).
- Tacrine will not be discussed in this overview since it has been withdrawn from the market. Several drug characteristics, the major ones being reversible hepatic toxicity and four times daily administration, made tacrine undesirable compared to the newer AChE inhibitors (*Drugs@FDA 2018*).
- Medispan class: Cholinomimetics – ACHE Inhibitors; Antidementia Agent Combinations; N-Methyl-D-Aspartate (NMDA) Receptor Antagonists

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Aricept (donepezil)	✔
Exelon (rivastigmine)	✔
Namenda (memantine)	✔
Namenda XR (memantine)	✔
Namzaric (donepezil/memantine)	-
Razadyne (galantamine)	✔
Razadyne ER (galantamine)	✔

(*Drugs@FDA 2018, Clinical Pharmacology 2018*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Aricept (donepezil)	Exelon (rivastigmine)	Namenda, Namenda XR (memantine)	Namzaric* (donepezil/ memantine)	Razadyne, Razadyne ER (galantamine)
Mild dementia of AD	✔	✔			✔
Moderate dementia of AD	✔	✔	✔	✔	✔
Severe dementia of AD	✔		✔	✔	
Mild to moderate dementia of PD		✔			

Abbreviations: XR = extended release; ER = extended release; AD = Alzheimer's disease, PD = Parkinson's disease
*Namzaric is indicated in patients with moderate to severe dementia of AD who are stabilized on certain doses of memantine and donepezil

(*Prescribing information: Aricept 2015, Exelon 2016, Namenda 2013, Namenda XR 2014, Namzaric 2014, Razadyne 2016, Razadyne ER 2016*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The following section highlights key studies associated with the treatment of AD, but does not represent the comprehensive body of evidence available.

Aricept

- A double-blind (DB), randomized controlled trial (RCT) (N = 290) in patients with moderate to severe AD evaluated the use of donepezil 5 to 10 mg/day compared with placebo for 24 weeks and was measured using the Clinician's Interview-Based Impression of Change with caregiver input (CIBIC+) as the primary outcome measure. The CIBIC+ least square scores for donepezil were above baseline severity until week 24, while it declined for placebo. A total of 63% of patients in the donepezil group and 42% of patients in the placebo group improved or had no change ($p < 0.0001$). Donepezil was favored over placebo for secondary outcome measures of the standardized Mini-Mental State Examination (sMME), the Severe Impairment Battery (SIB), Disability Assessment for Dementia (DAD), modified Instrumental Activities of Daily Living (IADL+), and the modified Physical Self-Maintenance Scale (PSMS+). Donepezil demonstrated consistent benefit in cognition, global function, behavior, and activities of daily living (ADL) in both primary and secondary outcome measures. Patients who withdrew from treatment due to adverse events represented 8% in the donepezil group and 6% in the placebo group (*Feldman et al 2001*).

Exelon

- An international RCT (N = 725) in patients with mild to moderately severe AD in Europe and North America evaluated the efficacy and safety of higher dose rivastigmine (6 to 12 mg/day) and lower dose rivastigmine (1 to 4 mg/day) vs placebo for an ITT population over 26 weeks. The outcome measures were the ADAS-cog, CIBIC+, and the progressive deterioration scale. On the ADAS-cog, more patients in the higher dose rivastigmine group improved clinically compared with placebo (24 vs 16%, respectively; $p < 0.1$). On the CIBIC+, more patients in both rivastigmine groups received ratings of marked, moderate, or minimal improvement than placebo (37% in higher dose group [$p < 0.001$] and 30% in lower dose group [$p < 0.05$] vs 20% placebo). On the progressive deterioration scale, more patients in the higher dose rivastigmine group significantly improved compared to placebo (29 vs 19%, respectively; $p < 0.01$). Rivastigmine improved cognition, global functioning, and ADL compared with placebo. More patients in the higher dose rivastigmine group (23%) withdrew from treatment due to adverse events compared to the lower dose rivastigmine group (7%) and the placebo group (7%) (*Rosler et al 1999*).
- One DB, RCT (N = 1195) of patients with mild to moderate AD evaluated the safety and efficacy of oral rivastigmine 12 mg daily or 2 doses of transdermal rivastigmine (10 and 20 cm^2) vs placebo for 6 months. The primary efficacy measures were the ADAS-cog and the AD Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC). At week 24, 27.4% of patients in the 10 cm^2 group, 32.8% in the 20 cm^2 group, and 28.5% in the oral rivastigmine group had clinical improvement (4 point improvement in ADAS-Cog) compared with 19.9% in the placebo group ($p < 0.05$). The 20 cm^2 patch had a higher mean improvement on the ADAS-cog vs the 10 cm^2 patch. Both doses of the transdermal rivastigmine were superior to placebo (better cognition, attention, ADL, motor processing speed, and visual tracking) and were non-inferior to oral rivastigmine. The incidence of adverse events was not statistically significantly different between the 10 cm^2 patch (51%) and placebo (46%), but was higher in the 20 cm^2 patch group (66%) and oral capsules (63%) compared to placebo ($p \leq 0.001$ for both) (*Winblad et al 2007*).
- A systematic review of 13 RCTs evaluated the use in patients with mild to moderate AD treated for ≥ 12 weeks. Results demonstrated rivastigmine was beneficial for ADL (standardized mean difference [SMD], 0.20; 95% confidence interval [CI], 0.13 to 0.27; N = 3230; 6 studies); cognitive function on the ADAS-cog (mean difference [MD], -1.79; 95% CI, -2.21 to -1.37, N = 3232, 6 studies) and on the MMSE (MD, 0.74; 95% CI, 0.52 to 0.97; N = 3205; 6 studies), and the clinician's global assessment compared with placebo. No differences were found in behavioral changes and impact on caregivers. In addition, oral rivastigmine was associated with a higher risk of adverse events compared to rivastigmine transdermal patch (odds ratio [OR], 0.68; 95% CI, 0.58 to 0.80) (*Birks et al 2015*).

Namenda

- A pooled analysis of 2 RCTs (Phase 2 dose-finding study [N = 315] and Phase 3 study [N = 432]) in patients with moderate to severe dementia in Japan over 24 weeks found that memantine (10 to 20 mg/day) was superior to placebo based on the Clinician's Interview-based Impression of Change plus Japanese (CIBIC plus-J) assessment. The outcome measures were CIBIC plus-J, Severe Impairment Battery-Japanese version (SIB-J), and the Behavioral Pathology in AD Rating Scale (BEHAVE-AD). At weeks 4, 12, and 24, memantine had statistically significantly better outcomes than placebo on the SIB-J ($p < 0.0001$ for all timepoints). At week 24, memantine had statistically significantly less worsening than placebo on the CIBIC plus-J ($p = 0.047$). At week 24, memantine had statistically significant improvements than placebo on the BEHAVE-AD ($p = 0.0040$). Memantine was associated with less worsening of behavioral symptoms, language ability, language function, attention, visuospatial, and praxis compared with placebo (*Nakamura et al 2014*).
- One meta-analysis of 9 RCTs (N = 2433) in patients with AD for ≥ 24 weeks demonstrated that memantine monotherapy (10 to 20 mg/day) was effective in improving cognitive function, ADL, behavioral disturbances, global function assessment, and stage of dementia compared with placebo. Memantine significantly improved the primary outcome measures of cognitive function (SMD, -0.27; 95% CI, -0.39 to -0.14; $p = 0.0001$) and behavioral disturbances (SMD, -0.12; 95% CI, -0.22 to -0.01; $p = 0.03$). Memantine did not worsen symptoms of AD and potentially reduced agitation vs placebo (RR, 0.68; 95% CI, 0.49 to 0.94; $p = 0.02$) (*Matsunaga et al 2015*).
- One DB, RCT (N = 404) evaluated memantine 20 mg daily and placebo in patients with moderate to severe AD for 24 weeks who were established on stable treatment with donepezil. The primary outcome measures were the SIB and the modified 19-item Alzheimer's Disease Cooperative Study-Activities of Daily Living ($ADCS\text{-}ADL_{19}$). Memantine demonstrated a statistically significant benefit over placebo for the SIB ($p < 0.001$) and $ADCS\text{-}ADL_{19}$ ($p = 0.03$) scales. Memantine had better outcomes in clinical global status, cognition, ADL, and behavior compared with placebo. A total of 12.4% of patients in the placebo group and 7.4% of patients in the memantine group withdrew treatment due to adverse events (*Tariot et al 2004*).

- In another RCT (N = 252) conducted over 28 weeks, patients with moderate to severe AD demonstrated superior outcomes for memantine 20 mg/day vs placebo in CIBIC+, SIB, and the Alzheimer's Disease Cooperative Study Activities of Daily Living modified for more severe dementia (ADCS-ADLsev). There was a high withdrawal rate (28.2%) noted within the trial; therefore, caution should be exercised with applying results. The primary outcome measures were CIBIC+ (MD, 0.3; p = 0.06) and ADCD-ADLsev (MD, 2.1; p = 0.02). The secondary outcome measures were SIB and other measures of cognition, function, and behavior. Patients treated with memantine had less deterioration and less time spent with caregivers. The proportion of patients who discontinued treatment due to adverse events were 17% within the placebo group and 10% within the memantine group (*Reisberg et al 2003*).

Namzaric

- One DB, RCT (N = 677) of patients with moderate to severe AD evaluated the use of memantine extended-release (ER) 28 mg vs placebo over 24 weeks. Patients were concomitantly administered cholinesterase inhibitors with 69% of patients co-administered donepezil. Of note, the donepezil plus memantine is the only combination treatment FDA-approved. For the primary outcome measures, combination treatment with memantine ER plus cholinesterase inhibitor was significantly better in CIBIC+ (p = 0.008), SIB (least square MD, 2.6; 95% CI, 1.0 to 4.2; p = 0.001), Neuropsychiatric Inventory (NPI, p = 0.005), and the Verbal Fluency Test (VFT, p = 0.004) vs placebo plus a cholinesterase inhibitor. No significant differences were found on the ADCS-ADL_{19} (p = 0.177). Approximately, 6% of patients in the placebo group and 10% of patients in the memantine ER group discontinued treatment because of adverse events. The populations that included memantine plus galantamine or rivastigmine were too small to draw any firm conclusions for treatment (*Grossberg et al 2013*). Evidence was consistent with other studies (*Boinpally et al 2015*).
- The DOMINO-AD study was a DB, placebo-controlled (PC), RCT (N = 295) in patients with moderate to severe AD treated with donepezil for at least 3 months. Patients were divided into 4 treatment groups: continuation of donepezil, discontinuation of donepezil, discontinuation of donepezil and initiation of memantine, or continuation of donepezil and initiation of memantine (using the sMMSE and the Bristol Activities of Daily Living Scale [BADLS]). The primary outcome measures were the sMMSE (with higher scores translating to better cognitive function) and BADLS (with higher scores translating to greater impairment). The continuation of donepezil group scored higher on the sMMSE by 1.9 points (95% CI, 1.3 to 2.5; p < 0.001) and lower on the BADLS by 3.0 points (95% CI, 1.8 to 4.3, p < 0.001) compared with the discontinuation of donepezil group. The continuation of memantine group scored higher on the sMMSE by 1.2 points (95% CI, 0.6 to 1.8, p < 0.001) and lower on the BADLS by 1.5 points (95% CI, 0.3 to 2.8, p = 0.02) compared with the discontinuation of memantine group. The combination of donepezil and memantine showed no significant benefit vs donepezil alone (*Howard et al 2012*).

Razadyne

- One DB, RCT (N = 653) evaluated use in patients with mild to moderate AD over the period of 6 months. Results demonstrated that galantamine had improvements in ADL, cognition, global function, and daily function compared to placebo. The primary outcome measures were the CIBIC+ and the ADAS-cog. Galantamine (at lower [24 mg] and higher [32 mg] doses) demonstrated better outcomes for CIBIC+ compared to placebo (p < 0.05). On the ADAS-cog, patients on galantamine had significantly better cognition than patients on placebo at 6 months (lower dose, 3.1; 95% CI, 1.7 to 4.5; p < 0.001 and higher dose, 4.1; 95% CI, 2.7 to 5.6; p < 0.001). Galantamine patients reported more (incidence ≥ 5% vs placebo) nausea, vomiting, diarrhea, dizziness, headache, anorexia, and weight loss. There were a total of 18% of patients on galantamine and 9% of patients on placebo who discontinued treatment due to adverse events (*Wilcock et al 2000*).
- One open label (OL) extension trial of 2 DB and OL studies (N = 491) evaluated the safety and efficacy of galantamine 24 mg in patients with mild to moderate AD for a total treatment period of 24 months (with exposures up to 36 months). Cognitive deterioration occurred slowly in patients treated with galantamine according to the Alzheimer's disease Assessment Scale-cognitive subscale (ADAS-cog), which was a co-primary outcome measure. On the ADAS-cog, 48.8% of patients on galantamine had ≤ 10 point increase, 15.3% maintained cognitive function at or above baseline, and majority of patients on galantamine had ≤ 20 point increase. For the additional co-primary endpoint, total DAD scores decreased significantly throughout the study (p < 0.002 at initial visit and p < 0.001 from baseline). The most common treatment emergent adverse events were agitation (16.1%), insomnia (12.4%), fall (11.2%), and urinary tract infection (10.2%) (*Pirttila et al 2004*).
- The SERAD study was a DB, PC, RCT (N = 407) in patients with severe AD treated with galantamine 24 mg vs placebo for 6 months. The primary outcome measures were the SIB and the minimum data set-activities of daily living (MDS-ADL). Patients who were treated with galantamine improved in the SIB score by week 26 (increased by 1.9 points),

while patients who were treated with placebo declined in the SIB score (decreased by 3.0 points) (least squares mean difference, 4.36; 95% CI, 1.3 to 7.5; p = 0.006). Both treatment groups declined in the MDS-ADL self-performance score at week 26 from baseline with 1.2 points in the galantamine group and 1.6 points in the placebo group; however, differences were not statistically significant (least squares mean difference, -0.41; 95% CI, -1.3 to 0.5; p = 0.38). Galantamine improved SIB domains of memory (p = 0.006), praxis (p = 0.01), and visuospatial ability (p = 0.002) compared with placebo. A total of 88% of patients in the galantamine group and 89% in the placebo group experienced at least 1 adverse event (*Burns at el 2009*).

- One PC, RCT (for 4 months) and OL extension (for an additional 4 months) in patients (N = 130) with mild to moderate AD evaluated galantamine 16 to 24 mg compared to placebo. Galantamine significantly improved the primary outcome measure of the Goal Attainment Scaling (GAS) on the clinician-rate GAS score vs placebo after 4 months (absolute difference, 4.0; p = 0.02; standardized response mean [SRM] = 0.41), but not on the patient-caregiver-rated GAS score (absolute difference between groups, 1.9; p = 0.27; SRM = 0.20). There were significant differences on the ADAS-cog scores and the CIBIC+ that favored galantamine. The most frequently reported adverse events (incidence > 10% vs placebo) were nausea and vomiting (*Rockwood et al 2009*).

Comparative Effectiveness Reviews

- One meta-analysis of 16 RCTs (5169 received AChE inhibitors [donepezil, galantine, and rivastigmine] and 2795 received a placebo) in patients with mild to moderate AD found that AChE inhibitors were effective compared with placebo in AD. AChE inhibitors demonstrated significantly better global improvement response than placebo for minimal improvement or better, marked improvement, and stabilization or better. However, AChE inhibitors also had significantly more adverse events compared with placebo (8%; 95% CI, 5 to 11%). The proportion of patients administered AChE inhibitors who dropped out due to adverse events were 7% (95% CI, 3 to 10%) (*Lanctot et al 2003*).
- One head-to-head RCT (N = 994) evaluated the efficacy, safety, and tolerability of donepezil 5 to 10 mg vs rivastigmine 3 to 12 mg in patients with moderate to moderately severe AD over a 2 year period. For the primary outcome of SIB, results were similar. A total of 34.8% of patients administered donepezil and 36.5% of patients administered rivastigmine had SIB scores equal or better than baseline at 26 months. However, it was not statistically significant. At 104 weeks, rivastigmine demonstrated better efficacy in ADL than donepezil on the ADCS-ADL (24.7 vs 19.4%, p = 0.047) as well as better efficacy in global deterioration than donepezil on the global deterioration scale (GDS; 53.1% vs 45.3%, p = 0.016). Only 57.9% of patients completed the study, mainly due to adverse events (gastrointestinal-related) with more patients in the rivastigmine group experiencing adverse events during the titration Phase. (*Bullock et al 2005*).
- One systemic review evaluated the cognitive decline and the benefits of inventions for clinical Alzheimer's type dementia across 10 studies. Based on results, AChE inhibitors may not reduce the incidence of clinical Alzheimer's type dementia or provide a significant effect on cognitive performance in patients with mild cognitive impairment; however, evidence was of lower quality. A study of patients with normal cognition (N = 28) demonstrated insufficient evidence and no cognitive benefits compared with placebo over 26 weeks. The study of patients with mild cognitive impairment (N = 769) demonstrated low-strength evidence in delaying progression of dementia over 18 months to 2 years and demonstrated no benefit at 3 years compared with placebo (*Kane et al 2017*).

CLINICAL GUIDELINES

Overall

- Several guidelines outline the goals for AD therapy are to delay the progression of symptoms and to preserve functional ability. In general, guidelines do not prefer one agent over another. The choice of treatment is based on tolerability, adverse events and ease of use (*APA 2007, Bond et al 2012, Bullock et al 2005, Hogan et al 2004, Hort et al 2010, Jones et al 2004, Rabins et al 2014, Wilcock et al 2003, Wilkinson et al 2002*).
- All AChE inhibitors are FDA-approved for mild and moderate disease. Donepezil is the only AChE inhibitor that is also approved for severe disease. Memantine is the only NMDA antagonist approved for use in AD and is only indicated for patient with moderate or severe disease. These treatments all show evidence of slowing cognitive decline and improving global outcome, behavior, and activities of daily living (ADL). There is no sufficient evidence to support the use of any medications for the primary prevention of AD (*APA 2007, Bond et al 2012, Hort et al 2010*).
- Medication(s) should be chosen based on the severity of the disease since FDA approval is dependent on disease severity. Guidelines recommend starting patients on one of the approved AChE inhibitors (donepezil, rivastigmine, and galantamine). If symptoms have not improved and the patient has moderate or severe disease, it is recommended to add memantine as adjunct therapy (*APA 2007*). This is due to multiple studies showing that use of an AChE inhibitor in

combination with memantine yields better outcomes than an AChE inhibitor alone (*Bond et al 2012, Bullock et al 2005, Hogan et al 2004, Jones et al 2004, Wilcock et al 2003, Wilkinson et al 2002*).

- AChE inhibitors all show similar efficacy rates with differing tolerability, but none have been shown to be superior (*Bond et al 2012, Bullock et al 2005, Hogan et al 2004, Jones et al 2004, Wilcock et al 2003, Wilkinson et al 2002*).

American Psychiatric Association (APA)

- The American Psychiatric Association (APA) guidelines for AD recommend initiating non-pharmacological management (i.e., occupational therapy, physiotherapy, mental stimulation, social services, speech and language therapy, aromatherapy, education) approaches before prescribing medication due to the modest benefit and varying levels of support for these pharmaceutical treatments. Upon failure of non-pharmacologic treatments, medication should be initiated, but it is recommended that doctors discuss the medication risks and benefits before initiating treatment (*APA 2007, Hort et al 2010*).
  - There is evidence of modest improvement in some patients treated with AChE inhibitors and therapy is appropriate in patients with mild or moderate AD for whom the medication is not contraindicated. Evidence suggests similar efficacy among agents; however, they may differ in tolerability.
  - Memantine should be considered in patients with moderate to severe AD. There is modest evidence that the combination of memantine and donepezil is better than donepezil alone, but there is no evidence that this combination is better than memantine monotherapy.
  - Due to reduced clearance in elderly individuals, medication should be started at low doses and slowly titrated until a reduction in symptoms is seen. This is done to minimize the occurrence of adverse reactions which tend to be mild and predominantly affect the gastrointestinal system but also include confusion, orthostatic hypotension, sedation, and more (*APA 2007*).
  - The APA guidelines discourage the use of NSAIDs, Vitamin E, *Ginko biloba*, and estrogen supplements for the management of AD. No evidence has demonstrated an effect on cognitive decline and some have been shown to be detrimental to cognition and can cause extraneous adverse effects (*APA 2007, Hort et al 2010, Rabins et al 2014*).
- An 2014 update to the APA guidelines stipulate that AD evidence remains modest for certain medications (eg, cholinesterase inhibitors and memantine):
  - No clinically meaningful advantages have been observed with higher doses of donepezil; however, higher doses of the rivastigmine patch may produce efficacy advantages. There is no evidence to support the use for cognitive symptomatic treatment or prevention *(Rabins et al 2014*).
  - New trials for memantine in mild to moderate AD demonstrated no benefit.
  - Caution should be exercised when considering mood stabilizing medications for comorbid conditions due to lack of evidence except for atypical antipsychotics. Upon implementation, these mood stabilizers should be reduced when symptoms have been controlled for 4 to 6 months to assess the need for continued use (*APA 2007, Rabins et al 2014*).

European Federation of Neurological Societies (EFNS)

- The EFNS guidelines are in agreement with the 2007 APA guidelines. Other recommendations include:
  - Recommend AChE inhibitors (donepezil, galantamine, or rivastigmine) be considered at the time of diagnosis for mild to severe disease. Memantine should be considered in patients with moderate to severe AD.
  - Where possible, initial treatment should be non-pharmacological.
  - Evidence does not support the use for any medications for the primary prevention of dementia. Cholinesterase inhibitors, vitamin E, gingko and estrogens should not be used as treatments for those with mild cognitive impairment.
  - Memantine may provide benefits for some non-cognitive symptoms (ie, agitation and delusions) *(Hort et al 2010*).

SAFETY SUMMARY

- Contraindications
  - Patients who have a history of application site reaction with rivastigmine transdermal patch is suggestive of allergic contact dermatitis.

- Warnings/Precautions
  - Namenda, Namenda XR, Namzaric: Increased plasma levels of memantine and decreased urinary elimination of memantine may result if patients have conditions that raise urine pH
  - Razadyne, Razadyne ER: Serious skin reactions (i.e., Stevens-Johnson syndrome) have been reported; patient should discontinue at the first appearance of a skin rash
  - Exelon: May worsen driving or use of machinery in addition to the patient's dementia
  - Cholinesterase inhibitors (donepezil, rivastigmine, galantamine):
    - May exaggerate the neuromuscular blocking effects of succinylcholine-type muscle relaxation during anesthesia
    - May have vagotonic effects on the sinoatrial and atrioventricular nodes, causing heart block or bradycardia in patients with or without underlying cardiac conduction abnormalities
    - May increase gastric acid secretion due to increased cholinergic activity, causing gastrointestinal bleeding or peptic ulcer disease in patients with underlying conditions or on nonsteroidal anti-inflammatory drugs (NSAIDs)
    - May have the potential to cause generalized convulsions, but it may also be a manifestation of Alzheimer's disease
    - Should be prescribed with care to patients with a history of asthma or chronic obstructive pulmonary disease

- The most common adverse events associated with each agent are:
  - Aricept: Nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, anorexia
  - Exelon: Nausea, vomiting, anorexia, dyspepsia, asthenia
  - Exelon patch: Nausea, vomiting, diarrhea
  - Namenda: Dizziness, headache, confusion, constipation
  - Namenda XR: Headache, diarrhea, dizziness
  - Razadyne, Razadyne ER: Nausea, vomiting, diarrhea, dizziness, headache, decreased appetite

- Key Drug Interactions
  - Cholinesterase inhibitors can interfere with the activity of anticholinergic medications
  - Cholinesterase inhibitors have a synergistic effect when given with succinylcholine, cholinergic agonists (ie, bethanechol), other neuromuscular blocking agents, or other cholinesterase inhibitors
  - Exelon and metoclopramide: Increased risk of extrapyramidal adverse effects
  - Exelon and beta blockers: May cause additive bradycardic effects leading to syncope
  - Namenda/Namenda XR and other NMDA antagonists: Approach with caution since it has not been systemically evaluated

- Other safety comments
  - Aricept, Razadyne, Razadyne ER: Pregnancy category C
  - Exelon, Namenda, Namenda XR: Pregnancy category B

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Aricept (donepezil)	Tablet, oral disintegrating tablet	Oral	Once daily in the evening	May be taken with or without food.
Exelon (rivastigmine)	Capsule, TD patch	Oral, TD	Capsule: Twice daily TD patch: Once in a 24 hour period	Capsule: Patients with moderate and severe renal impairment as well as mild and moderate hepatic impairment may only tolerate lower doses. TD patch: Consider dose adjustments in patients with mild to moderate hepatic impairment.
Namenda, Namenda XR (memantine)	Tablet, solution, capsule ER, titration pack	Oral	Once daily	May be taken with or without food. Capsule ER: May be taken whole, or sprinkled on applesauce. Lower doses are recommended in patients with severe renal impairment (CrCL 5 to 29 mL/min). Use with caution in patients with severe hepatic impairment.
Namzaric (donepezil/ memantine)	Capsule ER, therapy pack	Oral	Once daily in the evening	May be taken with or without food, whole, or sprinkled on applesauce.
Razadyne, Razadyne ER (galantamine)	Tablet, capsule ER	Oral	Tablet: Twice daily, Capsule ER: Once daily	Should not exceed 16 mg/day for moderate hepatic impairment (Child Pugh score of 7 to 9) or in patients with CrCL of 9 to 59 mL/min. Do not use for severe hepatic impairment (Child Pugh score of 10 to 15) or in patients with CrCL of < 9 mL/min.

Abbreviations: CrCL = creatinine clearance, ER = extended release, TD = transdermal
See the current prescribing information for full details

CONCLUSION

- AD is a progressive, degenerative neurological disease often presenting in later stages of life. Patients often present with memory loss, aphasia, apraxia, agnosia, and loss of abstract planning skills.
- Non-pharmacological approaches should be initiated before prescribing medication due to the modest benefit and varying levels of support for these pharmaceutical treatments. Upon failure of non-pharmacologic treatments, medication should be initiated, but it is recommended that doctors discuss the medication risks and benefits before initiating treatment.
- Management of AD includes an AChE inhibitor with or without a noncompetitive NMDA receptor antagonist depending on the severity stage diagnosis (mild, moderate, or severe), along with psychosocial treatment methods, have been

shown to be effective in managing patient symptoms with some evidence to support their effect on the behavioral symptoms of AD.

- Common adverse effects for the class include nausea, vomiting, and diarrhea.
- All AChE inhibitors are FDA-approved for mild and moderate disease. Donepezil is the only AChE inhibitor that is also approved for severe disease. Memantine is the only NMDA antagonist approved for use in AD and is only indicated for patient with moderate or severe disease. Evidence has demonstrated that memantine may be combined with a cholinesterase inhibitor. AChE inhibitors all show similar efficacy rates with differing tolerability, but none have been shown to be superior.
- Clinical trials evaluating the efficacy and safety of AD agents include over 40 measurement tools, which measure outcomes related to global function, cognition, behavior, and quality of life. Indirect comparisons between treatments are difficult as there are methodologic limitations including inconsistent results, different tools of measure, inadequately described follow up, and sometimes high dropout rates. None-the-less, current clinical trials, systematic reviews, and meta-analyses support the efficacy of these medications for their FDA-approved indications and have shown to be superior to placebo. There is limited evidence available head-to-head.
- Rivastigmine is available as a transdermal patch and may have less side effects than oral rivastigmine. There may be efficacy advantages with administering higher doses of the rivastigmine patch. Rivastigmine is the only agent in class which has an indication for the symptoms of dementia in PD (*Birks et al 2015, Rabins et al 2014*).
- Several guidelines outline the goals for AD therapy are to delay the progression of symptoms and to preserve functional ability. In general, guidelines do not prefer one agent over another. The choice of treatment is based on tolerability, adverse events and ease of use (*APA 2007, Bond et al 2012, Bullock et al 2005, Hogan et al 2004, Hort et al 2010*, *Jones et al 2004, Rabins et al 2014, Wilcock et al 2003, Wilkinson et al 2002*).
- AD treatments demonstrate evidence of slowing cognitive decline and improving global outcome, behavior, and ADL; however, improvements are modest. Other limitations include inconsistent evidence from large, well-designed trials and in many cases well-designed trials are generally conducted under a duration of 1 year. There is no sufficient evidence to support the use of any medications for the primary prevention of AD.

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Publication Date: May 7, 2018

Therapeutic Class Overview
Anti-migraine Agents (triptans)

INTRODUCTION

- Migraine is a common disabling primary headache disorder that can be divided into 2 major subtypes: without aura (the most common subtype and is associated with a higher average attack frequency) and with aura. According to the International Classification of Headache Disorder (IHS), migraine is a common primary headache disorder manifesting in attacks lasting 4 to 72 hours in adults and 1 to 72 hours in children. Migraines range from moderate to very severe and are sometimes debilitating. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia. When attacks occur ≥15 days/month for >3 months, patients are considered to have chronic migraines (Cutrer et al, 2017; Snow et al, 2002; IHS, 2018a; IHS, 2018b).
- The migraine 1-year prevalence rate in Americans is approximately 12% (17% of women and 6% of men) (Cutrer et al, 2017; Lipton et al, 2001).
- The Food and Drug Administration (FDA) Industry Guidance recommendations and the IHS recommend 2 co-primary endpoints for trials measuring efficacy of acute treatment of migraines. One is the proportion of patients who are pain-free at 2 hours and the other is the reduction of the most bothersome migraine-associated symptom at 2 hours (FDA Industry Guidance [migraine], 2018; Tfelt-Hansen et al, 2012).
- The serotonin (5-HT1) receptor agonists, also referred to as triptans, work in the management of migraine via the promotion of vasoconstriction, inhibition of dural vasodilation and inflammation, and blockade of pain pathways in the brainstem (Clinical Pharmacology, 2018). In contrast to analgesics, the triptans are considered to be "specific" migraine therapies because they act at the pathophysiologic mechanisms of headaches (Bajwa et al, 2018).
- In adults, all triptans are FDA-approved for the acute treatment of migraines with or without aura. In addition to the acute treatment of migraines, subcutaneous sumatriptan is also approved for cluster headaches. The agents FDA-approved in pediatric patients include almotriptan, sumatriptan/naproxen, zolmitriptan nasal spray (for ≥12 years of age), and rizatriptan (for ≥6 years of age).
- There is well-established evidence demonstrating the triptans to be an effective option for acute treatment of migraine; however, there is inconsistent head-to-head data demonstrating the superiority of any triptan, making it difficult to recommend the use of 1 over another (Bajwa et al, 2018). Some treatment guidelines do not differentiate among various formulations (Evers et al, 2009; Francis et al, 2010; Matchar et al, 2000; Silberstein, 2000; Silberstein et al, 2012 [guideline reaffirmed in 2015]; Erratum in Subcommittee of the American Academy of Neurology [AAN] and the American Headache Society [AHS], 2013; Snow et al, 2002). Additional key therapies for the treatment of migraines include nonsteroidal anti-inflammatory drugs (NSAIDs), dihydroergotamine (DHE nasal spray or inhaler), and opioid medications; however, some medications are not recommended for regular use (Marmura et al, 2015; Silberstein et al, 2012 [guideline reaffirmed in 2015]; Erratum in Subcommittee of the AAN and the AHS, 2013). For the treatment of cluster headaches, the 2016 AHS guidelines recommend subcutaneous sumatriptan and zolmitriptan nasal spray (Robbins et al, 2016). In pediatric patients, the Child Neurological Society recommends ibuprofen, followed by acetaminophen, and sumatriptan nasal spray when all other analgesics fail (Lewis et al, 2004). An update of the 2004 Child Neurological Society guideline is currently in progress.
- FDA-approved triptans are available as an oral tablet (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, sumatriptan/naproxen combination, zolmitriptan), orally disintegrating tablet (rizatriptan, zolmitriptan), nasal spray (sumatriptan, zolmitriptan), nasal powder (sumatriptan), and subcutaneous injection (sumatriptan) (DRUGS@FDA, 2018). Branded products are outlined in Table 1.
- According to DRUGS@FDA, the marketing status of ALSUMA and SUMAVEL DOSEPRO is discontinued; therefore, these products have been removed from the therapeutic class overview (DRUGS@FDA, 2018).
- In October 2017, the FDA announced Teva's voluntary discontinuation of ZECUITY (sumatriptan iontophoretic transdermal system) due to post-marketing reports of application site reactions, including severe redness, cracked skin, blistering/welts, and burns/scars associated with the product (FDA Drug Shortages and Discontinuations, 2017). Therefore, this product has been removed from the therapeutic class overview.

- Medispan class: Migraine Products – Selective Serotonin Agonists 5-HT(1); Selective Serotonin Agonist-NSAID Combinations

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
AMERGE (naratriptan hydrochloride tablet)	various	02/10/1998	✔
AXERT (almotriptan malate tablet)	various	05/07/2001	✔
FROVA (frovatriptan succinate tablet)	various	11/08/2001	✔
IMITREX (sumatriptan tablet, nasal spray, injection)	various	12/28/1992	✔
IMITREX STATDOSE (sumatriptan cartridges for injection)	various	12/23/1996	✔
MAXALT (rizatriptan benzoate tablet)	various	06/29/1998	✔
MAXALT MLT (rizatriptan benzoate orally disintegrating tablet)	various	06/29/1998	✔
ONZETRA XSAIL (sumatriptan nasal powder)	Merck & Co., Inc.	01/27/2016	-
RELPAX (eletriptan hydrobromide tablet)	Pfizer	12/26/2002	✔
TREXIMET (sumatriptan/naproxen sodium tablet)	GlaxoSmithKline	04/15/2008	✔
ZEMBRACE SYMTOUCH (sumatriptan injection)	Nupathe Inc.	01/28/2016	-
ZOMIG (zolmitriptan nasal spray, tablet)	various	09/30/2003	✔ (tablets only)
ZOMIG-ZMT (zolmitriptan orally disintegrating tablet)	various	02/13/2001	✔

(DRUGS@FDA, 2018; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2018)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

	AMERGE (naratriptan tablet)	AXERT (almotriptan tablet)	FROVA (frovatriptan tablet)	IMITREX (sumatriptan tablets, nasal spray, injection)	IMITREX STATDOSE (sumatriptan cartridges for injection)	MAXALT (rizatriptan tablet)	MAXALT MLT (rizatriptan ODT)	ONZETRA XSAIL (sumatriptan nasal powder)	RELPAX (eletriptan tablet)	ZEMBRACE SYMTOUCH (sumatriptan injection)	ZOMIG (zolmitriptan nasal spray, tablet)	ZOMIG ZMT (zolmitriptan ODT)	TREXIMET (sumatriptan/naproxen tablet)
Acute treatment of migraine with or without aura	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔ ‡	✔	✔
Acute treatment of cluster headache				✔ *	✔								
Acute treatment of migraine with or without aura (aged ≥ 6 years)						✔	✔						
Acute treatment of migraine headache pain in adolescents with a history of migraine with or without aura, and who have migraine attacks usually lasting ≥ 4 hours when untreated (aged ≥ 12 years)		✔ §											
Acute treatment of migraine with or without aura (aged ≥ 12 years)											✔ †‡		✔

Abbrv: ODT = orally disintegrating tablet
*Indication applies only to the injection formulation
†Indication applies only to the nasal spray formulation
Class Limitations of Use: All agents in class are not intended to be used as prophylactic migraine therapy. Use is recommended only after a clear diagnosis of migraine (or cluster headache, if FDA-approved for use) has been established. Agents are not indicated for the treatment of cluster headache unless FDA-approved.
Additional Limitations of Use:
‡Nasal spray is not recommended in patients with moderate to severe hepatic impairment
§For adolescents aged 12 to 17 years, efficacy on migraine-associated symptoms was not established.

(Prescribing information: AMERGE, 2016; AXERT, 2017; FROVA, 2013; IMITREX injection, 2017; IMITREX nasal spray, 2017; IMITREX tablets, 2017; MAXALT, 2015; MAXALT MLT, 2015; ONZETRA XSAIL, 2016; RELPAX, 2013; TREXIMET, 2016; ZEMBRACE SYMTOUCH, 2017; ZOMIG nasal spray, 2016; ZOMIG tablets, 2017; ZOMIG ZMT, 2017)

Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- In general, clinical trial data consistently demonstrate the superiority of the triptans over placebo in achieving headache pain relief and freedom from pain at 2 hours and sustained pain-free response, reducing rescue medication use and improving migraine-associated symptoms such as nausea, photophobia and phonophobia (Bird et al, 2014; Brandes et al, 2007; Cady et al, 2015; Derry et al, 2012 [a]; Derry et al, 2012[b]; Derry et al, 2012[c]; Derry et al, 2014; Ferrari et al, 2002; Law et al, 2016; Oldman et al, 2002; Pascual et al, 2007; Poolsup et al, 2005; Prescribing information: IMITREX, 2015; ZEMBRACE SYMTOUCH, 2017; Richer et al, 2016).
- While there appear to be differences in the relative efficacies among the triptans, direct head-to-head trials do not consistently support the use of 1 over another, suggesting that individual variations in response to different triptans exist. 5-HT_1 receptor agonists have been evaluated in numerous meta-analyses and comparative trials with sumatriptan often used as the benchmark standard as it has the most clinical experience available. All 5-HT_1 receptor agonists are effective at treating migraines and are well-tolerated; however, there are some notable differences between the different agents and formulations. Based on older evidence and reviews, the following conclusions were drawn (Derry et al, 2012[a]; Derry et al, 2012[b]; Derry et al, 2012[c]; Derry et al, 2014; Ferrari et al, 2002; Oldman et al, 2002; Pascual et al, 2007):
  - o Rizatriptan 10 mg has the fastest onset of action and the highest efficacy rates of pain-free and headache relief at 2 hours post-dose for oral agents (Oldman et al, 2002); however, the rate of recurrence at 24 hours appears to be higher with rizatriptan (Ferrari et al, 2002; Pascual et al, 2007). Naratriptan 2.5 mg has lower efficacy rates of pain-free and headache relief at 2 hours (Pascual et al, 2007) while eletriptan has a lower rate of recurrence (Ferrari et al, 2002).
  - o Subcutaneous sumatriptan is the most effective for migraine treatment but is associated with more adverse events (AEs) relative to the other 5-HT_1 receptor agonist formulations (Oldman et al, 2002; Derry et al, 2012[c]).
  - o Frovatriptan has the least number of head-to-head trials with active comparators. A recent pooled analysis of 3 studies showed similar efficacy at 2 hours post-dose with pain-free and pain relief responses between frovatriptan and the comparator group (consisting of almotriptan, rizatriptan, and zolmitriptan); however, frovatriptan had less recurrent episodes at 48 hours post-dose than the comparator group (P<0.001) (Cortelli et al, 2011).
  - o Sumatriptan/naproxen fixed-dose combination is more effective for migraine treatment than monotherapy or placebo when measuring headache relief at 2 hours and associated symptoms of migraine, with a similar AE profile to sumatriptan monotherapy (Brandes et al, 2007).
  - o Most 5-HT_1 receptor agonists are well-tolerated; however, naratriptan 2.5 mg and almotriptan 12.5 mg appear to have the lowest risk of causing an AE (Ferrari et al, 2002).
- Recent evidence is summarized below:
  - o The newest intranasal sumatriptan formulation, ONZETRA XSAIL, was evaluated in 2 double-blind (DB), randomized trials in 498 patients with moderate to severe migraines through the TARGET and COMPASS studies. The TARGET study (n=230) resulted in significantly more patients who experienced headache relief at 2 hours post-dose among those who received nasal powder sumatriptan 22 mg compared to placebo (68% vs. 45%, respectively; P=0.002). At 30 minutes post-dose, a significant difference in relief was maintained between treatment groups (42% vs. 27%; P=0.03) (Cady et al, 2015). The COMPASS study was a cross-over study with a high drop-out rate, which compared nasal powder sumatriptan 22 mg to oral sumatriptan 100 mg (n=275; 1,531 migraines assessed) in patients with 2 to 8 migraines/month at baseline. Primary endpoint results demonstrated a significant reduction in the adjusted mean difference in pain intensity scores (P<0.001). At 2 hours, the rates of pain relief (freedom) were comparable (Tepper et al, 2015).
  - o Data to support the approval of ZEMBRACE SYMTOUCH were based on subcutaneous sumatriptan succinate bioequivalence studies. The safety and efficacy of subcutaneous sumatriptan succinate were evaluated in 3 controlled, unpublished studies in over 1,000 patients with moderate to severe migraines. Studies demonstrated that the onset of relief began as early as 10 minutes following a 6 mg sumatriptan injection. Within 2 hours, headache relief was achieved in 82% of patients treated with a sumatriptan 6 mg injection, and 65% were pain free (Prescribing Information: ZEMBRACE SYMTOUCH, 2017; IMITREX, 2015).
  - o In a randomized, double-blind, crossover study, the efficacy and tolerability of 3 mg subcutaneous sumatriptan (ZEMBRACE SYMTOUCH) and 6 mg subcutaneous sumatriptan (SUMAVEL DOSEPRO – now discontinued) were compared in 20 patients with rapidly-escalating migraine attacks. The proportion of patients who were pain-free at 1-hour post-dose was similar following treatment with 3 mg and 6 mg subcutaneous sumatriptan (50% vs

52.6%, respectively; P=0.87). Tolerability was also similar for both doses; although, sumatriptan 3 mg was associated with fewer triptan sensations (ie, paresthesia, neck pain, flushing, and involuntary muscle contractions of the neck) when compared to the the 6-mg dose (1 patient vs 4 patients) (Cady et al, 2017).
  - A summary of Cochrane Reviews evaluating the various routes of administration for sumatriptan demonstrated that the injectable (particularly the 6 mg subcutaneous dose) routes of administration were most effective in reducing pain within the first 2 hours of treatment compared to placebo (number needed to treat [NNT], 2.3) and sustained pain-free after 24 hours (NNT, 6.1). Efficacy was dose-related with the oral sumatriptan 50 mg dose demonstrating the highest NNT for most endpoints. Compared to other triptans, only rizatriptan 5 mg (vs. sumatriptan 25 mg), rizatriptan 10 mg (vs. sumatriptan 25 to 100 mg), and eletriptan 40 to 80 mg (vs. sumatriptan 50 to 100 mg) were superior to sumatriptan for various endpoints. No differences in the incidence AEs were found (Derry et al, 2014).
  - A Cochrane Review of zolmitriptan trials concluded that zolmitriptan 2.5 to 5 mg benefited the same proportion of patients as sumatriptan 50 mg for headache relief at 2 hours (range 66 to 68%) with no significant difference in safety (Bird et al, 2014).
  - The TEENZ study assessed the efficacy and safety of zolmitriptan nasal spray for the acute treatment of a single migraine headache in 798 adolescents aged 12 to 17 years. The DB, 4-arm parallel study randomized patients in a ratio of 5:3:3:5 to placebo or zolmitriptan nasal spray in doses of 0.5 mg, 2.5 mg, or 5 mg, respectively. Zolmitriptan 5 mg nasal spray was statistically superior to placebo for the primary endpoint of pain-free status after 2 hours of administration (29.7% vs. 16.6%, respectively; P<0.001). Dysgeusia was the most frequently reported AE with zolmitriptan 5 mg nasal spray (occurring in 11.4% more of patients) (Winner et al, 2016).
  - In pediatric patients, 1 Cochrane review concluded that triptans (moderate quality of evidence) and ibuprofen (low quality evidence) are effective at providing pain freedom in children and adolescents. There are limited safety data available for AEs associated with ibuprofen use, and there may be with higher rates of minor AEs associated with triptan use. Further studies are needed in this population to validate conclusions (Richer et al, 2016).

SAFETY SUMMARY

- The manufacturer of sumatriptan iontophoretic TDS has received post-marketing reports of application site reactions described as burns and scars in patients treated with sumatriptan iontophoretic TDS. Distribution of sumatriptan iontophoretic TDS has been voluntarily suspended. Patients are recommended to discontinue sumatriptan iontophoretic TDS and discuss alternative treatment options with their physicians.
- All triptans are contraindicated in patients with significant underlying cardiovascular (CV) disease (eg, angina pectoris, history of myocardial infarction, documented silent ischemia, or coronary artery vasospasm); peripheral vascular disease; ischemic bowel disease; uncontrolled hypertension; a history of stroke, transient ischemic attack or history of hemiplegic or basilar migraine because these patients are at a higher risk of stroke; and recent use (ie, within 24 hours) of ergotamine-containing medication, ergot-type medication (such as DHE or methysergide) or another 5-HT_1 receptor agonist. Additional contraindications include:
  - Naratriptan, sumatriptan and sumatriptan/naproxen are contraindicated in severe hepatic impairment. Naratriptan is also contraindicated in severe renal impairment (creatinine clearance [CrCL] < 15 mL/min).
  - Frovatriptan, naratriptan, eletriptan, sumatriptan, sumatriptan/naproxen, or zolmitriptan are contraindicated in patients with Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders.
  - Concurrent administration of rizatriptan, sumatriptan, sumatriptan/naproxen, or zolmitriptan with a monoamine oxidase (MAO)-A inhibitor or recent (within 2 weeks) use of an MAO-A inhibitor.
  - Eletriptan is contraindicated in patients with recent use (within at least 72 hours) of potent cytochrome P450 (CYP) 3A4 inhibitors including ketoconazole, itraconazole, nefazodone, clarithromycin, ritonavir, or nelfinavir.
  - Sumatriptan/naproxen is contraindicated in the setting of coronary artery bypass graft (CABG) surgery; use during the third trimester of pregnancy; and in asthma, rhinitis, and in those patients with a history of asthma, urticaria, or allergic-type reactions after taking aspirin (ASA) or NSAIDs.
- Sumatriptan/naproxen has a boxed warning of potentially fatal CV and gastrointestinal (GI) risks associated with NSAID-use. NSAIDs can increase CV thrombotic events (eg, myocardial infarction and stroke); use is contraindicated in the setting of CABG; and increased reports of GI events such as bleeding, ulceration, and perforation of the stomach or intestines have been reported, including fatal events.

- The following warnings and precautions are associated with medications in class:
  - o Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, sumatriptan/naproxen, and zolmitriptan have a higher risk of myocardial ischemia, infarction, Prinzmetal angina, arrhythmias, and other adverse cardiac events in certain patients; cerebrovascular events and associated fatalities in certain patients; other vaso-spasm-related events (ie, GI ischemic and peripheral vasospastic); chest, throat, neck, and jaw pain, tightness and pressure; exacerbation of headache with medication overuse; and serotonin syndrome.
  - o Almotriptan has additional warnings of corneal opacities and possible accumulation and subsequent toxicity due to the binding of melanin-containing tissues in certain patients. Almotriptan should be used with caution in patients with hypersensitivity to sulfonamides. Almotriptan, rizatriptan, and zolmitriptan, have had reports of significant elevations of blood pressure.
  - o All sumatriptan-containing products have reports of seizures reported following administration. Sumatriptan/naproxen also has warnings associated with NSAID use, which include: increased exacerbations of asthma, nasal polyps, or fatal bronchospasm due to ASA-sensitivity or cross-reactivity; increases in fluid retention and edema may worsen heart failure or cause hyperkalemia and renal toxicity; serious skin reactions (eg, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis); the potential to mask inflammation and fever; and elevated liver enzymes have been reported with use.
  - o Zolmitriptan ODTs contain phenylalanine, in which the labeling warns of use in patients with phenylketonuria.
- Triptan-containing medications have a large number of potential AEs, but the incidence of most individual reactions is relatively low and often dose-related. Among the oral preparations, no triptan is clearly safer than the others. In general, the injectable triptans are associated with more AEs compared with the oral/topical dosage forms. Triptans are often associated with atypical sensations, including numbness tingling, flushing, heaviness/tightness of the chest and throat, heat, burning, cold, or pressure.
  - o Generally, the most common AEs associated with 5-HT_1 receptor agonists are dizziness, numbness, tingling, flushing, sleepiness, and fatigue.
  - o Serious cardiac events, including myocardial infarction and coronary artery vasospasm, have occurred following use of 5-HT_1 receptor agonists. These events are extremely rare and have been reported in patients with risk factors predictive of coronary artery disease. Other events reported in association with drugs in this class have included ventricular tachycardia and fibrillation.
- A 2017 meta-analysis including 141 trials compared the tolerability of 14 oral treatments for acute migraine. In indirect comparisons of PC trials utilizing triptans, naratriptan had the lowest odds of any AE (odds ratio [OR]=1.11; 95% confidence interval [CI], 0.84 to 1.43) and treatment-related AE (OR=0.86, 95% CI, 0.51 to 1.55); zolmitriptan had the highest odds of any AE (OR, 2.22; 95% CI, 1.83 to 2.70) and sumatriptan had the highest odds of treatment-related AE (OR=2.23, 95% CI, 1.83 to 2.73). Results from the meta-regression reported that the dose of triptans had a significant effect on the occurrence of any AE and treatment-related AE, with higher doses yielding a higher probability of AE occurrence and lower doses lessening the risk (Thorlund, 2017).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
Oral agents			
AMERGE (naratriptan)	Tablet: 1 mg 2.5 mg	Adult: 1 mg or 2.5 mg orally as a single dose; may repeat administration in 4 hours. Max daily dose: 5 mg.	Safety of treating > 4 migraines in 1 month has not been established.
AXERT (almotriptan)	Tablet: 6.25 mg 12.5 mg	Adult and adolescent (≥12 years): 6.25 mg or 12.5 mg orally as a single dose; may repeat administration in 2 hours. Max daily dose for adults: 25 mg.	Safety of treating >4 migraines in 1 month has not been established. In adults, 12.5 mg dose is more effective.
FROVA (frovatriptan)	Tablet: 2.5 mg	Adult: 2.5 mg orally as a single dose; may repeat administration in 2 hours. Max daily dose: 7.5 mg.	Safety of treating >4 migraines in 1 month has not been established.

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
IMITREX (sumatriptan)	Tablet: 25 mg 50 mg 100 mg	Adult: 25, 50, or 100 mg orally as a single dose; may repeat administration in 2 hours. Max daily dose: 200 mg.	Safety of treating >4 migraines in 1 month has not been established. Doses of 100 mg may not provide a greater effect than the 50 mg dose.
MAXALT, MAXALT MLT (rizatriptan)	Orally disintegrating tablet; Tablet: 5 mg 10 mg	Adult: 5 mg or 10 mg orally as a single dose. Max daily dose: 30 mg. Pediatric (≥6 years): Weight based dosing of 5 mg for <40 kg and 10 mg for ≥40 kg. May repeat administration in 2 hours in adults and 24 hours in pediatric patients. Dose adjustments are needed for patients taking propranolol concomitantly.	Safety of treating >4 migraines/month in adults or children, and >1 dose within 24 hours in patients 6 to 12 years of age have not been established.
RELPAX (eletriptan)	Tablet: 20 mg 40 mg	Adult: 20 or 40 mg orally as a single dose; may repeat administration in 2 hours. Max daily dose: 80 mg. Max single dose: 40 mg.	Safety of treating >3 migraines in 1 month has not been established.
TREXIMET (sumatriptan/ naproxen)	Tablet: 10/60 mg 85/500 mg	Adult and adolescent (≥12 years): 1 tablet (85/500 mg for adults and 10/60 mg for adolescents) orally as a single dose. Max daily dose: 2 tablets in 24 hours, taken at least 2 hours apart for adults and 1 tablet in a 24 hour period for adolescents.	Safety of treating >5 migraines in adults and >2 migraines in pediatric patients over the span of 1 month has not been established.
ZOMIG, ZOMIG-ZMT (zolmitriptan)	Orally disintegrating tablet; Tablet: 2.5 mg 5 mg	Adult: starting dose is 1.25 or 2.5 mg dose; may repeat administration in 2 hours. Max daily dose: 10 mg. Max single dose: 5 mg.	Safety of treating >3 migraines in 1 month has not been established.
Intranasal agents			
IMITREX nasal spray (sumatriptan)	Nasal spray: 5 or 20 mg/actuator unit-of-use inhaler	Adult: 5, 10, or 20 mg administered as a single dose intranasally; may repeat administration in 2 hours. Max daily dose: 40 mg. Max single dose: 20 mg.	Safety of treating >4 migraines in 1 month has not been established.
ONZETRA XSAIL (sumatriptan)	Nasal powder: 2 breath-powered delivery systems containing 11 mg sumatriptan per each nosepiece	Adult: 22 mg (2 nosepieces) administered using the breath-powered delivery device; may repeat administration in 2 hours. Max daily dose: 2 doses (44 mg/4 nosepieces).	Safety of treating >4 migraines in 1 month has not been established. Breath-powered powder delivery requiring a forceful blow into each nostril.
ZOMIG (zolmitriptan)	Nasal spray: 2.5 or 5 mg/spray single-use nasal spray units	Adult and adolescent (≥12 years): 2.5 mg administered as a single dose intranasally; may repeat administration in 2 hours. Max daily dose: 10 mg. Max single dose: 5 mg.	Safety of treating >4 migraines in 1 month has not been established.
Subcutaneous agents			
IMITREX (sumatriptan)	Subcutaneous injection: 6 mg single dose vial	Adult: 6 mg administered subcutaneously; may repeat administration in 1 hour. Max daily dose: 12 mg. Max single dose: 6 mg,	Administer the needle only to the skin; intramuscular (IM) or intravascular (IV)

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
		particularly for cluster headaches; however, lower doses (1 to 5 mg) may be administered for the treatment of migraine.	delivery should be avoided.
IMITREX STATDOSE (sumatriptan)	Subcutaneous injection: 4 and 6 mg single dose, prefilled cartridges for pen use	Adult: 6 mg administered subcutaneously; may repeat administration in 1 hour. Max daily dose: 12 mg. Max single dose: 6 mg, particularly for cluster headaches; however, lower doses (1 to 5 mg) may be administered for the treatment of migraine.	Administer where the needle penetrates ¼ inch of skin; IM or IV delivery should be avoided.
ZEMBRACE SYMTOUCH (sumatriptan)	Subcutaneous injection: 3 mg single dose, prefilled autoinjector	Adult: 3 mg injected subcutaneously; each dose should be separated by at least 1 hour. May administer up to 4 times per day. Max daily dose: 12 mg. Max single dose: 3 mg.	Administer where the needle penetrates ¼ inch of skin; IM or IV delivery should be avoided. Administer dose to the upper arm or thigh. May be administered at least 1 hour following a dose of another sumatriptan agent.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
AXERT (almotriptan)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric patients who have other CV risk factors.	Safety and efficacy have not been established in children <12 years of age.	For CrCL ≤30 mL/minute, an initial dose of 6.25 mg and a max dose of 12.5 mg/day are recommended.	Dosage adjustment required for moderate to severe impairment, reduce dose to 6.25 mg and a max dose of 12.5 mg/day.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.
RELPAX (eletriptan)	No overall difference in safety or efficacy between elderly and younger patients. BP was increased to a greater extent in elderly patients. Additionally, a statistically	Safety and efficacy have not been established.	No significant change in clearance for patients with mild, moderate, or severe impairment; although, BP elevations were observed in this population. No	Use in severe impairment is not recommended.	Pregnancy Category C* Excreted in breast milk. AAP classifies drug as compatible with breastfeeding. Drug would not be expected to cause any adverse effects in breastfed infants,

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	significant increased half-life (from 4.4 hours to 5.7 hours) was observed between elderly and younger patients. No dose adjustments are recommended.		dosage adjustment required.		especially if the infant is >2 months; use with caution.
FROVA (frovatriptan)	Mean blood concentrations were 1.5 to 2 times higher in elderly patients versus younger patients. No dose adjustments are recommended.	Safety and efficacy have not been established.	No dosage adjustment is required.	An estimated 2-fold increase in AUC is predicted with severe impairment; use with caution. No dosage adjustment is required for mild to moderate impairment.	Pregnancy Category C* Unknown whether excreted in breast milk. However, because of the long half-life, a shorter-acting drug may be preferred, especially while nursing a newborn or preterm infant; use with caution.
AMERGE (naratriptan)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric patients who have other CV risk factors.	Safety and efficacy have not been established.	For mild to moderate impairment, reduce initial dose to 1 mg and a max dose of 2.5 mg/day. Use in severe impairment (CrCL ≤15 mL/min) is contraindicated.	For mild to moderate impairment, reduce initial dose to 1 mg and a max dose of 2.5 mg/day. Use in severe impairment (Child-Pugh C) is contraindicated.	†Unclassified Several studies have suggested women with migraine may be at increased risk of preeclampsia. Post-marketing reports of naratriptan included mainly first trimester exposures. The incidence of major birth defects with naratriptan was similar to the incidence of the general US population (2.2% vs. 2.2 to 2.9%, respectively). Use with caution. Unknown whether excreted in breast milk; use with caution.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
MAXALT, MAXALT MLT (rizatriptan)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric patients who have other CV risk factors.	Safety and efficacy have not been established in children <6 years of age.	No dosage adjustment is required.	Drug plasma concentrations are 30% greater with moderate impairment. No dosage adjustment is required for mild to moderate impairment.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
IMITREX, IMITREX STATDOSE, ONZETRA XSAIL, ZEMBRACE SYMTOUCH (sumatriptan)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric patients who have other CV risk factors.	Safety and efficacy have not been established.	Not studied.	The maximum single oral dose should not exceed 50 mg. Use of IMITREX, IMITREX STATDOSE, ONZETRA XSAIL, and ZEMBRACE SYMTOUCH in severe impairment is contraindicated.	Pregnancy Category C* (ONZENTRA XSAIL, ZEMBRACE SYMTOUCH) †Unclassified (IMITREX, IMITREX STATDOSE) Overall, data from a pregnancy exposure registry have not detected an increased frequency of birth defects or a consistent pattern of birth defects associated with sumatriptan exposure during pregnancy. Several studies have suggested women with migraine may be at increased risk of preeclampsia. A registry study reported a 4.2% occurrence of major birth defects during first-trimester exposure and during any trimester of exposure which is numerically higher than the 2.2% to 2.9% rate of major birth defects among deliveries to women with migraine. ALL FORMULATIONS: Excreted in breast milk after subcutaneous administration. Unknown excretion after oral administration. Withhold breastfeeding for 12 hours after oral, nasal, or subcutaneous administration to minimize infant exposure.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
TREXIMET (sumatriptan/ naproxen)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric patients who have other CV risk factors.	Safety and efficacy have not been established in children <12 years of age.	No renal dosage adjustment required for mild to moderate impairment. Not recommended for severe impairment (CrCL ≤30 mL/min). Renal effects of the drug may hasten progression of renal dysfunction in pre-existing renal disease.	Administer 1 10/60 mg tablet in a 24 hour period for mild to moderate impairment. Use in severe impairment is contraindicated.	Pregnancy Category C during the first 2 trimesters; Pregnancy Category X during the third trimester* Both agents are excreted in breast milk. Limited information indicates that levels are low and adverse effects in breastfed infants are apparently uncommon. However, because of naproxen's long half-life and reported serious adverse reaction in a breastfed neonate, other agents may be preferred while nursing a newborn or preterm infant; use with caution.
ZOMIG, ZOMIG-ZMT (zolmitriptan)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric patients who have other CV risk factors.	Safety and efficacy have not been established for the nasal spray in children <12 years of age and <18 years of age for oral formulations.	Clearance was reduced by 25% in patients with severe impairment (CrCL ≤25 mL/min); no significant change in clearance was observed in moderate impairment (CrCL 26 to 50 mL/min). No dosage adjustment required.	Dosage adjustment required for moderate to severe impairment, reduce dose to 1.25 mg and a max dose of 5 mg/day.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.

Abbrv: AAP = American Academy of Pediatrics; AUC = area under the curve; BP = blood pressure; CrCL = creatinine clearance; CV = cardiovascular; ODT = orally disintegrating tablet

*Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Pregnancy Category X = Contraindicated in pregnant women due to evidence of fetal abnormalities from adverse effects data from investigational or marketing experience. Risks of use of the drug in pregnant women clearly outweigh potential benefits.

†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

(American Academy of Pediatrics, 2001; LactMed, 2018)

CONCLUSION

- The 5-HT_1 receptor agonists, commonly referred to as triptans, are a well-established therapy for the acute treatment of migraine attacks with or without aura. These agents work via the promotion of vasoconstriction, inhibition of dural vasodilation and inflammation and blockade of pain pathways in the brainstem. In contrast to analgesics, the triptans are considered to be specific migraine therapies because they act at the pathophysiologic mechanisms of headaches (Bajwa et al, 2018; Clinical Pharmacology, 2018).
- Currently, there are 7 single-entity triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) and 1 fixed-dose triptan/nonsteroidal anti-inflammatory combination product (sumatriptan/naproxen) available. All triptans are available as a tablet; however, some are available in a variety of other dosage formulations. Specifically, sumatriptan (nasal spray, nasal powder, subcutaneous injection, and tablet) and zolmitriptan (nasal spray, orally disintegrating tablet, and tablet) are available in the greatest number of dosage formulations. While it is noted that the subcutaneous sumatriptan injection has the fastest onset of action, there is no evidence to suggest that different oral triptan formulations have a faster onset of action than others (Francis et al, 2010). Almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, sumatriptan/naproxen and zolmitriptan are available generically in at least 1 dosage form or strength (DRUGS@FDA, 2018).
- Triptan selection is based on the characteristics of the headache, dosing convenience, and patient preference. All available triptans are FDA-approved for the acute treatment of migraine with or without aura. The subcutaneous sumatriptan injections (with the exception of ZEMBRACE SYMTOUCH) are also FDA-approved for the acute treatment of cluster headache episodes. In pediatric patients, almotriptan, zolmitriptan nasal spray (fastest onset), and sumatriptan/naproxen are approved for use in children 12 years of age and older, while rizatriptan is approved for use in children as young as 6 years of age.
- While there are data to suggest that the available triptans differ in comparative efficacy, because of the lack of consistent superiority of 1 triptan over another in direct head-to-head comparisons, it appears that individual variations in response to the different triptans exist. There are no pediatric comparative effectiveness data and studies are sparse. Based on pharmacokinetic and –dynamic data, subcutaneous and intranasal formulations generally have a quicker onset of action and subcutaneous formulations generally have a lower NNT but more AEs. Frovatriptan and naratriptan have the longest onset of action, which may be responsible for lower incidences of AE. Meta-analyses and systematic reviews point to a potential for lower efficacy with naratriptan and frovatriptan; however, more studies are needed to validate findings.
- Triptan-containing medications have a large number of potential AEs, but the incidence of most individual reactions is relatively low and often dose-related. Among the oral preparations, no triptan is clearly safer than the others. A 2017 meta-analysis including 141 trials compared the tolerability of 14 oral treatments for acute migraine. In indirect comparisons of placebo-controlled trials utilizing triptans, naratriptan had the lowest odds of any AE (odds ratio [OR]=1.11; 95% confidence interval [CI], 0.84 to 1.43) and treatment-related AE (OR=0.86, 95% CI, 0.51 to 1.55); zolmitriptan had the highest odds of any AE (OR, 2.22; 95% CI, 1.83 to 2.70) and sumatriptan had the highest odds of treatment-related AE (OR=2.23, 95% CI, 1.83 to 2.73). Results from the meta-regression reported that the dose of triptans had a significant effect on the occurrence of any AE and treatment-related AE, with higher doses yielding a higher probability of AE occurrence and lower doses lessening the risk (Thorlund, 2017).
- In general, the injectable triptans are associated with more AEs compared with the oral dosage forms. Triptans are often associated with atypical sensations, including numbness, tingling, flushing, heaviness/tightness in the chest and throat, heat, burning, cold, or pressure.
- According to the AAN, American College of Physicians-American Society of Internal Medicine, and U.S. Headache Consortium, 5-HT_1 receptor agonists are clinically interchangeable for the treatment of migraines. These guidelines do not provide a recommendation for the use of 1 agent over another. In addition, non-oral formulations provide relief for patients unable to swallow due to symptoms of nausea and vomiting (Evers et al, 2009; Francis et al, 2010; Matchar et al, 2000; Silberstein, 2000; Silberstein et al, 2012 (guideline reaffirmed in 2015); Erratum in Subcommittee of the AAN and the AHS, 2013; Snow et al, 2002). According to the 2015 AHS evidence assessment, triptans (regardless of formulation) and DHE (nasal spray or inhaler) have been established to be effective treatments for acute migraines in adults. Reaffirming the AAN migraine guidelines, the recommendation remains that clinicians should consider medication efficacy and potential AEs when prescribing acute medications

for migraine. Opioid medications are probably effective; however, they are not recommended for regular use (Marmura et al, 2015). For the treatment of cluster headaches, the 2016 AHS guideline provides an update to the 2010 AAN guidelines (Francis et al, 2010; Robbins et al, 2016). For acute treatment, subcutaneous sumatriptan and zolmitriptan nasal spray are recommended with a higher level of evidence; although zolmitriptan nasal spray is not FDA-approved for use (Robbins et al, 2016). In pediatric patients, older guidelines published by the Child Neurological Society recommend ibuprofen as first-line therapy for the treatment of migraines, followed by acetaminophen, and sumatriptan nasal spray when all other analgesics fail (Lewis et al, 2004). An update of the 2004 Child Neurological Society guideline is currently in progress.

- All 5-HT_1 receptor agonists are generally effective for the acute treatment of migraine attacks and are well-tolerated with a similar safety profile. Although some 5-HT_1 receptor agonists have been shown to be significantly superior to other 5-HT_1 receptor agonists in direct comparator studies, these results may not translate to significant differences within meta-analyses and systematic reviews. Additionally, the clinical superiority cannot be determined as an individual patient's response to a particular drug may vary. In general, injection treatments have been associated with the fastest onset of action; therefore, are amenable to quick relief. However, injectable triptans are associated with more AE compared to oral or topical dosage forms. Treatment guidelines do not recommend 1 agent over another; rather, choice of treatment should be individualized based on patient needs, response, and preference, migraine severity, and tolerability.

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Publication date: July 3, 2018

INTRODUCTION

- Blepharitis is a chronic inflammatory condition of the eyelids, often presenting with the symptoms of eye irritation and redness. Overgrowth of normal bacterial flora plays a role in the pathophysiology of blepharitis, with the most common causative organisms including *Staphylococcus* species, *Corynebacterium* species, and *Propionibacterium acnes*. The mainstay of the treatment of blepharitis is patient education regarding eyelid hygiene as well as the use of ophthalmic antibiotics. Of note, blepharitis is a chronic condition without definitive cure; therefore, satisfactory results require a long-term commitment to treatment and appropriate expectations. Ophthalmic corticosteroids may also be used acutely to treat exacerbations (*American Academy of Ophthalmology [AAO], 2013[b]).*
- Conjunctivitis occurs worldwide and affects all ages and social strata. This infection rarely causes permanent visual loss or structural damage, and mild cases may be self-limited, as many cases will resolve without treatment in immunocompetent individuals. The most common causative pathogens seen with bacterial conjunctivitis include *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis*. Use of ophthalmic antibiotics is associated with earlier clinical and microbiological remission when compared to placebo. The selection of an ophthalmic antibiotic is typically empirical, and the most convenient or least expensive ophthalmic antibiotic is typically effective for most cases of conjunctivitis (*AAO, 2013[c]; American Optometric Association [AOA], 2002*).
- Severe bacterial conjunctivitis is characterized by purulent discharge, pain, and marked eye inflammation. In these cases, cultures and slides for gram staining should be obtained, and the results of these laboratory tests should guide the choice of the antibiotic. Methicillin-resistant *S. aureus* has been isolated in patients with bacterial conjunctivitis with increasing frequency and may be resistant to many available ophthalmic antibiotics. In patients with conjunctivitis caused by *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, systemic antibiotic therapy is necessary, and while not necessary, ophthalmic antibiotics are also typically used (*AAO, 2013[c]; AOA, 2002*).
- Bacterial keratitis is characterized by an inflammation of the cornea and rarely occurs in the normal eye due to the cornea's natural resistance to infection. However, several predisposing factors such as contact lens wear, trauma, corneal surgery, ocular surface disease, systemic disease, and immunosuppression may alter the defense mechanisms of the ocular surface and allow for infection of the cornea (*Tauber et al, 2011*). Due to corneal scarring or topographic irregularity, many forms of this infection result in visual loss. Untreated or severe bacterial keratitis can result in corneal perforation and may develop into endophthalmitis and result in the loss of the eye. The most common causative organisms of bacterial keratitis include *Staphylococci* and gram-negative rods, of which the most frequent organisms identified are *Pseudomonas* species. Ophthalmic antibiotics are the preferred method of treatment in many cases, and antibiotic ointments may be useful at bedtime in less severe cases or as adjunctive therapy. In addition, broad-spectrum ophthalmic antibiotics are used initially as empiric treatment. In severe cases, patients should be followed daily until stabilization or clinical improvement is documented (*AAO, 2013[a]*).
- Though not Food and Drug Administration-approved, ophthalmic antibiotics are routinely used to prevent postoperative infections after eye surgeries such as refractive surgeries and cataract removal, while ophthalmic corticosteroids may also be used to reduce inflammation associated with surgeries (*AAO, 2016; AAO, 2017; AOA, 2004*).
- Ophthalmic antibiotic and steroid combinations are included in this review. Poly-Pred (neomycin/polymyxin/prednisolone) was discontinued by Allergan in 2011, and a generic product is not available (*Drugs@FDA, 2018; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2018*). However, other polymyxin/neomycin products are available with another corticosteroid.
- Medispan class: Ophthalmic Steroid Combinations

Table 1. Medications Included Within Class Review

Drug	Generic Availability
bacitracin/neomycin/polymyxin/hydrocortisone	✔
Blephamide* (sulfacetamide/prednisolone)	✔ (solution only)

Drug	Generic Availability
Maxitrol (neomycin/polymyxin/dexamethasone)	✔
neomycin/polymyxin/hydrocortisone	✔
Pred-G (gentamicin/prednisolone)	-
Tobradex, Tobradex ST (tobramycin/dexamethasone)	✔ (suspension only)
Zylet (tobramycin/loteprednol)	-

*Blephamide is available as suspension and ointment; solution is only available as a generic.

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

- Ocular corticosteroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe where the inherent risk of corticosteroid use in certain infective conjunctivitis is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation or thermal burns; or penetration of foreign bodies.

Indication	bacitracin/neomycin/polymyxin/hydrocortisone	Blephamide (sulfacetamide/prednisolone)	Maxitrol (neomycin/polymyxin/dexamethasone)	neomycin/polymyxin/hydrocortisone	Pred-G (gentamicin/prednisolone)	Tobradex, Tobradex ST (tobramycin/dexamethasone)	Zylet (tobramycin/loteprednol)
Steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where bacterial infection or a risk of bacterial ocular infection exists.	✔	✔	✔	✔	✔	✔	✔

(Prescribing information: bacitracin/neomycin/polymyxin/hydrocortisone, 2011; BLEPHAMIDE ointment, 2014; BLEPHAMIDE, suspension 2017; MAXITROL suspension, 2018; MAXITROL ointment, 2017; neomycin/polymyxin/hydrocortisone, 2011; PRED-G ointment, 2017; PRED-G suspension, 2017; sulfacetamide/prednisolone solution, 2013; TOBRADEX ointment, 2018; TOBRADEX suspension, 2015; TOBRADEX ST, 2011; ZYLET, 2016)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Clinical trials have demonstrated that ophthalmic antibiotic steroid combination products are effective in treating patients with external ocular infections, including bacterial blepharitis, conjunctivitis, and blepharokeratoconjunctivitis (*Rhee et al 2007; Shulman et al 1996; White et al 2008*).
- In one study involving patients with moderate blepharokeratoconjunctivitis, reductions in blepharitis and conjunctivitis symptom scores were greater with ophthalmic tobramycin/dexamethasone therapy compared to ophthalmic tobramycin/loteprednol therapy, while the reductions in keratitis symptom scores were similar between the 2 treatment groups (*Rhee et al 2007*).
- In another study, the reduction in composite symptom scores in patients with blepharokeratoconjunctivitis was similar between the tobramycin/dexamethasone and tobramycin/loteprednol groups; however, the increase in intraocular pressure was significantly greater with tobramycin/dexamethasone than tobramycin/loteprednol (*White et al 2008*). Another pooled analysis of data from 2 trials in patients with blepharokeratoconjunctivitis who were randomized to either

tobramycin/dexamethasone or tobramycin/loteprednol found similar effects on blepharitis severity; however, tobramycin/loteprednol demonstrated a better safety profile with respect to intraocular pressure (*Comstock 2017*).

- Another study involving patients with moderate to severe acute blepharitis/blepharoconjunctivitis showed initial therapy with the combination of tobramycin/dexamethasone ST provides faster inflammation relief than azithromycin ophthalmic based on a statistically significant lower mean global score (p = 0.0002) (*Torkildsen et al 2011*).
- One study showed that when compared to dexamethasone alone, neomycin/polymyxin B/dexamethasone resulted in significantly greater bacterial eradication and decrease in bacterial count in patients with bacterial blepharitis or conjunctivitis; however, the reduction in signs and symptoms of ocular infection was similar between the 2 treatment groups (*Shulman et al 1996*).
- In patients undergoing cataract and posterior chamber lens implant surgery, treatment with ophthalmic gentamicin resulted in lower bacterial colony count compared to ophthalmic neomycin/polymyxin B/dexamethasone at days 6 and 8 (p = 0.033); however, there was no significant difference between the 2 groups with regard to the degree of intraocular inflammation or the global assessment of the success of therapy and local tolerance (p value not reported) (*Van Endt et al 1997*). In a separate study involving patients undergoing cataract extraction by either manual extraction or phacoemulsification with intraocular lens implantation, ophthalmic tobramycin/dexamethasone was non-inferior to ophthalmic neomycin/polymyxin B/dexamethasone concerning inflammation scores at days 3, 8, 14, and 21. Inflammation scores in the ophthalmic tobramycin/dexamethasone group were significantly lower than scores seen in the ophthalmic neomycin/polymyxin B/gramicidin group at days 8, 14, and 21 (p < 0.05 for all), and scores in the ophthalmic neomycin/polymyxin B/dexamethasone group were significantly lower than those seen in the ophthalmic neomycin/polymyxin B/gramicidin group at day 8 (p < 0.05) (*Notivol et al 2004*).

CLINICAL GUIDELINES

- Guidelines published by the AAO recommend that blepharitis be treated with ophthalmic bacitracin or ophthalmic erythromycin and note that macrolide antibiotics may have anti-inflammatory activity with regard to the treatment of blepharitis. To prevent resistance, topical antibiotics with different mechanisms of action can be used intermittently if needed (*AAO, 2013[b]*).
- Guidelines state that keratitis should be treated with a broad-spectrum ophthalmic antibiotic that may be selected based on the isolated organism, and if no organism is identified, treatment with cefazolin plus either gentamicin or tobramycin or an ophthalmic fluoroquinolone alone is recommended. The AAO guideline also notes that fewer gram-positive cocci are resistant to ophthalmic gatifloxacin and moxifloxacin hydrochloride than other fluoroquinolones (*AAO 2013[a]*).
- For the treatment of bacterial conjunctivitis, it is recommended that the least expensive or most convenient broad-spectrum antibiotic be selected for a 5- to 7-day course of treatment (*AAO 2013[b]; AOA 2002*).
- Short-term use of ophthalmic corticosteroids is recommended by treatment guidelines to reduce inflammation in the treatment of blepharitis, conjunctivitis, and keratitis, and can be considered in postoperative prophylaxis (*AAO 2016; AAO 2013[a]; AAO 2013[b]; AAO 2013[c]*).

SAFETY SUMMARY

- Prolonged use of corticosteroids may result in the following: development of glaucoma, corneal or scleral thinning which can lead to perforation, suppression of host response causing secondary infection, and/or purulent infections of the eye may be masked or activity enhanced.
- If using these products for longer than 10 days, monitor intraocular pressure (IOP). Use after cataract surgery may delay healing. Overgrowth of nonsusceptible organisms, including fungi, may occur.
- Blephamide (sulfacetamide/prednisolone) may cause acute anterior uveitis in susceptible individuals, primarily Blacks. The p-aminobenzoic acid present in purulent exudates competes with sulfonamides and can reduce their effectiveness.
- Reactions occurring most often from the presence of the anti-infective ingredient are allergic sensitization reactions including itching, swelling, and conjunctival erythema. The reactions due to the corticosteroid component are elevation of IOP with possible development of glaucoma, and infrequent optic nerve damage; posterior subcapsular cataract formation; and delayed wound healing.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Usual Recommended Frequency	Comments
bacitracin/ neomycin/ polymyxin/ hydrocortisone	ophthalmic ointment: bacitracin zinc 400 units/neomycin sulfate 3.5 mg/polymyxin B sulfate 10,000 units/ hydrocortisone 10 mg/gram	Apply to the affected eye(s) every 3 or 4 hours, depending on the severity of the condition.	Not more than 8 grams should be prescribed initially.
Blephamide (sulfacetamide/ prednisolone)	ophthalmic ointment: sulfacetamide 10%/ prednisolone 0.2% ophthalmic solution: sulfacetamide 10%/ prednisolone sodium 0.23% ophthalmic suspension: sulfacetamide 10%/ prednisolone 0.2%	**Ointment** Apply ½ inch ribbon to the conjunctival sac(s) 3 or 4 times daily and once or twice at night. **Solution** Instill 2 drops into the eye(s) every 4 hours. **Suspension** Instill 2 drops into the conjunctival sac(s) every 4 hours during the day and at bedtime.	Ointment: Not more than 8 grams should be prescribed initially. Solution and suspension: Not more than 20 mL should be prescribed initially. Suspension: shake well before using.
Maxitrol (neomycin/ polymyxin/ dexamethasone)	ophthalmic ointment: neomycin 3.5 mg/ polymyxin B sulfate 10,000 units/ dexamethasone 0.1% per gram ophthalmic suspension: neomycin 3.5 mg/ polymyxin B sulfate 10,000 units/ dexamethasone 0.1% per mL	**Ointment** Apply a small amount into the conjunctival sac(s) up to 3 or 4 times daily. **Suspension** *Mild disease:* One to 2 drops in the conjunctival sac(s) up to 4 to 6 times daily. *Severe disease*: Drops may be used hourly, being tapered to discontinuation as the inflammation subsides.	Ointment: Not more than 8 grams should be prescribed initially. Suspension: Not more than 20 mL should be prescribed initially.
neomycin/ polymyxin/ hydrocortisone	ophthalmic suspension: neomycin sulfate 3.5 mg/polymyxin B sulfate 10,000 units/hydrocortisone10 mg/mL	Instill 1 or 2 drops into the affected eye(s) every 3 to 4 hours depending on the severity of the infection.	Not more than 20 mL should be prescribed initially.
Pred-G (gentamicin/ prednisolone)	ophthalmic ointment: gentamicin 0.3%/ prednisolone acetate 0.6% ophthalmic suspension: gentamicin 0.3%/ prednisolone acetate 1%	**Ointment** Apply ½ inch ribbon in the conjunctival sac(s) 1 to 3 times daily. **Suspension** Instill 1 drop into the conjunctival sac(s) 2 to 4 times daily. During the initial 24 to 48 hours, the dosing	Ointment: Not more than 8 grams should be prescribed initially. Suspension: Not more than 20 mL should be prescribed initially.

Drug	Available Formulations	Usual Recommended Frequency	Comments
		may be increased up to 1 drop every hour.	
Tobradex, Tobradex ST (tobramycin/ dexamethasone)	ophthalmic ointment: tobramycin 0.3%/ dexamethasone 0.1% ophthalmic suspension: tobramycin 0.3%/ dexamethasone 0.1% ophthalmic ST suspension: tobramycin 0.3%/ dexamethasone 0.05%	**Ointment** Apply ½ inch ribbon into the conjunctival sac(s) up to 3 or 4 times daily. **Suspension** Instill 1 or 2 drops into the conjunctival sac(s) every 4 to 6 hours. During the initial 24 to 48 hours, the dosage may be increased to 1 or 2 drops every 2 hours. **ST Suspension** Instill 1 drop into the conjunctival sac(s) every 4 to 6 hours. During the initial 24 to 48 hours, the dosage may be increased to 1 drop every 2 hours.	Ointment: Not more than 8 grams should be prescribed initially. Suspension, ST Suspension: Not more than 20 mL should be prescribed initially. Shake well before using.
Zylet (tobramycin/ loteprednol)	ophthalmic suspension: tobramycin 0.3%/ loteprednol etabonate 0.5%	Instill 1 or 2 drops into the conjunctival sac(s) every 4 to 6 hours. During the initial 24 to 48 hours, the dosing may be increased, to every 1 to 2 hours.	Not more than 20 mL should be prescribed initially. Shake vigorously before using.

See the current prescribing information for full details

CONCLUSION

- Ophthalmic antibiotic steroid combination products are indicated for the treatment of steroid-responsive ocular inflammatory conditions where the presence or risk of a superficial bacterial ocular infection exists. At least 1 generic is available in each formulation: ointment, solution, and suspension.
- In comparative clinical trials, no one ophthalmic antibiotic steroid combination product has been shown to be more effective than another with regard to symptom improvement or reduction of postoperative inflammation.
- In clinical studies, adverse events were mild with no significant difference seen with regard to the rate of adverse events. Common adverse events reported include burning, ocular discomfort, stinging, and tearing.
- Ophthalmic antibiotic steroid combinations are not intended to be used for prolonged periods of time in order to avoid overgrowth of non-susceptible organisms and reduce the risk of resistance. Should a super-infection occur, the ophthalmic antibiotic should be discontinued, and an alternative therapy should be initiated. Steroid-containing ophthalmic products may also increase the risk of intraocular pressure elevation, cataract formation, and delayed healing after cataract surgeries, and should be used with caution.
- Guidelines published by the AAO recommend that blepharitis be treated with ophthalmic bacitracin or ophthalmic erythromycin and note that macrolide antibiotics may have anti-inflammatory activity with regard to the treatment of blepharitis. To prevent resistance, topical antibiotics with different mechanisms of action can be used intermittently if needed (*AAO 2013[b]*).
- Guidelines state that keratitis should be treated with a broad-spectrum ophthalmic antibiotic that may be selected based on the isolated organism, and if no organism is identified, treatment with cefazolin plus either gentamicin or tobramycin or an ophthalmic fluoroquinolone alone is recommended. The AAO guideline also notes that fewer gram-positive cocci are resistant to ophthalmic gatifloxacin and moxifloxacin hydrochloride than other fluoroquinolones (*AAO 2013[a]*).

- For the treatment of bacterial conjunctivitis, it is recommended that the least expensive or most convenient broad-spectrum antibiotic be selected for a 5- to 7-day course of treatment (*AAO 2013[c], AOA 2002*).
- Short-term use of ophthalmic corticosteroids is recommended by treatment guidelines to reduce inflammation in the treatment of blepharitis, conjunctivitis, and keratitis and can be considered in postoperative prophylaxis (*AAO 2016; AAO 2013[a]; AAO 2013[b]; AAO 2013[c]*).

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Publication Date: June 28, 2018

Therapeutic Class Overview
Otic Antibiotics and Antibiotic-Steroid Combinations

INTRODUCTION

- Otitis externa (OE) is a broad term used to describe a condition characterized by inflammation of the external ear canal or auricle. Acute (diffuse) bacterial OE, also known as "swimmer's ear", is the most common infection of the external ear canal with *Pseudomonas (P.) aeruginosa* and *Staphylococcus (S.) aureus* being the most common causative pathogens of the condition. Infectious, allergic, and dermatologic disease may all lead to external otitis (*Hughes et al 2001, Rosenfeld et al 2014, Schaefer et al 2012, Wall et al 2009, Centers for Disease Control and Prevention [CDC] 2017, Goguen 2017*).
- A clinical diagnosis of acute otitis externa (AOE) is based on a characteristic history and physical examination. Patients with AOE typically experience otalgia (ear pain), pruritus, otorrhea (ear discharge), and hearing loss. Physical findings include pain with tragal pressure or pain when the auricle is pulled (*Rosenfeld et al 2014*). In contrast to acute disease, chronic OE can occur and is characterized as a persistent, low-grade infection and inflammation that leads to a thickening of the skin lining the ear canal (*Hughes et al 2001*).
- Acute otitis media (AOM) is another commonly occurring infection of the ear and is defined by the presence of fluid in the middle ear accompanied by acute signs of illness and signs and symptoms of middle ear inflammation (*Rosenfeld et al 2016*). Symptoms of AOM include otalgia, otorrhea, and swelling with additional nonspecific symptoms such as fever, irritability, and headache. Chronic otitis media is another type of middle ear infection diagnosed in an ear with a tympanic membrane perforation in the setting of chronic ear infections. Specifically, chronic suppurative otitis media is associated with chronic purulent drainage through the perforated membrane (*Micromedex 2018*).
- Controlling infection and inflammation are the 2 main management strategies for infections of the ear (*Hughes and Lee 2001*). Ototopical therapies have been demonstrated to be effective treatment options delivering a high concentration of medication to the infected tissue with minimal systemic side effects. The goals of such therapies are to lower the pH of the ear canal, eliminate the causative pathogens, and reduce inflammation (*Micromedex 2018*).
- Initial therapy for AOE includes topical preparations as the disease is typically limited to the skin of the external ear canal (*Rosenfeld et al 2014, Schaefer et al 2012, Rosenfeld et al 2016, Lieberthal et al 2013*).
- Based on current guidelines, topical preparations used in the treatment of AOE do not differ in terms of clinical outcomes. Therefore, the choice of agent should be based on tympanic membrane status, adverse events, adherence to therapy, and cost (*Rosenfeld et al 2014, Schaefer et al 2012, Jackson et al 2016*).
- Systemic antibiotics are rarely recommended for the treatment of AOM (*Rosenfeld et al 2014, Schaefer et al 2012, Rosenfeld et al 2016, Lieberthal et al 2013*). There is evidence to support the use of ototopical antibiotics as first-line therapy for patients with AOM and tympanostomy tube otorrhea in the absence of systemic infection or serious underlying disease (*Wall et al 2009*).
- Of note, Xtoro (finafloxacin otic suspension) is approved by the FDA for the treatment of AOE; however, Alcon, the company that manufacturers Xtoro, does not plan to market the product in the United States (*Brooks 2014*). Due to this, Xtoro is not included in this review.
- Medispan class: Otic Anti-infectives and Otic Steroid-Anti-infective Combinations

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Antibiotics	
Cetraxal (ciprofloxacin)	✔
Otiprio (ciprofloxacin)	-
ofloxacin*	✔
Antibiotic/Steroids	
Ciprodex (ciprofloxacin/dexamethasone)	-
Cipro-HC (ciprofloxacin/hydrocortisone)	-

Drug	Generic Availability
Coly-Mycin-S (colistin/neomycin/thonzonium/hydrocortisone)	-
neomycin/polymyxin/hydrocortisone**	✔
Otovel (ciprofloxacin/fluocinolone)*	-

*Brand Floxin otic has been discontinued by the manufacturer
**Brand Cortisporin otic solution and suspension are no longer available

(*Clinical Pharmacology 2018*, *Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Antibiotics			Antibiotic/Steroids				
	Cetraxal (ciprofloxacin)	Otiprio (ciprofloxacin)	ofloxacin	Ciprodex (ciprofloxacin/ dexamethasone)	Cipro HC (ciprofloxacin/ hydrocortisone)	Coly-Mycin-S (colistin/neomycin/ thonzonium/ hydrocortisone)	Cortisporin (neomycin/ polymyxin/ hydrocortisone)	Otovel (ciprofloxacin/ fluocinolone)
Treatment of superficial bacterial infections of the external auditory canal						✔	✔	
Treatment of infections of mastoidectomy and fenestration cavities						✔	✔ *	
Acute otitis externa	✔ †	✔ ‡	✔ ‡	✔ ‡	✔ †			
Acute otitis media, with tympanostomy tubes			✔ †	✔ ‡				✔ ‡
Chronic suppurative otitis media, ≥ 12 years of age with perforated tympanic membranes			✔					
Treatment of pediatric patients with bilateral otitis media with effusion, undergoing tympanostomy tube placement		✔ ‡						

*suspension only
† Aged ≥ 1 year
‡ Aged ≥ 6 months

(*Prescribing information: Cetraxal 2017, Ciprodex 2017, Cipro HC 2017, Coly-Mycin S 2016, Cortisporin suspension 2003, Cortisporin solution 2016, ofloxacin 2015, Otovel 2016, Otiprio 2018*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Ciprofloxacin has demonstrated non-inferiority to treatment with polymyxin B/neomycin/hydrocortisone for the treatment of AOE (*Drehobl et al 2008*).
- Pooled data from 2 trials demonstrate that when compared to polymyxin B/neomycin/hydrocortisone, treatment with ciprofloxacin/dexamethasone resulted in a shorter time to cure in patients with AOE (*Rahman et al 2007*). Another trial demonstrated that response to treatment and the microbiologic eradication rate with ciprofloxacin/hydrocortisone was

non-inferior to that of polymyxin B/neomycin/hydrocortisone when combined with oral amoxicillin (*Roland et al 2008*). This same trial also noted that for both treatments, the median time to end of pain was 6 days, and there were no significant differences between treatment groups in the mean change from baseline for any symptom. Although it is not approved for this indication, ciprofloxacin/fluocinolone was more effective than ciprofloxacin (p = 0.01) for achieving clinical cure in patients with diffuse OE (*Lorente et al 2014*).

- A systematic review of low quality studies evaluating interventions for the treatment of AOE found that topical treatments alone, as distinct from systemic treatments, are effective for uncomplicated AOE (*Kaushik et al 2010*). Furthermore, the choice of topical intervention does not generally appear to influence the therapeutic outcome significantly. Specifically, the review found that combination antimicrobial/steroid otic products were significantly more effective than placebo (odds ratio [OR], 11; 95% confidence interval [CI], 2 to 60.57) (*Kaushik et al 2010*).
- For the treatment of AOM, when compared to ciprofloxacin alone, the combination ciprofloxacin/dexamethasone resulted in a shorter mean time to cessation of otorrhea (p = 0.004) and a better clinical response on day 3 (p < 0.0001) and day 8 (p = 0.0499) (*Roland et al 2003*). However, the outcome difference between the 2 treatments in terms of microbiological eradication rates was not significantly different (p = 0.066). Two trials compared ciprofloxacin/dexamethasone to ofloxacin in patients with AOM and found that the combination treatment was superior (*Roland et al 2004a, Roland et al 2004b*). Specifically, combination treatment resulted in better clinical responses, a higher microbiologic eradication rate, and a shorter time to cessation of otorrhea. The combination treatment was also superior to ofloxacin for eradication of granulation tissue. Another study compared ciprofloxacin/dexamethasone to oral antimicrobial therapy and found that topical therapy was superior for time to cessation of otorrhea (intention to treat [ITT]; p = 0.0006, and modified intention to treat [MITT]; p = 0.0011) and proportion of patients cured (ITT; p = 0.01, and MITT; p = 0.034) (*Dohar et al 2006*). Compared to ciprofloxacin alone or fluocinolone alone, the combination of ciprofloxacin/fluocinolone demonstrated a shorter median time to cessation of otorrhea in pediatric AOM patients with tympanostomy tubes (p < 0.001 for both comparisons) (*Spektor et al 2017*). Ciprofloxacin/fluocinolone also demonstrated a higher clinical cure rate at the test-of-cure visit when compared to ciprofloxacin alone (p = 0.002) or fluocinolone alone (p < 0.001).
- The fluoroquinolones ofloxacin and ciprofloxacin provide excellent coverage against susceptible pathogens. In 2 clinical trials, ofloxacin appeared to be as effective as neomycin/polymyxin/hydrocortisone (Cortisporin otic suspension) (*Jones et al 1997, Schwartz 2006*).
  - Two randomized, evaluator-blinded trials compared the safety and efficacy of ofloxacin 0.25 to 0.50 mL twice daily with that of neomycin/polymyxin/hydrocortisone 0.15 to 0.20 mL 4 times daily otic solutions targeting mainly *P. aeruginosa, S. aureus*, and enteric bacilli in OE infections. Of the 601 patients included in the trial, a total of 474 patients were clinically evaluable (247 patients were aged ≥ 12 years and 227 children were aged < 12 years). Within the clinically evaluable population, cure was similar between groups in both age groups. In patients aged ≥ 12 years, cure was observed in 82% treated with ofloxacin vs 84% treated with neomycin/polymyxin/hydrocortisone. In children aged < 12 years, cure was observed in 97% of children treated with ofloxacin vs 95% treated with neomycin/polymyxin/hydrocortisone. There were no significant differences between treatment groups for microbiological and clinical cure or in the rates of adverse events (*Jones et al 1997*).
  - Another randomized, evaluator-blinded trial compared the efficacy and safety of ofloxacin 0.3% once daily versus neomycin/polymyxin/hydrocortisone 4 times daily otic solution in pediatric patients aged 6 months to 12 years diagnosed with OE. Of the 278 patients included in the trial, a total of 208 patients were clinically evaluable. For the clinically evaluable population, cure rates were similar with cure observed in 93.8% treated with ofloxacin and 94.7% treated with neomycin sulfate/polymyxin B sulfate/hydrocortisone. Decreases in pain severity were similar in both treatment groups. Treatment-related adverse events were similar between groups and there was no significant difference between groups (*Schwartz 2006*).
- When compared to ofloxacin for the treatment of chronic suppurative otitis media, polymyxin B/neomycin/hydrocortisone resulted in a smaller proportion of patients experiencing no otorrhea at day 14 (75% vs 46%; p = 0.06), but both treatments resulted in statistically significant improvements (p < 0.001 for all measures) (*Tong et al 1996*). A systematic review of 9 studies found that topical fluoroquinolones resulted in significantly higher rates of clinical cure compared to topical aminoglycosides for chronic suppurative otitis media in 2 studies and similar clinical cure rates in 4 studies (*Harris et al 2016*).
- Otiprio (ciprofloxacin) received FDA-approval based on 2 multicenter, placebo-controlled, randomized clinical trials in 532 pediatric patients with bilateral otitis media with effusion who were undergoing myringotomy with tympanostomy

tube placement. The primary endpoint was the cumulative proportion of study treatment failures through day 15. In both trials, a single intraoperative administration of Otiprio demonstrated a statistically significant reduction in the cumulative proportion of study treatment failures compared to tubes alone (21.3 to 24.6% vs 44.8% to 45.5%, p < 0.001) (*Mair et al 2016*). For the treatment of acute OE, the efficacy and safety of Otiprio were evaluated in a single MC, sham-controlled trial with 262 patients aged ≥ 6 months. At day 8, the proportion of patients who achieved the primary endpoint of clinical response, defined as the complete absence of any signs and symptoms of acute OE, were significantly greater for Otiprio-treated patients (69% vs 46%; p < 0.001 for ITT) (*Otiprio prescribing information 2018)*.

CLINICAL GUIDELINES

- Treatment guidelines for AOE recommend topical therapies as first-line treatment because of safety and efficacy over placebo in randomized controlled trials, and excellent clinical and bacteriologic outcomes in comparative studies. No one agent has been shown to be more effective than another. Therefore, the choice of topical antimicrobial agent should be based upon efficacy, low incidence of adverse events, likelihood of adherence to therapy, and cost (*Rosenfeld et al 2014*).
- Additional treatment guidelines for uncomplicated AOE describe topical antimicrobials with or without topical steroids as the mainstay of treatment. It is reasonable to initiate a topical otic preparation without a culture in cases of OE with mild symptoms. Corticosteroid-containing preparations are recommended for more rapid symptom relief when needed (*Schaefer et al 2012*).
- Treatment guidelines for AOM have not addressed the place in therapy for topical agents (*Lieberthal et al 2013, Rosenfeld et al 2016, Jackson et al 2016*).
- The American Academy of Otolaryngology – Head and Neck Surgery Foundation (AAO-HNSF) guidelines for tympanostomy tubes in children promote topical antibiotic therapy and discourage systemic antibiotics in managing uncomplicated acute tympanostomy tube otorrhea (TTO). Randomized controlled trials have demonstrated equal efficacy of topical vs oral antibiotics for otorrhea and fewer adverse effects with topical therapy. Only topical drops approved for use with tympanostomy tubes should be prescribed (eg, ofloxacin or ciprofloxacin-dexamethasone) to avoid potential ototoxicity from aminoglycoside-containing eardrops, which are often used to treat AOE. AAO-HNSF suggests cleaning the ear canal when necessary in otitis externa to improve the penetration of ototopical medications despite a lack of evidence from randomized trials (*Rosenfeld et al 2014, Rosenfeld et al 2016*).

SAFETY SUMMARY

- Prolonged treatment with any of these agents may result in overgrowth of nonsusceptible organisms and fungi.
- Permanent sensorineural hearing loss due to cochlear damage, cutaneous sensitization, and/or ototoxicity may occur with prolonged use of neomycin. The duration of therapy should be limited to 10 days.
- The products should not be used to treat viral infections or if patients have a hypersensitivity to any of the components.
- The most common adverse events from clinical trials included application site pain and reactions, itching, ear discomfort and redness.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended frequency	Comments
Antibiotics				
Cetraxal (ciprofloxacin)	Otic solution	otic	**AOE** twice daily for 7 days	Warm solution by holding the bottle in the hand for at least 1 minute to avoid dizziness, which may result from the instillation of a cold solution. The patient should lie with the affected ear upward and then the

Drug	Available Formulations	Route	Usual Recommended frequency	Comments
				drops should be instilled. This position should be maintained for at least 1 minute.
Otiprio (ciprofloxacin)	Otic suspension	otic	**Bilateral otitis media with effusion, undergoing tympanostomy tube placement** ≥ 6 months: Instill into each affected ear, following suctioning of middle ear effusion. **Otitis externa** ≥ 6 months: Instill into each affected ear as a single dose.	Keep solution cold during preparation. Hold the vial by the aluminum seal to prevent gelation. Shake for 5 to 8 seconds to mix well until suspension is homogenous. After preparation, syringes can be kept at room temperature or in the refrigerator prior to administration. Use a different syringe for each ear. Discard if not administered in 3 hours.
Ofloxacin	Otic solution	otic	**AOM** ≥ 1 to 12 years: twice daily for 10 days. **CSOM** ≥12 years: twice daily for 14 days. **Otitis externa** ≥ 13 years: once daily for 7 days. ≥ 6 months to 13 years: once daily for 7 days.	Warm solution by holding the bottle in the hand for 1 or 2 minutes to avoid dizziness, which may result from the instillation of a cold solution. The patient should lie with the affected ear upward and then the drops should be instilled. This position should be maintained for 5 minutes. **AOM and CSOM**: The tragus should then be pumped 4 times.
Antibiotic/Steroids				
Ciprodex (ciprofloxacin/ dexamethasone)	Otic suspension	otic	**AOE and AOM** ≥ 6 months: twice daily for 7 days.	Shake well. Warm suspension by holding the bottle in the hand for 1 or 2 minutes to avoid dizziness, which may result from the instillation of a cold suspension. The patient should lie with the affected ear upward and then the drops should be instilled. This position should be maintained for 60 seconds. **AOM**: The tragus should then be pumped 5 times by pushing inward to facilitate penetration of the drops into the middle ear.
Cipro HC (ciprofloxacin/ hydrocortisone)	Otic suspension	Otic	**AOE** ≥ 1 year: twice daily for 7 days.	Shake well. Warm suspension by holding the bottle in the hand for 1 or 2 minutes to avoid dizziness, which may result from the instillation of a cold suspension. The patient should lie with the affected ear upward and then the

Drug	Available Formulations	Route	Usual Recommended frequency	Comments
				drops should be instilled. This position should be maintained for 30 to 60 seconds.
Coly-Mycin S (colistin/ neomycin/ thonzonium/ hydrocortisone)	Otic suspension	Otic	**Adults**: 3 or 4 times daily. **Pediatric**: 3 or 4 times daily. **Wick**: Insert a cotton wick into the canal and then saturate with the suspension. Keep wick moist by adding solution every 4 hours. The wick should be replaced at least once every 24 hours. Therapy with this product should be limited to 10 days.	Shake well. The external auditory canal should be thoroughly cleansed and dried with a sterile cotton applicator. The patient should lie with the affected ear upward and then the drops should be instilled. This position should be maintained for 5 minutes.
neomycin/ polymyxin/ hydrocortisone	Otic solution and suspension	otic	**Adults**: 3 or 4 times daily. **Pediatric**: 3 or 4 times daily. **Wick**: Insert a cotton wick into the canal and then saturate with the solution or suspension. Keep wick moist by adding solution every 4 hours. The wick should be replaced at least once every 24 hours. Therapy with this product should be limited to 10 days.	Suspension: Shake well. The external auditory canal should be thoroughly cleansed and dried with a sterile cotton applicator. The patient should lie with the affected ear upward and then the drops should be instilled. This position should be maintained for 5 minutes.
Otovel (ciprofloxacin/ fluocinolone)	Otic solution	otic	**≥ 6 months:** twice daily (approximately every 12 hours) for 7 days	Warm solution by holding the bottle in the hand for 1 or 2 minutes to avoid dizziness, which may result from the instillation of a cold solution. The patient should lie with the affected ear upward and then the drops should be instilled. This position should be maintained for 1 minute. The tragus should then be pumped 4 times by pushing inward to facilitate penetration of the medication into the middle ear.

AOE = acute otitis externa; AOM = acute otitis media; CSOM = chronic suppurative otitis media
See the current prescribing information for full details

CONCLUSION

- For the treatment of AOE, limited trial data are available. The clinical trials conducted have not shown one agent to be more effective than another. Treatment guidelines recommend that choice of therapy should be based upon efficacy, low incidence of adverse events, likelihood of adherence to therapy, and cost.
- For the treatment of AOM, clinical trials have demonstrated that steroid-containing products provide a faster resolution of symptoms compared to antibiotic-only products. However, there is not an abundance of clinical studies. Treatment guidelines have not addressed the place in therapy of these topical agents.
- For the treatment of acute uncomplicated TTO, guidelines recommend topical antibiotic therapy with products approved for use with tympanostomy tubes (eg, ofloxacin or ciprofloxacin-dexamethasone).
- Antibiotic-only products, ciprofloxacin and ofloxacin, are available generically, except for Otiprio (ciprofloxacin). Otiprio (ciprofloxacin) may be administered via the external ear canal or via intratympanic route depending on indication.
- Antibiotic/steroid containing products, Ciprodex (ciprofloxacin/dexamethasone), Cipro HC (ciprofloxacin/hydrocortisone), Coly-Mycin S (colistin/neomycin/polymyxin/thonzonium), and Otovel (ciprofloxacin/fluocinolone) are available as brand only. Neomycin/polymyxin/hydrocortisone is available generically.

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Publication Date: June 29, 2018.

Therapeutic Class Overview
Antivirals, Herpes

INTRODUCTION

- Famvir (famciclovir), Sitavig (acyclovir), Valtrex (valacyclovir), and Zovirax (acyclovir) are nucleoside analogues that are Food and Drug Administration (FDA)-approved for the treatment of various herpes viruses.
- Herpes viruses contain double-stranded deoxyribonucleic acid (DNA), and human herpes viruses are subdivided into three subfamilies: α, β and γ herpes viruses. Specifically, the herpes viruses include herpes simplex virus (HSV)-1, HSV-2, varicella-zoster virus (VZV), and herpes B virus (*Cohen 2015*).
- HSV-1 and -2 cause a variety of illnesses, including mucocutaneous infections, central nervous system infections, and infections of the visceral organs. They are the causative agent in orolabial and genital lesions, commonly referred to as cold sores and genital herpes, respectively. Both viral subtypes can cause orolabial or genital infections and are clinically indistinguishable; however, cold sores are most often caused by HSV-1, and genital herpes is most often caused by HSV-2 (*Schiffer et al 2015*).
- Herpes simplex is typically transmitted through close contact with a person who is shedding virus at a peripheral site, mucosal surface, or in genital or oral secretions. Following transmission, the initial infection may not demonstrate any lesions; however, most are associated with systemic signs and symptoms and involve both mucosal and extramucosal sites.
  - Initial infections are also associated with higher complication rates and have a longer duration of symptoms and viral shedding from lesions.
  - After inoculation and initial infection, HSV settles into nerves near the spine and becomes latent. The virus can travel along the nerves, back to the skin, and either reactivate (ie, new blisters or lesions are formed) or shed (ie, no new blisters or lesions are formed) (*Schiffer et al 2015*).
  - Recurrent infections are typically localized to a defined mucocutaneous site. Recurrent infections may also be associated with prodromal symptoms, which can occur in the absence of lesions, and vary from mild tingling sensations to shooting pain in the buttocks, legs or hips (*Schiffer et al 2015*).
- VZV causes chickenpox and herpes zoster, commonly known as shingles. Chickenpox is the primary infection following exposure to VZV. Chickenpox is a common and highly contagious disease characterized by an exanthematous rash. Following resolution of the rash, the virus remains dormant in the dorsal root ganglia until reactivation. Reactivation of the virus leads to herpes zoster, or shingles. Herpes zoster is characterized by unilateral vesicular eruptions with a dermatomal distribution, but may have ophthalmic involvement that is sight-threatening. Herpes zoster is also associated with acute neuritis and postherpetic neuralgia (*Whitley 2015*).
- The oral antivirals acyclovir, famciclovir, and valacyclovir are well established treatment options for both HSV and VZV infections. All of the agents have demonstrated comparable efficacy for the treatment of primary or initial genital herpes, suppression of recurrent infection, and herpes zoster in immunocompetent patients (*Schiffer et al 2015, Whitley 2015*). In 2013, a buccal formulation of acyclovir, Sitavig, for recurrent herpes labialis was approved via the 505(b)(2) pathway.
- For the treatment of genital herpes, antiviral therapy offers clinical benefits to active infections, but does not eradicate latent virus or affect the risk, frequency, or severity of recurrences after therapy is discontinued (*Centers for Disease Control and Prevention [CDC] 2015*).
- The oral antiviral agents exert their effect against HSV and VZV by interfering with DNA and inhibiting viral replication. Acyclovir and famciclovir are synthetic purine and acyclic purine nucleoside analogs. Valacyclovir is a prodrug that is rapidly converted to acyclovir after oral administration. The bioavailability of oral acyclovir is relatively low compared to valacyclovir and famciclovir. Acyclovir is typically dosed 5 times daily, while famciclovir and valacyclovir are typically dosed 1 to 3 times daily.
- Oral acyclovir is available as a capsule, tablet, buccal tablet, and suspension for oral administration. Acyclovir is also available in intravenous, cream, and ointment formulations; the topical acyclovir products are included in the “Antivirals, topical” review. Famciclovir and valacyclovir are available as tablets. While brand Famvir is no longer marketed, generic famciclovir remains commercially available.
- Medispan class: Antivirals; Herpes agents

Table 1. Medications Included Within Class Review

Drug	Generic Availability
famciclovir*	✔
Sitavig (acyclovir) buccal tablet	-
Valtrex (valacyclovir)	✔
Zovirax (acyclovir)	✔

* Branded product, Famvir, is no longer marketed.

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. FDA Approved Indications

Indication(s)	famciclovir	Valtrex (valacyclovir)	Zovirax, Sitavig (acyclovir)
Chickenpox			
Treatment of chickenpox (VZV)	-	✔ *	✔ *
Genital Herpes			
Chronic suppressive therapy of recurrent episodes of genital herpes	✔ †,‡	✔ §,‖	-
Management of recurrent episodes of genital herpes	✔ †,¶	✔ †,#	✔
Reduction of transmission of genital herpes	-	✔ †,**	-
Treatment of initial episodes of genital herpes	-	✔ †,††	✔
Herpes Labialis (cold sores)			
Treatment of cold sores	-	✔ ‡‡,§§	-
Treatment of recurrent herpes labialis	✔ †	-	✔ † (Sitavig only)
Herpes Zoster			
Acute treatment of herpes zoster (shingles)	-	-	✔
Treatment of herpes zoster (shingles)	✔ †,‖ ‖	✔ †,¶¶	-
Orolabial or Genital Herpes			
Treatment of recurrent episodes of orolabial or genital herpes in human immunodeficiency virus infected adults	✔ ##	-	-

* In immunocompetent pediatric patients aged 2 to < 18 years. Based on efficacy data from clinical trials with oral acyclovir, treatment with valacyclovir should be initiated within 24 hours after onset of rash.
† In immunocompetent adults.
‡ The efficacy and safety of famciclovir for the suppression of recurrent genital herpes beyond 1 year have not been established.
§ In immunocompetent and in human immunodeficiency virus (HIV) 1 infected adults.
‖ The efficacy and safety of valacyclovir for the suppression of recurrent genital herpes beyond 1 year in immunocompetent patients and beyond 6 months in HIV 1 infected patients have not been established.
¶ The efficacy of famciclovir when initiated more than 6 hours after onset of symptoms or lesions has not been established.
# The efficacy of valacyclovir when initiated more than 24 hours after the onset of signs and symptoms has not been established.
** The efficacy of valacyclovir for the reduction of transmission of genital herpes beyond 8 months in discordant couples has not been established.
†† The efficacy of valacyclovir when initiated more than 72 hours after the onset of signs and symptoms has not been established.
‡‡ In patients ≥ 12 years.
§§ The efficacy of valacyclovir initiated after the development of clinical signs of a cold sore has not been established.
‖ ‖ The efficacy of famciclovir when initiated more than 72 hours after onset of rash has not been established.
¶¶ The efficacy of valacyclovir when initiated more than 72 hours after the onset of rash and the efficacy and safety of valacyclovir for treatment of disseminated herpes zoster have not been established
The efficacy of famciclovir when initiated more than 48 hours after onset of symptoms or lesions has not been established

(*Prescribing information: famciclovir 2016, Sitavig 2015, Valtrex 2013, Zovirax 2013*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Chickenpox

- A Cochrane review of 3 randomized controlled trials (RCTs) of acyclovir in healthy children with chickenpox found that acyclovir was associated with a reduction in the number of fever days (−1.1 days; 95% confidence interval [CI], −1.3 to −0.9) and the maximum number of lesions (−76 lesions; 95% CI, −145 to −8) compared to placebo. No differences were observed between acyclovir and placebo with respect to complications associated with chickenpox and adverse effects associated with treatment (*Klassen et al 2005*).
- The approval of valacyclovir for chickenpox was based on an open-label trial with single-dose pharmacokinetic and multiple-dose safety data, along with extrapolated data from the 3 acyclovir RCTs (*Valtrex prescribing information 2013*).

Genital Herpes

- A Cochrane review of 26 trials (N = 2084) was conducted to assess the safety and efficacy of existing treatments for the first episode of genital herpes. There was low quality evidence from 2 studies that oral acyclovir reduced the duration of symptoms in the primary treatment of genital herpes compared to placebo (−3.22; 95% CI, −5.91 to −0.54). Oral valacyclovir demonstrated similar efficacy to acyclovir when compared directly in 2 studies (*Heslop et al 2016*).
- A systematic review found high-quality evidence based on 1 RCT (N = 643) that oral acyclovir and valacyclovir were equally effective in reducing time to healing, time to resolution of all symptoms, and duration of viral shedding for first episodes of genital herpes in HIV-negative patients (*Hollier and Eppes 2015*).
- For the episodic treatment of genital herpes, acyclovir, famciclovir, and valacyclovir have demonstrated comparable efficacy to each other and superior efficacy to placebo (*Abudalu et al 2008, Chosidow et al 2001, Romanowski et al 2000, Warkentin et al 2002*).
- For chronic suppressive therapy of genital herpes, a systematic review of 22 trials with oral antivirals in immunocompetent and nonpregnant patients showed inconsistent and low quality evidence that suppressive therapy with acyclovir, famciclovir, and valacyclovir in patients with at least 4 recurrences per year decreased the number of patients with at least one recurrence compared to placebo. Based on indirect comparisons in a network meta-analysis, no oral antiviral was shown to be superior (*Le Cleach et al 2014*).

Herpes Labialis

- The efficacy of Sitavig (acyclovir) buccal tablets was established in a randomized, double-blind (DB), placebo-controlled, patient-initiated, multicenter (MC) trial comparing a single dose to placebo (N = 771). Enrolled patients had at least 4 recurrent herpes labialis episodes in the preceding 12 months. Median time to healing of primary vesicular lesion was reduced in the treatment group (7 days vs 7.3 days; p = 0.015). In a 9-month follow-up of 537 patients, a benefit was suggested in delaying and reducing frequency of herpes labialis lesion recurrence (*Bieber et al 2014*).
- A Cochrane review showed that oral acyclovir or oral valacyclovir may prevent herpes simplex labialis when used prophylactically for greater than 1 month. However, the clinical benefit was small, and it was not seen with short-term or long-term use of topical antivirals (*Chi et al 2015*). For the treatment of recurrent herpes labialis, a meta-analysis of 25 RCTs found that oral valacyclovir was more effective than oral acyclovir in reducing the time to healing of all lesions and time to resolution of pain. Both acyclovir and valacyclovir increased the percentage of aborted lesions, but the same benefit was not observed with famciclovir (*Chen et al 2017*).

Herpes Zoster

- There is conflicting evidence with respect to the comparative efficacy of the oral antivirals for herpes zoster treatment. In general, there were minimal differences between the agents with regard to time to complete healing and resolution of zoster-associated pain. While the results from some studies suggest within-class differences for certain outcomes, superiority of any agent was not consistently demonstrated (*Beutner et al 1995, Shafran et al 2004, Tyring et al 2000, Tyring et al 2001a, Tyring et al 2001b*).
  - In a DB, MC, RCT, famciclovir was directly compared with acyclovir in 559 immunocompetent adults with herpes zoster. Both antivirals resulted in similar efficacy with respect to the cutaneous healing of herpes zoster (eg, cessation of new lesion formation, 50% reduction in affected area, loss of acute pain) (*Shafran et al 2004*).

- In another DB, MC, RCT, famciclovir was directly compared with valacyclovir in 597 immunocompetent adults with herpes zoster. No statistically significant differences were detected between groups in the resolution of zoster-associated pain, rash healing, or postherpetic neuralgia (*Tyring et al 2000*).
- In a DB, MC, RCT, valacyclovir was directly compared with acyclovir in 1141 patients with herpes zoster. Valacyclovir for 7 days significantly accelerated the resolution of herpes zoster-associated pain vs acyclovir (p = 0.001). Valacyclovir also significantly reduced the duration of postherpetic neuralgia and the proportion of patients with pain persisting for 6 months. No differences were observed in pain intensity or quality-of-life measures (*Beutner et al 1995*).

- The results of a systematic review of 12 trials demonstrated that both famciclovir and valacyclovir reduced pain compared to acyclovir in patients with herpes zoster who presented within 72 hours of symptom onset (*McDonald et al 2012*). However, data are limited for the use of these agents for prevention of postherpetic neuralgia (*Chen et al 2014*).
- With regard to ocular manifestations in patients with herpes zoster infection, a head-to-head trial of acyclovir and famciclovir demonstrated no difference between treatments in the proportion of patients with at least one ocular manifestation (*Tyring et al 2001b*). Additionally, a Cochrane review comparing oral valacyclovir and acyclovir for the treatment of herpes zoster ophthalmicus found similar rates of ocular complications regardless of the agent utilized. The incidence of post-herpetic pain, tolerability of the medication, and side-effect profiles were also similar between both treatments (*Schuster et al 2016*).

- While various dosing regimens of antiviral therapy in genital herpes, herpes zoster, and herpes labialis were evaluated, no dosing regimen has consistently demonstrated better outcomes than another (*Abudalu et al 2008, Arora et al 2008, Bartlett et al 2008, Beutner et al, 1995, Bodsworth et al 2008, Chosidow et al 2001, Hull et al 2009, Romanowski et al 2000, Shafran et al 2004, Tyring et al 2000, Tyring et al 2001a, Tyring et al 2001b, Wald et al 2006, Warkentin et al 2002*).

CLINICAL GUIDELINES

- The American Academy of Pediatrics recommends against the routine use of oral acyclovir or valacyclovir for the treatment of chickenpox in otherwise healthy children, for whom antiviral therapy results in only a modest decrease in symptoms. For healthy patients with risk factors for moderate to severe varicella (ie, unvaccinated patients > 12 years old, chronic cutaneous or pulmonary disorders, long term salicylate therapy, patients receiving short or intermittent courses of oral or aerosolized corticosteroids), oral acyclovir or valacyclovir should be considered. Intravenous acyclovir is recommended for immunocompromised patients (*American Academy of Pediatrics 2015*).
  - Administration of oral acyclovir for post-exposure prophylaxis in healthy children may prevent or attenuate varicella. For exposed immunocompromised patients, varicella zoster immune globulin is the treatment of choice. There is limited data on the effectiveness of prophylactic oral acyclovir (*American Academy of Pediatrics 2015*).
- For the treatment of genital herpes, antiviral therapy should be used to treat all initial episodes, as well as recurrent episodes. For recurrent episodes, antiviral therapy can be administered as either suppressive therapy or episodically. Suppressive therapy has an advantage over episodic treatment in that it reduces the risk of transmission to susceptible sexual partners. Systemic antiviral therapy is preferred, and topical antiviral therapy is discouraged, as it offers minimal clinical benefit (*CDC 2015, Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents 2017*).
  - Acyclovir, famciclovir, and valacyclovir appear equally effective in the episodic treatment of genital herpes, but famciclovir may be less effective for suppression of viral shedding (*CDC 2015*).
- For the management of herpes zoster infection, acyclovir, valacyclovir, and famciclovir are all effective. Treatment should be initiated within 72 hours of the appearance of the rash to decrease the duration of symptoms and severity of pain (*Saguil et al 2017*).

SAFETY SUMMARY

- Acyclovir buccal tablets are contraindicated in patients with known hypersensitivity to milk protein concentrate.
- In patients with reduced renal function, underlying renal disease, concomitant nephrotoxic drug therapy, or in patients who are dehydrated, the development of acute renal failure has been reported with acyclovir, famciclovir, and valacyclovir. Dosage reductions are recommended for patients with renal impairment.
- Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome have been reported with acyclovir and valacyclovir in patients with advanced HIV-1 disease, allogeneic bone marrow transplant, and renal transplant recipients. Discontinue treatment immediately if clinical signs, symptoms, and laboratory abnormalities occur.

- Central nervous system adverse reactions (eg, agitation, hallucinations, confusion, and encephalopathy) have been reported with valacyclovir.
- The most common adverse events are nausea/vomiting, headache, and dizziness.
  - Application site reactions are associated with acyclovir buccal tablets.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
famciclovir	Tablet	Oral	1 to 3 times daily	
Sitavig (acyclovir) buccal tablet	Buccal tablet	Oral	Single dose	Apply within one hour of the onset of prodromal symptoms and before signs of lesions to the upper gum on the same side as the symptoms.
Valtrex (valacyclovir)	Tablet	Oral	1 to 3 times daily	
Zovirax (acyclovir)	Capsule, suspension, tablet Cream, ointment Injection	Oral Topical IV	2 to 5 times daily	Topical acyclovir products are included in the "Antivirals, topical" review. Intravenous acyclovir is indicated for the treatment of varicella-zoster infections in immunocompromised patients.

See the current prescribing information for full details

CONCLUSION

- Famciclovir, Sitavig (acyclovir), Valtrex (valacyclovir), and Zovirax (acyclovir) are antiviral agents FDA-approved for the treatment of the herpes viruses, HSV and/or VZV.
  - These agents exert their antiviral effect against HSV and VZV by interfering with DNA and inhibiting viral replication.
- The bioavailability of oral acyclovir is relatively low compared to valacyclovir and famciclovir. Acyclovir is typically dosed 5 times daily, compared to 1 to 3 times daily with famciclovir and valacyclovir. Oral acyclovir is available as a capsule, oral suspension, tablet and buccal tablet; famciclovir and valacyclovir are available as tablets.
- Acyclovir, famciclovir, and valacyclovir are all well-established treatment options for their FDA-approved indications. Comparative trials, meta-analyses, and treatment guidelines suggest acyclovir, famciclovir, and valacyclovir all provide clinical benefit to patients with HSV or VZV infection, and no one agent is preferred over another (*Abudalu et al 2008, Arora et al 2008, Bartlett et al 2008, Beutner et al, 1995, Bodsworth et al 2008, Chosidow et al 2001, Hull et al 2009, Romanowski et al 2000, Shafran et al 2004, Tyring et al 2000, Tyring et al 2001a, Tyring et al 2001b, Wald et al 2006, Warkentin et al 2002*). Furthermore, various dosing regimens of antiviral therapy have been evaluated in clinical trials, and results demonstrate that no one dosing regimen is consistently superior to another (*Arora et al 2008, Beutner et al, 1995, Shafran et al 2004, Tyring et al 2000, Tyring et al 2001a, Tyring et al 2001b*).
- For the treatment of genital herpes, antiviral therapy should be used to treat all initial episodes, as well as recurrent episodes. For recurrent episodes, antiviral therapy can be administered as either suppressive therapy or episodically. Suppressive therapy has the advantage over episodic treatment in decreasing the risk of transmission to susceptible sexual partners. Systemic antiviral therapy is preferred, and topical antiviral therapy is discouraged as it offers minimal clinical benefit (*Centers for Disease Control and Prevention 2015, Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents 2017*).

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Publication Date: July 3, 2018

Therapeutic Class Overview
Antivirals, Influenza

INTRODUCTION

- Influenza is an infectious respiratory illness caused by the influenza A and influenza B viruses. Influenza epidemics occur annually in the United States, typically from late fall to early spring. Although the majority of infected individuals recover without complications, some cases of influenza result in severe illness or death *(Grohskopf et al 2017)*.
- The virus is primarily transmitted through direct contact large-particle respiratory droplets from an infected individual's coughs and sneezes. It is also spread through contact with surfaces contaminated by infected respiratory droplets. Adults begin to shed virus 1 day prior to symptom onset, and they remain contagious for 5 to 7 days after falling ill *(Centers for Disease Control and Prevention [CDC] 2016[a])*.
- Signs and symptoms of uncomplicated influenza illness include fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis. Complications of influenza infection include sinusitis, otitis media, pneumonia, sepsis, and exacerbation of chronic medical conditions. Elderly adults, young children, pregnant women, and patients with chronic medical conditions have a higher risk of developing complications from influenza *(CDC 2016[b])*.
- Annual influenza vaccination is the most effective method for preventing seasonal influenza virus infection and its complications. Antiviral prescription medications are also available for influenza prophylaxis and treatment; however, antiviral chemoprophylaxis is not a substitute for annual influenza vaccination *(Grohskopf et al 2017)*.
- Initiation of antiviral therapy to treat influenza is recommended as early as possible for patients with confirmed or suspected influenza who are hospitalized, have severe, complicated, or progressive illness, or are at higher risk for influenza complications *(Fiore et al 2011)*. Additionally, due to the increased influenza activity and a lower vaccine effectiveness for the 2017-2018 influenza season, a December 2017 CDC advisory recommends that all hospitalized patients and all high-risk patients (hospitalized or outpatient) with suspected influenza should be treated as soon as possible with a neuraminidase inhibitor. Although initiation within 2 days of symptom onset is ideal, the CDC is stating that benefit may still be seen even when treatment is initiated later *(CDC 2017)*.
- Two classes of antiviral medications are available and will be reviewed. The adamantanes include amantadine and Flumadine (rimantadine). The neuraminidase inhibitors include Rapivab (peramivir), Relenza (zanamivir), and Tamiflu (oseltamivir).
- Although the adamantanes are active against influenza A virus, resistance is high amongst currently circulating virus strains. The adamantanes lack activity against influenza B virus. Therefore, amantadine and rimantadine are not recommended for treatment or chemoprophylaxis during the current influenza season *(CDC 2018)*.
- The neuraminidase inhibitors are active against both influenza A and influenza B viruses. Rapivab (peramivir), Relenza (zanamivir), and oseltamivir are the only antivirals recommended for the current influenza season in the United States *(CDC 2018)*.
- Circulating influenza viruses are constantly evolving, and drug-resistant influenza virus strains have been reported. Prescribers should refer to influenza drug susceptibility patterns and treatment effects when selecting an antiviral agent *(CDC 2018)*.
- Medispan class: Antiparkinson, Dopaminergic and Influenza Agents. The only agent from the Antiparkinson, Dopaminergic category that will be included in this review is amantadine for the influenza indication.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
amantadine	✔
Flumadine (rimantadine)	✔
Rapivab (peramivir)	-
Relenza (zanamivir)	-
Tamiflu (oseltamivir)	✔

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018)*

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication[1]	amantadine[2]	Flumadine (rimantadine)	Rapivab[3] (peramivir)	Relenza[4] (zanamivir)	Tamiflu[5] (oseltamivir)
Prophylaxis and treatment of signs and symptoms of infection caused by various strains of influenza A virus	✔				
Prophylaxis and treatment of illness caused by various strains of influenza A virus in adults (17 years and older)		✔			
Prophylaxis against influenza A virus in children (1 to 16 years of age)		✔			
Treatment of acute uncomplicated influenza in patients 2 years and older who have been symptomatic for no more than 2 days			✔		
Prophylaxis of influenza in adults and pediatric patients aged 5 years and older				✔	
Treatment of uncomplicated acute illness due to influenza A and B virus in adults and pediatric patients aged 7 years and older who have been symptomatic for no more than 2 days				✔	
Prophylaxis of influenza A and B in patients 1 year and older					✔
Treatment of acute, uncomplicated illness due to influenza A and B infection in patients 2 weeks of age and older who have been symptomatic for no more than 48 hours					✔

[1] The changing of viruses over time is a limitation of use for antivirals. The emergence of resistance mutations could decrease drug effectiveness. Other factors, such as changes in viral virulence, may also diminish clinical benefit of antivirals. Prescribers should consider available information on influenza drug susceptibility patterns and treatment effects when selecting an antiviral.

[2] Amantadine is also indicated in the treatment of parkinsonism and drug-induced extrapyramidal reactions.

[3] Limitations of use for Rapivab (peramivir):

- Efficacy is based on clinical trials of naturally occurring influenza in which the predominant influenza infections were influenza A virus; a limited number of subjects infected with influenza B virus were enrolled.
- Efficacy could not be established in patients with serious influenza requiring hospitalization.

[4] Limitations of use for Relenza (zanamivir):

- Not recommended for treatment or prophylaxis of influenza in individuals with underlying airways disease (such as asthma or chronic obstructive pulmonary disease) due to the risk of serious bronchospasm.
- Has not been proven effective for treatment of influenza in individuals with underlying airways disease.
- Has not been proven effective for prophylaxis of influenza in the nursing home setting.

[5] Limitations of use for Tamiflu (oseltamivir):

- Not recommended for patients with end-stage renal disease not undergoing dialysis.

(Prescribing information: amantadine capsules 2017, amantadine oral solution 2015, amantadine tablets 2017, Flumadine 2010, Rapivab 2018, Relenza 2016, Tamiflu 2018)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Adamantanes

- Clinical trials have demonstrated that the adamantanes are effective in both the prophylaxis and treatment of influenza A virus *(Bryson et al 1980, Crawford et al 1988, Dolin et al 1982, Hall et al 1987, Hayden et al 1989, Jackson et al 2011, Jefferson et al 2006[a], Jefferson et al 2006[b], Monto et al 1995, Reuman et al 1989)*.
- One systematic review assessed the efficacy and safety of adamantanes in healthy adults by analyzing 20 prophylaxis and 13 treatment randomized trials comparing amantadine or rimantadine with placebo. For prophylaxis, amantadine was 61% better than placebo at reducing influenza risk (P<0.001). Although rimantadine was 72% better than placebo at preventing influenza, statistical significance was not achieved. There was significant heterogeneity between the prophylaxis trials, and only a small sample size was available for rimantadine compared to amantadine. For treatment, amantadine and rimantadine both reduced the duration of fever by one day. Both agents caused gastrointestinal side effects, but amantadine caused significantly more adverse effects in the central nervous system than rimantadine *(Jefferson et al 2006[a])*.
- Influenza A virus resistance to amantadine and rimantadine has developed over the years. During the 2009 to 2010 influenza season, 100% of the 18 influenza H3N2 viruses tested in the United States were resistant to adamantanes. Similarly, 99.8% of the pandemic H1N1 viruses tested were resistant to adamantanes. Due to influenza A virus resistance and lack of activity against influenza B virus, the adamantanes are not recommended for the current influenza season *(CDC 2010[b], CDC 2018)*.

Neuraminidase inhibitors

- The neuraminidase inhibitors have demonstrated efficacy for their respective indications. Relenza (zanamivir) inhalation and oral oseltamivir are effective in both the prophylaxis and treatment of influenza A and B. Clinical trials have demonstrated a reduction in laboratory-confirmed influenza, illness, fever duration, secondary complications, and household contacts with influenza infection *(Aoki et al 2003, Chik et al 2004, Cooper et al 2003, Fry et al 2014, Halloran et al 2007, Hayden et al 1997, Hayden et al 1999, Hayden et al 2000, Hayden et al 2004, Hedrick et al 2000, Hiba et al 2011, Kaiser et al 2003, Kawai et al 2005, Kawai et al 2006, Lin et al 2006, MIST Study Group 1998, Monto et al 1999[a], Monto et al 1999[b], Monto et al 2002, Nicholson et al 2000, Peters et al 2001, Reuman et al 1989, Singh et al 2003, Treanor et al 2000, Turner et al 2003, Wang et al 2012, Welliver et al 2001, Whitley et al 2001)*.
- One systematic review analyzed 20 oseltamivir and 26 Relenza (zanamivir) randomized, placebo-controlled trials in order to better define their efficacy and safety. In prophylaxis trials, the risk of symptomatic influenza was reduced by 3.05% in patients treated with oseltamivir compared to placebo and 1.98% in patients treated with Relenza (zanamivir) compared to placebo. In adults, the time to first alleviation of symptoms was reduced by 0.7 days (P<0.0001) in patients receiving oseltamivir compared to placebo and 0.6 days (P<0.00001) in patients receiving Relenza (zanamivir) compared to placebo. Oseltamivir significantly reduced the time to alleviation of symptoms in non-asthmatic children and decreased the incidence of self-reported pneumonia. Relenza (zanamivir) significantly reduced the risk of bronchitis in adults with influenza. Neither treatment was a significant improvement over placebo in time to symptom alleviation in asthmatic children or risk of hospitalizations, otitis media, or sinusitis. Many studies included were at a high risk of selection bias due to inadequate reporting and a high risk of attrition bias due to selective reporting. All trials were sponsored by the manufacturers *(Jefferson et al 2014)*.
- In a systematic review of other published systematic reviews and meta-analyses, treatment of influenza with neuraminidase inhibitors (oseltamivir or zanamivir) was found to be likely effective in reducing mortality amongst hospitalized patients; the odds of mortality appeared especially lower when therapy was started early (≤ 48 hours of symptom onset). When used for treatment in the general population, these agents appear to reduce the duration of symptoms by approximately 0.5 to 1 day. Both oseltamivir and zanamivir were found likely to be effective at reducing secondary symptomatic influenza transmission when used prophylactically (*Doll et al 2017*).
- Rapivab (peramivir) intravenous (IV) infusion is approved for the treatment of influenza A and B in adults. The primary endpoint for the main clinical trial supporting Food and Drug Administration (FDA)-approval of Rapivab (peramivir) was time to alleviation of symptoms. The trial evaluated 296 previously healthy adults presenting with the onset of influenza-like illness within the previous 48 hours and a positive influenza rapid antigen test. In this multicenter, double-blind,

placebo-controlled clinical trial, patients were randomized to Rapivab (peramivir) 300 mg, 600 mg, or placebo as a single IV dose. Acetaminophen use was permitted. Patients self-reported body temperature, symptoms, and resumption of activities over 14 days. The primary endpoint, the median time to alleviation of symptoms, was significantly earlier with Rapivab (peramivir) 300 mg (59.1 hours) and 600 mg (59.9 hours) compared to placebo (81.8 hours; both P=0.0092). There was no significant difference in the incidence of all adverse events in patients receiving Rapivab (peramivir) compared to placebo. Diarrhea was the most common adverse event, occurring in 14.1%, 15.2% and 17% of the Rapivab (peramivir) 300 mg, 600 mg, and placebo groups, respectively *(Kohno et al 2010)*.

- Although studies have evaluated Rapivab (peramivir) in hospitalized patients and in children, both of these populations are not included in the FDA-approved labeling *(De Jong et al 2014, Ison et al 2014, Ison et al 2013, Sugaya et al 2012)*. The Phase 3 clinical trial of Rapivab (peramivir) in hospitalized influenza patients failed to meet its primary endpoint of reducing the time to clinical resolution compared to placebo. There are no clinical endpoints that have been validated for clinical trials of neuraminidase inhibitors treating hospitalized patients with influenza *(FDA 2014)*. In 2009, the United States issued an Emergency Use Authorization (EUA) program allowing Rapivab (peramivir) for the treatment of suspected or confirmed 2009 H1N1 influenza A virus infection in hospitalized patients *(Birnkrant 2009)*. Patients eligible for treatment were hospitalized, unable to tolerate or unresponsive to other available antivirals, or lacked a dependable oral or inhalation drug delivery route. The Public Health Emergency determination for the 2009 H1N1 influenza pandemic expired on June 23, 2010 *(CDC 2010[a])*.
- Numerous placebo-controlled trials have demonstrated the efficacy of neuraminidase inhibitors individually, but head-to-head trials directly comparing the agents are limited. One randomized, double-blind, placebo-controlled safety trial compared the use of oseltamivir, Relenza (zanamivir), and placebo in 390 healthy adults for influenza chemoprophylaxis over 16 weeks. The study showed that both treatments were well tolerated compared to placebo, and there were no discontinuations due to adverse events *(Anekthananon et al 2013)*.
- A Phase 3 multinational, multicenter, double-blind, randomized, noninferiority trial compared a single dose of 300 or 600 mg IV Rapivab (peramivir) to 5 days of oral oseltamivir in 1,091 patients with seasonal influenza. The primary endpoint, time to alleviation of influenza symptoms, had a median of 78.0 hours in patients receiving 300 mg of Rapivab (peramivir), 81.0 hours in patients receiving 600 mg of Rapivab (peramivir), and 81.8 hours in patients receiving oseltamivir. Both strengths of Rapivab (peramivir) were noninferior to oseltamivir with a noninferiority margin of 0.170. There was no significant difference between treatments in the incidence of complications of influenza infection *(Kohno et al 2011)*.
- A meta-analysis including 2 controlled clinical trials and 5 observational trials (N = 1676) examined the comparative efficacy of IV Rapivab (peramivir) and oral oseltamivir in the treatment of seasonal influenza. No significant differences between treatments were noted for the following outcomes: mortality, hospital length of stay, virus titer 48 hours after admission, and incidence of adverse events. However, the time to resolution of influenza symptoms or fever was shorter with Rapivab (peramivir) versus oseltamivir treatment (mean difference, -7.17 hours; $p < 0.01$) (*Lee et al 2017*).
- Observational studies comparing the clinical efficacy of Rapivab (peramivir), Relenza (zanamivir), and oseltamivir in treating influenza have demonstrated within-class variation in the time to alleviation of influenza symptoms. The lack of robust data from randomized, head-to-head trials prevents the recommendation of one neuraminidase inhibitor over another. Local and seasonal susceptibility trends, route of administration, and patient-specific factors such as age and compliance should be taken into account when selecting an agent for antiviral drug therapy *(Kawai et al 2008, Takemoto et al 2013)*.
- While influenza virus strains resistant to specific neuraminidase inhibitors have emerged, overall resistance remains low. According to surveillance data on seasonal influenza virus strains, the rate of resistance to oseltamivir is 1 to 3% and resistance to Relenza (zanamivir) is less than 1% *(Li et al 2015)*.

CLINICAL GUIDELINES

- Annual influenza vaccination is the most effective method for preventing seasonal influenza virus infection and its complications. All individuals six months of age and older should receive an influenza vaccination each year, unless contraindicated. The live attenuated intranasal influenza vaccine is not recommended during the 2017 to 2018 influenza season due to low effectiveness. The prophylactic antiviral administration is not a substitute for early influenza vaccination *(Grohskopf et al 2017)*.
- Amantadine and rimantadine are not recommended for antiviral treatment or prophylaxis of influenza A virus strains in the United States due to high rates of resistance *(American Academy of Pediatrics [AAP] 2017, Fiore et al 2011, CDC 2018)*.

- The antivirals recommended by the CDC for the current influenza season include oseltamivir, Relenza (zanamivir) and Rapivab (peramivir). Routine or widespread use of antivirals for chemoprophylaxis is not recommended due to concerns for viral resistance. Oseltamivir and Relenza (zanamivir) are recommended for post-exposure prophylaxis in patients who are severely immunosuppressed and in patients at a high risk for influenza complications who are either not a candidate for vaccination or received their annual vaccination less than 2 weeks prior to exposure *(CDC 2018)*.
- Treatment of influenza with antiviral therapy is recommended as early as possible for patients with confirmed or suspected influenza who are hospitalized, have severe, complicated, or progressive illness, or are at a high risk for complications *(CDC 2018)*.
- Populations at a high risk for influenza complications and recommended to receive antiviral treatment include children younger than 2 years old, adults age 65 and above, pregnant or postpartum women, American Indians, Alaska Natives, obese patients with a body mass index (BMI) of 40 kg/m^2 and above, patients younger than 19 years old receiving long-term treatment with aspirin, residents of nursing homes, and patients with immunosuppression, chronic disorders (eg, pulmonary, cardiovascular, renal, hepatic, hematological and metabolic), or neurologic conditions *(CDC 2018)*. Additionally, due to the increased influenza activity and a lower vaccine effectiveness for the 2017-2018 influenza season, a December 2017 CDC advisory recommends that all hospitalized patients and all high-risk patients (hospitalized or outpatient) with suspected influenza should be treated as soon as possible with a neuraminidase inhibitor. Although initiation within 2 days of symptom onset is ideal, the CDC is stating that benefit may still be seen even when treatment is initiated later *(CDC 2017)*.
- Antiviral therapy works best when administered within 48 hours of symptom onset. Treatment initiation should not be delayed for the results of diagnostic testing. Early administration of antivirals may shorten the duration of fever, reduce the risk of influenza-related complications such as otitis media and pneumonia, reduce death in hospitalized patients, and decrease the duration of hospitalization in hospitalized children *(CDC 2018)*.

SAFETY SUMMARY

- Common adverse events with adamantanes include nausea, dizziness, insomnia, headache, anorexia, dry mouth, and agitation.
- Amantadine and rimantadine should be used with caution in patients with epilepsy due to an increased risk for seizures.
- Amantadine has anticholinergic effects and is contraindicated in patients with untreated angle closure glaucoma. There have also been reports of death from overdose and suicide attempts with amantadine.
- Common adverse events with neuraminidase inhibitors include nausea, vomiting, and headache. The most common adverse effect with Rapivab (peramivir) is diarrhea.
- All three neuraminidase inhibitors have labeled warnings for neuropsychiatric events such as hallucinations and delirium. Patients should be monitored for signs of abnormal behavior.
- Oseltamivir and Rapivab (peramivir) have warnings for serious skin and hypersensitivity reactions, including Stevens-Johnson Syndrome.
- Relenza (zanamivir) has a warning for bronchospasm and should not be used in patients with asthma or chronic obstructive pulmonary disease. It is also contraindicated in patients with milk protein allergies.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration*

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
amantadine	Capsules, oral solution, tablets	Oral	Once daily or twice daily Adults: 200 mg once daily or 100 mg twice daily Pediatric patients: 1 to 9 years: 4.4 to 8.8 mg/kg/day not to exceed 150 mg per day	Should be taken for 10 days following a known exposure. If using in conjunction with vaccine until antibody response, then take for 2 to 4 weeks. Treatment of illness should be started within 24 to 48 hours of symptom onset and continued

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			9 to 12 years: 100 mg twice daily The safety and efficacy of amantadine in newborn infants and infants below the age of 1 year have not been established.	for 24 to 48 hours after symptoms disappear. For adult patients intolerant to 200 mg daily dose because of central nervous system or other toxicities: 100 mg daily dose Because amantadine is primarily excreted in the urine, it accumulates in the plasma and in the body when renal function declines. Thus, the dose of amantadine should be reduced in patients with renal impairment and in individuals who are 65 years of age or older according to the following: For CrCl = 30 to 50 mL/min: 200 mg 1st day, then 100 mg daily For CrCl = 15 to 29 mL/min: 200 mg 1st day, then 100 mg on alternate days For CrCl < 15 mL/min and HD: 200 mg every 7 days For patients ≥ 65 years: 100 mg once daily The dose of amantadine may need reduction in patients with congestive heart failure, peripheral edema, or orthostatic hypotension.
Flumadine (rimantadine)	Tablets	Oral	Twice daily **Adults (17 years and older)** Treatment: 100 mg twice daily for 7 days Prophylaxis: 100 mg twice daily **Pediatric patients** Prophylaxis in patients 1 to 9 years: 5 mg/kg/day, not to exceed 150 mg per day	Treatment of illness should be started within 48 hours of symptoms. A suspension can be made from the tablets and is stable for 14 days. Dose adjustment in patients ≥ 65 years: 100 mg once daily Dose adjustment in patients with CrCl < 29 mL/min: 100 mg daily Dose adjustment in patients with

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			10 to 16 years: Refer to the adult dose The safety and efficacy of rimantadine in pediatric patients below the age of 1 year have not been established.	severe hepatic dysfunction: 100 mg daily
Rapivab (peramivir)	Injection	IV	Patients ≥ 13 years: 600 mg as a single dose Patients < 13 years: 2 to 12 years: 12 mg/kg (maximum dose 600 mg) as a single dose Safety and effectiveness in pediatric patients < 2 years of age have not been established.	One time dose should be provided within 2 days of onset of influenza symptoms A single dose administered by IV infusion for a minimum of 15 minutes. Rapivab must be diluted prior to administration. Dose adjustment in adults and adolescents 13 years of age or older with CrCl = 30 to 49 mL/min: 200 mg Dose adjustment in pediatric patients 2 to 12 years of age with CrCl = 30 to 49 mL/min: 4 mg/kg Dose adjustment in adults and adolescents 13 years of age or older with CrCl = 10 to 29 mL/min: 100 mg Dose adjustment in pediatric patients 2 to 12 years of age with CrCl = 10 to 29 mL/min: 2 mg/kg HD: Administer after dialysis
Relenza (zanamivir)	Inhalation powder (in blisters)	Oral inhalation via Diskhaler device	Once daily or twice daily, depending on the indication Treatment (≥ 7 years): 10 mg twice daily for 5 days Prophylaxis in household setting (≥ 5 years): 10 mg once daily for 10 days	The 10-mg dose is provided by 2 inhalations (one 5-mg blister per inhalation). Patients scheduled to use an inhaled bronchodilator at the same time as Relenza should use their bronchodilator before taking Relenza.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Prophylaxis in community outbreak (adults and adolescents): 10 mg once daily for 28 days	If Relenza is prescribed for children, it should be used only under adult supervision and instruction, and the supervising adult should first be instructed by a healthcare professional. Due to the low systemic bioavailability of Relenza following oral inhalation, no dosage adjustments are necessary for patients with renal Impairment; however, the potential for drug accumulation should be considered.
Tamiflu (oseltamivir)	Capsules, powder for oral suspension	Oral	Once daily or twice daily, depending on the indication **Patients ≥ 13 years** Treatment: 75 mg twice daily for 5 days Prophylaxis: 75 mg once daily for at least 10 days following close contact with an infected individual and up to 6 weeks during a community outbreak. In immunocompromised patients, may be continued for up to 12 weeks. **Patients < 13 years** Treatment: • 2 weeks to < 1 year: 3 mg/kg twice daily for 5 days • 1 to 12 years: 30 to 75 mg twice daily for 5 days; specific weight-based dosing recommendations as follows: ○ ≤ 15 kg: 30 mg twice daily ○ 15.1 kg to 23 kg: 45 mg twice daily ○ 23.1 kg to 40 kg: 60 mg twice daily ○ ≥ 40.1 kg: 75 mg twice daily Prophylaxis: • 1 to 12 years: 30 to 75 mg	Start treatment within 48 hours of symptom onset or close contact with the infected individual. Taking with food may enhance tolerability. In an emergency, a suspension can be made from capsules. Dosage adjustment is recommended for patients with a CrCl between 10 and 60 mL/minute and for patients with ESRD undergoing routine HD or CAPD. Not recommended for patients with ESRD not undergoing dialysis. No dosage adjustment for mild to moderate hepatic impairment. Safety not evaluated in patients with severe hepatic impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			once daily for 10 days; specific weight-based dosing recommendations as follows: ○ ≤ 15 kg: 30 mg once daily ○ 15.1 kg to 23 kg: 45 mg once daily ○ 23.1 kg to 40 kg: 60 mg once daily ○ ≥ 40.1 kg: 75 mg once daily • During a community outbreak, can continue for up to 6 weeks (or up to 12 weeks in immuno-compromised patients).	

CAPD=continuous ambulatory peritoneal dialysis; CrCl =creatinine clearance; ESRD=end stage renal disease; HD=hemodialysis
*See the current prescribing information for full details

CONCLUSION

- The first line of protection against influenza is vaccination. All individuals six months of age and older without contraindications should receive yearly influenza vaccination *(AAP 2017, Fiore et al 2011, Grohskopf et al 2017)*.
- Antivirals are available for the prevention and treatment of influenza. Overall, the adamantanes and neuraminidase inhibitors have demonstrated safety and efficacy for their respective indications. However, amantadine and rimantadine are not currently recommended due to high rates of resistance in circulating influenza virus strains *(CDC 2018)*.
- Relenza (zanamivir) and oseltamivir are both effective in preventing influenza but are not substitutes for annual vaccination. They are recommended as post-exposure chemoprophylaxis in patients with a high risk for influenza complications who are not sufficiently protected by vaccination *(Fiore et al 2011, CDC 2018, Harper et al 2009, Panel on Opportunistic Infections 2013)*. Rapivab (peramivir) is not approved or recommended for influenza prophylaxis *(CDC 2018)*.
- Rapivab (peramivir), Relenza (zanamivir), and oseltamivir effectively treat influenza by reducing the duration of fever and illness. Initiation of treatment is recommended as soon as possible for patients with suspected influenza who are hospitalized, severely ill, or at high risk for influenza complications *(Fiore et al 2011, AAP 2017, CDC 2017, CDC 2018, Harper et al 2009, Panel on Opportunistic Infections 2013)*.
- Limited within-class comparisons prevent the recommendation of one neuraminidase inhibitor over another. Factors to consider when selecting an antiviral agent include the route of administration, seasonal and geographical susceptibility trends, and patient-specific factors such as age and compliance *(Takemoto et al 2013)*.
- The most common adverse events with amantadine and rimantadine are nausea, insomnia, dizziness, headache, anorexia, dry mouth, and agitation. The adamantanes are associated with an increased risk for seizures.
- The most common adverse events with Relenza (zanamivir) and oseltamivir are headache, nausea, and vomiting. Diarrhea is the most common adverse event with Rapivab (peramivir). The neuraminidase inhibitors have a labeled warning for neuropsychiatric events such as delirium and abnormal behavior leading to injury.

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Publication Date: July 2, 2018

Therapeutic Class Overview
Fluoroquinolones

INTRODUCTION

- The fluoroquinolones are broad-spectrum antibiotics grouped into generations based on their spectrum of activity *(Bolon 2011).*
  - First generation agents, which are structurally quinolones rather than fluoroquinolones, possess activity against aerobic gram-negative bacteria but are not effective against aerobic gram-positive bacteria or anaerobes.
    - The first generation agents (eg, nalidixic acid, cinoxacin) are no longer on the market.
  - Second generation agents, the original fluoroquinolones, contain a fluorine atom at position C-6. These agents offer improved coverage against gram-negative bacteria and moderately improved gram-positive coverage.
    - The available second generation fluoroquinolones include ciprofloxacin, levofloxacin, and ofloxacin. Lomefloxacin and norfloxacin are second generation agents which are no longer on the market.
  - Third generation agents achieve greater potency against gram-positive bacteria, particularly pneumococci, and also possess good activity against anaerobes.
    - All 3 of the third generation agents, gatifloxacin, grepafloxacin, and sparfloxacin, were removed from the market due to toxicities.
  - Fourth generation fluoroquinolones have superior coverage against pneumococci and anaerobes.
    - The available agent is moxifloxacin.
    - Trovafloxacin, was removed from the market due to toxicities, and there is a drug shortage of gemifloxacin.
  - The most recently approved fluoroquinolone, delafloxacin, has an even broader spectrum of antibiotic activity and is commonly referred to as a "next generation" fluoroquinolone.
- The fluoroquinolones have been used to treat a variety of infections including urinary tract infections, sinusitis, lower respiratory tract infections, intra-abdominal infections, infectious diarrhea, skin and skin structure infections, sexually transmitted diseases, and bacterial prostatitis. A few of the agents also have Food and Drug Administration (FDA) approval for inhalational anthrax and plague. There is also considerable off-label data for use in neutropenic patients and for treatment of tuberculosis and mycobacterial infections in patients with human immunodeficiency virus (HIV). Due to the boxed warning for disabling and potentially irreversible serious adverse reactions involving the tendons, muscles, joints, nerves, and central nervous system, fluoroquinolones should be reserved for patients with no other treatment options when used to treat acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections *(FDA press release 2016).*
- As with all antibiotics, local resistance patterns should be considered when prescribing these agents.
- Ciprofloxacin, delafloxacin, levofloxacin, and moxifloxacin are available as intravenous and oral formulations. Ciprofloxacin, levofloxacin, moxifloxacin, and ofloxacin are available in otic and/or ophthalmic formulations. Only the oral formulations and indications will be included in this review.
- Medispan class: Fluoroquinolones

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Avelox (moxifloxacin)	✔
Baxdela (delafloxacin)	-
Cipro (ciprofloxacin)	✔
ciprofloxacin extended release*	✔
Factive (gemifloxacin)π	-
Levaquin (levofloxacin)	✔
ofloxacin†	✔

* The branded product, Cipro XR, is no longer marketed.
† The branded product, Floxin, is no longer marketed.

ππThis product is currently unavailable due to a drug shortage.

(Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018, Lexicomp 2018, FDA Drug Shortages 2018)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Avelox (moxifloxacin)	Baxdela (delafloxacin)	Cipro (ciprofloxacin)	ciprofloxacin extended release	Factive (gemifloxacin)	Levaquin (levofloxacin)	ofloxacin
Acute bacterial sinusitis caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*.	✔ ∞		✔ ∞			✔ ∞	
Acute bacterial exacerbation of chronic bronchitis caused by *S. pneumoniae* or *H. influenzae.*							✔ ∞
Acute bacterial exacerbation of chronic bronchitis caused by *S. pneumoniae*, *H. influenzae*, *Haemophilus parainfluenzae, Klebsiella pneumoniae,* methicillin-susceptible *Staphylococcus aureus, or M. catarrhalis.*	✔ ∞				✔ ‡ ∞	✔ ǂ ∞	
Community acquired pneumonia caused by *S. pneumoniae* or *H. influenzae.*							✔
Community acquired pneumonia caused by *S. pneumoniae**, *H. influenzae*, *M. catarrhalis,* methicillin-susceptible *S. aureus, K. pneumoniae, Mycoplasma pneumoniae, or Chlamydia pneumoniae.*	✔				✔ ‡‡	✔ ∫	
Lower respiratory tract infections caused *by Escherichia coli, K. pneumoniae, Enterobacter cloacae, Proteus mirabilis, Pseudomonas aeruginosa, H. influenzae, H. parainfluenzae*, or penicillin-susceptible *S. pneumoniae*.** Also, *M. catarrhalis* for the treatment of acute exacerbations of chronic bronchitis.			✔				
Uncomplicated skin and skin structure infections caused by methicillin-susceptible *S. aureus* or *Streptococcus pyogenes.*	✔					✔	
Uncomplicated skin and skin structure infections caused by methicillin-susceptible *S. aureus*, *S. pyogenes,* or *P. mirabilis.*							✔
Complicated skin and skin structure infections caused by methicillin-susceptible *S. aureus, E. coli, K. pneumoniae, or E. cloacae.*	✔						
Complicated skin and skin structure infections caused by methicillin-susceptible *S. aureus, S. pyogenes, Enterococcus faecalis,* or *P. mirabilis.*						✔	
Skin and skin structure infections caused by *E. coli*, *K. pneumoniae*, *E. cloacae*, *P. aeruginosa*, methicillin-resistant and methicillin-susceptible *S. aureus*, *S. haemolyticus*, *S. lugdunensis*, *S. agalactiae*, *S. anginosus* Group, *S. pyogenes*, and *E. faecalis*		✔					
Skin and skin structure infections caused by *E. coli, K. pneumoniae, E. cloacae, P. mirabilis, Proteus vulgaris, Providencia stuartii, Morganella morganii, Citrobacter freundii, P. aeruginosa*, methicillin-susceptible *S. aureus*, methicillin-susceptible *Staphylococcus epidermidis,* or *S. pyogenes.*			✔				

Indication	Avelox (moxifloxacin)	Baxdela (delafloxacin)	Cipro (ciprofloxacin)	ciprofloxacin extended release	Factive (gemifloxacin)	Levaquin (levofloxacin)	ofloxacin
Bone and joint infections caused by *E. cloacae, Serratia marcescens*, or *P. aeruginosa*.			✔				
Complicated intra-abdominal infections caused by *E. coli, Bacteroides fragilis, Streptococcus anginosus, Streptococcus constellatus, E. faecalis, P. mirabilis, Clostridium perfringens, Bacteroides thetaiotaomicron,* or *Peptostreptococcus* species.	✔						
Complicated intra-abdominal infections (used in combination with metronidazole) caused by *E. coli, P. aeruginosa, P. mirabilis, K. pneumoniae*, or *B. fragilis*.			✔				
Uncomplicated urinary tract infection (acute cystitis) caused by *E. coli, P. mirabilis, E. faecalis,* or *Staphylococcus saprophyticus.*				✔ ∞			
Uncomplicated urinary tract infection caused by *E. coli, K. pneumoniae,* or *S. saprophyticus.*						✔ ∞	
Complicated urinary tract infection caused by *E. coli, P. mirabilis, K. pneumoniae, E. faecalis,* or *P. aeruginosa.*				✔		✔ ǂǂ	
Complicated urinary tract infection caused by *E. coli, P. mirabilis, K. pneumoniae, P. aeruginosa, or Citrobacter diversus.*							✔
Acute uncomplicated pyelonephritis caused by *E. coli.*				✔		✔	
Urinary tract infection caused by *E. coli, K. pneumoniae, E. cloacae, Serratia marcescens, P. mirabilis, Providencia rettgeri, Morganella morganii, Citrobacter koseri* (*diversus*), *Citrobacter freundii, P. aeruginosa,* methicillin-susceptible *S. epidermidis, S. saprophyticus*, or vancomycin-susceptible *E. faecalis*.			✔ †				
Acute uncomplicated cystitis in females caused by *E. coli* or *S. saprophyticus*.			✔ ∞				
Acute uncomplicated cystitis caused by *C.diversus, Enterobacter aerogenes, E. coli, K. pneumoniae, P. mirabilis,* or *P. aeruginosa.*							✔ ∞
Chronic bacterial prostatitis caused *by E. coli* or *P. mirabilis.*			✔				
Chronic bacterial prostatitis caused *by E. coli, E. faecalis* or methicillin-susceptible *S. epidermidis.*						✔	
Prostatitis caused by *E. coli.*							✔
Infectious diarrhea caused by *E. coli* (enterotoxigenic isolates), *Campylobacter jejuni, Shigella boydii, Shigella dysenteriae, Shigella flexneri* or *Shigella sonnei*.			✔				
Typhoid fever (enteric fever) caused by *Salmonella typhi*.			✔				
Uncomplicated cervical and urethral gonorrhea caused by *Neisseria gonorrhoeae*.			✔				✔
Inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*.			✔ ††			✔	
Plague caused by *Yersinia pestis* (treatment and prophylaxis).	✔		✔ ††			✔	

Indication	Avelox (moxifloxacin)	Baxdela (delafloxacin)	Cipro (ciprofloxacin)	ciprofloxacin extended release	Factive (gemifloxacin)	Levaquin (levofloxacin)	ofloxacin
Urethritis and cervicitis caused by *Chlamydia trachomatis*							✔
Mixed infections of the urethra and cervix or pelvic inflammatory disease due to *N. gonorrhoeae and C. trachomatis.*							✔

* Multi-drug resistant isolates
∫ Also indicated for *H. parainfluenzae* and *Legionella pneumophilia*. Also indicated for nosocomial pneumonia caused by methicillin-susceptible *S. aureus*, *P. aeruginosa*, *S. marcescens, E. coli, K. pneumoniae, H. influenzae*, or *S. pneumoniae*. Adjunctive therapy should be used as clinically indicated. Where *P. aeruginosa* is a documented or presumptive pathogen, combination therapy with an anti-pseudomonal β-lactam is recommended.
‡ Not indicated for *K. pneumoniae* or methicillin-susceptible *S. aureus.*
‡‡ Not indicated for methicillin-susceptible *S. aureus.*
ǂ Not indicated for *K. pneumoniae*.
ǂǂ Also indicated for *E. cloacae.*
** Ciprofloxacin is not a drug of first choice in the treatment of presumed or confirmed pneumonia secondary to *S. pneumoniae.*
† Complicated urinary tract infections and pyelonephritis due to *E. coli* for children one to 17 years but not drug of first choice.
†† For adults and children
∞ Reserve for use in patients who have no alternative treatment options.

(Prescribing information: Avelox 2017, Baxdela 2017, Cipro 2017, ciprofloxacin extended release tablet 2016, Factive 2016, Levaquin 2017, ofloxacin 2016)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The efficacy of the fluoroquinolones has been well documented in the treatment of genitourinary, respiratory, dermatological, and other miscellaneous infections, including typhoid fever and complicated intra-abdominal infections.
- A meta-analysis demonstrated no significant differences in clinical or microbiological efficacy between the quinolones for the treatment of acute cystitis *(Rafalsky et al 2006)*. Another meta-analysis found no difference between fluoroquinolones and other classes of antibiotics for uncomplicated cystitis with regard to symptomatic cure (*Zalmanovici-Trestioreanu et al 2010*). For the treatment of urinary tract infections, 2 randomized clinical trials were conducted that directly compared the once-daily, extended-release formulation of ciprofloxacin with the equivalent dose of the twice-daily immediate release formulation (*Fourcroy et al 2005, Talan et al 2004*). Overall, the extended-release formulation was found to provide comparable bacteriological eradication rates and/or clinical cure rates as the immediate-release formulation with comparable rates of adverse reactions.
- Several head-to-head trials have demonstrated no significant differences between fluoroquinolone agents for the treatment of urinary tract infections (*Arredondo-Garcia et al 2004, Auquer et al 2002, Peterson et al 2008, Raz et al 2000, Richard et al 2008, Schaeffer et al 1992*). In one study, cefpodoxime did not demonstrate non-inferiority vs ciprofloxacin in the treatment of acute cystitis (*Hooten et al 2012*).
- Both levofloxacin and ciprofloxacin have demonstrated efficacy in the treatment of bacterial prostatitis (*Bundrick et al 2003, Naber et al 2008*). In a meta-analysis, no fluoroquinolone demonstrated consistent superiority over another for the treatment of chronic bacterial prostatitis (*Perletti et al 2013*).
- Four meta-analyses have been conducted comparing quinolones to other antibiotics for the treatment of acute sinusitis and community-acquired pneumonia (*Karageorgopoulos et al 2008, Salkind et al 2002, Varadakas et al 2008, Raz-*

Pasteur et al 2015). Results from these analyses established the efficacy of the quinolones in respiratory infections. When compared to other antibiotics (β-lactams, macrolides, β-lactams/macrolide combination therapy, doxycycline, or a ketolide), treatment with quinolones was generally clinically comparable or superior. However, the majority of trials assessed in the meta-analysis by *Salkind et al* included sparfloxacin, trovafloxacin, and grepafloxacin, which are not currently available in the United States. In another meta-analysis, gemifloxacin was shown to have a higher treatment success rate than other fluoroquinolones and similar rates to β-lactams and macrolides in the treatment of community-acquired pneumonia and acute exacerbations of chronic bronchitis (*Zhang et al 2012*). Eradication rates were similar between gemifloxacin and other fluoroquinolones, β-lactams, and macrolides.

- A meta-analysis in patients with acute chronic obstructive pulmonary disease (COPD) exacerbations did not find a consistent significant benefit of antibiotics across outcomes with the exception of patients admitted to the intensive care unit (*Vollenweider et al 2012*). Additionally, a network meta-analysis in patients with acute COPD exacerbations showed that ofloxacin and ciprofloxacin had high clinical cure rates with median rates of adverse effects (*Zhang et al 2017*).
- For patients with skin and skin structure infections, 2 trials demonstrated similar clinical success and eradication rates with levofloxacin and ciprofloxacin (*Nichols et al 1997, Nicodemo et al 1998*). Additionally, results from clinical trials have revealed similar cure rates for delafloxacin compared to tigecycline, linezolid, and the combination of vancomycin/aztreonam in the treatment of acute bacterial skin and skin structure infections (*O'Riordan et al 2015, Kingsley et al 2016, O'Riordan et al 2016, Pullman et al 2017*).
- A meta-analysis of 4 randomized, controlled trials evaluated moxifloxacin vs other combination antibiotic regimens for the treatment of intra-abdominal infections (*Mu et al 2012*). This analysis showed that moxifloxacin had similar clinical cure rates, bacteriological success rates, and mortality compared with those of the control group.

CLINICAL GUIDELINES

- Treatment guidelines for the treatment of community-acquired pneumonia, urinary tract infections, skin and soft tissue infections, and vertebral osteomyelitis recommend fluoroquinolones as alternative agents (*Berbari et al 2015, Chow et al 2012, Gupta et al 2011, Mandell et al 2007, Stevens et al 2014*). An update of the Infectious Diseases Society of America (IDSA) community-acquired pneumonia in adults guideline is currently in progress.
- Fluoroquinolones may be considered first-line therapy for bacterial prostatitis, inhalational anthrax, and some types of infectious diarrhea *(Shane et al 2017, Stern et al 2008, Khan 2017*).
- The Centers for Disease Control and Prevention has determined that fluoroquinolones should no longer be used for the treatment of gonorrhea due to resistant organisms. They are not recommended for routine use in pelvic inflammatory disease unless antimicrobial susceptibility testing is performed and the fluoroquinolone will be administered in combination with metronidazole (*CDC 2015*).

SAFETY SUMMARY

- All fluoroquinolones carry a boxed warning for disabling and potentially irreversible serious adverse reactions from different body systems that can occur together in the same patient. Commonly observed adverse reactions include tendinitis, tendon rupture, arthralgia, myalgia, peripheral neuropathy, and central nervous system effects (ie, hallucinations, anxiety, depression, insomnia, severe headaches, confusion).
  - The risk for fluoroquinolone-associated tendinitis and tendon rupture is increased in patients over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart, or lung transplants.
- Due to the potentially permanent serious adverse events involving the tendons, muscles, joints, nerves, and central nervous system, the FDA published a safety communication, which recommends reserving the use of fluoroquinolones in acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections for patients with no alternative treatment options (*FDA press release 2016*). A subsequent safety alert released by the FDA stated that after review, it did not find that use of fluoroquinolones resulted in detached retina, aortic aneurysm, or aortic dissection (*FDA press release 2017*).
- Fluoroquinolones may cause QT interval prolongation, anaphylactic reactions, phototoxicity, *Clostridium difficile* diarrhea, and blood glucose disturbances. Additionally, fluoroquinolones may exacerbate muscle weakness in patients with myasthenia gravis and should therefore be avoided.
- In a recent systematic review and meta-analysis, the use of fluoroquinolones was found to potentially increase the risk of serious arrhythmias and cardiovascular death. Moxifloxacin and levofloxacin showed a higher risk of serious arrhythmias (*Liu et al 2017*).

- The most common adverse events with fluoroquinolones include gastrointestinal (eg, nausea, vomiting, diarrhea) and central nervous system (eg, dizziness, headache) toxicities. Rash is frequently observed with fluoroquinolones and is especially common with gemifloxacin.
- All fluoroquinolones bind to multivalent cations. Administration of a fluoroquinolone should be separated by at least two hours from products containing aluminum, magnesium, iron, or zinc.
- Additional drug interactions include Class IA and Class III antiarrhythmics, nonsteroidal anti-inflammatory drugs, phenytoin, probenecid, sulfonylureas, theophylline, tizanidine, and warfarin.
- Oral dosing of ciprofloxacin, gemifloxacin, levofloxacin, and ofloxacin should be adjusted in renal impairment. Delafloxacin is not recommended for use in patients with end stage renal disease. The daily dose of ofloxacin should not exceed 400 mg in patients with severe liver dysfunction.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Avelox (moxifloxacin)*,†	Tablet	Oral	Every 24 hours	
Baxdela (delafloxacin)*	Tablet	Oral	Every 12 hours	Not recommended in ESRD (eGFR < 15 including hemodialysis)
Cipro (ciprofloxacin)*,†	Tablet, suspension	Oral	Every 12 hours	Oral dose adjustments are recommended in renal impairment. Ofloxacin dose should not exceed 400 mg per day in patients with severe liver dysfunction disorders.
ciprofloxacin extended release	Tablet	Oral	Every 24 hours	
Factive (gemifloxacin)	Tablet	Oral	Every 24 hours	
Levaquin (levofloxacin)* ,†	Tablet, oral solution	Oral	Every 24 hours	
ofloxacin†	Tablet	Oral	Every 12 hours	

Abbreviations: eGFR = estimated glomerular filtration rate; ESRD = end stage renal disease
* Also available as intravenous solution
† Also available as otic and/or ophthalmic formulations
See the current prescribing information for full details

CONCLUSION

- Fluoroquinolones have a broad spectrum of activity and may be used to treat a variety of infections. Current clinical evidence supports the efficacy of all products in this class for their FDA-approved indications, and efficacy appears comparable among agents. No fluoroquinolone has consistently demonstrated superiority over another.
- Fluoroquinolones should be considered first-line therapy for bacterial prostatitis, inhalational anthrax, and some types of infectious diarrhea (*Shane et al 2017, Stern et al 2008, Khan 2017*).
  - Treatment guidelines recommend fluoroquinolones as alternative agents for the treatment of community-acquired pneumonia, urinary tract infections, skin and soft tissue infections, and vertebral osteomyelitis (*Berberi et al 2015, Gupta et al 2011, Mandell et al 2007, Solomkin et al 2010, Stevens et al 2014*). They are not generally recommended for the treatment of bacterial sinusitis (*Chow et al 2012*). The Centers for Disease Control and Prevention has determined that fluoroquinolones should no longer be used for the treatment of gonorrhea due to resistant organisms (*CDC 2015*).
- All fluoroquinolones share a boxed warning for disabling and potentially irreversible serious adverse reactions such as tendinitis, tendon rupture, arthralgia, myalgia, peripheral neuropathy, and central nervous system effects (ie, hallucinations, anxiety, depression, insomnia, severe headaches, confusion). Due to the risk for permanent adverse effects, the FDA warns that fluoroquinolones should be reserved for patients with no other treatment options when used to treat acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections (*FDA press release 2016*).
- Additional warnings for the class include QT prolongation, blood glucose disturbances, *Clostridium difficile*-associated diarrhea, and phototoxicity. Fluoroquinolones should be avoided in patients with a history of myasthenia gravis.

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Publication Date: June 4, 2018

Therapeutic Class Overview
Pulmonary Arterial Hypertension Agents

INTRODUCTION

- Pulmonary arterial hypertension (PAH), a subtype of pulmonary hypertension (PH), is a chronic, life-threatening disease that is characterized by increased resistance in the pulmonary circulation caused by progressive pulmonary artery remodeling and constriction of the pulmonary vasculature (*Buckley et al 2013, Wu et al 2013*).
  - o PH is defined as a mean pulmonary arterial pressure (mPAP) of ≥ 25 mmHg at rest. Normal pulmonary arterial systolic pressure ranges from 15 to 30 mmHg, diastolic pressure from 4 to 12 mmHg, and normal mPAP is ≤ 20 mmHg (*Rubin et al 2017*).
  - o PAH often manifests with clinical symptoms such as shortness of breath and decreased functional capacity, and eventually leads to right heart failure and death (Gomberg-Maitland et al 2011).
- Early recognition of PAH is essential and the gold standard for the clinical diagnosis of PAH is right heart catheterization (*Buckley et al 2013*).
- The World Health Organization (WHO) classifies PH into 5 groups:
  - o Group 1 – PAH
  - o Group 2 – PH secondary to heart disease
  - o Group 3 – PH secondary to lung diseases and/or hypoxia
  - o Group 4 – Chronic thromboembolic PH (CTEPH)
  - o Group 5 – PH with unclear or multifactorial etiologies
- WHO Group I encompasses PAH, including idiopathic PAH, heritable PAH, drug- and toxin-induced PAH, and PAH associated with other disorders such as connective tissue disease, portal hypertension, human immunodeficiency virus infection, congenital heart disease, and schistosomiasis (*Simonneau et al 2013*).
- In addition to the diagnostic classification, patients may be stratified according to their WHO functional capacity, which was adapted from the New York Heart Association (NYHA) classification of left heart failure. A brief description of these functional classes (FC) is as follows (*Stringham et al 2010*):
  - o Class I: No limitation of physical activity
  - o Class II: Slight limitation of physical activity
  - o Class III: Marked limitation of physical activity
  - o Class IV: Inability to carry out any physical activity without symptoms
- The prevalence of WHO Group 1 PAH has been estimated at 7 to 26 cases per million adults (*Pogue et al 2016*). The disease has a poor prognosis and an approximate mortality rate of 15% within 1 year on therapy (*McLaughlin et al 2009*). The median survival in the 1980s was 2.8 years; this has improved to 7 years in the late 2000s (*Pogue et al 2016*).
- CTEPH (WHO Group 4) is a leading cause of severe PH that results from thrombus formation leading to fibrous stenosis or complete obliteration of pulmonary arteries.
  - o The incidence of CTEPH is uncertain, but it occurs in up to 4% of patients after an acute pulmonary embolism (*Simonneau et al 2009*).
- Specific agents to treat PAH primarily target 3 pathways critical to its pathobiology: the prostacyclin, endothelin, and nitric oxide pathways (*Wu et al 2013*). There are currently 10 molecular entities within 5 therapeutic classes that are Food and Drug Administration (FDA)-approved for the treatment of PAH (*Facts and Comparisons 2018*).
  - o Drugs active within the prostacyclin pathway are the prostacyclin analogues (PCAs) or prostanoids (intravenous [IV] epoprostenol; inhaled iloprost; and IV, subcutaneous [SC], inhaled, and oral treprostinil) and a prostacyclin receptor agonist (oral selexipag).
  - o Drugs active within the endothelin pathway are the endothelin receptor antagonists (ERAs) (oral ambrisentan, oral bosentan, and oral macitentan).
  - o Drugs active within the nitric oxide pathway are the phosphodiesterase-type-5 (PDE-5) inhibitors (IV and oral sildenafil and oral tadalafil) and a soluble guanylate cyclase (sGC) stimulator (oral riociguat).
- The goals of treatment include improvement in the patient's symptoms, quality of life (QOL), and survival. The optimal therapy for a patient should be individualized, taking into account many factors including severity of illness, route of administration, side effects, comorbid illness, treatment goals, and clinician preference (*McLaughlin et al 2009*).

- Initial management of PAH includes the use of warfarin, diuretics, and/or oxygen depending on the patient's diagnosis and symptoms. Prior to the initiation of advanced therapy, patients with PAH should undergo a vasoreactivity test. Oral calcium channel blockers (CCBs) are indicated only for patients who have a positive acute vasodilator response to testing (*Galiè et al 2015[b], McLaughlin et al 2009, Taichman et al 2014*).
- For patients who do not have a positive acute vasodilator response to testing and are considered low to moderate risk based on clinical assessment, oral mono- or combination therapy with certain agents are recommended. These include ERAs, PDE-5 inhibitors, an sGC stimulator, and a prostacyclin receptor (IP) agonist. In patients with high risk disease, continuous treatment with an IV PCA therapy (epoprostenol or treprostinil) would be recommended. Combination therapy may be considered if patients are not responding adequately to monotherapy or are not candidates for monotherapy (*Barst, 2009, Galiè et al 2015[b], McLaughlin et al 2009, Taichman et al 2014*).
- The PAH agents are FDA-approved for the treatment of patients with WHO Group I PAH; however, there are differences in the study populations for which their FDA-approvals were based (*McLaughlin et al 2009*).
- Adempas (riociguat) is a first-in-class sGC stimulator with a dual mode of action involving endogenous nitric oxide that leads to increased generation of cyclic guanosine monophosphate (cGMP) with subsequent vasodilation. Adempas (riociguat) has the additional FDA approval for treating adults with persistent/recurrent CTEPH (WHO Group 4) after surgical treatment or inoperable CTEPH. Adempas is the first and only drug to be FDA-approved in the treatment of CTEPH. Pulmonary endarterectomy is curative for CTEPH, but it is technically demanding which may limit access to its use as a treatment (*Archer 2013*).
- In PAH, prostacyclin synthase is reduced resulting in inadequate production of prostacyclin I_2, a potent vasodilator with antiproliferative effects and an inhibitor of platelet aggregation (*McLaughlin et al 2009*). The PCAs iloprost and treprostinil were developed as chemically stable alternatives to epoprostenol, which requires continuous IV infusion due to its lack of stability (*Asaki et al 2015*). Orenitram (treprostinil) is the first FDA-approved oral PCA. It may represent a more convenient dosage form to the other treprostinil formulations (Remodulin and Tyvaso). However, patients with more severe PAH are likely to receive infused PCA rather than oral therapy (*McLaughlin et al 2009*). Among these agents, epoprostenol IV is the only agent which has demonstrated improved patient survival in high risk PAH patients (*Galiè et al 2015[b]*). Uptravi (selexipag) works at the same pathway as the PCAs, but activates the IP receptor, also known as the prostacyclin receptor. Orenitram and Uptravi are the only orally administered agents that work within the prostacyclin pathway (*Asaki et al 2015*).
- Endothelial dysfunction in PAH causes increased production of endothelin-1 resulting in vasoconstriction, which is mediated by the endothelin receptors, ET_A and ET_B. Stimulation of ET_A causes vasoconstriction and cell proliferation, while stimulation of ET_B results in vasodilatation, antiproliferation and endothelin-1 clearance. The ERAs (Letairis [ambrisentan], Opsumit [macitentan], and Tracleer [bosentan]) competitively bind to both receptors with different affinities. Letairis and Opsumit are highly selective for the ET_A receptor, while Tracleer is slightly selective for the ET_A receptor over the ET_B receptor. In addition, Opsumit has a pharmacologically active metabolite and is considered "tissue-targeting" because it displays high affinity and sustained occupancy at the ET receptors in human pulmonary arterial smooth muscles. However, the clinical significance of receptor affinities of the ERAs has not been established (*McLaughlin et al 2009*).
- In patients with PAH, there is also an impaired release of nitric oxide by the vascular endothelium, thereby reducing cGMP concentrations. The PDE-5 enzyme is the predominant phosphodiesterase in the pulmonary vasculature and is responsible for the degradation of cGMP. The PDE-5 inhibitors, Revatio (sildenafil) and Adcirca (tadalafil), increase the concentrations of cGMP resulting in relaxation of the pulmonary vascular bed.
- Medispan class: Cardiovascular Agents, Miscellaneous – Prostaglandin Vasodilators; Pulmonary Hypertension: Endothelin Receptor Antagonists, Phosphodiesterase Inhibitors, Prostacyclin Receptor Agonist, and Soluble Guanylate Cyclase Stimulator.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
ERAs	
Letairis (ambrisentan)	-
Opsumit (macitentan)	-
Tracleer (bosentan)	-
PDE-5 inhibitors	
Adcirca (tadalafil)	-
Revatio (sildenafil)	✔ *
Prostacyclin receptor agonist	
Uptravi (selexipag)	-
PCAs	
Flolan (epoprostenol)	✔
Veletri (epoprostenol)	-
Orenitram (treprostinil)	-
Remodulin (treprostinil)	-**
Tyvaso (treprostinil)	-
Ventavis (iloprost)	-
sGC stimulator	
Adempas (riociguat)	-

*Revatio tablet and IV formulations are currently available generically; however, the oral suspension is brand-only.
**Under a settlement agreement, United Therapeutics granted Sandoz a non-exclusive license to manufacture and commercialize the generic version of Remodulin beginning on June 26, 2018; however, Sandoz may be permitted to enter the market earlier under certain circumstances.

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. FDA-approved Indications

Indication	Adcirca (tadalafil)	Adempas (riociguat)	Flolan (epoprostenol)	Letairis (ambrisentan)	Opsumit (macitentan)	Orenitram (treprostinil)	Remodulin (treprostinil)	Revatio (sildenafil)	Tracleer (bosentan)	Tyvaso (treprostinil)	Uptravi (selexipag)	Veletri (epoprostenol)	Ventavis (iloprost)
Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening				✔ *				✔ §	✔ †				
Treatment of PAH (WHO Group I) to improve exercise ability	✔ ¶		✔ ≠			✔ ¶¶	✔ ⨾			✔ Ω		✔ ₳	
Treatment of PAH (WHO Group I) to delay disease progression and reduce hospitalization					✔ **						✔ ‡		
Treatment of PAH (WHO Group I) to improve exercise capacity, to improve WHO FC, and to delay clinical worsening		✔											✔ ¥

Indication	Adcirca (tadalafil)	Adempas (riociguat)	Flolan (epoprostenol)	Letairis (ambrisentan)	Opsumit (macitentan)	Orenitram (treprostinil)	Remodulin (treprostinil)	Revatio (sildenafil)	Tracleer (bosentan)	Tyvaso (treprostinil)	Uptravi (selexipag)	Veletri (epoprostenol)	Ventavis (iloprost)
Treatment of persistent/recurrent CTEPH (WHO Group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO FC		✔											
Treatment of PAH (WHO Group I), in combination with Adcirca to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability				✔ *									
Treatment of PAH (WHO Group I) in pediatric patients aged ≥ 3 years with idiopathic or congenital PAH to improve pulmonary vascular resistance, which is expected to improve exercise ability									✔				

Abbrv: NYHA=New York Heart Association, PAH=pulmonary arterial hypertension, WHO=World Health Organization, CTEPH=chronic thromboembolic pulmonary hypertension

*Studies establishing effectiveness included predominantly patients with WHO FC II to III symptoms and etiologies of idiopathic or heritable pulmonary arterial hypertension (PAH) (60%) or PAH associated with connective tissue diseases (34%).

†Studies establishing effectiveness included predominately patients with New York Heart Association (NYHA) FC II to IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%).

‡Studies included predominantly WHO FC II to III. Patients had idiopathic PAH (58%), PAH associated with connective tissue diseases (29%), and PAH associated with congenital systemic-to-pulmonary shunts (10%).

§Studies included predominately patients with NYHA class II or III symptoms and etiologies of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%).

¶Studies included predominately patients with NYHA class II or III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

¥Studies included predominately patients with NYHA class III or IV symptoms and etiologies of idiopathic or heritable PAH (65%) or PAH associated with connective tissue diseases (23%).

ΩStudies included predominately patients with NYHA class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

₳Studies included predominately patients with NYHA class III or IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.

≠Studies included predominately patients with NYHA class III or IV symptoms and etiologies of idiopathic or heritable PAH (49%) or PAH associated with connective tissue diseases (51%).

ƧStudies establishing effectiveness included predominately patients with New York Heart Association (NYHA) FC II to IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with connective tissue diseases (19%), and PAH associated with congenital systemic-to-pulmonary shunts (23%).** Disease progression included death, initiation of IV or SC prostacyclin vasodilators, or clinical worsening of PAH (decreased 6-minute walk distance (6MWD), worsened PAH symptoms, and need for additional PAH treatment).

¶¶The study that established effectiveness included predominantly patients with WHO FC II and III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%). As the sole vasodilator, Orenitram has not been shown to add to other vasodilator therapy.

(*Prescribing information: Adcirca 2017, Adempas 2018, Flolan 2016, Letairis, 2015, Opsumit 2017, Orenitram 2017, Remodulin 2018, Revatio 2018, Tracleer 2017, Tyvaso 2017, Uptravi 2018, Veletri 2017, Ventavis 2017*)

NOTE: Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Adcirca (tadalafil)

- Adcirca was evaluated in the PHIRST study, a 16-week, randomized, double-blind, placebo-controlled trial consisting of 405 patients with predominantly WHO FC II or III symptoms. Treatment with Adcirca significantly improved exercise capacity, as measured by the 6MWD and reduced clinical worsening compared to placebo (*Galiè et al 2009*). In a 52-week extension trial, PHIRST-2, the improvements in 6MWD observed at the end of PHIRST appeared to be maintained through week 52 of PHIRST-2 (68 weeks total). In addition, 34% of patients enrolled in PHIRST-2 experienced an improvement in WHO FC compared to baseline of the PHIRST trial (*Oudiz et al 2012*).

Adempas (riociguat)

- The efficacy and safety of Adempas were evaluated in CHEST-1, a multinational, multicenter, double-blind,16-week trial in 261 adult patients with CTEPH. The majority of patients were WHO FC II (31%) or class III (64%). The primary endpoint of CHEST-1 was change from baseline in 6MWD after 16 weeks. Secondary endpoints included changes from baseline in pulmonary vascular resistance (PVR), N-terminal pro-brain natriuretic peptide (NT-proBNP) level, WHO FC, time to clinical worsening, Borg dyspnea score, QOL variables, and safety. Improvements in walking distance occurred beginning at week 2. At week 16, the placebo adjusted mean increase in 6MWD within the Adempas group was 46 m (95% confidence interval [CI], 25 m to 67 m; p < 0.001) (*Ghofrani et al 2013[a]*).
  - An open-label, non-comparative, extension study (CHEST-2) included 237 patients who completed CHEST-1. CHEST-2 consisted of an 8-week, double-blind dose-adjustment phase, followed by an open-label study phase that continued until Adempas received official approval and became commercially available. At the March 2013 cut-off date, 211 patients (89%) were receiving ongoing treatment, and 179 (76%) had received over 1 year of treatment. The safety profile of Adempas in CHEST-2 was similar to CHEST-1, with no new safety signals. Improvements in 6MWD and WHO FC observed in CHEST-1 persisted for up to 1 year in CHEST-2. In the observed population at 1 year, mean±standard deviation (SD) 6MWD had changed by 51±62 m (n = 172) versus CHEST-1 baseline (n = 237), and WHO FC had improved, stabilized, or worsened in 47, 50, or 3% of patients (n = 176) versus CHEST-1 baseline (n = 236). Of patients treated for 1 year in CHEST-2, 145 (92%) out of 157 were continuing to receive monotherapy, and 12 (8%) patients were receiving additional PH-specific medication (8 [5%] were receiving ERAs and 4 [3%] were receiving prostanoids). No patient required additional treatment with both an ERA and prostanoid at 1 year (Simmoneau et al 2015). An exploratory analysis noted a significant association with overall survival for 6MWD and NT-proBNP concentration at baseline (p = 0.0199, and 0.0183, respectively), and at follow-up (p = 0.0385, and 0.0068, respectively). Additionally, short-term improvements were associated with long-term survival and worsening-free survival. At 2 years, the overall survival rate was 93% (95% CI, 89 to 96%) and the rate of clinical worsening-free survival was 82% (95% CI, 77 to 87%) (*Simonneau et al 2016*). Due to lack of a control group and because certain outcomes were considered exploratory, data from this study must be interpreted cautiously.
- The efficacy and safety of Adempas were also evaluated in PATENT-1, a multinational, multicenter, double-blind, 12-week trial in 443 adult patients with PAH as defined by PVR > 300 dyn*sec*cm^{-5} and a PAP_{mean} > 25 mmHg. In this study, 50% of the patients were treatment-naïve with respect to PAH therapy, 44% were pre-treated with an ERA, and 6% were pretreated with a PCA (inhaled, oral, or SC). Patients were randomized to 1 of 3 treatment groups: placebo (n = 126), an exploratory capped titration arm of Adempas 1.5 mg 3 times daily (n = 63), or a capped maximum dose of Adempas 2.5 mg 3 times daily (n = 254). The primary endpoint of PATENT-1 was change from baseline in 6MWD after 12 weeks in the Adempas 2.5 mg group compared to placebo. Secondary endpoints included changes from baseline in PVR, NT-proBNP level, WHO FC, time to clinical worsening, Borg dyspnea score, QOL variables, and safety. At week 12, the placebo-adjusted mean increase in 6MWD within the Adempas 2.5 mg treatment group was

36 m (95% CI, 20 m to 52 m, p < 0.001). The group receiving the capped dose at 1.5 mg was excluded from the efficacy analysis (*Ghofrani et al 2013[b]*).

- An open-label, non-comparative, extension study (PATENT-2) included 396 patients who completed PATENT-1. PATENT-2 consisted of an 8-week, double-blind dose-adjustment phase, followed by an open-label study phase that continues until all patients have transitioned to the commercially available drug. A total of 197 patients received Adempas monotherapy and 199 received Adempas in combination with an ERA or prostanoid, or both. The primary objective of the study was to assess the safety and tolerability of long-term Adempas treatment. Assessments took place at entry to PATENT-2, at weeks 2, 4, 6, 8, and 12, and every 3 months thereafter. At the March 2013 data cut-off, 324 patients (82%) were receiving ongoing treatment and 84% had received 1 year or more of treatment. Mean treatment duration was 95 weeks (median 91 weeks), and cumulative treatment exposure was 718 patient-years (Rubin et al 2015). An exploratory analysis concluded that there was a significant association between overall survival and 6MWD, NT-proBNP concentration, and WHO FC at baseline (p = 0.0006, 0.0225, and 0.0191, respectively), and at follow-up (p = 0.021, 0.0056, and 0.0048, respectively). Additionally, short-term improvements were associated with long-term survival and worsening-free survival. The estimated survival rate was 97% (95% CI, 95 to 98%) and rate of clinical worsening-free survival was 88% (95% CI, 85 to 91%) at 1 year and 79% (95% CI, 74 to 82%) at 2 years (*Ghofrani et al 2016*). Certain outcomes were considered exploratory, so data from this study must be interpreted cautiously.

Flolan (epoprostenol)

- The safety and efficacy of chronically-infused Flolan were evaluated in 2 similar, open-label, randomized trials of 8 to12 weeks' duration comparing Flolan plus conventional therapy (eg, anticoagulants, oral vasodilators, diuretics, digoxin, oxygen) with conventional therapy alone in idiopathic or heritable PAH (NYHA Class II to IV) patients (n = 106). The average Flolan dose was 9.2 ng/kg/min at the trials' end. A statistically significant improvement was observed in the 6MWD in patients receiving Flolan plus conventional therapy for 8 to 12 weeks compared with those receiving conventional therapy alone. Improvements were noted as early as week 1. Increases in exercise capacity were accompanied by statistically significant improvement in dyspnea and fatigue, as measured by the Chronic Heart Failure Questionnaire and the Dyspnea Fatigue Index, respectively.
- The efficacy of chronically-infused Flolan in PAH and scleroderma spectrum of diseases (NYHA Class II to IV) was evaluated in an open-label, randomized, 12-week trial (n = 111) comparing Flolan plus conventional therapy with conventional therapy alone. The mean Flolan dose was 11.2 ng/kg/min at the end of week 12. Statistically significant improvement was observed in the 6MWD in patients receiving continuous Flolan plus conventional therapy for 12 weeks compared to those receiving conventional therapy alone. Increases in exercise capacity were accompanied by statistically significant improvement in dyspnea and fatigue, as measured by Borg Dyspnea Index and Dyspnea Fatigue Index. At week 12, the NYHA FC improved in 41% of patients treated with Flolan plus conventional therapy compared to none of the patients treated with conventional therapy alone. However, the majority of patients in both treatment groups showed no change in FC, with 4% of the Flolan plus conventional therapy group and 27% of conventional therapy group alone worsening.

Letairis (ambrisentan)

- The safety and efficacy of Letairis in the treatment of PAH were established in the ARIES trials. ARIES-1 and ARIES-2 were 12-week, randomized, double-blind, placebo-controlled trials that compared Letairis to placebo in 394 patients. Compared to placebo, treatment with Letairis resulted in a significant increase in exercise capacity as measured by 6MWD (*Galiè et al 2008[a]*). ARIES-E was the open-label extension study for ARIES-1 and ARIES-2. After 1 year of treatment, there was an improvement in 6MWD in the 2.5, 5 and 10 mg Letairis groups (25, 28 and 37 m, respectively). After 2 years of treatment, the improvement was sustained in the 5 and 10 mg groups (23 and 28 m), but not the 2.5 mg group (7 m) (*Oudiz et al 2009*).
- ARIES-3 was a long-term, open-label, single-arm, safety, and efficacy study of Letairis in patients with PH receiving Letairis 5 mg once daily for 24 weeks. The primary endpoint was change from baseline in 6MWD at week 24. Secondary efficacy endpoints included change in plasma NT-proBNP, Borg Dyspnea Index, WHO FC, time to clinical worsening of PAH, survival and adverse events (AEs). A total of 224 patients with PH due to idiopathic and familial PAH (31%), connective tissue disease (18%), chronic hypoxemia (22%), chronic thromboembolic disease (13%), or other etiologies (16%) were enrolled, and 53% of patients received stable background PAH therapies. After 24 weeks of therapy, there was an increase in 6MWD of 21 m (95% CI, 12 to 29), and a decrease in NT-proBNP of -26% (95% CI, -34 to -16%) observed in the overall population compared to baseline. However, increases in 6MWD were not

observed in several non-Group 1 PH subpopulations. Peripheral edema, headache, and dyspnea were the most common AEs (*Badesch et al 2012*).

- The AMBITION trial (n = 610) was a double-blind, randomized, Phase 3/4 trial which compared combination treatment with Letairis plus Adcirca to monotherapy with each in patients with WHO FC II or III symptoms. The study protocol was amended during the trial resulting in 17% of the initial protocol patients being excluded from the analysis, and treatment was administered significantly longer in the combination group vs. monotherapy groups (p = 0.03). Results demonstrated that patients receiving combination therapy had significantly fewer clinical failure events (defined as death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response) compared to patients receiving individual monotherapy (combination vs. pooled-monotherapy group, hazard ratio [HR] 0.5; 95% CI, 0.35 to 0.72; p < 0.001). Primary event outcomes were primarily driven by hospitalization. No significant differences were observed in terms of change in FC or all-cause death. The most common AEs that occurred more often with combination treatment included peripheral edema, headache, nasal congestion, anemia, and bronchitis (*Galiè et al 2015[a]*). Based on results from the AMBITION trial, the FDA-approved Letairis in combination with Adcirca to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability.

Opsumit (macitentan)

- The efficacy and safety of Opsumit on progression of PAH were demonstrated in a multicenter, Phase 3, event-driven, placebo-controlled trial (SERAPHIN) in 742 patients with symptomatic PAH (WHO FC II, III, or IV) with or without concomitant use of oral PDE-5 inhibitors, oral or inhaled PCAs, CCBs, or L-arginine for the 3 month period prior to randomization. Patients were randomized to placebo (n = 250), Opsumit 3 mg once daily (n = 250), or Opsumit 10 mg once daily (n = 242). The mean treatment durations were 85.3, 99.5, and 103.9 weeks in the placebo, Opsumit 3 mg, and Opsumit 10 mg groups, respectively. The primary study endpoint was time to the first occurrence of death, a significant morbidity event (defined as atrial septostomy, lung transplantation, initiation of IV or SC PCAs), or other worsening of PAH (defined as a sustained ≥ 15% decrease from baseline in 6MWD, worsening of PAH symptoms as determined by worsening of WHO FC, and need for additional treatment of PAH) during the double-blind treatment plus 7 days. Pre-specified secondary endpoints included change from baseline to month 6 in the 6MWD and percentage of patients with improvement in WHO FC. Other critical pre-specified secondary endpoints were time to PAH death or PAH hospitalization. The primary endpoint occurred in 46.4%, 38%, and 31.4% of the patients in the placebo, Opsumit 3 mg, and Opsumit 10 mg groups, respectively. Opsumit 10 mg once daily therapy resulted in a 45% reduction compared to placebo (HR, 0.55; 97.5% CI, 0.39 to 0.76; p < 0.001) in the occurrence of the primary endpoint to the end of the double-blind treatment. The beneficial effect of Opsumit 10 mg was primarily due to its reduction in clinical worsening (*Pulido et al 2013*).
  - In a sub-group analysis of the effect of Opsumit on hospitalizations, there were 117 (46.8%), 104 (41.6%), and 90 (37.2%) patients in the placebo, Opsumit 3 mg and 10 mg groups, respectively, who were hospitalized for any cause at least once during double-blind treatment, and they experienced a total of 171, 159, and 135 all-cause hospitalizations, respectively. Compared with that of placebo, the risk of all-cause hospitalization with Opsumit 3 mg was reduced by 18.9% (HR, 0.811; 95% CI, 0.623 to 1.057; p = 0.1208) and with Opsumit 10 mg by 32.3% (HR, 0.677; 95% CI, 0.514 to 0.891; p = 0.0051). Compared with placebo, the rate of PAH-related hospitalization was reduced by 44.5% in the Opsumit 3 mg group (p = 0.0004) and by 49.8% in the Opsumit 10 mg group (p < 0.0001). The mean number of annual hospital days for PAH-related hospitalizations was reduced by 53.3% in the Opsumit 3 mg arm (p = 0.0001) and by 52.3% in the Opsumit 10 mg arm (p = 0.0003). Due to the exploratory nature of this endpoint and small population, data from this study must be interpreted cautiously (*Channick et al 2015*).

Remodulin (treprostinil)

- The safety and efficacy of Remodulin were evaluated in 2 identical 12-week, multi-center, randomized, placebo-controlled, double-blind trials in a total of 470 patients with NYHA Class II, III, and IV PAH. Remodulin was administered SC at an average dose of 9.3 ng/kg/min. The effect on the 6MWD was small and did not achieve statistical significance at 12 weeks. For the combined populations, the median change from baseline for patients on Remodulin was 10 m and the median change from baseline on placebo was 0 m from a baseline of approximately 345 m. The Borg dyspnea score was significantly improved by Remodulin during the 6-minute walk test. Remodulin also consistently improved indices of dyspnea, fatigue, and signs and symptoms of PH. However, these results were difficult to interpret in the context of incomplete blinding to treatment assignment resulting from infusion site symptoms.

Orenitram (treprostinil)

- The efficacy and safety of Orenitram were evaluated in 3 multi-center, randomized, placebo-controlled, double-blind trials in 349 patients (FREEDOM-M), 350 patients (FREEDOM-C), and 310 patients (FREEDOM-C2).
  - o FREEDOM-M compared twice daily administration of Orenitram with placebo in patients newly diagnosed with PAH and not receiving any background PAH treatment. The dose titration was based on patient's clinical response and tolerability. The primary endpoint was change in 6MWD over 12 weeks. The Orenitram group showed a significant improvement in 6MWD of 23 m (p = 0.0125). More than 50% of patients had an improvement of ≥ 20 m, and over 30% of patients had an improvement of > 50 m (*Jing et al 2013*). Orenitram demonstrated AEs typical of prostacyclin treatments (*Waxman 2013*).
  - o FREEDOM-C and FREEDOM-C2 failed to meet the primary endpoint of improved 6MWD (*Tapson et al 2012, Tapson et al 2013*).

Revatio (sildenafil)

- The safety and efficacy of Revatio were evaluated in the SUPER-1 study, a 12-week, randomized, double-blind, placebo-controlled trial consisting of 278 patients with predominantly WHO FC II or III symptoms. Compared to placebo, Revatio significantly improved exercise capacity, as measured by the 6MWD, WHO FC symptoms and hemodynamics (*Galiè et al 2005*). In a 3-year extension study (SUPER-2), 46% of patients increased 6MWD relative to SUPER-1 baseline, 18% decreased 6MWD from baseline, 19% had died and 17% discontinued treatment or were lost to follow-up (*Rubin et al 2011*). The addition of Revatio to epoprostenol was evaluated in PACES, a 16-week, randomized, double-blind, placebo-controlled trial consisting of 267 patients receiving epoprostenol with predominantly WHO FC II or III symptoms. Revatio added to epoprostenol improved exercise capacity, hemodynamic measurements and time to clinical worsening more than epoprostenol plus placebo (*Simonneau et al 2008*).

Tracleer (bosentan)

- Tracleer was originally FDA-approved in PAH patients with WHO FC III and IV symptoms based on the results from 2 randomized, double-blind, placebo-controlled trials in 32 (Study 351) and 213 (BREATHE-1) patients treated for 16 and 12 weeks, respectively. In both studies, significant increases in the 6MWD were observed in all Tracleer groups compared to placebo. Tracleer was also associated with a significant reduction in dyspnea during walk tests and a significant improvement in WHO FC symptoms (*Channick et al 2001, Rubin et al 2002*). The FDA-approved indication was subsequently expanded to include patients with WHO FC II symptoms based on the results of the EARLY study consisting of 168 patients. In this 26-week study, treatment with Tracleer resulted in an increase in the 6MWD of 11.2 m compared to a decrease of 7.9 m in the placebo group; however, the difference was not statistically significant. The study did show a significant delay in clinical worsening and a lower incidence of worsening FC symptoms in the Tracleer group compared to placebo (*Galiè et al 2008[b], McLaughlin et al 2006*).
  - o The results of an open-label extension phase of the EARLY trial suggested that the majority of patients exposed to long-term Tracleer therapy maintained or improved their FC. Approximately 20% of patients discontinued treatment because of AEs which were most commonly PAH worsening (defined as death or initiation of IV or SC PCAs) and elevated liver enzymes. Due to lack of a control group, data from this study must be interpreted cautiously (*Simmoneau et al 2014*).
- The COMPASS-2 trial (n = 334) was a prospective, double-blind, randomized controlled trial consisting of symptomatic PAH patients ranging from WHO FC II to IV who were taking stable Revatio doses (mean dose, 60 mg) for ≥ 3 months. Patients were randomized to Tracleer 125 mg twice daily plus Revatio or placebo plus Revatio for 16 weeks. There was no difference in the primary endpoint, time to the first morbidity/mortality event (defined as time to all-cause death, hospitalization for worsening PAH, initiation of IV prostanoid, atrial septostomy, lung transplant, or worsening PAH). There were also no significant differences in the individual measures of the primary endpoint; however, observed benefits were seen in terms of the mean 6MWD test. A high drop-out rate was observed during the trial; therefore, study power was reduced (*McLaughlin et al 2015*).

Tyvaso (treprostinil)

- The safety and efficacy of Tyvaso were evaluated in TRIUMPH I, a 12-week, multi-center, randomized, placebo-controlled, double-blind trial in WHO Group I PAH (98% NYHA Class III) patients who were receiving either Tracleer or Revatio (n = 235) for at least 3 months prior to study initiation. Patients received either placebo or Tyvaso in 4 daily

treatments with a target dose of 9 breaths (54 mcg) per session. The primary endpoint, 6MWD, was measured at peak exposure (10 to 60 minutes post dose) and 3 to 5 hours after Tracleer or 30 to 120 minutes after Revatio. Patients receiving Tyvaso had a placebo-corrected median change from baseline in peak 6MWD of 20 meters (m) at week 12 ($p < 0.001$). The 6MWD measured at trough exposure (measured 4 hours after dosing) improved by 14 m.
- In a long-term follow-up of patients who were treated with Tyvaso in the pivotal study and the open-label extension (n = 206), Kaplan-Meier estimates of survival at 1, 2, and 3 years were 97%, 91%, and 82%, respectively. Of note, these observations were uncontrolled and therefore cannot be compared to the control group to determine the long-term effect of Tyvaso on mortality.

Uptravi (selexipag)
- The safety and efficacy of Uptravi were evaluated in the GRIPHON study (n = 1,156), a randomized, double-blind, placebo-controlled trial consisting of patients with predominantly idiopathic PAH, and WHO FC II or III symptoms. The median duration of treatment varied from 1.2 to 1.4 years for placebo and Uptravi, respectively, and treatment end was defined as 7 days after the last day of treatment intake. Compared to placebo, Uptravi significantly reduced the composite endpoint signifying the time to progression of PAH, defined as all-cause death or a PAH complication (27% vs. 41.6%; HR, 0.6; 99% CI, 0.46 to 0.78; $p < 0.001$); however, there were no differences in mortality between groups. The reduction in PAH complications was primarily driven by a reduction in disease progression (17.2% vs. 6.6%) and PAH-related hospitalization (18.7% vs. 13.6%). The safety of Uptravi compared to other agents in class is not clear. The GRIPHON pre-specified sub-group analysis did not stratify AEs by background treatment, but the study allowed stable doses of PDE-5 inhibitors and/or an ERA which accounted for ~80% of patients within the placebo baseline group. Those AEs that occurred significantly more often with Uptravi treatment included headache, diarrhea, jaw pain, nausea, myalgia, vomiting, extremity pain, flushing ($p < 0.001$ for all AEs), anemia ($p = 0.05$), and hyperthyroidism ($p = 0.004$) (*Sitbon et al 2015*).

Veletri (epoprostenol)
- Please refer to the clinical efficacy summary for Flolan above.

Ventavis (iloprost)
- The efficacy of Ventavis was evaluated in a 12-week, randomized, multicenter, double-blind, placebo-controlled trial consisting of 203 patients with NYHA Class III PAH (majority), Class IV PAH, or CTEPH. Patients received 2.5 or 5 mcg of Ventavis 6 to 9 times daily during waking hours. The difference in the primary composite endpoint (10% increase in 6MWD 30 minutes after dose, improvement by at least one NYHA class compared to baseline, and no death or deterioration of PH) was statistically significant (19% vs. 4% placebo, $p = 0.0033$). The results for the CTEPH patients were not included in the aforementioned results, since there was inadequate evidence of benefit in this patient population. The placebo-corrected difference in the 6MWD in Ventavis patients at 12 weeks was 40 m ($p < 0.01$).
- The safety of Ventavis was evaluated in a prospective, 2 year, open-label study with 63 PAH patients. Patients received Ventavis 2 to 4 mcg 6 to 9 times daily. Thirty-six patients completed at least 630 days of therapy, 19 patients dropped out prematurely, and 8 patients died. AEs were mild to moderate, the most common of which were cough and flushing. Two-year survival was found to be 87% [95% CI, 76% to 98%] (*Olschewski et al 2010*).

Meta-analyses and systematic reviews
- The results of a meta-analysis of 18 randomized controlled trials (n = 4,363) suggested that all oral PAH therapies confer a therapeutic benefit. More specifically, the findings showed:
  - PDE-5 inhibitors were associated with a statically significant reduction in mortality (relative risk [RR], 0.22; 95% CI, 0.07 to 0.71; $p = 0.011$), while other drugs only showed a trend toward reducing mortality.
  - Compared with placebo, ERAs, PDE-5 inhibitors, and riociguat significantly reduced clinical worsening, ameliorated WHO function class, and increased 6MWD. Oral prostanoids only showed a mild effect on 6MWD (19.88 m; 95% CI, 10.12 to 29.64, $p = 0$), and did not have any effect on reducing mortality and clinical worsening. Additionally, oral prostanoids significantly increased the incidence of treatment discontinuation due to AEs (RR, 3.41; 95% CI, 2.06 to 5.63; $p = 0$) (*Zheng et al 2014[a]*).
- A meta-analysis of 14 randomized controlled trials (n = 2,244) that evaluated the improvement in overall survival with use of oral, SC, IV, and inhaled PCAs, suggested the following:

- Only IV PCAs showed a survival benefit (RR, 0.36; 95% CI, 0.16 to 0.79; p = 0.011), while oral (RR, 0.73; 95% CI, 0.32 to 1.66; p = 0.446), inhaled (RR, 0.28; 95% CI, 0.05 to 1.67; p = 0.162), and SC administration (RR, 0.91; 95% CI, 0.38 to 2.20; p = 0.837) did not show a benefit.
- Overall mortality in the 14 studies was 3.30% (74 of 2,244 patients) with 2.52% (30 of 1,189 patients) mortality in the PCA-treated group and 4.17% (44 of 1,055 patients) mortality in the placebo group. The cumulative RR estimate of death showed a significant reduction of 44% (RR, 0.56; 95% CI, 0.35 to 0.88; p = 0.01), and no heterogeneity (I^2 = 0.0%; p = 0.84) was detected among studies (*Zheng et al 2014[b]*).

- The results of a meta-analysis of 21 randomized controlled trials (n = 5,105) suggested that there was a reduction in the number of combined clinical worsening events (defined as all-cause mortality, lung or heart-lung transplant, hospitalization for PAH, and escalation of treatment) in patients with PAH with oral treatments, but showed less favorable effects on life expectancy in the short-term follow-up. Results demonstrated:
  - All classes reduced clinical worsening compared to placebo, including oral prostanoids (odds ratio [OR], 0.616; 95% CI, 0.419 to 0.906; p = 0.014), ERAs (OR, 0.504; 95% CI, 0.409 to 0.621; p < 0.001), PDE-5 inhibitors (OR, 0.468; 95% CI, 0.329 to 0.664; p < 0.001), and Adempas (OR, 0.277; 95% CI, 0.098 to 0.782; p = 0.015).
  - There were no significant reductions in mortality with any class versus placebo (*Zhang et al 2015*).
- A meta-analysis of 5 randomized controlled trials (n = 962) of < 16 weeks duration in adults and children treated with an sGC stimulator determined the following (all comparisons are vs. placebo):
  - sGC stimulators improve PAP in patients with PAH (who are treatment naïve or receiving a prostanoid or ERA) or those with recurrent or inoperable CTEPH.
  - Pooled analysis showed a mean difference in 6MWD of 30.13 m (95% CI, 5.29 to 54.96; I^2 = 64%). On subgroup analysis, for PAH, there was no effect on 6MWD (11.91 m; 95% CI, -44.92 to 68.75; I^2 = 77%), and for CTEPH, sGC stimulators improved 6MWD by a mean difference of 45 m (95% CI, 23.87 to 66.13; I^2 = 0%).
  - The secondary outcome of mortality showed no change on pooled analysis.
  - Although pooled results demonstrated an increase (improvement) in WHO functional class (OR, 1.53; 95% CI, 0.87 to 2.72; I^2 = 49%), the results did not reach statistical significance. Also, there was no effect on clinical worsening (OR, 0.45; 95% CI, 0.17 to 1.14; I^2 = 54%) or a reduction in MAP (−2.77 mmHg; 95% CI, −4.96 to −0.58; I^2 = 49%). The pooled analysis did not show any significant difference in serious AEs (OR, 1.12; 95% CI, 0.66 to 1.90; I^2 = 39%).
  - sGC stimulators should not be taken by people also receiving PDE-5 inhibitors or nitrates due to the risks of hypotension, and there is currently no evidence supporting their use in pulmonary hypertension associated with left heart disease (*Wardle et al 2016*).
- Several additional meta-analyses have been conducted evaluating ERAs, PDE-5 inhibitors, and PCAs. Notable observations in meta-analyses include the following:
  - Survival benefit was seen more with IV PCAs, especially in patients with more severe disease, compared with other routes such as oral and inhalation (*Ryerson et al 2010*).
  - ERAs (Letairis and Tracleer) may have a somewhat lower effect on exercise tolerance in patients with connective tissue diseases, whereas PDE-5 inhibitors (Revatio and Adcirca) and the PCA epoprostenol showed consistent effects regardless of the presence or absence of connective tissue diseases (*Kuwana et al 2013*).
  - Combination therapy appears to improve exercise capacity and reduce the risk of clinical worsening in PAH patients compared with monotherapy (*Zhu et al 2012*).
  - Favorable effects on clinical events were not predicted by changes in the 6MWD (*Savarese et al 2012*). In addition, pulmonary hemodynamics correlated with exercise capacity, but not with clinical events (*Savarese et al 2013*).
  - According to an Agency for Healthcare Research and Quality meta-analysis, prostacyclin analogues showed a statistically significant improvement in mortality. In addition, all drug classes improved 6MWD, but comparisons between agents were inconclusive. Combination therapy also improved 6MWD compared with monotherapy, but comparisons between specific regimens were inconclusive. Patients taking ERAs and PDE-5 inhibitors had a lower risk of hospitalization than those taking placebo, while the reduction in patients taking PCAs compared with placebo was similar, but not statistically significant (*McCrory et al 2013*).
  - A meta-analysis including 15 RCTs comparing combination and monotherapy for the treatment of PAH found that the absolute risk reduction of clinical worsening was relatively constant beyond a 6 to 12-month treatment duration, and cast doubt on the need for trials of longer duration for measuring treatment efficacy in this population (*Lajoie et al 2017*).

CLINICAL GUIDELINES

- Several recently published clinical guidelines on PAH are available.
  - The Chest Guideline and Expert Panel Report on pharmacologic therapy for PAH provides several options for initial and subsequent therapy (*Taichman et al 2014*).
    - Initial therapy: For patients in WHO FC II or III, monotherapy with an ERA, PDE-5 inhibitor, or sGC stimulator is recommended. In WHO FC III patients with evidence of rapid progression or markers of poor prognosis, a parenteral prostanoid should be considered. For patients in WHO FC IV, a parenteral PCA is recommended; however, if patients are unable or unwilling to manage a parenteral product, an alternative is an inhaled PCA combined with an ERA.
    - Subsequent therapy: For patients in WHO FC III who have evidence of progression or markers of poor prognosis, addition of an inhaled or parenteral prostanoid should be considered. In patients in WHO FC III or IV, if clinical status is unacceptable, a second (and if needed, a third) class of PAH therapy can be added.
  - The European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines for the diagnosis and treatment of PH (*Galiè et al 2015[b]*) provide several options for both monotherapy and combination therapy of PAH.
    - Monotherapy: For patients in WHO FC II, recommendations include an ERA, a PDE-5 inhibitor, an sGC stimulator, or a prostacyclin receptor agonist. For patients in WHO FC III, the same medications may be used, and another option is a PCA. PCAs (eg, epoprostenol) are generally preferred for patients in WHO FC IV.
    - Initial drug combination therapy: Only the combination of Adcirca and Letairis has a category I recommendation for patients in WHO FC II and III; this combination also has a category IIb recommendation for patients in WHO FC IV. Other double- and triple-therapy combinations are also options, including other ERA and PDE-5 inhibitor combinations (WHO FC II, III, and IV) and some combinations of oral therapies with parenteral PCAs (WHO FC III and IV).
    - Sequential drug combination therapy: Several options are provided for sequential combination therapy. Oral combinations are commonly recommended for patients in WHO FC II and III, including Opsumit added to Revatio, Adempas added to Tracleer, and Uptravi added to an ERA and/or a PDE-5 inhibitor. Other oral combinations and combinations of oral therapies with inhaled or parenteral agents may also be used in patients in WHO FC II, III, and/or IV, but in most cases these recommendations are not as strong.
  - A 2018 scientific statement on the evaluation and management of right-sided heart failure from the American Heart Association (AHA) summarizes data for the use of prostacyclin analogs, PDE-5 inhibitors, and endothelin receptor agonists in patients with PAH (*Konstam et al 2018*). However, specific recommendations concerning the use of these agents in the PAH population are not provided in this document.
  - Reputable society groups agree that evidence supporting pediatric treatment is lacking. The AHA and American Thoracic Society (ATS) recently published a guideline on pediatric PH. This guideline states that in pediatric patients with lower-risk PAH, oral therapy with either a PDE-5 inhibitor or an ERA is recommended, and in pediatric patients with higher-risk PAH, IV or SC PCAs should be initiated without delay (*Abman et al 2015*). A recent expert consensus statement from the European Pediatric Pulmonary Vascular Disease Network, the International Society of Heart and Lung Transplantation, and the German Society of Pediatric Cardiology reaffirm the AHA/ATS guideline. Additionally, early combination therapy with oral PAH drugs in treatment-naïve children who are FC II or III may be considered (*Hansmann et al 2016*).

SAFETY SUMMARY

- sGC Stimulator
  - Adempas has a boxed warning due to embryo-fetal toxicity. It is contraindicated in pregnancy (Pregnancy Category X) because it may cause fetal harm when administered to pregnant women.
  - Females can only receive Adempas through the Adempas REMS Program, a restricted distribution program that requires enrollment and certification of prescribers, patients, and pharmacies. The program also requires females of reproductive potential to comply with pregnancy testing and contraception requirements.
  - Adempas is contraindicated in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias.
  - Additional contraindications for Adempas include co-administration with nitrates or nitric oxide donors and PDE-inhibitors (specific and non-specific).

- Warnings and precautions for Adempas include symptomatic hypotension, bleeding, and pulmonary edema in patients with veno-occlusive disease (if confirmed, treatment should be discontinued).
- The most common AEs associated with Adempas include headache, dyspepsia and gastritis, dizziness, nausea, diarrhea, hypotension, vomiting, anemia, gastroesophageal reflux disease, and constipation.

- ERAs
  - The ERAs (Letairis, Opsumit, and Tracleer) have boxed warnings for embryo-fetal toxicity and/or risks of teratogenicity due to the potential for fetal harm when administered to women who are or may become pregnant.
  - The Letairis and Opsumit REMS programs, respectively, are designed in the same manner as the Adempas REMS program described above.
  - The Tracleer Access Program (T.A.P.) program has been re-listed as the Tracleer REMS program. As a requirement of the REMS, healthcare professionals who prescribe or dispense Tracleer must enroll and comply with the requirements. Requirements include monthly reviews of pregnancy tests in women of reproductive potential, and liver enzymes and bilirubin in all patients. All patients must understand the risks and complete an enrollment form.
  - Letairis has an additional contraindication for idiopathic pulmonary fibrosis (IPF).
  - Tracleer has an additional boxed warning for risks of hepatotoxicity and birth defects. Throughout treatment and for 1 month after stopping Tracleer, females of reproductive potential must use 2 reliable methods of contraception unless the patient has had a tubal sterilization or had an intrauterine device (IUD) inserted.
  - Drug Reaction with Eosinophilia and Systematic Symptoms (DRESS), anaphylaxis, rash, and angioedema have been reported with Tracleer.
  - Warnings and precautions for Adcirca and Revatio include prolonged erection (for more than 4 hours), hearing loss, and vision loss (in 1 or both eyes), all of which require immediate medical attention.
  - Pulmonary edema has been reported during postmarketing surveillance of Letairis and Tracleer. Pulmonary edema may occur within weeks after starting Letairis and is more common when Letairis is used in combination with Adcirca than with Letairis or Adcirca alone.
  - Use of Opsumit and Tracleer should be avoided in patients taking potent inhibitors or inducers of CYP3A.
  - Decreases in sperm count, decreased hemoglobin and hematocrit levels, and pulmonary edema (associated with pulmonary veno-occlusive disease (PVOD) have been observed in patients taking ERAs.
- PDE-5 Inhibitors
  - All PDE-5 inhibitor products have a contraindication for use in patients on nitrates as well as a warning with concomitant alpha blocker use due to resulting hypotension. The patient should allow 48 hours to elapse between the last dose of Adcirca and taking nitrates. Additionally, Revatio and Adcirca are contraindicated for concomitant use with the sGC stimulator, Adempas.
  - In August 2012, the prescribing information for Revatio was updated with a warning stating that the use of Revatio in pediatric patients is not recommended due to increased mortality associated with higher doses and noted that lower doses are not effective in improving exercise capacity. The FDA clarified the warning related to pediatric use of Revatio in March 2014, stating it was not intended to suggest that Revatio never be used in children. The FDA acknowledged there may be situations in which the benefit-to-risk profile may be acceptable in individual children, for example, when other treatment options are limited, in which case Revatio can be used with close monitoring (FDA Drug Safety Communication, 2014).
  - Co-administration of Revatio or Adcirca with potent CYP3A4 inhibitors is not recommended. Co-administration of Adcirca with potent CYP3A4 inducers is not recommended.
  - Blood pressure lowering effects are increased when Adcirca is taken with alcohol.
  - Revatio and Adcirca are generally well tolerated with headaches, myalgia, flushing, and dyspepsia being the most common AEs reported for both products.
  - Stevens-Johnson syndrome and exfoliative dermatitis have been reported with Adcirca, and anaphylactic reaction, anaphylactic shock and anaphylactoid reaction have been reported with Revatio.
  - Vision loss, including permanent vision loss because of non-arteritic anterior ischemic optic neuropathy has been reported with the use of PDE-5 inhibitors.
- Prostacyclin Receptor Agonist
  - Uptravi has a warning/precaution to consider PVOD if acute pulmonary edema develops.
  - Uptravi is not recommended in patients with severe hepatic impairment (Child-Pugh Class C) and has not been studied in dialysis patients (or with eGFR < 15 mL/min/1.73m^2).
  - Concomitant administration of Uptravi is contraindicated with strong inhibitors of CYP2C8 (eg, gemfibrozil).

- The most common AEs reported with Uptravi are headache, diarrhea, jaw pain, nausea, myalgia, vomiting, pain in extremity, and flushing. These AEs are more frequent during the dose titration phase.

- PCAs
  - Orenitram is contraindicated for use in patients with severe hepatic impairment (Child-Pugh Class C).
  - Flolan and Veletri are contraindicated in patients with congestive heart failure due to severe left ventricular dysfunction. Additionally, Veletri is contraindicated in patients with pulmonary edema, stating that the development of pulmonary edema during dose initiation may be associated with pulmonary veno-occlusive disease.
  - Orenitram and Tyvaso both carry a warning/precaution related to an increased risk of bleeding, particularly in patients receiving anticoagulants. Additional warnings and precautions for Tyvaso include symptomatic hypotension, possible Tyvaso dose changes when inhibitors or inducers of CYP2C8 are added or withdrawn, and a possible increase in exposure or a decrease in tolerability with hepatic or renal impairment. Orenitram should be avoided in patients with blind-end pouches (diverticulosis).
  - The safety of Tyvaso and Ventavis has not been established in patients with significant underlying lung disease (eg, asthma, chronic obstructive pulmonary disease, acute pulmonary infections). Patients with acute pulmonary infections who are taking Tyvaso should be carefully monitored to detect any worsening of lung disease and loss of drug effect. Ventavis can induce bronchospasm.
  - Hypotension leading to syncope has been observed with Ventavis. It should not be administered in patients with a systolic blood pressure below 85 mmHg.
  - Flolan and Ventavis carry additional warnings and precautions regarding pulmonary edema. If signs of pulmonary edema occur, treatment should be stopped because this could be a sign of pulmonary venous hypertension or pulmonary veno-occlusive disease.
  - With Flolan, Orenitram, Remodulin, and Veletri, abrupt withdrawal (including interruptions in drug delivery) or sudden large reductions in the dose can worsen PAH symptoms (or cause rebound PH in patients taking Flolan).
  - Flolan carries additional warnings and precautions that include vasodilation reactions and an increased risk of bleeding.
  - Flolan, Remodulin, and Veletri are administered via an indwelling central venous catheter. This route of administration is associated with blood stream infections (BSI) and sepsis, which may be fatal. During long-term follow-up, sepsis was reported at a rate of 0.3 infections per patient per year in patients treated with Flolan. In an open-label study of IV Remodulin (n = 47), there were 7 catheter-related line infections during approximately 35 patient years, or about one BSI event per 5 years of use. A Centers for Disease Control and Prevention survey of 7 sites that used IV Remodulin for the treatment of PAH found approximately one BSI event per 3 years of use. Continuous SC infusion (undiluted) is the preferred mode of administration of Remodulin. VELTERI was associated with chills/fever/sepsis/flu-like symptoms in 25% of patients in controlled trials for idiopathic or heritable PAH.
  - Remodulin and Tyvaso exposure may increase or decrease when administered with strong inhibitors or inducers of CYP2C8.
  - AEs reported with Tyvaso include cough, headache, throat irritation/pharyngolaryngeal pain, nausea, flushing, and syncope. AEs with Remodulin include infusion site pain, infusion site reaction, headache, diarrhea, nausea, rash, jaw pain, vasodilation, dizziness, edema, pruritus, and hypotension. The most common AEs reported with Orenitram include headache, diarrhea, nausea, and flushing.
  - AEs associated with Ventavis include vasodilation (flushing), increased cough, headache, trismus, insomnia, nausea, hypotension, vomiting, increased alkaline phosphatase, flu syndrome, back pain, tongue pain, palpitations, syncope, increased gamma-glutamyl transpeptidase, muscle cramps, hemoptysis, and pneumonia.
  - The most common AEs reported with Flolan and Veletri include dizziness, jaw pain, nausea, vomiting, headache, hypotension, flushing, and musculoskeletal pain.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Adcirca (tadalafil)	Tablet: 20 mg	Oral	Daily	Dividing the dose over the course of the day is not recommended.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Adempas (riociguat)	Tablet (film-coated): 0.5, 1, 1.5, 2, and 2.5 mg	Oral	Three times daily	Patients who smoke may tolerate higher doses. If they stop smoking, dose decreases may be required. Lower starting doses should be considered in patients unable to tolerate the hypotensive effects and patients receiving strong CYP and P-gp/BCRP inhibitors. Adempas may be crushed and mixed with water or soft foods immediately before administration. Discontinue at least 24 hours prior to administering a PDE-5 inhibitor. Pregnancy test required prior to treatment initiation and monthly during treatment.
Flolan (epoprostenol)	Powder for injection: 0.5 and 1.5 mg	IV	Continuous infusion; Increase in increments of 1 to 2 ng/kg/min every 15 minutes based on clinical response.	Abrupt withdrawal or sudden large reductions in infusion rates should be avoided. Continuous chronic infusion is administered through a central venous catheter. Temporary peripheral IV infusion may be used until central access is established.
Letairis (ambrisentan)	Tablet: 5 and 10 mg	Oral	Once daily (with or without Adcirca daily. Titrate at 4-week intervals.	Doses > 10 mg once daily have not been studied. Tablets should not be split, crushed, or chewed. Pregnancy test required prior to treatment initiation and monthly during treatment.
Opsumit (macitentan)	Tablet: 10 mg	Oral	Once daily	Doses > 10 mg once daily are not recommended
Orenitram (treprostinil)	Extended-release tablet: 0.125, 0.25, 1, 2.5 mg, and 5 mg	Oral	Twice or 3 times daily. Maximum dose is determined by tolerability. Titrate not more than every 3 to 4 days as tolerated.	Should be taken with food. Tablets should be swallowed whole. Coadministration with CYP2C8 inhibitors (eg, gemfibrozil) requires a lower starting dose.
Remodulin (treprostinil)	Multi-dose vials for injection: 1, 2.5, 5, 10 mg/mL	SC, IV	Continuous infusion; Increase in increments of 1.25 to 2.5 ng/kg/min	SC is preferred, although it can be administered by a central IV line if SC administration is not tolerated.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			slowly (per week/month increments).	
Revatio (sildenafil)	Tablet: 20 mg Powder for oral suspension: 10 mg/mL Solution for injection: 10 mg/12.5 mL	Oral, IV	Oral: 3 times daily approximately 4 to 6 hours apart Injection: IV bolus 3 times daily	Doses above 20 mg 3 times daily are not recommended. Revatio 10 mg injection dose is predicted to be the equivalent of a 20 mg oral dose. Revatio injection is for continued treatment of patients who are temporarily unable to take oral treatment. Oral suspension expires within 60 days of reconstitution.
Tracleer (bosentan)	Tablet: 62.5 and 125 mg Tablet for oral suspension: 32 mg	Oral	Twice daily (age and weigh based dosing) Concurrent ritonavir: Once daily or every other day in patients who have been receiving ritonavir for ≥ 10 days. Discontinue Tracleer at least 36 hours prior to initiation of ritonavir. Resume Tracleer 10 days following ritonavir initiation.	Tablets for oral suspension should be dispersed in a minimal amount of water immediately before administration. Pregnancy test required prior to treatment initiation and monthly during treatment. Initiation should be avoided in patients with aminotransferases > 3x ULN. Doses > 125 mg twice daily do not have additional benefit sufficient to offset the increased risk of hepatotoxicity.
Tyvaso (treprostinil)	Inhalation solution (solution, refill, and starter solution): 0.6 mg/mL (1.74 mg per 2.9 mL)	Inhale	3 breaths per treatment session, 4 times a day (4 hours apart). Titrate by an additional 3 breaths in 1 to 2 week intervals. Maximum: 9 breaths per treatment session, 4 times daily.	Inhalation system consists of an ultrasonic, pulsed delivery device and its accessories.
Uptravi (selexipag)	Tablet: 200, 400, 600, 800, 1000, 1200, 1400, and 1600 mcg Therapy pack: 200/800 mcg	Oral	Twice daily. Titrate dose weekly.	Swallow tablets whole. Food may improve tolerability.
Veletri (epoprostenol)	Powder for injection: 0.5 and 1.5 mg	IV	Continuous infusion; Increase in increments of 1 to 2 ng/kg/min every 15 minutes based on clinical response.	Abrupt withdrawal or sudden large reductions in infusion rates should be avoided. Continuous chronic infusion is administered through a central venous

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				catheter. Temporary peripheral IV infusion may be used until central access is established.
Ventavis (Iloprost)	Inhalation solution: 10 and 20 mcg	Inhale	Administered 6 to 9 times per day (no more than once every 2 hours). Maximum: 9 times daily.	Ventavis is intended to be inhaled using the I-neb Adaptive Aerosol Delivery (AAD) System. The 20 mcg/mL concentration is for patients who are maintained at the 5 mcg dose and who have repeatedly experienced extended treatment times, which could result in incomplete dosing. Vital signs should be monitored while initiating Ventavis.

Abbrv: CYP = cytochrome P450; IV = intravenous; P-gp/BCRP = P-glycoprotein/breast cancer resistance protein; SC = subcutaneous

CONCLUSION

- Pulmonary arterial hypertension (PAH) is a life-threatening disorder that is associated with a poor prognosis.
- There are 5 classes of drugs that are used in the management of PAH, including endothelin receptor antagonists (ERAs), phosphodiesterase (PDE)-5 inhibitors, a prostacyclin analog (PCA), a prostacyclin receptor agonist, and a soluble guanylate cyclase (sGC) stimulator.
- All of the PAH agents have shown improved pulmonary hemodynamics and exercise capacity in PAH patients as compared to placebo. Their effects on mortality have not been adequately demonstrated.
- Most trials for PAH have been relatively short-term trials (12 to 18 weeks) that evaluated changes in exercise capacity using the 6-minute walk distance (6MWD) as a primary endpoint. However, recently there has been a preference toward longer, event-driven trials that evaluate composite clinical worsening events (*LeVarge et al 2015*). Published event-driven trials include SERAPHIN, GRIPHON, AMBITION, and COMPASS-2 (*Galiè et al 2015[a], McLaughlin et al 2015, Pulido et al 2013, Sitbon et al 2015*).
- Clinical trials have demonstrated the safety and efficacy of the individual PAH agents; however, there is limited data comparing the agents within classes or between classes. Data is conflicting regarding the benefits of combination vs. monotherapy (*Barst, 2009, McLaughlin et al 2009, Galiè et al 2015[b], Taichman et al 2014*). Two recent trials evaluating this include the AMBITION and COMPASS-2 trials. The AMBITION trial has demonstrated that combination treatment with Letairis and Adcirca resulted in reduced disease progression and hospitalization in mainly FC II and III PAH patients compared to monotherapy (*Galiè et al 2015[a]*). However, the COMPASS-2 trial demonstrated no difference between Tracleer plus Revatio versus Revatio monotherapy for most endpoints with the exception of the mean 6MWD test (*McLaughlin et al 2015*).
- Adempas is the first and only drug to be FDA-approved in the treatment of CTEPH. Pulmonary endarterectomy can be curative for CTEPH, but it is technically demanding which may limit access to its use as a treatment. Adempas is dosed 3 times daily, which is more frequent than several other oral treatments for PAH.
- The ERAs (Letairis, Opsumit, and Tracleer) competitively bind to both receptors with different affinities. Letairis and Opsumit are highly selective for the ET_A receptor, while Tracleer is slightly selective for the ET_A receptor over the ET_B receptor. In addition, Opsumit has a pharmacologically active metabolite and is considered “tissue-targeting” because it displays high affinity and sustained occupancy at the ET receptors in human pulmonary arterial smooth muscles. However, the clinical significance of receptor affinities of the ERAs has not been established.
- The PDE-5 inhibitors (Adcirca and Revatio) are generally well tolerated; the most common side effects include headache, myalgia, flushing, dizziness, and gastrointestinal upset. Both products are contraindicated for use in patients on nitrates and have warnings about their use in patients on alpha-adrenergic inhibitors. Use of Adcirca with potent CYP3A4 inhibitors or inducers may significantly alter serum levels of Adcirca and is not recommended. Use of Adcirca in patients who are using an sGC stimulator may potentiate the hypotensive effects of sGC stimulators and is

not recommended. Use of Revatio with potent CYP3A4 inhibitors is not recommended as they may significantly alter serum levels of Revatio.

- In addition to the oral formulation, Revatio is available in an oral suspension formulation and an intravenous formulation. Currently, Revatio tablets and intravenous formulation are available generically.
- Adcirca is taken just once a day compared to 3 times a day with Revatio.
- Orenitram is the first oral PCA approved by the FDA. The PCAs are frequently reserved for more severe forms of PAH. As the first oral option in this subclass for treatment of PAH, Orenitram may offer a more convenient alternative dosage form leading to earlier PCA initiation in treatment. Orenitram is dosed twice daily and requires dosage titration every 3 to 4 days. Orenitram did not demonstrate added benefit when added to other vasodilator therapy.
- Uptravi is a first-in-class prostacyclin receptor agonist, which works within the same pathway as Orenitram. Based on results from the GRIPHON trial, Uptravi has reduced disease progression and hospitalization. This is in contrast to Orenitram, which has only improved exercise tolerability. Unlike Orenitram, Uptravi has also demonstrated efficacy when combined with a PDE-5 inhibitor and/or an ERA. The safety of Uptravi compared to other oral agents in class is not clear. The GRIPHON pre-specified sub-group analysis did not stratify AEs by background treatment, but the study allowed stable doses of PDE-5 inhibitors and/or an ERA throughout the trial. Background treatment was used by ~80% of patients within the placebo baseline group. Those AEs reported significantly more often with Uptravi treatment include headache, diarrhea, jaw pain, nausea, myalgia, vomiting, extremity pain, flushing, anemia, and hyperthyroidism (*Sitbon et al 2015*). Based on indirect trial evidence, the proportion of patients discontinuing Uptravi vs. placebo (14% vs. 7%) due to AEs in the GRIPHON trial was higher than those within the Orenitram labeling vs. placebo (4% vs. 3%) (*Orenitram prescribing information 2014, Sitbon et al 2015*). Overall, it is not clear how the Uptravi safety profile compares to other agents in class due to different study populations. Head-to-head trials are needed to confirm safety risks and differences.
- The 2014 CHEST Guideline and Expert Panel Report update identifies PDE-5 inhibitors, ERAs, the oral PCA, and the sGC stimulator as viable alternatives in treating PAH adults with varying severity levels (FC II to IV) based primarily on consensus opinions (*Taichman et al 2014*).
- The 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines stratifies PAH treatment by low or intermediate risk or high risk patients. In adult patients with low or intermediate risk (FC II to III), initial monotherapy or initial oral combination therapy is recommended. Based on the AMBITION trial, guidelines state that initial combination treatment with ambrisentan plus tadalafil has proven to be superior to initial monotherapy with ambrisentan or tadalafil in delaying clinical failure. In adult patients with high risk (FC IV), initial combination therapy including IV PCAs are recommended with epoprostenol IV considered first-line due to the mortality benefits in trials (*Galiè et al 2015[b]*).
- Reputable society group guidelines agree that there is a lack of randomized trials in pediatric patients, making it difficult to deliver strong guidelines (*Abman et al 2015, Galiè et al 2015[b], Hansmann et al 2016*). The 2015 American Heart Association and American Thoracic Society guidelines recommend oral therapy with either a PDE-5 inhibitor or an ERA in lower risk PAH pediatric patients. In pediatric patients with higher-risk PAH, IV and SC PCAs should be initiated immediately with a goal to transition patients to oral or inhaled therapy after the patient is asymptomatic and stable (*Abman et al 2015*). The 2015 ESC/ERS guidelines recommend that pediatric treatment follows adult guidelines taking in account risks (*Galiè et al 2015[b]*). The European Pediatric Pulmonary Vascular Disease Network, the International Society of Heart and Lung Transplantation, and the German Society of Pediatric Cardiology reaffirm much of the aforementioned guidance, but also stipulate that early combination therapy with two oral PAH drugs in treatment-naïve children who are FC II or III may be considered (*Hansmann et al 2016*).
- A 2018 scientific statement on the evaluation and management of right-sided heart failure from the American Heart Association (AHA) summarizes data for the use of prostacyclin analogs, PDE-5 inhibitors, and endothelin receptor agonists in patients with PAH (*Konstam et al 2018*). However, specific recommendations concerning the use of these agents in the PAH population are not provided in this document.

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Publication Date: July 2, 2018

Therapeutic Class Overview
Antipsoriatic Agents

INTRODUCTION

- The goal of treatment for patients with psoriasis is to control the disease. There are three main treatment modalities available at present for the treatment of psoriasis: topical agents, phototherapy, and systemic agents. Topical therapies are the mainstay for mild disease either as monotherapy or in combination, and topical therapies are also commonly used in conjunction with phototherapy, traditional systemic agents, or biologic agents for moderate to severe disease. Phototherapy, photochemotherapy, and traditional systemic agents are generally used for moderate or severe disease and in situations in which topical therapy is ineffective or otherwise contraindicated (Menter et al, 2011; Feldman 2017).
- Topical corticosteroids (e.g., betamethasone, clobetasol, triamcinolone, etc.) are the cornerstone of treatment for the majority of patients with psoriasis. Their effectiveness in treating psoriasis is due to anti-inflammatory, antiproliferative, immunosuppressive, and vasoconstrictive effects. Drawbacks associated with topical corticosteroid treatment are local cutaneous side effects and more serious systemic side effects that are associated with long-term use over a large body surface area (Menter et al, 2011). Due to these side effects, several agents have been developed and tested as monotherapy or in combination with topical corticosteroids in the hopes of reducing the duration of corticosteroid treatment.
- Other topical antipsoriatic agents include anthralin, calcitriol, calcipotriene, and tazarotene. These agents are available in a variety of vehicles. Early forms of treatment also included coal tar. In the United States, coal tar use has declined due to lack of standardization of available compounds and the development of other agents with less cosmetic issues such as odor and staining.
- Oral antipsoriatic systemic agents are typically reserved for moderate to severe psoriasis and are often combined with other therapies. Acitretin, a topical retinoid, modulates the cellular differentiation of the epidermis and is known to have immunomodulatory and anti-inflammatory activity (Menter et al, 2009[b]). Acitretin is most effective as a maintenance therapy, usually after the disease has been stabilized, or in combination with other treatments such as phototherapy (Villasenor-Park et al, 2012). Methoxsalen is a naturally occurring photosensitivity agent (psoralen) that enhances skin reactivity to ultraviolet light A (UVA). The combination of psoralen and UVA is referred to as photochemotherapy or PUVA. PUVA is an option for psoriasis that does not respond to topical medications alone or for lesions that are too extensive for topical treatment (Menter et al, 2010).
- Agents included in this review are the topical and oral antipsoriatics, which are listed in Table 1. Biologics (i.e., adalimumab, adalimumab-adbm, adalimumab-atto, brodalumab, etanercept, etanercept-szzs, guselkumab, infliximab, infliximab-abda, infliximab-dyyb, infliximab-qbtx, ixekizumab, secukinumab, and ustekinumab) that are used to treat psoriasis and other inflammatory/immunologic diseases are not included in this review. Topical corticosteroids are also not included in this review.
- Medispan Class: Antipsoriatics, Antipsoriatic – Systemic, and Topical Steroid Combinations

Table 1. Medications Included Within Class Review

Generic	Brand	Manufacturer	FDA Approval Date	Generic Availability
Topical Agents				
Anthralin	DRITHO-CREME® HP cream	Summers	-*	-
	ZITHRANOL® shampoo	Elorac	-*	-
Calcipotriene	DOVONEX® cream	Leo Pharma	07/22/1996	✔
	SORILUX® foam	Stiefel	10/06/2010	-
	Topical ointment	Glenmark Generics	03/24/2010	✔
	Topical scalp solution	various	03/03/1997	✔
Calcitriol	VECTICAL® ointment	Galderma	01/23/2009	✔
Tazarotene**	TAZORAC® cream	Allergan	09/29/2000	✔
	TAZORAC® gel		06/13/1997	-
Calcipotriene/ Betamethasone dipropionate	ENSTILAR® foam	Leo Pharm	10/16/2015	-
	TACLONEX® suspension		05/09/2008	-
	TACLONEX® ointment		01/09/2006	✔
Oral Systemic Agents				
Acitretin	SORIATANE® capsules	Stiefel	10/28/1996	✔
Methoxsalen	OXSORALEN-ULTRA® capsules	Valeant	10/30/1986	✔

*Anthralin products are unapproved marketed drugs that have not been formally evaluated by the Food and Drug Administration (FDA) as it was initially marketed before the Federal, Food, Drug, and Cosmetic Act was passed.
**Tazarotene 0.1% topical foam (FABIOR®) is approved for the treatment of acne. The AVAGE® brand of tazarotene 0.1% topical cream is approved for cosmetic indications.

(DRUGS@FDA.com, 2018; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2018; Clinical Pharmacology, 2018)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Drug(s)	Psoriasis (Quiescent or Chronic)	Severe Psoriasis	Plaque Psoriasis	Photo-chemotherapy	Acne Vulgaris
Topical Agents					
Anthralin (DRITHRO-CREME, ZITHRANOL)	✔				
Calcipotriene (DOVONEX, SORILUX, Calcipotriene ointment)			✔ *		
Calcitriol (VECTICAL)			✔ **		
Tazarotene (TAZORAC)			✔		✔ †
Calcipotriene/ betamethasone dipropionate (ENSTILAR foam)			✔		
Calcipotriene/ betamethasone dipropionate (TACLONEX suspension)			✔ ‡		
Calcipotriene/ betamethasone dipropionate (TACLONEX ointment)			✔ ‖		
Oral Systemic Agents					
Acitretin (SORIATANE)		✔			
Methoxsalen (OXSORALEN-ULTRA)				✔ ¥	

*SORILUX indicated for plaque psoriasis of scalp and body in patients 18 years or older; Calcipotriene Topical Solution, 0.005% (Scalp Solution) is indicated for the treatment of chronic, moderately severe psoriasis of the scalp.
**Mild to moderate plaque psoriasis in adults 18 years and older.
†TAZORAC 0.1% cream and gel
‡TACLONEX suspension indicated for plaque psoriasis of the scalp and body in patients 18 years and older. Additionally, the suspension is indicated for plaque psoriasis of the scalp in patients ages 12 to 17 years.
‖TACLONEX ointment is indicated for plaque psoriasis in patients 12 years of age and older. Limitations of use: Do not use on face, axillae or groin and do not use if skin atrophy is present at the treatment site.
¥For control of severe, recalcitrant, disabling psoriasis not adequately responsive to other forms of therapy and when the diagnosis has been supported by biopsy.

(Prescribing Information: Calcipotriene ointment, 2015; Calcipotriene solution, 2015; DOVONEX, 2017; DRITHOCREME, 2014; ENSTILAR, 2017; OXSORALEN-ULTRA, 2015; SORIATANE, 2017; SORILUX, 2016; TACLONEX ointment, 2017; TACLONEX suspension, 2017; TAZORAC cream, 2017; TAZORAC gel, 2017; VECTICAL, 2012; ZITHRANOL, 2011)

Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Various strengths and formulations of anthralin or dithranol have been evaluated (Fredriksson, 1983; Jones et al, 1985). Results from these trials support efficacy of anthralin in the treatment of psoriasis with no significant differences identified between dosage strength, formulation, or administration.
- Topical calcipotriene has demonstrated favorable efficacy in treating psoriasis in several studies with marked improvements in clearing of psoriatic lesions occurring in approximately 50 to 70% of patients (Highton et al 1995; Dubertret et al, 1992; Thaci et al, 2001). Treatment success was reported in patients with psoriasis who were treated with topical calcipotriene foam in two eight-week, multicenter, randomized, double-blind, vehicle-controlled clinical trials (Feldman et al, 2012; Feldman et al, 2013).
- For the treatment of plaque psoriasis, topical calcipotriene has demonstrated favorable efficacy when combined with betamethasone, psoralen plus ultraviolet A (PUVA), and methotrexate (Buckley et al, 2008; De Jong et al, 2003; Kragballe et al, 2009; Luger et al, 2008; Ortonnne et al, 2009; Ozkan et al, 2012; Torras et al, 2014; van de Kerkhof et al, 2009). The combination of calcipotriene plus betamethasone has demonstrated superior efficacy when compared to monotherapy with either calcipotriene or betamethasone or placebo in several clinical trials (Buckley et al, 2008; Douglas et al, 2002; Guenther et al, 2002; Jemec et al, 2008; Kaufman et al, 2002; Kragballe et al, 2004; Kragballe et al, 2009; Luger et al, 2008; Ortonne et al, 2009; Papp et al, 2003; Parslew et al, 2005; Singh et al, 2000; van de Kerkhof et al, 2005; van de Kerkhof et al, 2009; van de Kerkhoff et al, 2004).
- The efficacy of calcitriol ointment for the treatment of mild to moderate plaque psoriasis was demonstrated in two double-blind, randomized controlled studies involving 839 patients. Calcitriol applied twice daily for eight weeks was significantly more effective than the vehicle. Additionally, there were no clinically relevant changes in calcium homeostasis or other routine laboratory parameters in calcitriol-treated patients (Lebwohl et al, 2007).
- Head-to-head trials comparing the vitamin D analogues have been conducted. Ortonne et al found calcitriol to be significantly better tolerated than calcipotriol in sensitive skin fold areas (Ortonne et al, 2003). In another 12-week, randomized trial in patients with chronic plaque psoriasis, calcitriol demonstrated similar efficacy to calcipotriol and had a significantly better safety profile (Zhu et al, 2007).
- Head-to-head trials comparing therapies from different medication classes for the treatment of psoriasis also exist. Veronikis et al compared calcipotriene to coal tar and found that both agents were effective in the treatment of plaque psoriasis with no significant differences found between treatment groups (P value not reported) (Veronikis et al, 1999). Calcipotriol solution has been compared to clobetasol shampoo, with clobetasol being found to be significantly more efficacious in terms of total severity score measures as well as global severity score ($P<0.05$ for all) (Reygagne, 2005).
- Tazarotene was shown to be more effective than placebo in treating plaque psoriasis (Weinstein et al, 1997). Results demonstrated that both tazarotene 0.1% and 0.5% gel were significantly more effective than placebo in reducing the severity of signs and symptoms of target lesions ($P<0.05$). A second, placebo-controlled trial with the same methodology found similar results (Weinstein et al, 2003). Topical tazarotene in combination with a low-, mid-, and high-potency topical corticosteroid has been evaluated in patients with mild to moderate plaque psoriasis (Guenther et al, 2000; Lebwohl et al, 1998). While all treatments were effective, the tazarotene and topical corticosteroid combination produced significantly higher treatment success rates at weeks two, eight, and 12 vs tazarotene monotherapy (all $P<0.05$). Bowman et al compared the combination of tazarotene gel plus calcipotriene ointment to clobetasol ointment in patients with stable psoriasis and found

that both treatments were effective in reducing scaling, plaque elevation, and overall lesion severity with no significant differences between the two groups (P=0.93, P=0.76, and P=0.29, respectively) (Bowman et al, 2002).

- Acitretin has been shown to be effective in the treatment of patients with moderate to severe psoriasis in open-label studies and controlled clinical trials (Olsen et al, 1989; Tosti et al, 2009). In combination with calcipotriol, acitretin demonstrated improved clinical outcomes compared to acitretin alone or placebo (Rim et al, 2003; van de Kerkhof et al, 1998). Acitretin in combination with phototherapy can enhance treatment efficacy for patients with moderate to severe chronic plaque psoriasis that does not clear using UVB, PUVA, or acitretin alone. Compared with acitretin or UV light monotherapy, the combination regimen enhances efficacy and limits treatment frequency, duration, and cumulative doses (Lebwohl et al, 2001).
- Several large multicenter trials have demonstrated the efficacy of oral methoxsalen with UVA (PUVA) in psoriasis, indicating clearance of lesions in 70% to 89% of patients (Henseler et al, 1981; Roenigk et al, 1979; Melski et al, 1977). Two systematic reviews of the large majority of PUVA studies verified these findings demonstrating that between 70% and 100% of patients treated with PUVA achieved clearing of psoriasis lesions (Griffiths et al, 2000; Spuls et al, 1997).
- The Agency for Healthcare Quality and Research (AHRQ) published a comparative effectiveness review of the biologic systemic agents compared to nonbiologic systemic agents or phototherapy on an individual drug level for the treatment of chronic plaque psoriasis. A total of five randomized clinical trials and four observational studies were identified. In summary, limited data exist that compare agents. Existing data were considered to be low strength of evidence, which in general favored the biological agents over the non-biologic agents (Lee et al, 2012).
- A Cochrane Review was conducted to compare the effectiveness, tolerability, and safety of topical treatments for chronic plaque psoriasis, relative to placebo, and to similarly compare vitamin D analogues (alone or in combination) with other topical treatments. A total of 177 randomized controlled trials with 34,808 participants were included. When used on the body, most vitamin D analogues were significantly more effective than placebo. Dithranol, combined treatment with vitamin D/corticosteroid, and tazarotene all performed significantly better than placebo. Head-to-head comparisons of vitamin D for psoriasis of the body against potent or very potent corticosteroids had mixed findings. For both the body and scalp psoriasis, combined vitamin D and corticosteroid treatment performed significantly better than vitamin D alone or corticosteroid alone. When applied to psoriasis of the scalp, vitamin D was significantly less effective than both potent corticosteroids and very potent corticosteroids. Vitamin D generally performed better than coal tar, but findings compared to dithranol were mixed. For both body and scalp psoriasis, potent corticosteroids were less likely than vitamin D to cause local adverse events, such as burning or irritation. No comparison of topical agents found a significant difference in systemic adverse effects (Mason et al, 2013).
- In addition to its FDA approval for the treatment of psoriasis, tazarotene, a topical retinoid agent, is also FDA-approved for the treatment of acne vulgaris. In a placebo-controlled trial by Bershad et al, tazarotene 0.1% gel was compared with tazarotene 0.1% gel plus a vehicle gel, or vehicle gel alone (Bershad et al, 2002). The primary efficacy endpoint, reduction in acne vulgaris lesions, was significant in both tazarotene treatment groups compared to the vehicle group (P=0.002). Clinical trials comparing tazarotene to other topical retinoid agents have shown conflicting results, with tazarotene being at equivalent or more effective than other topical retinoids (Pariser et al, 2008; Tanghetti et al, 2010).
- The current guidelines for the management of psoriasis and psoriatic arthritis from the American Academy of Dermatology (AAD) recommend topical agents for mild to moderate psoriasis. Topical agents are also used adjunctively with ultraviolet light or systemic medications for resistant lesions or more severe disease. Topical corticosteroids are recommended as first-line treatment for most patients. Other topical agents included in the guidelines are vitamin D analogues, tazarotene, tacrolimus, pimecrolimus, anthralin, coal tar, and combination products. Combination products include corticosteroid and salicylic acid, corticosteroid and vitamin D analogue, corticosteroid and tazarotene, and tacrolimus and salicylic acid. When used in conjunction with ultraviolet radiation B or psoralen and UVA phototherapy or biologics, acitretin is effective for psoriasis and the treatment of choice in human immunodeficiency virus-positive patients with severe psoriasis due to its lack of significant immunosuppression (Gottlieb et al, 2008; Menter et al, 2009[a]; Menter et al, 2009[b]; Menter et al, 2010; Menter et al, 2011).
- In a 2013 position paper published by the AAD, psoriasis patients with moderate to severe psoriasis may avoid stepwise-therapy (i.e., first phototherapy, then oral systemic therapies, followed by biologic therapies) and be moved to later line therapy based on disease severity (AAD, 2013). Treatment needs vary depending on the severity of disease, body location of disease, characteristics of the psoriasis being treated including lesion thickness, degree of erythema and amount of scaling, as well as patient preferences.

- Topical retinoids such as tazarotene are also effective in the treatment of acne vulgaris. Guidelines do not recommend one retinoid over another but do generally recommend these agents as a first-line combination option (Thiboutot et al, 2009; Eichenfield et al, 2013).
    - According to the AAD, topical retinoids (e.g., tretinoin, adapalene, tazarotene) are recommended among the first-line treatment options for the management of acne (strength of recommendation: A [based on consistent and good-quality patient-oriented evidence]; level of evidence I [good-quality patient-oriented evidence, i.e., evidence measuring outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life], and II [limited-quality patient-oriented evidence]) (Zaenglein et al, 2016). Topical retinoids are important in addressing the development and maintenance of acne and are recommended as monotherapy in primarily comedonal acne, or in combination with topical or oral antimicrobials in patients with mixed or primarily inflammatory acne lesions. The guidelines do not prefer one topical retinoid over another.
        - There are several head-to-head studies with retinoid products. Some support greater efficacy of tazarotene over adapalene and tretinoin, and adapalene over tretinoin, but the concentrations and formulations were varied. Overall, the limitations of the existing studies prohibit direct efficacy comparisons of topical retinoids.
    - According to the Medical Letter, topical retinoids can be used alone or in combination with antibiotics to treat both inflamed and noninflamed acne lesions, or for maintenance treatment of acne (Medical Letter, 2016).

SAFETY SUMMARY

- Topical calcipotriene is contraindicated in individuals with hypersensitivity to any components of the preparation. Additionally, calcipotriene administration in patients with vitamin D toxicity or hypercalcemia is also contraindicated. Calcipotriene should not be used for the treatment of the face, and the scalp solution is contraindicated in acute psoriatic eruptions. The most common adverse effects of calcipotriene are local effects including burning, pruritus, edema, peeling, stinging, dryness, skin irritation, and erythema. Contact dermatitis has been reported to occur with use of topical calcipotriene. Systemic side effects of vitamin D analogs, including hypercalcemia, are rare unless patients apply more than the recommended dosage of 100 g per week (Clinical Pharmacology, 2018).
- There are no known contraindications to topical calcitriol. Among patients receiving laboratory monitoring, hypercalcemia was observed in 24% (18/74) of patients exposed to active drug and in 16% of (13/79) patients exposed to vehicle. This increase in calcium and albumin-adjusted calcium levels was <10% above the upper limit of normal. The effects of calcitriol on calcium metabolism have not been evaluated for treatment durations of >52 weeks. Additionally, increased absorption of calcitriol may occur with the use of occlusive dressings. Avoid exposure of treated areas to artificial or natural sunlight. The safety and efficacy of topical calcitriol in patients with disorders of calcium metabolism and patients with erythrodermic, exfoliative, or pustular psoriasis have not been evaluated. The most common adverse effects include hypercalciuria, pruritus, and lab test abnormalities (not otherwise specified).
- There are no known contraindications to calcipotriene/betamethasone suspension, ointment, or foam. Caution should be used with all formulations in patients with elevated serum calcium levels. Additionally, hypothalamic-pituitary-adrenal axis suppression has occurred due to systemic absorption of the topical corticosteroid. Avoid exposure of treated areas to artificial or natural sunlight. Local adverse reactions such as atrophy, irritation, and allergic contact dermatitis are more likely to occur with occlusive use. Common adverse effects include pruritus, worsening of psoriasis, erythema, and burning sensation.
- Topical tazarotene is contraindicated in patients who are pregnant or who have a documented hypersensitivity reaction to any component of the formulation. Tazarotene should not be used on eczematous skin as severe irritation may occur. Additionally, increased photosensitivity may occur with concurrent administration of fluoroquinolones, phenothiazines, sulfonamides, tetracyclines, and thiazides. Patients should be cautioned to take protective measures (e.g., sunscreens, protective clothing) against exposure to sunlight or ultraviolet light (e.g., tanning beds) until tolerance is determined. Excessive pruritus, burning, skin redness or peeling may occur. Discontinue tazarotene until skin integrity is restored, or reduce the dosing interval or switch to a lower concentration. The most common adverse effects include burning, erythema, and pruritus.
- Topical anthralin is contraindicated in acute or actively inflamed psoriatic eruptions. Additionally, the agent should not be used if there is a hypersensitivity to the active ingredient or any of its components. The most common side effects of anthralin are skin irritation and staining of lesional and adjoining skin, nails, and clothing.

- Acitretin is teratogenic and its use, therefore, is limited to male and female patients of nonchildbearing potential. Acitretin should only be considered for women of childbearing potential with severe psoriasis unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments. Other contraindications for acitretin include severe liver or kidney impairment, chronic elevation of lipid profile, and use in combination with methotrexate or tetracyclines. Potential adverse effects of acitretin include dry skin and mucus membranes, alopecia, skin peeling, pruritus, cheilitis, rhinitis, hyperlipidemia, liver toxicity, and teratogenicity. Periodic monitoring of bones, lipid profile, and eyes is recommended.
- Methoxsalen is contraindicated with a history of light sensitivity, melanoma, invasive squamous cell carcinoma or aphakia. Skin irritation, including severe edema, erythema, blistering, and exfoliative dermatitis, can occur during PUVA therapy. Pruritus and other dermatological effects may occur as well. Nausea occurs in 10% of patients receiving methoxsalen, and central nervous system (CNS) effects including depression, dizziness, and headache have been reported. Patients who have received PUVA therapy should be monitored throughout their lives for the development of cutaneous malignancies.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Topical Therapy				
DRITHO-CREME (anthralin)	Cream: 1%	Treatment of psoriasis (quiescent or chronic): Cream: Apply once a day to psoriatic lesions for 5 to 10 minutes using the lowest strength possible for at least one week; may increase contact time up to 20 to 30 minutes as tolerated		Avoid spreading cream onto the forehead; remove by washing or showering. For scalp psoriasis, comb hair to remove scalar debris; wet and part hair; rub cream into lesions.
ZITHRANOL (anthralin)	Shampoo: 1%	Scalp Psoriasis: Apply onto wet scalp 3 to 4 times per week. Leave on scalp for 3 to 5 minutes and then rinse thoroughly.		
DOVONEX (calcipotriene)	Cream: 0.005%	Plaque psoriasis: Apply a thin layer to affected area 1 to 2 times per day and rub in completely.	Safety and effectiveness of DOVONEX cream have been demonstrated in patients treated for 8 weeks.	
SORILUX (calcipotriene)	Foam: 0.005%	Plaque psoriasis: Apply a thin layer twice daily to the affected areas and rub in gently and completely.		Avoid contact with the face and eyes. Not for oral, ophthalmic, or intravaginal use.
Calcipotriene ointment	Ointment: 0.005%	Plaque psoriasis: Apply a thin layer to affected area 1 to 2 times per day and rub in gently and completely.		
Calcipotriene scalp solution	Solution: 0.005%	Severe Psoriasis of the scalp: Comb hair to remove scaly debris and apply twice daily,	Safety and efficacy have been	Do not spread to forehead. Keep well away from

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		only to lesions, and rub in gently and completely.	demonstrated in patients treated for 8 weeks.	eyes. Avoid applying to uninvolved scalp margins.
VECTICAL (calcitriol)	Ointment: 3 mcg/g	Plaque psoriasis: Apply to affected areas twice daily, morning and evening.	The maximum weekly dose should not exceed 200 g.	Not for oral, ophthalmic, or intravaginal use.
ENSTILAR (calcipotriene/ betamethasone dipropionate)	Foam: 0.005%/ 0.064%	Plaque psoriasis: Apply to affected area once daily for up to 4 weeks.	Do not use more than 60 g every 4 days.	Do not use with occlusive dressings unless directed by a physician. Not for oral, ophthalmic, or intravaginal use. Avoid use on face, groin, axillae, or if skin atrophy is present at treatment site.
TACLONEX (calcipotriene/ betamethasone dipropionate)	Ointment: 0.005%/ 0.064% Topical Suspension: 0.005%/ 0.064%	Ointment: Psoriasis: Apply to affected areas once daily for up to 4 weeks. Topical Suspension: Plaque Psoriasis: Apply to affected areas once daily for up to 8 weeks.	Maximum weekly dose should not exceed 100 g for patients ≥18 years of age. For patients 12 to 17 years of age, maximum weekly use should not exceed 60 g. Treatment of >30% of body surface area is not recommended.	Do not use on face, axillae, or groin. Do not use with occlusive dressings unless directed by a physician. Do not use if skin atrophy is present at treatment site. Shake topical suspension before use. Not for oral, ophthalmic, or intravaginal use.
TAZORAC (tazarotene)	Cream: 0.05%, 0.1% Gel: 0.05%, 0.1%	Psoriasis: Cream, gel: Apply a thin film to affected area once daily in the evening. Acne vulgaris for ages ≥12 years old: Cream (0.1%), gel (0.1%): Apply a thin film to affected area once daily in the evening.	Psoriasis: Start with 0.05% cream/gel, then increase to 0.1% if tolerated and medically indicated. Treatment of >20% of body surface area is not recommended	Not for oral, ophthalmic, or intravaginal use. Avoid contact with eyes, mouth, or other mucous membranes. Apply to dry skin and at least an hour after using

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			(gel only).	emollients.
Oral Agents				
SORIATANE (acitretin)	Capsules: 10 mg, 17.5 mg, 25 mg	Psoriasis: Initiate at 25 to 50 mg per day, given as a single dose with the main meal. Maintenance doses of 25 to 50 mg per day may be given dependent upon response to initial treatment.		
OXSORALEN (methoxsalen)	Capsules: 10 mg	Psoriasis: Take 2 hours before UVA exposure with food or milk according to following table: <30 kg: 10 mg 30-50 kg: 20 mg 51-65 kg: 30 mg 66-80 kg: 40 mg 81-90 kg: 50 mg 91-115 kg: 60 mg >115 kg: 70 mg	If weight changes during treatment, no change in dose is usually required. The number of doses per week will be determined by the schedule of UVA exposures. Dosages may be increased by 10 mg after the 15th treatment.	

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Topical Therapy					
DRITHO-CREME, ZITHRANOL (anthralin)	No data	Safety and efficacy have not been established.	No data	No data	Pregnancy category C* Unknown whether excreted in breast milk; discontinue nursing or discontinue drug
DOVONEX, SORILUX, calcipotriene ointment, calcipotriene scalp solution (calcipotriene)	DOVONEX, calcipotriene scalp solution: No differences in adverse events for subjects >65 years. However, greater sensitivity cannot be ruled out.	Safety and efficacy have not been established.	No data	No data	DOVONEX: Unclassified† Only use if potential benefit justifies risk to fetus

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	SORILUX: Trials did not include sufficient numbers of subjects >65 years. Calcipotriene ointment: Severity of skin-related adverse events showed a significant difference for subjects >65 years.				SORILUX, calcipotriene ointment, calcipotriene scalp solution: Pregnancy category C* Unknown whether excreted in breast milk; use with caution.
VECTICAL (calcitriol)	Trials did not include sufficient numbers of subjects >65 years.	Safety and efficacy have not been established.	No data	No data	Pregnancy category C* Unknown whether excreted in breast milk; use with caution.
ENSTILAR, TACLONEX (calcipotriene/ betamethasone)	No differences in safety and effectiveness for subjects >65 years; however, greater sensitivity cannot be ruled out.	Safety and efficacy have not been established in children <12 years (suspension, ointment).	No data	No data	Pregnancy category C* Unknown whether excreted in breast milk; use with caution. Do not apply to breast when nursing.
TAZORAC (tazarotene)	Cream: No overall differences in safety or effectiveness were observed between subjects >65 years and younger subjects; however, greater sensitivity of some older individuals cannot be ruled out. Gel: Subjects >65 years of age had more adverse events and lower treatment success rates after 12 weeks.	Safety and efficacy have not been established in patients with psoriasis under the age of 18 years and patients with acne under the age of 12 years.	No data	No data	Unclassified† Contraindicated in pregnancy due to the risk of fetal malformation. Unknown whether excreted in breast milk; use with caution.
Oral Therapy					
SORIATANE (acitretin)	Trials did not include sufficient numbers of	Safety and efficacy have not been	Plasma concen-	Elevations of liver function	Pregnancy category X*

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	subjects >65 years. Initial dose should be at the low end of the dosing range.	established.	trations significantly lower in end-stage renal failure.	tests (AST, ALT or LDH) were experienced by 1 in 3 patients. Perform LFTs prior to initiation and at 1- and 2-week intervals until stable.	Do not use prior to or during nursing.
OXSORALEN (methoxsalen)	Trials did not include sufficient numbers of subjects >65 years. Initial dose should be at the low end of the dosing range. Use with caution, especially those with a pre-existing history of cataracts, cardiovascular conditions, kidney and/or liver dysfunction, or skin cancer.	Safety in children has not been established.	No data	Treat with caution since hepatic biotransfor-mation is necessary for drug urinary excretion.	Pregnancy category C* Unknown whether excreted in breast milk; discontinue nursing or discontinue drug.

* Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Pregnancy Category X = Contraindicated in pregnant women due to evidence of fetal abnormalities from adverse effects data from investigational or marketing experience. Risks of use of the drug in pregnant women clearly outweigh potential benefits.
†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

CONCLUSION

- Numerous topical and systemic therapies are available for the treatment of psoriasis. Topical treatment is considered to be the safest option and is widely used for mild psoriasis, followed by systemic and phototherapies, which are used for moderate to severe psoriasis. Selection of medication must take into account severity of disease, thickness and scaling of the lesions, relevant comorbidities, patient preference, efficacy, and evaluation of individual patient response (AAD, 2013; Hsu et al, 2012; Menter et al, 2009[b]).
- Topical corticosteroids are the cornerstone of treatment for the majority of patients with psoriasis. Drawbacks associated with topical corticosteroid treatment are local cutaneous side effects and more serious systemic side effects that are associated with long-term use over a large body surface area (Menter et al, 2011). Several agents have been developed and tested as monotherapy or in combination with topical corticosteroids in the hopes of reducing the duration of corticosteroid treatment.
- The vitamin D analogs, calcipotriene and calcitriol, are other first-line topical agents with proven efficacy in the treatment of psoriasis. Although less effective than topical corticosteroids, they are often used in combination with topical corticosteroids to enhance efficacy and reduce the risk of atrophy, especially over the long term. One potential advantage of calcitriol is that there are no known contraindications for use, whereas calcipotriene (alone, but not in combination with betamethasone) is contraindicated in patients with hypercalcemia and vitamin D toxicity and in acute or actively inflamed psoriatic lesions. Another possible advantage of calcitriol is that it has been shown to be better

tolerated in sensitive skin fold areas as well as associated with less stinging, burning, edema and erythema (Weinstein et al, 2003; Zhu et al, 2007).

- The combination of calcipotriene and betamethasone (ENSTILAR and TACLONEX) has been evaluated in several studies for the treatment of psoriasis compared to placebo and to its individual components. Overall, results indicated that the combination product was more effective in reducing psoriasis area and severity index scores, and it increased the percentage of patients with clear or almost clear disease compared to either agent alone or placebo (Douglas et al, 2002; Guenthe et al, 2002, Kaufman et al, 2002; Kragballe et al, 2004; Papp et al, 2003; Parslew et al, 2005; Singh et al, 2000; van de Kerkhof et al, 2004; van de Kerkhof et al, 2005). The combination is available as a suspension, ointment, and foam.
- Tazarotene is the only retinoid agent that is FDA-approved for the treatment of psoriasis. Clinical trials have demonstrated its efficacy alone as well as in combination with other antipsoriatic agents. Guidelines recommend its use as an adjunct to topical corticosteroids (Menter et al, 2009[b]). No significant differences were observed between calcipotriene or calcitriol and tazarotene in several head-to-head studies (Guenther et al, 2000; Schiener et al, 2000; Tzung et al, 2005). Other topical preparations, including anthralin, have taken on more secondary roles and are particularly challenging as they stain clothing and skin.
- Of the systemic therapies, acitretin is the least effective as monotherapy and is therefore often used in conjunction with ultraviolet B or psoralen plus UVA phototherapy. Acitretin does not lead to immunosuppression or the associated risk of infection like biologic agents. Guidelines recommend the use of acitretin in combination with phototherapy as first-line treatment for psoriasis when not contraindicated, before resorting to other agents including methotrexate, cyclosporine, or biologic treatments (Lebwohl, 2001; Menter et al, 2009; Menter et al, 2010). Acitretin should not be used in women of childbearing potential.
- Methoxsalen and ultraviolet light (PUVA) is an effective method of treating psoriasis. PUVA is indicated in patients with moderate to severe psoriasis that is unresponsive to other forms of therapy or for lesions that are too extensive for topical treatment (Menter et al, 2010).
- In a position paper published by the AAD, psoriasis patients with moderate to severe psoriasis may avoid stepwise-therapy (i.e., first phototherapy, then oral systemic therapies, followed by biologic therapies) and be moved to later line therapy based on disease severity (AAD, 2013). Consensus guidelines agree that the decision for treatment should be based on efficacy, potential adverse effects, prior treatments, patient preference, duration and severity of disease, medical risk factors**,** co-morbidities, and potential impact on quality of life (AAD, 2013).
- Topical retinoids such as tazarotene are also effective in the treatment of acne vulgaris. Guidelines do not recommend one retinoid over another but do generally recommend these agents as a first-line combination option (Thiboutot et al, 2009; Zaenglein et al, 2016; Eichenfield et al, 2013).

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Publication date: March 8, 2018

Therapeutic Class Overview

Antifungals, Topical

INTRODUCTION

- The topical antifungals are available in multiple dosage forms and are indicated for a number of fungal infections and related conditions. In general, these agents are Food and Drug Administration (FDA)-approved for the treatment of cutaneous candidiasis, onychomycosis, seborrheic dermatitis, tinea corporis, tinea cruris, tinea pedis, and tinea versicolor (*Clinical Pharmacology 2018*).
- The antifungals may be further classified into the following categories based upon their chemical structures: allylamines (naftifine, terbinafine [only available over the counter (OTC)]), azoles (clotrimazole, econazole, efinaconazole, ketoconazole, luliconazole, miconazole, oxiconazole, sertaconazole, sulconazole), benzylamines (butenafine), hydroxypyridones (ciclopirox), oxaborole (tavaborole), polyenes (nystatin), thiocarbamates (tolnaftate [no FDA-approved formulations]), and miscellaneous (undecylenic acid [no FDA-approved formulations]) (*Micromedex 2018*).
- The topical antifungals are available as single entity and/or combination products. Two combination products, nystatin/triamcinolone and Lotrisone (clotrimazole/betamethasone), contain an antifungal and a corticosteroid preparation. The corticosteroid helps to decrease inflammation and indirectly hasten healing time. The other combination product, Vusion (miconazole/zinc oxide/white petrolatum), contains an antifungal and zinc oxide. Zinc oxide acts as a skin protectant and mild astringent with weak antiseptic properties and helps to promote healing.
- Ciclopirox, clotrimazole, clotrimazole/betamethasone, econazole (cream only), ketoconazole, naftifine (cream only), nystatin, nystatin/triamcinolone, and oxyconazole (cream only) are available generically in several dosage forms.
- Ecoza (econazole nitrate 1% foam) and Luzu (luliconazole) cream were approved in 2013.
- Two molecular entities were approved in 2014 for the topical treatment of adult patients with onychomycosis of the toenails due to select strains of *Trichophyton*, Jublia (efinaconazole 10% topical solution) and Kerydin (tavaborole 5% topical solution). Prior to 2014, ciclopirox 8% solution was the only topical agent available for the treatment of onychomycosis (*Rosen et al 2016*).
- This review focuses primarily on topical antifungal products that are available by prescription. Antifungal products that are used for the treatment of oropharyngeal or vulvovaginal candidiasis are not included. There are several topical antifungal products that are available OTC, and some products are available OTC as well as by prescription. Additionally, some agents within this class have been used safely and effectively for many years; however, there are limited published data evaluating the efficacy of these products for their approved indications.
- Medispan class: Antifungals - Topical.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single-entity Products	
clotrimazole	✔ (cream and solution)
econazole (Ecoza [foam] and creams)	✔ (cream)
Ertaczo (sertaconazole)	-
Exelderm (sulconazole)	-
Extina, Nizoral (ketoconazole)	✔ (cream, foam, and shampoo 2%)
Jublia (efinaconazole)	-
Kerydin (tavaborole)	-
Loprox, Penlac (ciclopirox)	✔ (all formulations*)
Luzu (luliconazole)	-
Mentax (butenafine)	-
Naftin (naftifine)	✔ (cream only)
nystatin	✔ (cream, ointment and powder)
Oxistat (oxiconazole)	✔ (cream only)
Xolegel (ketoconazole)	-
Combination Products	
Lotrisone (clotrimazole/betamethasone)	✔ (cream and lotion)
nystatin/triamcinolone	✔ (cream and ointment)
Vusion (miconazole/zinc oxide/white petrolatum)	-

* cream 0.77%, gel 0.77%, shampoo 1%, solution 8%, suspension 0.77%

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018, Clinical Pharmacology 2018*)

INDICATIONS

Table 2. Food and Drug Administration-Approved Indications for Single-Entity Products

Drug	Tinea corporis	Tinea cruris	Tinea pedis	Tinea versicolor	Seborrheic dermatitis	Diaper dermatitis	Cutaneous candidiasis	Onychomycosis
clotrimazole				✔			✔	
econazole (cream)	✔	✔	✔	✔			✔	
Ecoza (econazole) foam			✔ *					
Ertaczo (sertaconazole)			✔ *					
Exelderm (sulconazole)	✔	✔	✔ †	✔				
Extina (ketoconazole)					✔ *			
Jublia (efinaconazole)								✔
Kerydin (tavaborole)								✔
Loprox (ciclopirox)	✔ ‡	✔ §	✔ ‡	✔ §	✔ **		✔ §	
Luzu (luliconazole)	✔	✔	✔					
Mentax (butenafine)				✔				
Naftin†† (naftifine)	✔	✔ *	✔ *					
Nizoral (ketoconazole) cream	✔	✔	✔	✔	✔		✔	
Nizoral (ketoconazole) shampoo				✔ ‡‡				
nystatin							✔	
Oxistat (oxiconazole) §§	✔	✔	✔	✔ ***				
Penlac (ciclopirox lotion)								✔ †††
Xolegel (ketoconazole)					✔ *			

* Indicated for ≥ 12 years
† The cream is indicated for all tinea infections, but the solution is not indicated for tinea pedis
‡ Cream, gel, and lotion
§ Cream and lotion
** Gel and shampoo
†† 2% gel only indicated for tinea pedis in patients ≥ 12 years. 2% cream may be used for tinea corporis in patients age ≥ 2 years.
‡‡ Shampoo 2%
§§ The cream is approved for pediatric patients for all indications
*** Cream only
††† Indicated as a component of a comprehensive management program, as topical treatment in immunocompetent patients with mild to moderate onychomycosis of fingernails and toenails without lunula involvement.

Table 3. Food and Drug Administration-Approved Indications for Combination Products

Drug	Tinea corporis	Tinea cruris	Tinea pedis	Diaper dermatitis	Cutaneous candidiasis
Lotrisone* (clotrimazole/betamethasone)	✔	✔	✔		
nystatin/triamcinolone					✔
Vusion (miconazole/zinc oxide/white petrolatum)				✔ †	

* Indicated for >17 years for inflammatory conditions

† For the adjunctive treatment of diaper dermatitis only when complicated by documented candidiasis (microscopic evidence of pseudohyphae and/or budding yeast), in immunocompetent pediatric patients 4 weeks and older

(*Prescribing information: ciclopirox gel 2017, ciclopirox lotion 2014, ciclopirox olamine cream 2015, ciclopirox shampoo 2017, ciclopirox solution 2017, clotrimazole cream 2014, clotrimazole solution 2012, clotrimazole/betamethasone 2016, econazole 2015, Ecoza 2016, Ertaczo 2017, Exelderm cream 2017, Exelderm solution 2017, Extina 2014, Jublia 2016, Kerydin 2017, ketoconazole 2016, Lotrisone 2017, Luzu 2018, Mentax 2013, Naftin 1% gel 2018, Naftin 2% cream 2018, Naftin 2% gel 2018, Nizoral 2017, Nizoral A-D 2015, nystatin cream 2017, nystatin ointment 2017, nystatin powder 2017, nystatin/triamcinolone cream 2017, nystatin/triamcinolone ointment 2016, Oxistat 2016, Vusion 2013, Xolegel 2012*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Several clinical trials have demonstrated that topical azoles (clotrimazole, miconazole, sulconazole), ciclopirox, and nystatin were effective in the management of cutaneous candidiasis (*Bagatell et al 1985, Beveridge et al 1977, Rajan et al 1983, Tanenbaum et al 1983*). Clinical studies have reported no significant difference in efficacy between sulconazole cream and clotrimazole or miconazole cream for cutaneous candidiasis. Nystatin/triamcinolone was compared to the administration of nystatin monotherapy (*Beveridge et al 1977*). The results of this study demonstrated that nystatin/triamcinolone was as effective as nystatin monotherapy. Also, there was no difference reported in the patient or physician preference for either agent.
- There are limited data evaluating the efficacy of the combination of miconazole/zinc oxide for the treatment of patients with diaper dermatitis complicated by candidiasis. In 2 clinical trials, this combination product was compared to patients receiving zinc oxide monotherapy. In 1 study, miconazole/zinc oxide demonstrated statistically significant reductions in total rash scores in patients with mild-to-moderate diaper dermatitis as compared to zinc oxide monotherapy (*Concannon et al 2001*). A second study determined that miconazole/zinc oxide had a lower incidence of diaper dermatitis and a higher clinical microbiological and overall cure rate as compared to patients treated with zinc oxide alone (*Spraker et al 2006*).
- Topical antifungal agents are the mainstay of treatment for seborrheic dermatitis. During clinical trials, ciclopirox gel and shampoo formulations demonstrated statistically significant improvements in symptom scores and clinical cure compared to placebo vehicles (*Aly et al 2003[a], 2003[b], Vardy et al 2000*). Ketoconazole cream, foam, gel, and shampoo formulations were also associated with statistically significant improvements in symptom scores and clinical cure compared to placebo vehicles (*Carr et al 1987, Cauwenbergh et al 1986, Elewski et al 2006, Elewski et al 2007, Green et al 1987)*. There are limited data comparing ciclopirox to ketoconazole. One study reported significantly higher rates of remission with ciclopirox cream (twice daily for 28 days then once daily for 28 days) than ketoconazole gel (twice weekly for 28 days then once weekly for 28 days) for the treatment of facial seborrheic dermatitis (*Naldi and Rebora 2009*). The results were difficult to interpret because ciclopirox was dosed more frequently than ketoconazole. In a recent systematic review, ciclopirox and ketoconazole were both strongly recommended for facial seborrheic dermatitis due to their consistent effectiveness across multiple high-quality trials (*Gupta and Versteeg 2017*).
- Noninvasive tinea fungal infections may be treated with appropriate skin care and a topical antifungal agent (*Andrews et al 2008, Brown and Dresser 2017, Drake et al 1996[a]*). Based on data obtained from clinical trials on tinea pedis, there was a statistically significant improvement in efficacy (microbiological and clinical cure) in patients treated with the following agents compared to placebo: butenafine, ciclopirox, econazole foam, luliconazole, naftifine, oxiconazole, sertaconazole, and tolnaftate (*Aly et al 1989, Aly et al 2003, Ecoza prescribing information, 2013, Gupta et al 2005, Jarratt et al 2013, Jones et al 2014, Pariser et al 1994, Reyes et al 1997, Stein Gold et al 2013, Tschen et al 1997*). In a

meta-analysis of placebo-controlled trials, the pooled relative risks of failure to cure skin infections of the foot were as follows for the topical antifungal agents: allylamines 0.33, azoles 0.3, butenafine 0.33, ciclopirox 0.27, and tolnaftate 0.19 (*Crawford et al 2007*). No differences were detected between individual azoles and allylamines. Meta-analysis of data collected in 9 trials comparing 4 to 6 weeks of treatment with allylamines and azoles showed a risk ratio for treatment failure of 0.63 in favor of allylamines. In another meta-analysis, allylamines, azoles and other antifungals were found to be more effective in mycological cure and sustained cure vs. placebo (*Rotta et al 2012*). No differences were found between the classes of agents.

- Based on data obtained from clinical trials on various tinea infections (which included patients with tinea pedis, corporis, cruris, and/or versicolor), there was a statistically significant improvement in efficacy (microbiological and clinical cure) in patients treated with the following agents compared to placebo: miconazole, naftifine, oxiconazole, and terbinafine (*Jordan et al 1990, Kagawa et al 1989, Mandy and Garrott 1974, Pariser et al 1994, Ramelet et al 1987*). In a meta-analysis of 27 trials, terbinafine demonstrated 70 to 90% and 70 to 80% efficacy in the treatment of dermatomycoses and tinea versicolor, respectively (*Villars et al 1989*). Most of the head-to-head trials comparing one antifungal to another were conducted in a small number of patients. In general, direct comparative trials did not demonstrate that one antifungal was safer or more efficacious than another.
- The combination product consisting of clotrimazole/betamethasone has been evaluated for the treatment of tinea infections. In 2 double-blind, placebo-controlled trials, patients were randomized to clotrimazole/betamethasone, clotrimazole monotherapy, or betamethasone monotherapy. One trial enrolled patients with only a confirmed diagnosis of tinea cruris (*Wortzel et al 1982*). This study showed that 80, 20, and 13% of patients achieved either complete cure or excellent response to therapy with the combination product, clotrimazole monotherapy, and betamethasone monotherapy, respectively. The other study enrolled patients with a confirmed diagnosis of moderate-to-severe tinea cruris or tinea corporis (*Katz et al 1984*). This study showed that for the treatment of tinea cruris and tinea corporis, patients treated with the combination product had significantly better total sign and symptom reductions compared to each individual component administered as monotherapy.
- A Cochrane review of 129 trials (N = 18,086) assessed the effects of topical antifungal treatments in tinea cruris and tinea corporis (*El Gohary et al 2014*). Mycological cure rates favored naftifine 1% compared to placebo in 3 studies (risk ratio [RR] 2.38, 95% confidence interval [CI] 1.80 to 3.14, number needed to treat [NNT] 3, 95% CI 2 to 4) (low quality evidence). In 1 study, naftifine 1% was more effective than placebo in achieving clinical cure (RR 2.42, 95% CI 1.41 to 4.16, NNT 3, 95% CI 2 to 5) (low quality evidence). Across 2 studies, mycological cure rates were superior for clotrimazole 1% compared to placebo (RR 2.87, 95% CI 2.28 to 3.62, NNT 2, 95% CI 2 to 3). There was no difference in mycological cure between azoles and benzylamines (RR 1.01, 95% CI 0.94 to 1.07) (low quality evidence). There was no evidence for a difference in cure rates between tinea cruris and tinea corporis.
- Ciclopirox solution (lacquer) is a topical antifungal that is FDA-approved for onychomycosis. Two double-blind, placebo-controlled clinical trials reported significantly higher mycologic cure rates for ciclopirox (29 to 36%) compared to vehicle (9 to 11%) (*Katz et al 1984*). Both studies reported significantly higher treatment successes (≤ 10% nail involvement and negative mycology) with ciclopirox (6.5 to 12%) than placebo (0.9%). One of the 2 studies reported a significantly higher treatment cure (clear nail and negative mycology) with ciclopirox (5.5 to 8.5%) vs placebo (0 to 0.9%). A meta-analysis of randomized trials concluded that there was some evidence that ciclopirox was effective for the management of onychomycosis, but ciclopirox had to be applied daily for prolonged periods (1 year) (*Crawford et al 2007*). Oral antifungals are generally recommended for the treatment of onychomycosis (*de Berker 2009, Drake et al 1996[c], Ameen et al 2014*). Topical antifungals should be considered for patients who have contraindications to systemic therapy. There is inconsistent evidence that combining topical and oral antifungals leads to better cure rates than monotherapy with oral antifungals.
- The safety and efficacy of Jublia applied once daily for the treatment of onychomycosis of the toenail were assessed in 2 identical, 52-week prospective, multi-center, randomized, double-blind, vehicle-controlled clinical trials in patients 18 years and older (18 to 70 years of age) with 20% to 50% clinical involvement of the target toenail, without dermatophytomas or lunula (matrix) involvement. The primary endpoint was complete cure rate defined as 0% clinical involvement of target toenail (no clinical evidence of onychomycosis) in addition to mycologic cure (defined as both negative potassium hydroxide [KOH] examination and fungal culture) at week 52. Complete cure was significantly greater for patients treated with Jublia compared to vehicle in both studies (17.8% in study 1 and 15.2% in study 2 compared with 3.3% and 5.5% for vehicle, respectively; $p < 0.001$ for both studies). Similarly, mycologic cure rates were also significantly greater for patients treated with Jublia compared to vehicle in both studies (55.2% in study 1 and

53.4% in study 2 compared with 16.8% and 16.9% for vehicle, respectively; p < 0.001 for both studies). Similar adverse events were reported between the 2 groups (*Elewski et al 2013, Valeant Pharmaceuticals press release 2014*).

- The safety and efficacy of Kerydin were demonstrated in two phase 3, randomized, parallel-group, double-blind, vehicle-controlled trials: Study 301 and 302. Both studies were identically designed and patients (N = 1194) had 20 to 60% of clinical involvement of the target toenail at baseline. Patients were randomized to receive either Kerydin 5% topical solution or a vehicle-control which was applied topically once daily for 48 weeks. The primary endpoint, which was complete cure (defined as 0% clinical involvement of the target nail plus a negative KOH and fungal culture) was observed in 6.5% of Kerydin-treated patients vs 0.5% in the vehicle-controlled group for Study 301, and 9.1% vs 1.5%, respectively, in Study 302 (p ≤ 0.001 for both studies). Mycologic cure (defined as a negative KOH wet mount and a negative fungal culture) was observed in 31.1% of Kerydin-treated patients vs. 7.2% in the vehicle-controlled group for Study 301, and 35.9% vs 12.2%, respectively, in Study 302 (p ≤ 0.001 for both studies). The most common treatment-related adverse events in the Kerydin and vehicle-control groups were application site exfoliation (2.7% and 0.3%, respectively), erythema (1.6% and 0%), and dermatitis (1.3% and 0%) (*Elewski et al 2015*). In a pooled analysis of patients with complete or almost clear nails who completed an additional 8 weeks of post-study follow-up (N = 62), complete cure was maintained in 28.6% of Keridyn-treated patients compared to 7.7% of the vehicle-controlled group (*Gupta et al 2018*).
- In a 2014 evidence-based review of topical therapy for toenail onychomycosis, 28 studies evaluating complete and mycological cure demonstrated that topical amorolfine (not available in the US), ciclopirox, tavaborole, and efinaconazole were effective for patients with less than 50 to 65% toenail involvement. A treatment duration of 48 weeks led to the most successful outcomes. Complete cure (generally defined as mycological cure with no nail involvement) rates were 17.8% with efinaconazole vs 8.5% with ciclopirox (*Gupta et al 2014b*).

Table 4. Results from Phase 3 Trials of FDA-Approved Topical Treatments for Onychomycosis
This table provides an indirect comparison of data collected from different clinical trials. Because study populations and trial methods may vary across trials, this information should not be used to draw conclusions about the relative efficacy or safety of individual treatments.*†

Antifungal	Dosing and Duration	Complete or Clinical Cure	Mycologic Cure
Jublia (efinaconazole) Baseline: 20 to 50% clinical involvement	Once daily applications for 48 weeks of treatment with a 4 week follow-up period	15.2 to 17.8% Difference from vehicle-control, 9.7 to 14.5%	53.5 to 55.2% Difference from vehicle-control, 36.5 to 38.4%
Kerydin (tavaborole) Baseline: 20 to 60% clinical involvement	Once daily applications for 48 weeks of treatment with a 4 week follow-up period	6.5 to 9.1% Difference from vehicle-control, 6 to 7.6%	31.1 to 35.9% Difference from vehicle-control, 23.8%
Penlac (ciclopirox) nail lacquer Baseline: 20 to 65% clinical involvement	Applied for 48 weeks	5.5 to 8.5% Difference from vehicle-control, 4.6 to 8.5%	29 to 36% Difference from vehicle-control, 18 to 27%

*Only first-to-market topical drug formulations are included for comparison.
†According to the Penlac prescribing information, concomitant use of ciclopirox 8% topical solution and systemic antifungal agents for onychomycosis is not recommended because studies have not been conducted to determine whether ciclopirox might reduce the effectiveness of systemic antifungal agents. Some experts support the recommendation of combination therapy; however, this has not been explicitly studied by the manufacturer or evaluated by the FDA.

(*Poulakos et al 2017, Rosen et al 2016, Westerberg et al 2013*)

CLINICAL GUIDELINES

- National and international recommendations which discuss the management of fungal infections focus primarily on superficial mycotic infections. Several recommendations list topical antifungal agents or subclasses, and generally do

not give preference to one agent vs. another (*Brown and Dresser 2017, de Berker 2009, Drake et al 1996[a], Drake et al 1996[b], Naldi and Rebora 2009, Ameen et al 2014, Stevens et al 2014*). According to these guidelines, mycological and clinical cure of noninvasive fungal infections are often achieved with topical therapy alone. Oral therapy is preferred for the treatment of extensive or severe infection and those with tinea capitis or onychomycosis.

- New topical antifungal agents Jublia (efinaconazole) and Kerydin (tavaborole) are recommended for mild-moderate toenail fungal infections (*Brown and Dresser 2017*).

SAFETY SUMMARY

- If patients experience hypersensitivity to an agent, therapy should be discontinued. Cross-sensitivity can also occur among the imidazole-containing agents.
- Products containing corticosteroids should be used with caution because systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticoid insufficiency after withdrawal of treatment. Conditions which augment systemic absorption include use over large surface areas, prolonged use, use under occlusive dressings, and use in pediatric patients.
- The most common adverse events are erythema, stinging, blistering, peeling, edema, pruritus, urticaria, burning, and general irritation of the skin.
- Several products are flammable: Ecoza (econazole), Extina (ketoconazole), Penlac (ciclopirox), Xolegel (ketoconazole), Jublia (efinconazole), and Kerydin (tavaborole). They should not be used near heat or flame.

DOSING AND ADMINISTRATION

- For all products: enough cream/ointment/lotion should be applied to cover the affected areas and the immediately surrounding skin. If a patient shows no clinical improvement after the treatment period, the diagnosis and therapy should be reviewed.

Table 5. Dosing and Administration

Drug	Available Formulations	Usual Recommended Frequency	Comments
Single-entity products			
clotrimazole	Topical cream, solution	Apply twice daily for up to 4 weeks.	External use only; not for ophthalmic use.
econazole (Ecoza and generics)	Topical cream: (generics) Topical foam: (Ecoza)	**Cream** *Candidiasis:* Apply twice daily for 2 weeks. *Other uses:* Apply once daily for 2 weeks; except pedis, for 4 weeks. **Foam** *Tinea pedis:* Apply once daily for 4 weeks.	Topical use only; not for oral, ophthalmic, or intravaginal use.
Ertaczo (sertaconazole)	Topical cream	Apply twice daily for 4 weeks.	Topical use only; not for oral, ophthalmic, or intravaginal use.
Exelderm (sulconazole)	Topical cream Topical solution	**Cream** *Corporis, cruris, versicolor:* Apply once or twice daily for 3 weeks. *Pedis*: Apply twice daily for 4 weeks. **Solution** *Corporis, cruris, versicolor*: Apply once or twice daily for 3 weeks	Topical use only; not for ophthalmic use.
Extina, Nizoral, Xolegel (ketoconazole)	Topical cream, foam, shampoo, gel	**Cream** *Dermatitis*: Apply twice daily for 4 weeks or until clinical clearing. *Other uses*: Apply once daily for 2 weeks; except for tinea pedis for 6 weeks. **Foam**: Apply twice daily for 4 weeks.	Topical use only; not for oral, ophthalmic, or intravaginal use.

Drug	Available Formulations	Usual Recommended Frequency	Comments
		Shampoo 2%: Apply to damp skin of the affected area. Lather, leave in place for 5 minutes, and then rinse off with water. One application of the shampoo should be sufficient. **Shampoo 1% (OTC):** Apply to wet hair. Generously lather, rinse, and repeat. Use every 3 to 4 days for up to 8 weeks. **Topical Gel:** Apply once daily for 2 weeks.	
Jublia (efinaconazole)	Topical solution	Apply to affected toenails once daily for 48 weeks.	Topical use only; not for oral, ophthalmic, or intravaginal use. Ensure the toenail, the toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate, are completely covered.
Kerydin (tavaborole)	Topical solution	Apply to the affected toenails once daily for 48 weeks.	Topical use only; not for oral, ophthalmic, or intravaginal use. Should be applied to the entire toenail surface and under the tip of each toenail being treated.
Loprox, Penlac (ciclopirox)	Topical cream, gel, lotion, shampoo, solution	**Cream and lotion**: Apply twice daily for up to 4 weeks. **Gel**: Apply twice daily for 4 weeks. **Shampoo:** Treatment should be repeated twice per week for 4 weeks, with a minimum of 3 days between applications. **Solution**: Apply once daily (preferably at bedtime or 8 hours before washing) to all affected nails, evenly over the entire nail plate. Do not remove on a daily basis. Daily applications should be made over the previous coat and removed with alcohol every 7 days.	Solution: Should be applied to the nail bed, hyponychium, and under the surface of the nail plate when it is free of the nail bed. Topical use only; not for oral, ophthalmic, or intravaginal use
Luzu (luliconazole)	Topical cream	**Interdigital tinea pedis:** Apply once daily for 2 weeks. **Tinea cruris or tinea corporis:** Apply once daily for 1 week.	Topical use only; not for oral, ophthalmic, or intravaginal use
Mentax (butenafine)	Topical cream	Apply once daily for 2 weeks.	Topical use only; not for oral, ophthalmic, or intravaginal use
Naftin (naftifine)	Topical cream, gel	**Cream/Gel 2%:** Apply once daily for 2 weeks.	Topical use only; not for oral, ophthalmic, or intravaginal use

Drug	Available Formulations	Usual Recommended Frequency	Comments
		Gel 1%: Apply twice daily for up to 4 weeks.	
nystatin	Topical cream, ointment, powder	**Cream and ointment**: Apply twice daily until complete healing. **Powder**: Apply 2 to 3 times daily until complete healing.	Topical use only; not for oral, ophthalmic, or intravaginal use Cream is usually preferred to ointment in candidiasis involving intertriginous areas. Very moist lesions are best treated with topical powder.
Oxistat (oxiconazole)	Topical cream, lotion	**Corporis and cruris**: Apply once or twice daily for 2 weeks. **Versicolor**: Apply once daily for 2 weeks. **Pedis**: Apply once or twice daily for one month.	Shake lotion well before using. Topical use only; not for oral, ophthalmic, or intravaginal use
Combination products			
Lotrisone (clotrimazole/ betamethasone)	Topical cream, lotion	**Corporis, cruris**: Apply twice daily for up to 2 weeks. **Pedis**: Apply twice daily for up to 4 weeks.	Do not use more than 45 grams or 45 mL per week. Shake lotion well before each use. Topical use only; not for oral, ophthalmic, or intravaginal use
nystatin/ triamcinolone	Topical cream and ointment: nystatin 100,000 units/ triamcinolone 1 mg/gram	Apply twice daily for up to 25 days.	For external use only; Not for ophthalmic use
Vusion (miconazole/zinc oxide/white petrolatum)	Topical ointment: 0.25% miconazole nitrate/15% zinc oxide/81.35% white petrolatum	Apply with each diaper change for 7 days.	Topical use only; not for oral, ophthalmic, or intravaginal use

See the current prescribing information for full details.

CONCLUSION

- Many of the products are available generically, including ciclopirox, clotrimazole, clotrimazole/betamethasone, econazole cream, ketoconazole, naftifine cream, nystatin, nystatin/triamcinolone, and oxyconazole cream.
- Several topical antifungal products are available OTC and some are available both as prescription and OTC.
- The limited clinical trials available do not differentiate one product from another in terms of mycological and clinical cure.
- Vusion (miconazole/zinc oxide/white petrolatum) is a combination product indicated for diaper dermatitis when complicated by documented candidiasis. It has been shown to be more effective than zinc oxide therapy alone (*Concannon et al 2001, Spraker et al 2006*). Comparative trials to other active agents have not been conducted.
- Jublia is the first FDA-approved triazole antifungal indicated for the topical treatment of adult patients with onychomycosis of the toenails due to *Trichophyton rubrum* and *Trichophyton mentagrophytes.* Jublia is also the first triazole antifungal to be developed for the treatment of distal lateral subungual onychomycosis (DLSO) (*Valeant Pharmaceuticals press release 2014*).

- Kerydin is a first-in-class oxaborole topical antifungal approved for the treatment of toenail onychomycosis (*MarketWatch press release 2014*).
- National and international recommendations which discuss the management of fungal infections focus primarily on superficial mycotic infections. Several recommendations list topical antifungal agents or subclasses, and generally do not give preference to one agent vs another (*Brown and Dresser 2017, de Berker, 2009, Drake et al 1996[a], Drake et al 1996[b], Naldi and Rebora 2009, Ameen et al 2014, Stevens et al 2014*). According to these guidelines, mycological and clinical cure of noninvasive fungal infections are often achieved with topical therapy alone.
- Dosing and administration of these agents are dependent upon the condition being treated and the patient population.
- Adverse effects for the topical antifungals are primarily dermatological with allergic or contact dermatitis, burning, dry skin, erythema, pruritus, skin irritation, and stinging as the most common reactions reported.

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Publication Date: July 3, 2018

INTRODUCTION

Phosphate Binders

- Hyperphosphatemia, an important and inevitable clinical consequence of advanced stages of chronic kidney disease (CKD), requires appropriate management due to the risk for secondary hyperparathyroidism and cardiovascular disease. Persistent or chronic hyperphosphatemia, along with an elevated calcium times phosphorus (Ca x P) product, is associated with an increased risk of vascular, valvular, and other soft-tissue calcification in patients with CKD. Elevated phosphorus levels may also directly influence several components of CKD-Mineral and Bone Disorder such as secondary hyperparathyroidism, bone abnormalities, calcitriol deficiency, and extra skeletal calcification. In addition, there is evidence consistently demonstrating that hyperphosphatemia is a predictor of mortality in CKD stage 5 patients who are receiving dialysis. Because of these reasons, control of serum phosphorus levels in patients with CKD is an important component of care (*Kidney Disease Improving Global Outcomes [KDIGO] 2009, KDIGO 2017, National Kidney Foundation [NKF] 2003, Kestenbaum et al 2005, Voormolen et al 2007*).
- The two principal modalities used to control serum phosphorus levels in patients with CKD include restricting dietary phosphorus intake and administering phosphorus binders (or phosphorus depleters). When dietary phosphorus restriction is inadequate in controlling serum phosphorus levels, the administration of phosphorus binders is recommended. There are several currently available phosphorus binders and the class can be divided into two subcategories: calcium- and non-calcium-containing products. Calcium-based phosphate binders include calcium carbonate and calcium acetate, and calcium-free binders include aluminum hydroxide, lanthanum carbonate, magnesium carbonate, sevelamer hydrochloride, sevelamer carbonate, ferric citrate, and sucroferric oxyhydroxide.
- The 2017 KDIGO guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD) does not specifically recommend one type of phosphate-binder as first-line therapy, but suggests restricting the dose of calcium-based phosphate binders in adult patients with CKD stage 3a to 5 (with or without dialysis) receiving phosphate-lowering treatment. In children, it is reasonable to base the choice of phosphate-lowering treatment on serum calcium levels *(KDIGO 2017).*
- The sevelamer hydrochloride salt was the initial sevelamer formulation developed; however, because of the incidence of metabolic acidosis associated with its use, a buffered formulation was created. The sevelamer carbonate formulation has advantages compared to sevelamer hydrochloride because it does not lower a patient's bicarbonate level and does not result in the development of metabolic acidosis *(Perry and Plosker 2014)*. An advantage to the use of lanthanum carbonate is a decrease in the pill burden compared to other products (*Prescribing information: Fosrenol 2016, Renagel 2017, Renvela 2017*). Two iron-based, calcium-free phosphate binders are Velphoro (sucroferric oxyhydroxide) and Auryxia (ferric citrate). Velphoro may reduce the pill burden for those patients that require higher doses of sevelamer as demonstrated in trials (*Prescribing information: Auryxia 2017, Velphoro 2018, Wuthrich et al 2013*).
- Available evidence supports the efficacy of all of the phosphorus binders in controlling serum phosphorus levels. It is generally accepted that no one product is effective and acceptable to every patient. Although treatment guidelines recommend serum phosphorus levels to be maintained within or slightly above the normal range (depending on CKD stage), there is currently no evidence to demonstrate that lowering phosphorus to a specific target range results in improved clinical outcomes in patients with CKD. Despite this lack of evidence, it is still reasonable to use phosphorus binders to lower phosphorus levels in CKD patients with hyperphosphatemia to prevent the development of secondary hyperparathyroidism and cardiovascular disease.
- The main considerations for selection of phosphate binders include absorbability, adequate gastrointestinal tolerability, and cost or cost-effectiveness (*Frazao et al 2012*).
- Medispan Therapeutic Class: Phosphate Binder Agents

Table 1. Medications Included Within Class Review (Phosphate Binders)

Drug	Generic Availability
Auryxia (ferric citrate)	-
Calphron (calcium acetate)*,†	-
Eliphos (calcium acetate)	✔
Fosrenol (lanthanum carbonate)	✔ ‡
PhosLo (calcium acetate)	✔
Phoslyra (calcium acetate)	-
Renagel (sevelamer hydrochloride)	-
Renvela (sevelamer carbonate)	✔
Velphoro (sucroferric oxyhydroxide)	-

*This product is not intended to diagnose, treat, cure or prevent any disease.
†Calphron is available as an over-the-counter nutritional supplement.
‡Fosrenol chewable tablets are available generically; however, the Fosrenol oral packet is not generically available.

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018; Calphron 2016*)

Potassium Removing Agents

- Hyperkalemia is a common clinical problem that is most often a result of impaired urinary potassium excretion due to acute or CKD and/or disorders or drugs that inhibit the renin-angiotensin-aldosterone system (RAAS). The most serious manifestations of hyperkalemia are muscle weakness or paralysis, cardiac conduction abnormalities, and cardiac arrhythmias, including sinus bradycardia, sinus arrest, slow idioventricular rhythms, ventricular tachycardia, ventricular fibrillation, and asystole. These manifestations usually occur when the serum potassium concentration is ≥ 7 mEq/L with chronic hyperkalemia or possibly at lower levels with an acute rise in serum potassium or in patients with an underlying cardiac conduction disorder (*Mount 2017*).
- There are no clear guidelines regarding the appropriate setting for the treatment of hyperkalemia. The decision for hospital admission for continuous electrocardiograph monitoring is a matter of clinical judgment in each case. Patients believed to have a rapid rise in potassium commonly need inpatient care, whereas patients whose hyperkalemia has developed over a period of weeks can often be managed in an outpatient setting with close follow-up (*Hollander-Rodriquez and Calvert 2006*).
  - Urgent treatment of hyperkalemia includes 3 main phases: 1) antagonizing cardiac effects of potassium (using intravenous calcium gluconate); 2) redistributing potassium into cells (using insulin with dextrose, beta-2-adrenergic agonists, or sodium bicarbonate); and 3) removing excess potassium from the body (ie, using hemodialysis, loop diuretics, or cation exchange resins) (*Hollander-Rodriquez and Calvert 2006, Mount 2017, Raebel 2012*).
  - In patients who do not require urgent treatment, lowering total body potassium may be the only step necessary (*Hollander-Rodriquez and Calvert 2006*).
- Long-term treatment or prevention of hyperkalemia should be tailored to correcting the underlying cause of hyperkalemia (*Hollander-Rodriquez and Calvert 2006*).
- Cation exchange resins are used in clinical practice for removing excess potassium from the body. Prior to 2015, Kayexalate (sodium polystyrene sulfonate) was the only potassium binding agent approved in the U.S. for the treatment of hyperkalemia; however, the use of sodium polystyrene sulfonate has been limited by tolerability and safety concerns (ie, colonic necrosis and sodium absorption leading to volume overload) and questions about efficacy (*Veltassa FDA Summary Review 2015*).
- In October 2015, the Food and Drug Administration (FDA) approved Veltassa (patiromer), a non-absorbed, cation exchange polymer that contains a calcium-sorbitol counterion, for the treatment of hyperkalemia.
- In May 2018, the FDA approved Lokelma (sodium zirconium cyclosilicate), a non-absorbed zirconium silicate, for the treatment of hyperkalemia in adults.
- Medispan Therapeutic Class: Potassium Removing Agents

Table 2. Medications Included Within Class Review (Potassium Removing Agents)

Drug	Generic Availability
Lokelma (sodium zirconium cyclosilicate)	-
Sodium polystyrene sulfonate*	✔
Veltassa (patiromer)	-

*Sodium polystyrene sulfonate is generically available; brand Kayexalate is no longer available; Kionex, Kalexate, and SPS are branded generics.

INDICATIONS

Table 3. FDA-Approved Indications for Phosphate Binders

Generic name	Reduce absorption of dietary phosphate	Reduce serum phosphate in end stage renal disease	Control serum phosphorus in patients with CKD on dialysis	Iron deficiency anemia in CKD in patients not on dialysis
Calcium acetate	✔ (Calphron)	✔ (Eliphos, PhosLo, Phoslyra)		
Ferric citrate			✔	✔
Lanthanum carbonate		✔		
Sevelamer carbonate			✔	
Sevelamer hydrochloride			✔ †	
Sucroferric oxyhydroxide			✔	

†Safety and efficacy in CKD patients who are not on dialysis have not been studied.

(Prescribing information: Auryxia 2017, Calphron 2016, Eliphos 2015, Fosrenol 2016, PhosLo 2013, Phoslyra 2015, Renagel 2017, Renvela 2017, Velphoro 2018)

Table 4. FDA-Approved Indications for Potassium Removing Agents

Generic name	Treatment of hyperkalemia
Patiromer	✔
Sodium polystyrene sulfonate	✔
Sodium zirconium cyclosilicate	✔

(Prescribing information: Lokelma 2018, sodium polystyrene sulfonate powder for suspension 2017, sodium polystyrene sulfonate suspension 2016, Veltassa 2018)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Phosphate Binders

- Available evidence supports the efficacy of all of the phosphate binders controlling serum phosphorus levels (*Shigematsu et al, 2010, Almirall et al 2012, Finn et al 2005, Hutchison et al 2008, Finn et al 2004, Joy et al 2003, Sprague et al 2009, Shigematsu et al 2008, Al-Baaj et al 2005, Mehrotra et al 2008, Ketteler et al 2008, Fischer et al 2006, Ouellet et al 2009, Iwasaki et al 2005, Qunibi et al 2004, Finn et al 2006, Wilson et al 2009, Hutchison et al 2006, Kasai et al 2012, Delmez et al 2007, Fan et al 2009, Fishbane et al 2010, Suki et al 2007, St. Peter et al 2008, Pieper et*

al 2006, Evenepoel et al 2009, Hervas et al 2003, Bleyer et al 1999, Navaneethan et al 2011, Block et al 2015, Dwyer et al 2013, Lewis et al 2015).

- In general, the true benefits of phosphorus lowering with respect to hard clinical outcomes have not been established, and most clinical trials evaluate surrogate end points. A systematic review of 18 studies evaluated the rate of all-cause mortality among those treated with non-calcium based phosphate binders compared to calcium-based phosphate binders in patients with CKD (*Jamal et al 2013*). The non-calcium based group which included sevelamer and lanthanum had a statistically significant reduction of 22% in all-cause mortality compared to calcium-based phosphate binders (RR 0.78, 95% CI, 0.61 to 0.98, I^2=43%; 11 randomized clinical trials, N=4,622). Note that two observational studies and one cross-sectional study were included. No significant reduction in cardiovascular events was observed.
- Clinical trials have consistently demonstrated that sevelamer hydrochloride is effective at lowering phosphorus levels and maintaining phosphate control comparable to calcium acetate and calcium carbonate therapy (*Qunibi et al 2004 Evenepoel et al 2009, Hervas et al 2003, Bleyer et al 1999, Pieper et al 2006*). A 2011 systematic review concluded that sevelamer significantly decreases the risk of hypercalcemia compared with calcium-based agents (*Navaneethan et al 2011*). A 2016 meta-analysis of 25 studies with 88% of patients on hemodialysis found lower all-cause mortality with sevelamer (risk ratio 0.54, 95% confidence interval [CI], 0.32 to 0.93) compared to calcium-based binders, but no statistical difference for cardiovascular mortality was observed (*Patel et al 2016*).
- Clinical trials demonstrate that lanthanum carbonate and sevelamer show comparable efficacy in lowering phosphorous although limited studies have compared the two therapies for efficacy (*Kasai et al 2012*). Findings from a meta-analysis showed that, compared with calcium-based agents, lanthanum significantly decreased end of treatment serum calcium and calcium phosphorus product levels but with similar end of treatment phosphorus levels (*Navaneethan et al 2011*).
- The efficacy and safety of Velphoro were evaluated in three trials: a fixed dose study, a dose titration study, and a dose titration extension study. Velphoro demonstrated efficacy by significantly reducing serum phosphorus in hemodialysis and peritoneal dialysis patients from six to 52 weeks (*Velphoro prescribing information 2017, Wuthrich et al 2013*).
  - In the fixed dose study, all Velphoro dose groups showed a significant decrease in serum phosphorus (P≤0.02), except the 250 mg/day group. The proportion of Velphoro patients achieving goal phosphorus levels after six weeks of treatment ranged from 35 to 60% for 1,000 to 2,500 mg/day, and 42.1% in the sevelamer control arm. The median time to reach first controlled serum phosphorus levels was not different for Velphoro (one week) vs the sevelamer (two weeks) control arm (P>0.16) (*Wuthrich et al 2013*).
  - In the dose titration study, Velphoro 1,000 to 3,000 mg/day was statistically superior to the Velphoro low dose (250 mg) control in maintaining the phosphorus lowering effect in hemodialysis patients at week 27 (P<0.001) (*Floege et al 2014*). In the extension trial, Velphoro demonstrated a greater change from baseline in serum phosphorus when compared to sevelamer carbonate from weeks 32 to 40. However from weeks 44 to 52, changes in serum phosphorus between sevelamer carbonate and Velphoro were similar (*Floege et al 2015*). The greatest changes from baseline for serum phosphorus occur up to week 12 for sevelamer carbonate and up to week 20 for Velphoro (*Velphoro prescribing information 2017*).
  - The most frequent adverse events were hypophosphatemia and discolored feces for the Velphoro groups. Velphoro patients experienced more discolored feces, hypophosphatemia, muscle spasms, and constipation compared to sevelamer HCl in the active comparator trial (*Wuthrich et al 2013*).
- Auryxia is an iron-based, calcium-free phosphate binder that has been studied in several published trials. Ferric citrate is similarly safe and effective to two current first-line phosphate binders, calcium acetate and sevelamer (*Lewis et al 2015*). Ferric citrate offers a reduced pill burden vs sevelamer carbonate but not vs calcium acetate. In addition to reducing serum phosphorus, ferric citrate raises iron stores (evidenced by increased hemoglobin, serum ferritin and serum transferrin saturation) and decreases intravenous iron and erythropoietin stimulating agent usage (*Block et al 2015, Lewis et al 2015, Umanath et al 2015, Prescribing information: Auryxia 2017*).

Potassium Removing Agents

- The FDA first approved sodium polystyrene sulfonate in 1958, 4 years before passage of the Kefauver-Harris Drug Amendments, which requires drug manufacturers to prove the effectiveness of their products before marketing (*Sterns et al 2010*).
- In 1961, *Scherr et al* reported the largest clinical experience with sodium polystyrene sulfonate suspended in water in an uncontrolled study of hyperkalemic patients with acute and chronic renal failure, using the newly approved sodium polystyrene sulfonate. In 23 of 30 cases, the plasma potassium fell by at least 0.4 mEq/L in the first 24 hours. Two patients with pre-treatment potassium levels of 6.1 and 7.4 mEq/L developed hypokalemia (3.3 and 2.3 mEq/L) while

receiving 40 g/day of oral resin for 2 and 6 days. On the strength of this study and several smaller case series, the FDA's Drug Efficacy Study Implementation (DESI) Program, charged with reviewing pre-1962 drugs that were already on the market, ruled sodium polystyrene sulfonate powder "effective" (*Sterns et al 2010*).

- A recent randomized, double-blind (DB), placebo-controlled (PC), single-center study (N = 33) evaluated the safety and efficacy of a 7-day course of sodium polystyrene sulfonate in the treatment of mild hyperkalemia (potassium levels of 5.0 to 5.9 mEq/L) in patients with CKD (*Lepage et al 2015*).
  - Sodium polystyrene sulfonate was superior to placebo in the reduction of serum potassium levels (mean difference between groups: −1.04 mEq/L; 95% confidence interval [CI]: −1.37 to −0.71).
  - A higher proportion of patients in the sodium polystyrene sulfonate group attained normokalemia at the end of their treatment compared with those in the placebo group, but the difference did not reach statistical significance (73% vs 38%, p = 0.07).
- The safety and efficacy of patiromer were based primarily on 2 pivotal trials in hyperkalemic patients (potassium levels of 5.1 to < 6.5 mEq/L).
  - OPAL-HK was a 2-part, single-blind, Phase 3 study that evaluated the efficacy and safety of patiromer in 237 patients with CKD receiving RAAS inhibitors. During the initial treatment phase (Part A), patiromer therapy resulted in a mean (± standard error [SE]) change from baseline to week 4 in serum potassium of −1.01 ± 0.03 mEq/L (95% CI: −1.07 to −0.95; p < 0.001) (*Weir et al 2015*).
    - Patients with moderate to severe hyperkalemia at baseline who achieved a target potassium level with initial treatment during Part A were randomized to receive patiromer (n = 55) or placebo (n = 52) in Part B (randomized withdrawal phase). The median increase in potassium level from baseline of Part B through week 4 was greater with placebo compared with patiromer (0.72 mEq/L vs 0 mEq/L, 95% CI: 0.46 to 0.99; p < 0.001).
  - AMETHYST-DN was a long-term, Phase 2, randomized study in patients with CKD and diabetes mellitus receiving a RAAS inhibitor. Patiromer demonstrated a mean change from baseline to week 4 or at first patiromer dose titration in serum potassium of −0.35 mEq/L (95% CI: −0.22 to −0.48, p < 0.001) in patients with mild hyperkalemia receiving 8.4 g/day and −0.87 mEq/L (95% CI: −0.60 to −1.14, p < 0.001) in patients with moderate hyperkalemia receiving 16.8 g/day. The efficacy of patiromer was maintained for 1 year (*Bakris et al 2015*).
- The safety and efficacy of sodium zirconium cyclosilicate were based on data from 2 DB, PC studies and 2 open-label studies in adult patients with hyperkalemia.
  - Study 1 was a 2-part, Phase 3, DB, RCT in patients with hyperkalemia (> 5 mmol/L). Patients were randomly assigned to receive either sodium zirconium cyclosilicate (at a dose of 1.25 g, 2.5 g, 5 g, or 10 g) or placebo 3 times daily for 48 hours. Patients with normokalemia (serum potassium level, 3.5 to 4.9 mmol per liter) at 48 hours were randomly assigned to receive either sodium zirconium cyclosilicate or placebo once daily on days 3 to 14 (maintenance phase). The primary end point was the exponential rate of change in the mean serum potassium level at 48 hours *(Packham et al 2015)*.
    - At 48 hours, the mean serum potassium level had decreased from 5.3 mmol/L at baseline to 4.9 mmol/L in the group of patients who received 2.5 g of sodium zirconium cyclosilicate, 4.8 mmol/L in the 5-g group, and 4.6 mmol/L in the 10-g group, for mean reductions of 0.5, 0.5, and 0.7 mmol/L, respectively (p < 0.001 for all comparisons) and to 5.1 mmol/L in the 1.25-g group and the placebo group (mean reduction, 0.3 mmol/L). In patients who received 5 g of sodium zirconium cyclosilicate and those who received 10 g of sodium zirconium cyclosilicate, serum potassium levels were maintained at 4.7 mmol/L and 4.5 mmol/L, respectively, during the maintenance phase, as compared with a level of more than 5.0 mmol/L in the placebo group (p < 0.01 for all comparisons).
  - Study 2 (HARMONIZE) was a Phase 3, randomized, DB, PC trial evaluating sodium zirconium cyclosilicate in outpatients with hyperkalemia (serum potassium ≥ 5.1 mEq/L). Patients (n = 258) received 10 g of sodium zirconium cyclosilicate 3 times daily in the initial 48-hour open-label phase. Patients (n = 237) achieving normokalemia (3.5 to 5.0 mEq/L) were then randomized to receive sodium zirconium cyclosilicate, 5 g (n = 45 patients), 10 g (n = 51), or 15 g (n = 56), or placebo (n = 85) daily for 28 days *(Kosiborod et al 2014)*.
    - In the open-label phase, serum potassium levels declined from 5.6 mEq/L at baseline to 4.5 mEq/L at 48 hours, with 84% of patients (95% CI, 79 to 88) achieving normokalemia by 24 hours and 98% (95% CI, 96 to 99) by 48 hours. In the randomized phase, serum potassium was significantly lower during days 8 to 29 with all 3 zirconium cyclosilicate doses vs placebo (4.8 mEq/L [95% CI, 4.6 to 4.9], 4.5 mEq/L [95% CI, 4.4 to 4.6], and 4.4 mEq/L [95% CI, 4.3 to 4.5] for 5 g, 10 g, and 15 g; 5.1 mEq/L [95% CI, 5.0 to 5.2] for placebo; p < 0.001 for all comparisons).

- Patients who completed the 28-day randomized withdrawal phase had the option to continue treatment with sodium zirconium cyclosilicate, in an open-label extension phase for up to 11 months (n = 123). The treatment effect on serum potassium was maintained during continued therapy *(Prescribing information: Lokelma 2018)*.

- Sodium zirconium cyclosilicate was also evaluated in an open-label 12-month study in 751 hyperkalemic patients. The mean baseline potassium level in this study was 5.6 mEq/L. Following the acute phase treatment of sodium zirconium cyclosilicate 10 g three times a day, patients who achieved normokalemia (3.5 to 5.0 mEq/L) within 72 hours (n = 746; 99%) entered the maintenance phase. For maintenance treatment, the initial dosage was 5 g once daily and was adjusted to a minimum of 5 g every other day up to maximum of 15 g once daily, based on serum potassium level. The treatment effect on serum potassium was maintained during continued therapy *(Prescribing information: Lokelma 2018)*.

CLINICAL GUIDELINES

KDIGO - Clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of CKD-MBD *(KDIGO 2009, KDIGO 2017)*

- KDIGO published treatment guidelines in 2009 and these were updated again in 2017. The update revised recommendations for treatment of elevated phosphate levels. The recommendations include:
  - In patients with CKD stage 3a to 5 (with or without dialysis), KDIGO suggests lowering elevated phosphate levels toward the normal range. There is insufficient evidence that maintaining phosphate in the normal range is of clinical benefit to CKD stage 3a to stage 4 patients. Due to safety concerns with pharmacologic therapy, treatment should be reserved for overt hyperphosphatemia.
  - In patients with CKD stage 3 to stage 5 (with or without dialysis), decisions about phosphate-lowering treatment should be based on progressively or persistently elevated serum phosphate. The broader term “phosphate-lowering” treatment is used instead of phosphate binding agents since all possible approaches (ie, binders, diet, or dialysis) can be effective.
  - In adult patients with CKD stage 3a to 5 (with or without dialysis) receiving phosphate-lowering treatment, KDIGO suggests restricting the dose of calcium-based phosphate binder. In children, it is reasonable to base the choice of phosphate-lowering treatment on serum calcium levels.

- **KDOQI – US Commentary on the 2017 KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of CKD-MBD** *(Isakova 2017)*
  - The KDOQI CKD-MBD work group published a commentary on the 2017 KDIGO guideline update recommendations.
  - The majority of the KDOQI work group supported the recommendation from the 2017 KDIGO guideline to limit calcium-based binders *when possible*, and discussed that there are multiple non-calcium phosphate-lowering therapies that are effective with similar adverse event profiles to calcium-based phosphate binders. The work group endorsed the recommendation to base the choice of phosphate-lowering therapy in children on serum calcium levels.

SAFETY SUMMARY

Phosphate Binders

- Sevelamer carbonate and sevelamer hydrochloride are contraindicated in patients with bowel obstruction. Cases of dysphagia and esophageal tablet retention have been reported in association with use of the tablet formulation of sevelamer, some requiring hospitalization and intervention. The sevelamer suspension formulation should be considered in patients with a history of swallowing disorders. Adverse reactions possibly related to sevelamer included nausea, vomiting, dyspepsia, diarrhea, flatulence, abdominal pain, and constipation. Ciprofloxacin should be taken at least two hours before or six hours after sevelamer and mycophenolate mofetil should be taken at least two hours before sevelamer.
- Calcium acetate is contraindicated in patients with hypercalcemia. Calcium supplements should be used with caution in patients with chronic renal failure due to the increased risk of developing hypercalcemia. The most common adverse effects include hypercalcemia, nausea, and vomiting. Diarrhea has been reported with calcium acetate oral solution. The administration of calcium acetate may decrease the bioavailability of tetracyclines or fluoroquinolones.
- Ferric citrate is contraindicated in patients with iron overload. Ferric citrate should be kept out of the reach of children to lower the risk of accidental overdose of iron. Adverse events reported in more than 5% of patients treated with ferric citrate in clinical trials included diarrhea, nausea, constipation, vomiting, discolored feces, and cough. Doxycycline

should be taken at least one hour before ferric citrate. Ciprofloxacin should be taken at least two hours before or after ferric citrate.

- Bowel obstruction, ileus, and fecal impaction are contraindications to lanthanum carbonate therapy. Serious adverse events consisting of gastrointestinal obstruction, ileus, subileus, gastrointestinal perforation, and/or fecal impaction have been reported with this medication, and some of these events required surgery or hospitalization. Adverse events that were more commonly associated with lanthanum carbonate therapy included nausea, vomiting, and abdominal pain. Compounds that bind aluminum-, magnesium-, or calcium-based cationic antacids and thyroid hormone replacement therapy should be separated by at least two hours from lanthanum carbonate. Fluoroquinolones should be taken at least one hour before or four hours after lanthanum.
- Sucroferric oxyhydroxide does not have any contraindications. Due to the potential for drug interactions, levothyroxine should be taken at least four hours before sucroferric oxyhydroxide. Doxycycline, acetylsalicylic acid and cephalexin must be taken at least one hour before sucroferric oxyhydroxide. Common adverse events include dark/discolored feces, nausea, and diarrhea.

Potassium Removing Agents

- Patiromer is contraindicated in patients with known hypersensitivity to patiromer or any of its components. Warnings and precautions of patiromer include worsening of gastrointestinal motility and hypomagnesemia. The most common adverse reactions (≥ 2%) with patiromer use were constipation, hypomagnesemia, diarrhea, nausea, abdominal discomfort, and flatulence.
- Sodium polystyrene sulfonate powder for suspension is contraindicated in patients with obstructive bowel disease and neonates with reduced gut motility. Sodium polystyrene sulfonate suspension is contraindicated in patients with hypokalemia, obstructive bowel disease, and as oral or rectal administration in neonates. Warnings and precautions for sodium polystyrene sulfonate include intestinal necrosis; development of hypokalemia or other electrolyte disturbances; fluid overload in patient sensitive to high sodium intake; and risk of aspiration.
- Sodium polystyrene sulfonate may cause some degree of gastric irritation. Anorexia, nausea, vomiting, and constipation may occur especially if high doses are given. Occasionally diarrhea develops.
- Warnings and precautions for sodium zirconium cyclosilicate include gastrointestinal adverse events in patients with motility disorders and edema. The most common adverse reactions were mild to moderate edema.

DOSING AND ADMINISTRATION

Table 5. Dosing and Administration of Phosphate Binders

Generic name	Available Formulations	Route	Usual Recommended Frequency	Comments
Calcium acetate	Capsule, tablet, solution	Oral	Administered with each meal	--
Ferric citrate	Tablet	Oral	Three times daily with meals	--
Lanthanum carbonate	Chewable tablet, powder	Oral	Administered with meals or immediately after meals	• Use is not recommended in children. In animal studies, lanthanum was deposited into developing bone including the growth plate. Consequences of lanthanum bone deposition are unknown.
Sevelamer carbonate	Powder for oral suspension, tablet	Oral	Three times daily with meals	--
Sevelamer hydrochloride	Tablet	Oral	Three times daily with meals	--
Sucroferric oxyhydroxide	Chewable tablet	Oral	Three times daily with meals	--

See the current prescribing information for full details

Table 6. Dosing and Administration of Potassium Removing Agents

Generic name	Available Formulations	Route	Usual Recommended Frequency	Comments
Patiromer	Powder for suspension	Oral	Once daily with or without food	• Administer at least 3 hrs before or 3 hrs after other oral medications.
Sodium polystyrene sulfonate	Powder for suspension; suspension	Oral; rectal (enema)	Oral: 1 to 4 times daily Rectal: Every 6 hours	• Administer at least 3 hrs before or 3 hrs after other oral medications. • Patients with gastroparesis may require a 6 hr separation.
Sodium zirconium cyclosilicate	Powder for suspension	Oral	Starting dose is 10 g administered 3 times a day for up to 48 hours; for maintenance, recommended dose is 10 g once daily	• Other oral medications should be administered at least 2 hours before or 2 hours after sodium zirconium cyclosilicate

CONCLUSION

Phosphate Binders

- The phosphorus binders (or phosphorus depleters) class is an important aspect of the medical management of patients with CKD; these agents are used to lower a patient's phosphorus level. If phosphorus levels remain elevated in this population, the patient is at a greater risk for the development of secondary hyperparathyroidism or cardiovascular disease. In addition, there is available evidence to demonstrate that hyperphosphatemia is a predictor of mortality in CKD stage 5 patients who are receiving dialysis. In patients with CKD stage 3 to stage 5 (with or without dialysis), decisions about phosphate-lowering treatment should be based on progressively or persistently elevated serum phosphate. The broader term "phosphate-lowering" treatment is used instead of phosphate binding agents since all possible approaches (ie, binders, diet, or dialysis) can be effective (*NKF 2003, KDIGO 2009, KDIGO 2017*).
- The two subgroups of phosphorus binders currently available include the calcium and non-calcium containing products. Available evidence supports the efficacy of all of the phosphorus binders in controlling serum phosphorus levels. It is important to note that although the true benefits of these agents, with respect to hard clinical outcomes, have not been established, it is still reasonable to prescribe these products in patients with CKD who have elevated phosphorus levels to prevent the development of secondary hyperparathyroidism and cardiovascular disease.
- In adult patients with CKD stage 3a to 5 (with or without dialysis) receiving phosphate-lowering treatment, KDIGO suggests restricting the dose of calcium-based phosphate binder. In children, it is reasonable to base the choice of phosphate-lowering treatment on serum calcium levels *(KDIGO 2017).*
- Sevelamer, a non-calcium-containing phosphate binder, is available in two salt formulations: hydrochloride (Renagel) and carbonate (Renvela). The hydrochloride formulation was developed first, but due to the incidence of metabolic acidosis associated with its use, a buffered sevelamer formulation was later developed. The newer sevelamer carbonate product will most likely be preferred in this patient population due to a decrease in the incidence of metabolic acidosis associated with its use. Additionally, sevelamer carbonate is the only phosphate binder that is FDA-approved for use in children (6 years of age and older).
- Lanthanum carbonate (Fosrenol) is another non-calcium-containing phosphorus binder available. An advantage to this agent, in addition to not causing an increase in serum calcium levels, appears to be its decreased pill burden compared to the other products (*NKF 2003, KDIGO 2009*). Two iron-based, calcium-free phosphate binders are now available. Velphoro provides long-term control of hyperphosphatemia, as demonstrated by the unpublished 52-week extension trial. Velphoro may reduce the pill burden for those patients that require higher doses of sevelamer as demonstrated in trials (*Wuthrich et al 2013*). Ferric citrate has shown to provide significant reductions in serum phosphate levels in three studies (*Block et al 2015, Dwyer et al 2013, Lewis et al 2015*). Based on secondary study endpoints, ferric citrate raises iron stores (evidenced by increased serum ferritin and serum transferrin saturation) and decreases intravenous iron and erythropoietin stimulating agent usage (*Lewis et al 2015, Umanath et al 2015*).
- Ferric citrate's effects may make it an attractive option for dialysis patients who require concomitant use of a phosphate binder and anemia treatments.
- The main considerations for selection of phosphate binders include absorbability, adequate gastrointestinal tolerability, and cost or cost-effectiveness (*Frazao et al 2012*).

Potassium Removing Agents

- Hyperkalemia is a common clinical problem that is most often a result of impaired urinary potassium excretion due to acute or CKD and/or disorders or drugs that inhibit the RAAS may also cause hyperkalemia *(Mount 2017)*.
- Acute or urgent treatment of hyperkalemia includes 3 main phases: 1) antagonizing cardiac effects of potassium by using intravenous calcium gluconate; 2) redistributing potassium into cells using insulin with dextrose, beta-2-adrenergic agonists, or sodium bicarbonate; and 3) removing excess potassium from the body using hemodialysis, loop diuretics, or cation exchange resins (ie, sodium polystyrene sulfonate) (*Hollander-Rodriquez et al 2006, Mount 2017, Raebel 2012*).
  - In patients who do not require urgent treatment, lowering total body potassium may be the only step necessary (*Hollander-Rodriquez et al 2006*).
- In October 2015, the FDA approved Veltassa (patiromer), a non-absorbed, cation exchange polymer that contains a calcium-sorbitol counterion, for the treatment of hyperkalemia. Patiromer should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action.
- Patiromer has been shown to be effective in lowering serum potassium levels in patients with CKD receiving RAAS inhibitor therapy. Patiromer has also been shown to provide sustained reductions of serum potassium for up to 1 year.
  - Compared with sodium polystyrene sulfonate, patiromer has more robust prospective long-term data and may have a more favorable adverse event profile (sodium polystyrene sulfonate is associated with intestinal necrosis and sodium retention); however, studies used for the approval of patiromer did not address the relative efficacy and safety of patiromer vs sodium polystyrene sulfonate.
  - In addition, the role of patiromer for the outpatient treatment of hyperkalemia is unknown, as chronic management of hyperkalemia is generally accomplished through dietary modifications, discontinuation or dose lowering of hyperkalemia-exacerbating agents, or the use of diuretics.
- In May 2018, the FDA also approved Lokelma (sodium zirconium cyclosilicate), a non-absorbed zirconium silicate that acts as a highly-selective potassium-removing agent, for the treatment of hyperkalemia. Similar to patiromer, sodium zirconium cyclosilicate should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action. The safety and efficacy of sodium zirconium cyclosilicate were based on data from 2 DB, PC studies and two open-label studies in adult patients with hyperkalemia.
  - The PC studies demonstrated that patients treated with sodium zirconium cyclosilicate had significant reductions in serum potassium levels vs placebo-treated patients. The two open-label studies showed that the treatment effect of sodium zirconium cyclosilicate on serum potassium was maintained during continued therapy.

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Publication Date: July 3, 2018

INTRODUCTION

- Benign prostatic hyperplasia (BPH) is a histologic diagnosis that refers to the proliferation of smooth muscle and epithelial cells of the prostate. A different but related term is benign prostatic enlargement, which is used when the prostate has an increased size *(McVary et al 2011).*
- BPH causes bladder outlet obstruction that leads to lower urinary tract symptoms (LUTS). The obstruction is caused by 2 main factors:
  - A static, structural component due to the bulk of the enlarged prostate impinging upon the urethra
  - A dynamic, reversible component due to the tension of smooth muscle in the prostate *(McVary et al 2011).*
- LUTS include storage and voiding symptoms *(Cunningham et al 2017a, McVary et al 2011).*
  - Storage symptoms may include increased frequency of daytime urination, nocturia, urgency, and urinary incontinence.
  - Voiding symptoms may include a slow urinary stream, splitting or spraying of the urinary stream, intermittent urinary stream, hesitancy, straining to void, and terminal dribbling.
- The exact etiology of BPH is unknown *(McVary et al 2011).* Increased age is a major risk factor; the prevalence of BPH is 8% in men 31 to 40 years of age, 40 to 50% in men 51 to 60 years of age, and over 80% in men older than 80 years of age *(Cunningham et al 2017b).*
- The primary goals of treatment are to alleviate bothersome LUTS secondary to prostate enlargement, to alter the disease progression, and to prevent complications associated with BPH and LUTS *(McVary et al 2011).*
- Current treatment options include watchful waiting, surgical interventions, and pharmacological therapies *(McVary et al 2011).*
  - Watchful waiting is the preferred management strategy for men with mild symptoms and for those with moderate to severe symptoms who are not bothered by their LUTS.
  - Surgical and minimally invasive therapies, such as transurethral resection of the prostate and transurethral microwave thermotherapy, are recognized as the most effective strategies for BPH management. Surgical therapy is an appropriate treatment alternative for patients with moderate-to-severe LUTS and for patients who have developed acute urinary retention or other complications.
  - Pharmacological therapies are appropriate for less frequent and severe symptom management. These therapies may include alpha $(\alpha)_1$-adrenergic blocking agents, five-alpha (5-α)-reductase inhibitors, anticholinergic agents, and phosphodiesterase-5 (PDE5) inhibitors.
- This review focuses on the pharmacological agents that are Food and Drug Administration (FDA)-approved for the management of BPH and include the following drug classes:
  - α_1-adrenergic blocking agents: Cardura (doxazosin), Cardura XL (doxazosin extended-release), Flomax (tamsulosin), Hytrin (terazosin), Rapaflo (silodosin), and Uroxatral (alfuzosin)
    - Doxazosin and terazosin are non-uroselective α_1-adrenergic blocking agents. They cause relaxation in both the prostatic and vascular smooth muscles and are therefore associated with a higher incidence of orthostatic hypotension. Both agents are FDA-approved for the management of BPH and hypertension.
    - Cardura XL, an extended-release tablet, is only indicated for the management of BPH.
    - Tamsulosin, silodosin, and alfuzosin are uroselective α_1-adrenergic blocking agents and are therefore associated with a lower risk of orthostatic hypotension. They are FDA-approved for the management of BPH.
    - Minipress (prazosin) is also included in this review since it is an α_1-adrenergic blocking agent that could be used for the management of BPH, but it is only FDA-approved for the treatment of hypertension.
  - 5-α-reductase inhibitors: Avodart (dutasteride) and Proscar (finasteride)
    - Both agents are indicated for the treatment of BPH in men with enlarged prostate to improve symptoms, reduce the risk of acute urinary retention, and reduce the risk of BPH-related surgery. Finasteride is also indicated in combination with doxazosin to reduce the risk of symptomatic progression of BPH, and dutasteride is indicated in combination with tamsulosin for the treatment of symptomatic BPH in men with an enlarged prostate.

- PDE5 inhibitor: Cialis (tadalafil)
  - In addition to the management of BPH symptoms in men with or without concomitant erectile dysfunction, Cialis is FDA-approved for the treatment of erectile dysfunction.
- Combination product: Jalyn (dutasteride/tamsulosin) is indicated for the treatment of symptomatic BPH in men with an enlarged prostate.

- Currently, doxazosin, prazosin, tamsulosin, terazosin, finasteride, dutasteride, alfuzosin, and the combination product dutasteride/tamsulosin are available generically. The brand product for Hytrin is no longer marketed; the product is only available generically.
- Medispan Therapeutic Class: Prostatic Hypertrophy Agents (tadalafil is classified with "Impotence Agents" but is also approved for BPH. Terazosin and doxazosin are classified with "antiadrenergic antihypertensives" but are also approved for BPH).

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single Entity Agents: α_1-Adrenergic Blocking Agents	
Cardura (doxazosin)	✔
Cardura XL (doxazosin extended-release)	-
Flomax (tamsulosin)	✔
Hytrin (terazosin)†	✔
Minipress (prazosin)	✔
Rapaflo (silodosin)	-*
Uroxatral (alfuzosin)	✔
Single Entity Agents: 5-α-Reductase Inhibitors	
Avodart (dutasteride)	✔
Proscar (finasteride)	✔
Single Entity Agents: PDE5 Inhibitors	
Cialis (tadalafil)	-
Combination Product	
Jalyn (dutasteride/tamsulosin)	✔

*A generic product is listed in the FDA Orange Book but is not currently marketed.
†Brand product no longer marketed; product only available generically

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2a. Food and Drug Administration Approved Indications

Indication	Cardura (doxazosin)	Cardura XL (doxazosin extended-release)	Flomax (tamsulosin)	Minipress (prazosin)	Hytrin (terazosin)	Rapaflo (silodosin)	Uroxatral (alfuzosin)
Treatment of signs and symptoms of BPH	✔	✔	✔		✔	✔	✔
Treatment of hypertension	✔			✔	✔		

(Prescribing Information: Cardura 2016, Cardura XL 2017, Flomax 2017, Minipress 2016, Terazosin 2014, Rapaflo 2017, Uroxatral 2015)

Table 2b. FDA-Approved Indications: 5-α-Reductase Inhibitors

Indication	Avodart (dutasteride)	Proscar* (finasteride)
Treatment of symptomatic BPH in men with an enlarged prostate to improve symptoms, reduce the risk of acute urinary retention, and to reduce the risk of need for BPH-related surgery	✔	✔
Treatment of symptomatic BPH in men with enlarged prostate in combination with tamsulosin	✔	
Reduction of the risk of symptomatic progression of BPH in combination with doxazosin		✔

*If finasteride is used with Cialis to initiate BPH treatment, such use is recommended for up to 26 weeks because the incremental benefit of Cialis decreases from 4 weeks until 26 weeks, and the incremental benefit of Cialis beyond 26 weeks is unknown.

(Prescribing information: Avodart 2014, Proscar 2013)

Table 2c. FDA-Approved Indications: PDE5 Inhibitors

Indication	Cialis* (tadalafil)
Treatment of erectile dysfunction	✔
Treatment of signs and symptoms of BPH	✔
Treatment of signs and symptoms of BPH and erectile dysfunction	✔

*If Cialis is used with finasteride to initiate BPH treatment, such use is recommended for up to 26 weeks because the incremental benefit of Cialis decreases from 4 weeks until 26 weeks, and the incremental benefit of Cialis beyond 26 weeks is unknown.

(Cialis prescribing information 2017)

Table 2d. FDA Approved Indications: Combination Product

Indication	Jalyn (dutasteride/tamsulosin)
Treatment of symptomatic BPH in men with enlarged prostate	✔

(Jalyn prescribing information)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Alpha-Adrenergic Blocking Agents

- Overall, doxazosin, Cardura XL, tamsulosin, terazosin, silodosin, and alfuzosin have been shown in clinical trials to decrease International Prostate Symptom Score (IPSS) and improve LUTS in men with BPH *(Chang et al 2010, Choo et al 2014, Demir et al 2009, Kawabe et al 2006, Kojima et al 2012, Leungwattanakij et al 2010, Marks et al 2013, Matsukawa et al 2009, Permpongkosol et al 2011, Ren et al 2010, Song et al 2011, Sun et al 2010, Sun et al 2011, Yamanishi et al 2010, Yokoyama et al 2011).*
- Although some studies showed small differences among agents on selected efficacy endpoints, most randomized controlled trials and reviews demonstrated very similar efficacy among products.
- A meta-analysis of α_1-adrenergic blocking agents (doxazosin, tamsulosin, terazosin, and alfuzosin) in men with LUTS secondary to benign prostatic obstruction did not identify any difference among agents in improving total urinary symptom scores or maximum urinary flow rate. However, tamsulosin and alfuzosin were better tolerated than doxazosin and terazosin *(Djavan et al 1999).*
- A systematic review of studies comparing alfuzosin to doxazosin and tamsulosin showed that doxazosin was associated with the greatest improvement in IPSS *(MacDonald et al 2005).*

- Cardura XL was associated with greater improvement in IPSS compared to tamsulosin in 2 randomized controlled trials *(Chung et al 2011, Kirby et al 2003a);* however, 2 other randomized controlled trials showed no difference between the 2 agents in the improvement in IPSS, nocturia, or quality of life *(Xue et al 2007, Zhang et al 2011).*
- Other head-to-head studies comparing the various α_1-adrenergic blocking agents have demonstrated no difference among these agents in the improvement of BPH symptoms *(Kaplan et al 1995, Kaplan et al 1997, Karadag et al 2011, Kirby et al 2001, Lapitan et al 2005, Rahardjo et al 2006, Samli et al 2004, Tsai et al 2007).*
- Results from a meta-analysis and 2 crossover studies demonstrated that the efficacy of silodosin was similar to tamsulosin in improving IPSS and maximum urinary flow rate *(Cui et al 2012, Miyakita et al 2010, Shirakawa et al 2013, Watanabe et al 2011).* A 2017 Cochrane review reported the efficacy of silodosin is similar to other α_1-adrenergic blockers (tamsulosin and alfuzosin), but it is associated with a higher rate of sexual adverse effects (*Jung et al 2017*).
- Another meta-analysis examined combination therapy with an anticholinergic medication (eg, tolterodine, oxybutynin ER, solifenacin, fesoterodine) plus an α_1-adrenergic blocker (eg, doxazosin, tamsulosin) versus α_1-adrenergic blocker monotherapy in men with BPH. Study results demonstrated the addition of an anticholinergic to an α_1-adrenergic blocker slightly reduced storage symptoms and urinary frequency; however, this combination may increase the risk of acute urinary retention *(Filson et al 2013).*
- A systematic review of 48 studies concluded that older α_1-adrenergic blocking agents had similar outcomes as newer α_1-adrenergic blocking agents, PDE5 inhibitors, antimuscarinics, and combination therapy with agents from more than one medication class. However, older α_1-adrenergic blocking agents had more adverse events than comparators *(Dahm et al 2017).*

5-α-Reductase Inhibitors

- Dutasteride has been shown to reduce prostate volume in men with BPH *(Na et al 2012, Page et al 2011).* Dutasteride has also been demonstrated to reduce the incidence of clinical progression of BPH compared to placebo in men with enlarged prostates *(Toren et al 2013).*
- In a Cochrane review, finasteride improved total BPH symptom scores compared to placebo *(Tacklind et al 2010).* One clinical study also showed that finasteride reduced the risk of clinical progression of BPH compared to placebo in men with large prostate volume *(Kaplan et al 2011).*
- The Enlarged Prostate International Comparator Study (N = 1630) showed that there was no significant difference between dutasteride and finasteride in reducing prostate volume and improving LUTS and maximum urinary flow rate in men with BPH over a period of 12 months *(Nickel et al 2011).* A smaller head-to-head study and a meta-analysis of 4 studies showed similar results *(Jun et al 2017, Ravish et al 2007).* A network meta-analysis of 21 studies found that dutasteride may improve BPH symptoms but not urinary flow or prostate volume compared to finasteride *(Yin et al 2017).* When compared to α_1-adrenergic blocking agents, finasteride was shown in one study to be comparable to tamsulosin in improving LUTS; however, improvements were seen earlier with tamsulosin compared to finasteride *(Lee 2002).*

Combination Therapy with an α1-Adrenergic Blocking Agent Plus a 5-α Reductase Inhibitor

- In men with an enlarged prostate, combination therapy may lead to improved symptom control compared to monotherapy with either an α_1-adrenergic blocking agent or a 5-α reductase inhibitor *(Kaplan et al 2006).* However, available data are inconsistent in this area, with another study demonstrating symptom control with combination therapy to be no better than with α_1-adrenergic blocking monotherapy *(Kirby et al 2003b).*
- In the 4-year, double-blind, randomized, parallel-group study known as the Combination of Avodart and Tamsulosin (CombAT) trial (N = 4844), Jalyn significantly reduced the risk of acute urinary retention or BPH-related surgery compared to tamsulosin monotherapy and demonstrated significantly greater symptom benefit *(Roehrborn et al 2010).* Jalyn was also associated with greater reduction in voiding and storage symptoms compared to dutasteride or tamsulosin monotherapy *(Becher et al 2009).*
- The 2-year, open-label CONDUCT trial compared Jalyn to watchful waiting with the addition of tamsulosin if symptoms did not improve in treatment-naïve men with moderately symptomatic BPH. Jalyn was shown to significantly improve the rate of clinical progression, health-related quality of life, and IPSS scores compared to the watchful waiting/tamsulosin group *(Roehrborn et al 2015).*

PDE5 Inhibitors

- A meta-analysis showed that PDE5 inhibitors (Cialis, Levitra [vardenafil], and Viagra [sildenafil]) were safe and effective in improving IPSS and LUTS secondary to BPH. However, no statistically significant difference was detected in maximum urine flow rate (Q_{max}) or postvoid residual urine volume *(Gacci et al 2016)*.

- Several clinical studies have also demonstrated the efficacy of Cialis in improving LUTS secondary to BPH in men with or without concomitant erectile dysfunction *(Broderick et al 2010, Dmochowski et al 2013, Donatucci et al 2011, Egerdie et al 2012, Goldfischer et al 2012, Oelke et al 2012, Porst et al 2011, Roehrborn et al 2008, Takahashi et al 2018).* A meta-analysis of 13 clinical studies also confirmed the efficacy of Cialis in improving LUTS associated with BPH and treating erectile dysfunction over 12 weeks *(Wang et al 2018).*

Combination Therapy with a PDE5 Inhibitor

- A randomized, double-blind trial showed combination therapy with a 5-α reductase inhibitor, finasteride, combined with the PDE5 inhibitor, Cialis, was associated with modest improvements in urinary symptoms and significantly improved patient, but not clinician, global impression of improvement when compared with finasteride monotherapy *(Casabe et al 2014).*
- A meta-analysis demonstrated that combination therapy with a PDE5 inhibitor and an α_1-adrenergic blocking agent statistically significantly improved IPSS, international index of erectile function (IIEF) score, and Q_{max} compared to an α_1-adrenergic blocking agent alone *(Gacci et al 2012).*
- A randomized controlled trial with a primary objective of evaluating the occurrence of dizziness when tadalafil was added to α_1-adrenergic blocking therapy demonstrated that changes in hemodynamic signs and symptoms were similar for tadalafil- and placebo-treated patients. There was a trend toward increased hemodynamic signs and symptoms in men treated with concomitant tadalafil and non-uroselective α_1-adrenergic blocking agents. Notably, this study did not demonstrate increased effectiveness with the combination therapy compared to α_1-adrenergic blocking agent monotherapy, with an IPSS reduction of 2.2 in the tadalafil group and 1.33 in the placebo group (p = 0.13) *(Goldfischer et al 2012).*

CLINICAL GUIDELINES

- The American Urological Association guideline has noted no differences in efficacy among doxazosin, tamsulosin, terazosin and alfuzosin in the management of BPH *(McVary et al 2011).* The European Association of Urology guideline notes that all α_1-adrenergic blocking agents have similar efficacy at appropriate doses *(Gravas et al 2017).*
- The American Urological Association guideline notes that there is no evidence to suggest that the clinical efficacy of 5-α reductase inhibitors differs when used for the appropriate indication *(McVary et al 2011).* Similarly, the European Association of Urology guideline notes that available evidence indicates that dutasteride and finasteride are equally effective in the treatment of LUTS *(Gravas et al 2017).*
- The American Urological Association guideline currently does not have a recommendation for the place in therapy for PDE5 inhibitors *(McVary et al 2011)*; however, the European Association of Urology guideline suggests that PDE5 inhibitors are effective for reducing moderate-to-severe LUTS symptoms *(Gravas et al 2017).*

SAFETY SUMMARY

- Alpha $(\alpha)_1$-adrenergic blocking agents:
  - Use of α_1-adrenergic blocking agents may lead to intraoperative floppy iris syndrome during cataract and glaucoma surgery and warrant modification in surgical techniques as needed.
  - Orthostatic hypotension may occur with all agents, but is more common with doxazosin, prazosin and terazosin, especially after the first dose.
  - Doxazosin, prazosin, and Cardura XL are contraindicated in patients with hypersensitivity to quinazolines (eg, prazosin, terazosin).
  - Use of α_1-adrenergic blocking agents has been associated with priapism. Patients must be advised about the seriousness of this condition.
  - Tamsulosin may cause serious allergic reactions in patients allergic to sulfa.
  - Silodosin and alfuzosin are contraindicated in patients with severe hepatic impairment and in those who are taking strong cytochrome P450 (CYP) 3A4 inhibitors. Tamsulosin also should not be used with strong CYP3A4 inhibitors.
  - Silodosin is contraindicated in patients with creatinine clearance of less than 30 mL/minute. Silodosin may also increase the risk of QT prolongation. Silodosin should not be used with concurrent strong inhibitors of P-glycoprotein.
- Five-alpha (5-α)-reductase inhibitors:

- Dutasteride and finasteride are contraindicated in women who are pregnant or have child-bearing potential; these agents should also be avoided in pediatric patients.
- These agents may increase the risk of high-grade prostate cancer. Since these agents can decrease plasma prostate specific antigen (PSA) levels, a new PSA baseline should be obtained after at least 3 months of therapy and used for monitoring of prostate cancer.
- Blood donation should be avoided during and for at least 6 months after therapy discontinuation.

- PDE5 inhibitors:
  - Cialis is contraindicated with regular or intermittent use of any form of organic nitrates. Cialis should not be used in patients using a guanylate cyclase inhibitor, such as riociguat.
  - Cialis may cause vasodilation and should be used with caution with alcohol and avoided in patients with preexisting cardiac conditions.
  - The lowest PDE5 inhibitor dose should be used when starting therapy with concurrent α_1-adrenergic blocking agents due to the risk of additive hypotension, although the manufacturer of Cialis recommends against its use with concurrent α_1-adrenergic blocking agents for the treatment of BPH.
  - Patients should be advised to stop Cialis and seek immediate medical attention if they experience sudden hearing or vision loss, which could be a sign of nonarteritic anterior ischemic optic neuropathy (NAION). In patients with a history of NAION, Cialis should be used only if benefits outweigh the risks.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single Entity Agents: a_1-Adrenergic Blocking Agents				
Cardura (doxazosin)	Tablets	Oral	Daily	Not recommended in severe hepatic impairment. Use with caution and monitor blood pressure for hypotensive symptoms in mild or moderate hepatic impairment.
Cardura XL (doxazosin extended-release)	Tablets (extended-release)	Oral	Daily	
Minipress (prazosin)	Capsules	Oral	Twice daily	
Flomax (tamsulosin)	Capsule	Oral	Daily	Should be taken 30 minutes following the same meal each day.
Hytrin (terazosin)	Capsules	Oral	Daily at bedtime	Dosage adjustment may be required in hepatic impairment.
Rapaflo (silodosin)	Capsules	Oral	Daily	Contraindicated in severe renal and/or hepatic impairment. Dosage adjustment required in moderate renal impairment.
Uroxatral (alfuzosin)	Tablet (extended-release)	Oral	Daily	Contraindicated in moderate to severe hepatic impairment. Use with caution in severe renal impairment.
Single Entity Agents – 5-α-Reductase Inhibitors				
Avodart (dutasteride)	Capsule	Oral	Daily	Pregnancy Category X*†
Proscar (finasteride)	Tablet	Oral	Daily	Pregnancy Category X*† Use with caution in hepatic impairment.
Single Entity Agents – PDE5 Inhibitors				
Cialis (tadalafil)	Tablets	Oral	Daily	Dosage adjustment may be required in renal and/or hepatic impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Combination Product				
Jalyn (dutasteride/tamsulosin)	Capsule	Oral	Daily	Pregnancy Category X*† Should be taken 30 minutes following the same meal each day.

*Pregnancy Category X = contraindicated in pregnant women due to evidence of fetal abnormalities from adverse effects data from investigational or marketing experience. Risks of use of the drug in pregnant women clearly outweigh potential benefits.
†Not indicated for use in women.
See the current prescribing information for full details.

CONCLUSION

- BPH contributes to LUTS such as increased frequency of urination, nocturia, urinary hesitancy, and weak urinary streams *(Cunningham et al 2017a, McVary et al 2011).*
- Current treatment options include watchful waiting, surgical interventions and pharmacological therapies *(McVary et al 2011).*
- Alpha$_1$-adrenergic blocking agents are the most widely used agents for the management of BPH *(McVary et al 2011).*
  - Cardura (doxazosin), Minipress (prazosin), and Hytrin (terazosin) are non-uroselective and are associated with a higher risk of orthostatic hypotension; therefore, therapy should be started at the lowest possible dose and titrated to the maximally tolerated dose.
  - Flomax (tamsulosin), Rapaflo (silodosin), and Uroxatral (alfuzosin) are uroselective and are therefore associated with a lower risk of orthostatic hypotension.
  - The American Urological Association treatment guideline and a meta-analysis have indicated no differences in efficacy among doxazosin, tamsulosin, terazosin, and alfuzosin in the management of BPH *(Djavan et al 1999, McVary et al 2011).*
  - Silodosin was also shown to be similarly effective to tamsulosin in improving IPSS and LUTS secondary to BPH *(Choo et al 2014, Cui et al 2012, Jung et al 2017, Miyakita et al 2010, Shirakawa et al 2013, Watanabe et al 2011).*
- The 5-α-reductase inhibitors are FDA-approved for the management of BPH symptoms in men with an enlarged prostate and may be used to prevent clinical progression of BPH *(McVary et al 2011).*
  - Avodart (dutasteride) and Proscar (finasteride) are teratogenic and contraindicated in women. Therapy may increase the risk of high-grade prostatic cancer; therefore, evaluation for prostatic cancer should be performed prior to initiation of therapy and periodically during treatment.
  - Clinical trials have shown no significant differences between dutasteride and finasteride in reducing prostate volume and improving LUTS and maximum flow rate in men with BPH *(Nickel et al 2011).*
  - When compared to α$_1$-adrenergic blocking agents, 5-α-reductase inhibitors were associated with a slower onset of improvement in BPH symptoms *(Lee 2002).*
- Combination therapy with an α$_1$-adrenergic blocking agent and a 5-α-reductase inhibitor may be used in men with an enlarged prostate *(McVary et al 2011).*
  - In men with an enlarged prostate, combination therapy may lead to improved symptom control compared to monotherapy with either an α$_1$-adrenergic blocker or a 5-α reductase inhibitor *(Kaplan et al 2006).* However, available data are inconsistent in this area, with another study demonstrating symptom control with combination therapy to be no better than with α$_1$-adrenergic blocker monotherapy *(Kirby et al 2003b).*
  - Jalyn (dutasteride/tamsulosin) has been shown to reduce the risk of acute urinary retention or BPH-related surgery compared to tamsulosin monotherapy and watchful waiting (*Becher et al 2009, Roehrborn et al 2015).*
- Cialis (tadalafil), a PDE5 inhibitor, was approved by the FDA for the management of BPH. The American Urological Association treatment guideline currently does not have a recommendation for the place in therapy for PDE5 inhibitors *(McVary et al 2011)*; however, the European Association of Urology treatment guideline suggests that PDE5 inhibitors are effective in patients with moderate-to-severe LUTS *(Gravas et al 2017).*
  - Cialis may cause hypotension and should not be administered within 48 hours of nitrate use.
  - Three meta-analyses and several other clinical studies have shown that Cialis was safe and effective in improving IPSS and LUTS secondary to BPH in men with or without concomitant erectile dysfunction *(Broderick et al 2010, Dmochowski et al 2013, Donatucci et al 2011, Egerdie et al 2012, Gacci et al 2012, Gacci et al 2016, Goldfischer et al 2012, Oelke et al 2012, Porst et al 2011, Roehrborn et al 2008, Takahashi et al 2018, Wang et al 2018).*

- Combination therapy with the 5-α reductase inhibitor finasteride and Cialis was associated with modest improvements in urinary symptoms and significantly improved patient, but not clinician, global impression of improvement when compared with finasteride monotherapy *(Casabe et al 2014).* Guidance has been added to the Cialis prescribing information regarding dosing for this combination.

- Currently, Avodart, Cardura, Minipress, Flomax, Hytrin, Jalyn, Proscar, and Uroxatral are available generically. The brand product for Hytrin is no longer on the market; the product is only available generically.

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Publication Date: March 26, 2018

Therapeutic Class Overview
Injectable Anticoagulants

INTRODUCTION

- Venous thromboembolism (VTE) can lead to significant health problems, which may become potentially fatal. It may occur in young, otherwise healthy adults, although it often occurs in patients who sustain multiple traumas, undergo major surgery, are immobile for a lengthy period of time, or have a hypercoagulable disorder (such as cancer). Due to clot formation within the venous circulation, VTE manifests as a stroke, deep vein thrombosis (DVT) and/or a pulmonary embolism (PE). The disease is often clinically silent, and death from PE can occur within minutes after the onset of symptoms, before treatment can be given (*Blann et al 2006*).
- The estimated incidence of VTE is 300,000 to 600,000 annually. This estimate is considered to be an underestimate due to missed or wrong diagnoses, also data is ≥ 10 years old. The VTE incidence is similar or higher among African Americans and lower among Asian Americans and Native Americans than among whites. Most PE deaths are sudden and both DVTs and PEs are usually attributed to underlying diseases (eg, cancer, other chronic heart, lung, or renal disease) (*Benjamin et al 2018)*.
- Stroke also causes significant morbidity and mortality. Stroke is the fifth leading cause of death after heart disease, cancer, chronic lower respiratory disease, and injuries/accidents. Each year, approximately 795,000 people experience a new or recurrent stroke. Of all strokes, 87% are ischemic, 10% are intracerebral hemorrhage (ICH) strokes, and 3% are subarachnoid hemorrhage (SAH) strokes (*Benjamin et al 2018*).
- The injectable anticoagulants include Arixtra, Fragmin, Lovenox, and unfractionated heparin (UFH) and, in general, are Food and Drug Administration (FDA)-approved for prophylaxis and/or treatment of VTE.
  - Certain agents in the class are also FDA-approved for the treatment of acute ST-segment elevation myocardial infarction (STEMI) or for prophylaxis of ischemic complications in unstable angina (UA) and non-Q-wave MI.
  - Additional labeled indications for use of UFH include disseminated intravascular coagulation, prophylaxis and treatment of arterial embolism, use in blood transfusions, extracorporeal circulation, and dialysis procedures. Heparin is also used as an anticoagulant for several other off-label indications (*Micromedex 2018*).
- UFH is a mucopolysaccharide molecule that ranges in molecular weight from 3,000 to 30,000 daltons. Its primary effect as an anticoagulant is a result of its binding to antithrombin which inhibits clot formation. Additional anticoagulant effects of UFH include inhibition of factors (F) IIa (thrombin), Xa, IXa, XIa, and XIIa (*Garcia et al 2012*).
- Fragmin and Lovenox are classified as low molecular weight heparins (LMWH) and exert their anticoagulant effect by binding to antithrombin, an endogenous inhibitor of various activated clotting factors, including FXa and thrombin.
  - LMWH is a smaller fragment of UFH that is formed by enzymatic or chemical depolymerization processes. The difference in the average size of LMWH (5,000 daltons) compared to UFH contributes to the pharmacologic differences between the agents. The LMWH agents primarily inhibit FXa, and do so with much less effect on thrombin compared to UFH. The inhibition of thrombin requires a heparin molecule to bind simultaneously to antithrombin and thrombin to form a ternary complex. The UFH molecules are large enough for this while the LMWH molecules typically are not (*Hirsh et al 2008, Weitz1997*).
- Because the LMWH agents are prepared using different methods of depolymerization, they differ somewhat in their pharmacokinetic properties and anticoagulant profiles. Therefore, these agents are not clinically interchangeable (*Hirsh et al 2008*).
- Arixtra is a synthetic, selective FXa inhibitor that was developed to have an increased affinity to antithrombin. Its specific anti-FXa activity is higher than that of the LMWH agents (*Hirsh et al 2008*).
- Medispan class: Anticoagulants; Heparins and Heparinoid-like agents

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Arixtra (fondaparinux)	✔
Fragmin (dalteparin)	-
Heparin Sodium (unfractionated heparin)	✔
Lovenox (enoxaparin)	✔

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

- In general, the injectable anticoagulants are FDA-approved for prophylaxis and/or treatment of VTE. The labeled indications for Arixtra, Fragmin, and Lovenox are more specific than the labeled indications for UFH. However, UFH is considered an option for a number of off-label uses, including UA, NSTEMI, STEMI, and bridging in patients with atrial fibrillation (AF) and mechanical heart valves, by various guidelines.
- For most indications, UFH is administered IV; however, the subcutaneous (SC) route can be used for prophylaxis and/or treatment of VTE.
- Both Lovenox and Fragmin are approved for prophylaxis of ischemic complications in UA and non-Q-wave MI.
- Fragmin is the only LMWH agent that is not approved for the treatment of acute VTE, yet it is the only agent in the class that is approved for the extended treatment of symptomatic VTE in patients with cancer.

Table 2. Food and Drug Administration Approved Indications

Indication	Arixtra (fondaparinux)	Fragmin (dalteparin)	Heparin sodium (unfractionated heparin)	Lovenox (enoxaparin)
Treatment of acute DVT with or without PE	✔ ‡			✔ *
Treatment of acute STEMI managed medically or with subsequent percutaneous coronary intervention (PCI)				✔ §
Prophylaxis of ischemic complications in UA and non-Q-wave MI		✔ ¶		✔ ¶
Extended treatment of symptomatic VTE (proximal DVT and/or PE) in patients with cancer		✔ ‖		
Prophylaxis and treatment of venous thrombosis and PE			✔	
Prophylaxis and treatment of thromboembolic complications associated with AF			✔	
Treatment of acute and chronic consumption coagulopathies (disseminated intravascular coagulation)			✔	
Prevention of clotting in arterial and cardiac surgery			✔	
Prophylaxis and treatment of peripheral arterial embolism			✔	
Anticoagulant use in blood transfusions, extracorporeal circulation, and dialysis procedures			✔	
Prophylaxis of DVT				
Medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness		✔		✔

Indication	Arixtra (fondaparinux)	Fragmin (dalteparin)	Heparin sodium (unfractionated heparin)	Lovenox (enoxaparin)
Patients undergoing abdominal surgery who are at risk for thromboembolic complications	✔	✔		✔
Patients undergoing hip fracture surgery	✔ †			
Patients undergoing hip replacement surgery	✔	✔		✔ #
Patients undergoing knee replacement surgery	✔			✔
Limitations of use				
Not indicated for the acute treatment of VTE		✔		

*Indicated for inpatient treatment of acute DVT with or without PE, when administered in conjunction with warfarin, and for outpatient treatment of acute DVT without PE when administered in conjunction with warfarin.
†Including extended prophylaxis.
‡When administered in conjunction with warfarin.
§When administered in conjunction with aspirin when initial therapy is administered in the hospital.
‖In these patients therapy begins with the initial VTE treatment and continues for 6 months.
¶When concurrently administered with aspirin therapy.
#During and following hospitalization.
††When administered concurrently with aspirin, enoxaparin has been shown to reduce the rate of the combined endpoint of recurrent MI or death in patients with acute STEMI receiving thrombolysis and being managed medically or with percutaneous coronary intervention.

(Prescribing information: Arixtra 2017, Fragmin 2017, Lovenox 2017, Lovenox (preservative-free) 2017, Heparin sodium 2017)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The evidence demonstrating the safety and efficacy of the injectable anticoagulants in FDA-approved indications is well established, and as mentioned previously, clinical guidelines support the use of these agents for these indications. Patients experiencing an acute coronary syndrome will generally receive treatment with an injectable anticoagulant in an acute hospital setting as recommended per current clinical guidelines (*Levine et al 2011, O'Gara et al 2013, Guyatt et al 2012*). When compared to UFH and placebo, LMWH was found to be superior or comparable to UFH treatment in patients with acute coronary syndrome.
- Currently, Fragmin is the only injectable anticoagulant approved for the extended treatment of VTE in patients with cancer. In a trial comparing Fragmin to oral anticoagulation (warfarin or acenocoumarol [not available in the United States]) in patients with symptomatic VTE, the incidence of symptomatic, recurrent VTE was significantly lower with Fragmin at 6 months. At 6 months, there was no difference in mortality rates between the 2 treatments; however, a 12 month follow-up revealed a significant benefit in mortality with Fragmin in patients without known metastases of their cancer (*Lee et al 2003, Lee et al 2005*). The DALTECAN study found that the frequency of major bleeding events was lower during months 6 through 12 as compared to the first 6 months of Fragmin therapy in patients with cancer (*Francis et al 2015*). A Cochcrane review comparing LMWH, UFH, and Arixtra for VTE treatment in cancer patients found that LMWH may possibly be superior to UFH in reducing mortality at 3 months but it doesn't ensure a clinically significant decrease in VTE recurrence (*Hakoum et al 2018*). An AHRQ Comparative Effectiveness Review found for the minority of patients at low or intermediate risk of recurrent ischemia, MI, or death, an initial conservative approach is recommended as Lovenox reduced composite ischemic events and MI with mixed effects on bleeding when compared to UFH or Arixtra (*Melloni et al 2013*).
- The evidence establishing the safety and efficacy of the injectable anticoagulants for VTE treatment and/or thromboprophylaxis is well established. Several placebo-controlled trials, meta-analyses (MAs), and systematic reviews (SRs) with the various injectable anticoagulants in medical patients, immobilized patients, and those undergoing orthopedic surgery have been conducted and consistently demonstrate their efficacy (*Alikhan et al 2003, Bergqvist et al 1996, Bergqvist et al 2002, Eriksson et al 2003, Fuji et al 2008, Hull et al 2010, Lassen et al 1998, Leizorovicz et al 2004, Michot et al 2002, Planes et al 1996, Samama et al 1999, Testroote et al 2014, Torholm et al 1991, Uchino et al 2012, Anderson et al 2013*). When the injectable anticoagulants are compared to other methods of treatment and

thromboprophylaxis which include heparin, UFH, aspirin, and warfarin, “superiority” in terms of recurrent VTE and safety is not always consistent, which supports recommendations from current clinical guidelines (*Andras et al 2012, Bhutia et al2013, Colwell et al1994, Colwell et al1999, Cook et al 2011, De et al 2010, DeCarolis et al 2012, Eriksson et al 1991, Erkens et al 2010, Ferres et al 2011, Fitzgerald et al 2001, Francis et al 1997, Handoll et al 2002, Kanaan et al 2007, Kleber et al 2003, Leclerc et al 1996, McLeod et al 2001, No authors listed 1991, Othieno et al 2007, Rasmussen et al 2009, Salazar et al 2010, Senaran et al 2006, Anderson et al 2013, Akl et al 2014*). For treatment and thromboprophylaxis in these patients, any of these options may be appropriate; however, LMWH or low-dose UFH are generally suggested in preference to the other agents recommended as alternatives (*Guyatt et al 2012*). In a recent update to a Cochrane review comparing fixed dose LMWH with adjusted dose IV or SC UFH for initial VTE treatment, LMWH reduced the incidence of both recurrent VTE and major hemorrhage compared to UFH. Additionally, low-quality evidence suggested that LMWH also reduced the thrombus size compared to UFH. No difference in overall mortality was observed (*Robertson et al 2017*).

- Although data comparing the LMWH agents to Arixtra has not demonstrated significant “superiority” for one therapy in all outcomes, treatment with Arixtra appears to be associated with a lower incidence of VTE, and the incidence of major bleeding compared to Lovenox has had mixed reports (*Bauer et al 2001, Eriksson et al 2001, Lassen et al 2002, Turpie et al 2002b*). In a MA of randomized-controlled trials (RCTs) comparing Arixtra to LMWH therapy (Lovenox), the incidence of VTE was significantly less and the incidence of major bleeding was significantly greater with Arixtra (*Turpie et al 2002a*). One MA/SR assessed the peri-operative use of Arixtra vs Lovenox in patients with acute coronary syndrome and found that mortality was similar between groups after a 10 day (Odds ratio [OR], 1.05; P = 0.84) and 30 day follow-up (OR, 0.90; P = 0.66); however, major bleeding was significantly lower with Arixtra after a 10 day (OR, 0.46; P = 0.0001) and 30 day follow-up (OR, 0.49; P = 0.03) (*Bundhun et al 2017*). Another trial noted no difference between Arixtra and Fragmin for the incidence of VTE and major bleeding (*Agnelli et al 2005*).

CLINICAL GUIDELINES

- In general, recommendations from other clinical guidelines for other populations are in line with the American College of Chest Physicians (ACCP) guidelines (*AAOS 2011, Amsterdam et al 2014, Levine et al 2011, Kernan et al 2014, Guyatt et al 2012, Jaff et al 2011, Bushnell et al 2014, Lyman et al 2015, O’Gara et al 2013, January et al 2014, Kernan et al 2014, Mazzolai et al 2017, Powers et al 2018*). Treatment recommendations vary according to the indication.
  - For orthopedic (eg, total hip or knee replacement) surgery, the American Academy of Orthopedic Surgeons (AAOS) does not recommend a specific medication (*AAOS 2011*). The ACCP does favor LMWH over Arixtra, Eliquis, Xarelto, or UFH (*Guyatt et al 2012*).
  - For non-orthopedic (eg, general and abdominal-pelvic surgery) surgical patients requiring thromboprophylaxis who are at moderate to high risk for VTE and who are not at high risk for bleeding complications, LMWH and low dose UFH are both recommended as options (*Guyatt et al 2012*).
  - In patients with UA, NSTEMI, or STEMI, the American College of Cardiology (ACC) recommends anticoagulant therapy for a minimum of 48 hours and up to 8 days or until revascularization is performed in patients undergoing reperfusion. The recommended treatment options include UFH, Lovenox and Arixtra (*O’Gara et al 2013, Kernan et al 2014*). For those patients undergoing PCI, Lovenox, Arixtra, or UFH are recommended by most reputable guidelines. However, Arixtra should not be used as the sole anticoagulant administered due to risk of catheter thrombosis (*Amsterdam et al 2014, Levine et al 2011*). Bridging therapy with UFH or LMWH is recommended for patients with AF and a mechanical heart valve undergoing procedures or for various procedures (*January et al 2014*).
  - In acutely ill hospitalized (ie, non-surgical) patients at increased risk of thrombosis, LMWH, low dose UFH, and Arixtra are recommended (*Guyatt et al 2012*).
  - For acute VTE (eg, DVT or PE), LMWH or Arixtra is preferred over UFH (*Guyatt et al 2012, Lyman et al 2015*). For chronic management of VTE in patients with cancer, the American Society of Clinical Oncology (ASCO) guideline recommends LMWH for the initial 6 months due to its improved efficacy over warfarin. The guideline states that warfarin is an acceptable alternative for long-term therapy if LMWH is not readily available (*Lyman et al 2015*). The most recent ACCP guidelines recommend Pradaxa (dabigatran), Xarelto (rivaroxaban), Eliquis (apixaban), or Savaysa (edoxaban) over warfarin for long-term VTE therapy (*Kearon et al 2016*). They also recommend warfarin over LMWH; however, LMWH is preferred in patients with cancer. In patients with a VTE recurrence while on warfarin, Pradaxa, Xarelto, Eliquis, or Savaysa, treatment with a LMWH is recommended. Duration of anticoagulation after treatment of an acute thromboembolic event will depend on whether the patient was currently receiving

anticoagulation therapy, if the event was provoked or unprovoked and/or caused by surgery or a nonsurgical transient risk factor, and if it was the first or second thromboembolic event (*Guyatt et al 2012*).
  - In general, pregnant women and women who are breast-feeding with a high-risk condition that would require anticoagulation outside of pregnancy, it is reasonable to use UFH, or LMWH (*Bushnell et al 2014, Kernan et al 2014*).
  - Patients with mechanical heart valves, AF, or VTE at high risk of developing thromboembolism, whose oral anticoagulation therapy is to be interrupted prior to an invasive procedure, would require bridging therapy with LMWH or UFH. Providers need to carefully consider risks and benefits of bridging in patients with the above mentioned conditions and moderate risk for thromboembolism. No bridging is indicated for patients at low risk for thromboembolism (*Douketis et al 2012, Douketis et al 2015, Clark et al 2015*).
  - In patients with acute ischemic stroke, urgent anticoagulation with the goal of preventing early recurrent stroke, stopping neurological worsening, or improving outcomes after an acute ischemic stroke is not recommended. The benefit of urgent anticoagulation in some patients may be warranted; however, use is not well established. In patients undergoing DVT prophylaxis after an acute ischemic stroke when prophylactic anticoagulation is used, the use benefit of prophylactic LMWH over prophylactic UFH is uncertain (*Powers et al 2018)*.

SAFETY SUMMARY

- A boxed warning exists for the injectable anticoagulants (eg, Arixtra, Fragmin, and Lovenox) warning of spinal or epidural hematomas when anticoagulated with LMWH or heparinoids and in patients who are receiving neuraxial anesthesia or undergoing spinal puncture. Optimal timing between the administration of Arixtra, Fragmin or Lovenox and neuraxial procedures is not known.
- The injectable anticoagulants (ie, Arixtra, Fragmin, and Lovenox) are contraindicated with active major bleeding. These agents are associated with an increased risk of bleeding and hemorrhage; therefore, use with caution in conditions with increased risk of hemorrhage. In addition, thrombocytopenia can occur with these agents. Lovenox, UFH, and Fragmin are contraindicated in patients with hypersensitivity to heparin or pork products.
- Arixtra is also contraindicated in patients with bacterial endocarditis, thrombocytopenia in the presence of Arixtra, patients with body weight of less than 50 kg if using it for VTE prophylaxis, and in patients with CrCL less than 30 mL/min when using it for treatment or prophylaxis of VTE.
- Contraindications to the use of UFH include severe thrombocytopenia, and uncontrolled active bleeding unless it is due to disseminated intravascular coagulation.
- Lovenox is contraindicated in patients with a history of hepain-induced thrombocytopenia (HIT) within the past 100 days. Lovenox is contraindicated in patients with hypersensitivity to benzyl alcohol.
- Fragmin is contraindicated in patients with a history of HIT or HIT with thrombosis. It is also not to be used for treatment of unstable angina and non-Q-wave MI or for prolonged VTE prophylaxis in patients undergoing Epidural/Neuraxial anesthesia.
- All injectable anticoagulants warn of drug interactions with medications that may enhance the risk of hemorrhage, which should be discontinued prior to initiation of therapy with any of the injectable anticoagulants, unless these medications are essential. However, in clinical trials, Arixtra in combination with oral anticoagulants, platelet inhibitors, nonsteroidal anti-inflammatory drugs, and digoxin did not significantly affect the pharmacokinetics and pharmacodynamics of any of the medications.
- Warnings and Precautions and adverse reactions associated with agents in class include:
  - Injection site reaction, rash, and fever as adverse events commonly observed; and serious adverse events include bleeding-related adverse events with Arixtra use. An increased bleeding risk is associated in patients with renal impairment and in patients with a low body weight (< 50 kg). Do not use Arixtra for VTE prophylaxis and treatment in patients with creatinine clearance (CrCL) < 30 mL/min or as prophylactic therapy in patients < 50 kg undergoing hip, abdominal, or knee surgery.
  - Injection site reaction, pain, and hematomas as adverse events commonly observed; and serious adverse events include anaphylaxis, abnormal liver function tests, and those bleeding-related adverse events with Fragmin use.
  - Gastrointestinal reactions, abnormal liver function tests, fever, thrombocytopenia, and bleeding-related events as adverse events commonly observed; and serious adverse events include AF, heart failure, dermatologic reactions, pneumonia, and those adverse events related to bleeding with Lovenox use.
  - Hemorrhage, thrombocytopenia, hypersensitivity, and local injection reactions with UFH use.
  - “Gasping syndrome,” characterized by CNS depression, metabolic acidosis, and gasping respirations, which is reported in infants and neonates due to the benzyl alcohol content in multiple-dose formulations of Fragmin and UFH.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Arixtra(fondaparinux)	Injection	SC	Once daily	Usual duration is 5 to 9 days; extended durations up to 24 additional days may be warranted for DVT prophylaxis after a hip fracture surgery. A total of 32 days (perioperative and extended prophylaxis) was administered in clinical trials. Administer 6 to 8 hours after surgery. A higher incidence of hemorrhage was observed in patients with moderate hepatic impairment. Caution in patients with CrCL 30 to 50 mL/min and use is contraindicated in CrCL < 30 mL/min.
Fragmin (dalteparin)	Injection	SC	Once or twice daily	Usual duration is 5 to 10 days; extended durations up to 6 additional months may be warranted. Administer 4 to 8 hours after surgery. Dosage reductions may be required in patients with cancer and acute symptomatic VTE who develop thrombocytopenia. Use caution with multiple-dose vials in pregnancy, nursing mothers and pediatric patients due to benzyl alcohol content. Monitor anti-Xa levels in patients with CrCL < 30 mL/min.
Heparin sodium (unfractionated heparin)	Injection (including benzyl alcohol and preservative-free formulations)	IV, SC	Once to 6 times daily; continuous infusion or as needed use may also be warranted.	Dosing recommendations are based on a 68 kg patient. The preservative-free formulation should be used in pregnancy, nursing mothers, neonates, and infants to avoid benzyl alcohol toxicity. Caution should be exercised in patients with severe renal impairment

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				or liver disease due to an increased risk of hemorrhage.
Lovenox (enoxaparin)	Injection	IV, SC	Once or twice daily	Usual duration is 2 to 11 days; extended durations of up to 17 days have been studied in trials. Multiple-dose vials are not approved for use in neonates and infants due to the benzyl alcohol content. Pregnant women and nursing mothers should use preservative-free formulations, when available. For IV administration, Lovenox can be mixed with normal saline solution or 5% dextrose in water.

See the current prescribing information for full details

CONCLUSION

- The injectable anticoagulants include UFH, LMWH agents (ie, Fragmin, Lovenox) and FXa inhibitors (ie, Arixtra). The primary effect of UFH as an anticoagulant is a result of its binding to antithrombin which inhibits clot formation. Additional anticoagulant effects of UFH include inhibition of FIIa (thrombin), Xa, IXa, XIa, and XIIa (*Garcia et al, 2012*). The FXa inhibitors and LMWH agents work by binding to antithrombin, causing inhibition of the clotting factors, thrombin and FXa. These agents have a greater inhibitory effect on FXa compared to thrombin (*Hirsh et al 2008, Weitz 1997*).
- Because the LMWH agents are prepared using different methods of depolymerization, the various agents in this class differ and are not clinically interchangeable (*Hirsh et al 2008*).
- Currently, Arixtra, UFH, and Lovenox are available generically (*Micromedex 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*).
- In general, the injectable anticoagulants are FDA-approved for prophylaxis and/or treatment of VTE. Certain agents in the class are also FDA-approved for the treatment of acute STEMI or for prophylaxis of ischemic complications in UA and non-Q-wave MI; however, treatment for these indications will most likely be initiated in an acute hospital setting.
- UFH is considered an option for a number of off-label uses, including UA, NSTEMI, STEMI and use during PCI, by various guidelines. For most indications, UFH is administered IV; however, the SC route can be used for prophylaxis and/or treatment of VTE. For prophylaxis, the SC dose is administered 2 or 3 times daily and for treatment, the SC dose is administered twice daily.
- Outpatient or inpatient administration of the injectable anticoagulants for prophylaxis and treatment of VTE may be appropriate depending on the specific clinical situation. The most recent ACCP guidelines recommend Pradaxa, Xarelto, Eliquis, or Savaysa over warfarin for long-term VTE therapy (*Kearon et al 2016*). They also recommend warfarin over LMWH; however, LMWH is preferred in patients with cancer.
- Evidence from clinical trials and recommendations from clinical guidelines support the use of the injectable anticoagulants in FDA-approved indications.
- Several placebo-controlled trials have consistently demonstrated the efficacy of the injectable anticoagulants, but when compared to other methods of anticoagulation (eg, heparin, rivaroxaban, UFH, warfarin), their superiority in terms of recurrent VTE and safety has not always been demonstrated (*Alikhan et al 2003, Andras et al 2012, Bergqvist et al 1996, Bergqvist et al 2002, Brookenthal et al 2001, Colwell et al 1994, Colwell et al 1999, Cook et al 2013, De et al 2010, Eriksson et al 1991, Eriksson et al 2008, Erkens et al 2010, Fitzgerald et al 2001, Francis et al 1997, Fuji et al 2008, Handoll et al 2002, Hull et al 2010, Kakkar et al 2008, Kanaan et al 2007, Bauersachs 2010, Büller 2012, Kleber et al 2003, Anderson et al 2013, Lassen et al 1998, Lassen et al 2008, Leclerc et al 1996, Leizorovicz et al 2004, McLeod et al 2001, Michot et al 2002, No authors listed 1991, Othieno et al 2007, Planes et al 1996, Rasmussen et al 2009, Salazar et al 2010, Samama et al 1999, Senaran et al 2006, Torholm et al 1991, Turpie et al 2009, Uchino et al*

2012, Melloni et al 2013, van der Heijden 2001, Akl et al 2014). In a recent update to a Cochrane review comparing fixed dose LMWH with adjusted dose IV or SC UFH for initial VTE treatment, LMWH reduced the incidence of both recurrent VTE and major hemorrhage compared to UFH. Additionally, low-quality evidence suggested that LMWH also reduced the thrombus size compared to UFH. No difference in overall mortality was observed (*Robertson et al 2017*).

- When comparing Arixtra to the LMWH agents, treatment with Arixtra has demonstrated superiority in terms of the incidence of VTE in the majority of clinical trials; however, the risk of major bleeding is not clear (*Agnelli et al 2005, Bauer et al 2001, Bauer et al 2002, Bundhun et al 2017, Eriksson et al 2001, Eriksson et al 2003, Lassen et al 2002, Turpie et al 2002, Turpie AG et al 2002*). Data from 2 clinical trials revealed no difference between treatment with Arixtra compared to Fragminand Lovenox in the development of VTE (*Eriksson et al 2003, Turpie et al, 2002*).
- One trial revealed no difference between Fragmin compared to UFH treatment in critically ill patients in decreasing the incidence of proximal DVT; however, the trial found a statistically lower incidence of PE (definite or probable) with Fragmin. This result did require a large number needed to treat of 111 patients in order to achieve this outcome (*Cook et al 2011*).
- In terms of safety measures, 1 trial comparing patients who were given Lovenox with moderate renal impairment to those with normal renal function resulted in significantly more major bleeds in patients with moderate renal impairment (*DeCarolis et al 2012*). In women who met criteria for thromboprophylaxis (patients at high-risk for VTE) after cesarean, 1 study resulted in a greater proportion of women who had wound separation when given Lovenox compared to those women who were not given Lovenox (*Ferres et al 2011*).

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Publication Date: March 28, 2018

Therapeutic Class Overview
Oral Anticoagulants

INTRODUCTION

- The oral anticoagulants include Bevyxxa (betrixaban), Eliquis (apixaban), Pradaxa (dabigatran), Savaysa (edoxaban), Xarelto (rivaroxaban), and warfarin (Coumadin, Jantoven).
- Warfarin has been the principal oral anticoagulant for more than 60 years and has extensive, well established data demonstrating its safety and efficacy. However, warfarin is associated with challenges including a slow on- and offset of action, unpredictable variability in response, a narrow therapeutic window, frequent monitoring, and numerous food and drug interactions. In addition, maintenance of a therapeutic level of anticoagulation may be difficult for patients and requires a good understanding of the pharmacokinetic and pharmacodynamic properties of warfarin.
- Four target-specific oral anticoagulants (TSOACs), Eliquis, Pradaxa, Savaysa, and Xarelto, are indicated for the reduction of stroke and systemic embolism in non-valvular atrial fibrillation (NVAF) and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), otherwise known as events caused by a venous thromboembolism (VTE). Pradaxa, Xarelto, and Eliquis are indicated for the reduction in the risk of recurrence of DVT and PE. Pradaxa, Xarelto, and Eliquis are indicated for DVT and PE prophylaxis in patients undergoing hip replacement surgery and Xarelto and Eliquis have further indications for knee replacement surgery. Bevyxxa is the only agent in class indicated for patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE.
- Atrial fibrillation (AF) is one of the most common cardiac arrhythmias in the US, affecting approximately 2.7 to 6.1 million people in 2010. AF has been associated with death either directly or cited as an underlying cause contributing to mortality. Stroke is the most concerning complication of AF. AF is associated with a 5-fold increased risk of stroke throughout all ages (*Benjamin et al 2018*). Approximately 5 to 8% of patients who require percutaneous coronary intervention (PCI) with stents have AF (*Gibson et al 2016*).
- In patients with AF, oral anticoagulants are recommended for those who are at an intermediate or greater risk of stroke and selection should be based on individual patient characteristics (*Anderson et al 2013, Bushnell et al 2014, Culebras et al 2014, Doherty et al 2017, Furie et al 2012, Guyatt et al 2012, January et al 2014, Kernan et al 2014, Nishimura et al 2017, Otto et al 2017, Ravel et al 2017, Smith et al 2017*).
- VTE encompasses both DVT and PE. The precise number of people affected is unknown, but it is estimated to affect ~900,000 US patients (*CDC 2018*). Of those who suffer a DVT, approximately a third will have a recurrence within 10 years. Knee and hip replacement surgeries are associated with a high risk of VTE, which can lead to recurrent VTE events as well as post-thrombotic syndrome, and PE, which can be fatal. Without anticoagulant therapy, 40% to 50% of patients undergoing hip replacement surgery suffer VTE. This rises to 70% to 80% in hip fracture (*American Academy of Orthopaedic Surgeons [AAOS] 2011, Guyatt et al 2012, Kearon et al 2016*).
- Hospitalization is a risk factor for VTE with an estimated 22% of VTE occurrences following non-surgical hospital admissions (*Heit et al 2002*). Additionally, an estimated 4.6 per 1000 admissions are complicated by symptomatic VTE, which can lead to a higher risk of morbidity and mortality (*Zakai et al 2013*).
- Pharmacological anticoagulants available for the treatment of VTE (not due to orthopedic surgery) include parenteral anticoagulation (low molecular weight heparin [LMWH], fondaparinux, or intravenous [IV] or subcutaneous [SC] unfractionated heparin [UFH]) typically administered with warfarin, and the TSOACs (Xarelto, Eliquis, Pradaxa, or Savaysa) (*Guyatt et al 2012, Kearon et al 2016, Micromedex 2018*).
- Thromboprophylaxis is recommended to prevent VTE in patients undergoing total hip or knee replacement. Pharmacological anticoagulants available for the prophylaxis of VTE after orthopedic surgery include aspirin, LMWHs, warfarin, Pradaxa, and factor (F) Xa inhibitors (Arixtra [fondaparinux], Xarelto, or Eliquis) (*AAOS 2011, Guyatt et al 2012*).
- The oral anticoagulants work through varied mechanisms of action. Xarelto, Savaysa, Bevyxxa, and Eliquis are selective FXa inhibitors, while Pradaxa is a direct thrombin inhibitor. Warfarin is a vitamin K antagonist (VKA) that works by interfering with the synthesis of vitamin K dependent clotting factors. Vitamin K, therefore, serves as a reversal agent for warfarin.

- In 2015, the first TSOAC reversal agent, Praxbind (idarucizumab), was FDA-approved. Praxbind is indicated for the reversal of Pradaxa's anticoagulation effects as needed for emergency surgery, urgent procedures, and in life-threatening or uncontrolled bleeding (*Praxbind prescribing information 2015*).
- There are no specific antidotes for Bevyxxa, Eliquis, Savaysa or Xarelto. Andexxa (andexanet alfa) is an investigational agent that was submitted to the FDA for approval. Studies currently support use with Eliquis and Xarelto. In August 2016, the FDA issued a complete response letter (CRL) requesting additional information. In August 2017, Portola Pharmaceuticals announced that they re-submitted the biologics licensing application (BLA) addressing deficiencies noted in the CRL. In 2018, interim results from the ANNEXA-4, a Phase 3b/4 trial, were announced supporting reversal of anti-FXa activity when administered as a bolus and 120 minute infusion. The anticipated FDA decision date is May 4, 2018 (*Portola Pharmaceuticals press release 2018*).

- Medispan class: Anticoagulants; Thrombin Inhibitors - Dabigatran; Coumarin Anticoagulants; Direct FXa Inhibitors

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Bevyxxa (betrixaban)	-
Eliquis (apixaban)	-
Pradaxa (dabigatran)	-
Savaysa (edoxaban)	-
Xarelto (rivaroxaban)	-
Coumadin, Jantoven (warfarin)	✔

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Bevyxxa (betrixaban)	Eliquis (apixaban)	Pradaxa (dabigatran)	Savaysa (edoxaban)	Xarelto (rivaroxaban)	Coumadin Jantoven (warfarin)†
Prophylaxis and treatment of the thromboembolic complications associated with AF and/or cardiac valve replacement						✔
Prophylaxis and treatment of venous thrombosis and its extension, PE						✔
Reduce the risk of death, recurrent myocardial infarction (MI), and thromboembolic events such as stroke or systemic embolization after MI						✔
Reduce the risk of stroke and systemic embolism in patients with NVAF		✔	✔	✔ ‡	✔	
Prophylaxis of DVT, which may lead to PE, in patients undergoing knee (TKR) or hip (THR) replacement surgery		✔			✔	
Prophylaxis of DVT and PE in patients undergoing THR surgery			✔			
Treatment of DVT and PE		✔	✔ *	✔ *	✔	
Reduction in the risk of recurrence of DVT and PE following initial therapy		✔	✔		✔ ‖	
Prophylaxis of VTE in adult patients hospitalized for acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE	✔ §					

*Prior to treatment, patients should have been treated with parenteral anticoagulant for 5 to 10 days.
†Limitation of use: Warfarin has no direct effect on an established thrombus, nor does it reverse ischemic tissue damage.
‡Not indicated in NVAF patients with creatinine clearance (CrCL) > 95 mL/min due to increased rates of ischemic stroke.
§Limitation of use: Use has not been established in patients with prosthetic heart valves.
‖ Indicated after the completion of initial treatment lasting at least 6 months.

(*Prescribing information: Bevyxxa 2017, Coumadin 2016, Eliquis 2018, Jantoven 2011, Pradaxa 2018, Savaysa 2017, Xarelto 2018*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Warfarin has been the principal oral anticoagulant for more than 60 years and the evidence demonstrating the safety and efficacy in Food and Drug Administration (FDA)-approved indications is well established (*Aguilar 2005, Cundiff et al 2006, DiNisio et al 2012, Hutten 2006, Lopes et al 2013, Middeldorp et al 2014, Salazar et al 2010, Saxena 2004, van der Heijden et al 2001*).
- There is no direct comparator evidence of the TSOACs; therefore, caution should be exercised when drawing conclusions based on indirect data.

Non-valvular Atrial Fibrillation:

- Four large randomized controlled trials (RE-LY, ARISTOTLE, ENGAGE AF-TIMI 48, and ROCKET AF) were the basis for clinical efficacy and safety for Pradaxa, Eliquis, Savaysa, and Xarelto vs warfarin, respectively. Baseline populations varied for the Pradaxa, Eliquis, Savaysa, and Xarelto trials, with a mean proportion of 64%, 62%, 65%, and 55% time in therapeutic range (TTR) for warfarin patients and a mean baseline $CHADS_2$ score of 2.1, 2.1, 2.8, and 3.5, respectively (*Connolly et al 2009, Connolly et al 2011; Connolly et al 2014; Giugliano et al 2013; Granger et al 2011, Patel et al 2011*).
- The primary efficacy endpoint was stroke or systemic embolism, in which the following outcomes were reported:
  - Pradaxa was superior (relative risk [RR] for Pradaxa 150 mg twice daily vs warfarin, 0.66 [95% confidence interval {CI}, 0.53 to 0.82], P < 0.001).
  - Eliquis was superior (hazard ratio [HR] for Eliquis 5 mg twice daily vs warfarin, 0.79 [95% CI, 0.66 to 0.95], P = 0.01).
  - Savaysa was non-inferior (HR for Savaysa 60 mg once daily vs warfarin, 0.79 [97.5% CI, 0.63 to 0.99], P < 0.001; HR for Savaysa 30 mg once daily vs warfarin, 1.07 [97.5% CI, 0.87 to 1.31], P = 0.005).
  - Xarelto was non-inferior (HR for Xarelto 15 to 20 mg once daily vs warfarin, 0.88 [95% CI, 0.75 to 1.03], P < 0.001).
- In terms of safety, the following important outcomes were observed in trials:
  - All TSOACs had fewer intracranial hemorrhages (ICH) compared to warfarin.
  - For major bleeds, Eliquis and Savaysa were superior to warfarin (Eliquis HR, 0.69 [95% CI, 0.6 to 0.8], P < 0.001; Savaysa HR, 0.8 [95% CI, 0.71 to 0.91], P < 0.001) and Pradaxa and Xarelto were non-inferior to warfarin (Pradaxa RR, 0.93 [95% CI, 0.81 to 1.07], P = 0.31; Xarelto HR, 1.04 [95% CI, 0.9 to 1.2], P = 0.58).
  - For gastrointestinal (GI) bleeds, warfarin significantly out-performed Pradaxa, Savaysa, and Xarelto (Pradaxa RR, 1.5 [95% CI, 1.19 to 1.89], P < 0.001; Savaysa HR, 1.23 [95% CI, 1.02 to 1.5], P = 0.03; Xarelto HR, not reported [incidence, Xarelto 3.2% vs warfarin 2.2%], P < 0.001); however, Eliquis had a similar incidence of GI bleeds when compared to warfarin (Eliquis HR 0.89 [95% CI, 0.7 to 1.15], P = 0.37).
- In 2016, the Alere INRatio device, which was used in the ROCKET AF trial, was recalled due to the potential for falsely low international normalized ratio (INR) results. An article from the British Medical Journal (BMJ) suggested that an independent assessment of trial data should be performed. Researchers from the FDA, Bayer, Johnson and Johnson, and the Duke Clinical Research Institute performed a post-hoc data analysis and concluded that the recalled devices did not have significant clinical effects on the primary efficacy and safety trial outcomes. The FDA and European Medicines Agency (EMA) concluded that any incorrect INR measures would have marginal effects on the study outcomes; therefore, they should not impact the safety or benefit-risk balance of Xarelto (*Cohen 2016, EMA press release 2016, FDA press release 2016*).
- Extension trials and additional analyses were conducted for the thromboprophylaxis of NVAF and the following key results were demonstrated:
  - After 2.3 years of Pradaxa treatment, slightly higher rates of stroke and systemic embolism, in addition to increased rates of major bleeding were observed in the long-term trial, RELAY-ABLE, compared to the RE-LY trial, particularly in the FDA-approved 150 mg dose (*Connolly et al 2013*).
  - One pre-specified secondary analysis of the ENGAGE AF-TIMI 48 trial demonstrated ischemic cerebrovascular event rates were similar with Savaysa 60 mg and warfarin, whereas Savaysa 30 mg was less effective than warfarin (*Giugliano et al 2014*). Another pre-specified analysis found that patients with genetic variants of CYP2C9 and VKORC1 derived a greater early safety benefit in bleeding rates with edoxaban over warfarin (*Mega et al 2015*). An

analysis of the ENGAGE-AF-TIMI 48 trial found that patients with valvular heart disease had an increased risk of death (P < 0.001), major adverse cardiovascular events (P < 0.001), and major bleeding (P = 0.02) than patients without valvular heart disease, but did not change the efficacy and safety result of the higher Savaysa dose vs warfarin (*De Caterina et al 2017*).
  - Data regarding GI adverse events and myocardial infarction with Pradaxa treatment have been conflicting. A subgroup analysis of GI adverse events found that Pradaxa demonstrated a statistically significant risk of non-bleeding upper GI effects, which also resulted in a statistically larger proportion of patients discontinuing Pradaxa due to these effects (*Bytzer et al 2013*).
  - A subgroup analysis demonstrated a nonsignificant increase in MI with Pradaxa compared to warfarin but other myocardial ischemic events were not increased. In addition, results revealed that treatment effects of Pradaxa were consistent in patients at higher and lower risk of myocardial ischemic events (*Hohnloser et al 2012*). In contrast, a meta-analysis demonstrated that Pradaxa is associated with an increased risk of MI or acute coronary syndrome (ACS) in a broad spectrum of patients (e.g., stroke prophylaxis in AF, acute VTE, ACS, short term prophylaxis of DVT) when compared against different controls (warfarin, enoxaparin, or placebo). It was not accompanied by an increase in mortality (*Uchino, 2012*).
  - One observational cohort study of 134,000 Medicare patients was conducted by the FDA to compare Pradaxa to warfarin for risk of stroke, major GI bleeding, MI and death. Patients were newly diagnosed with AF within six months of medication claim for anticoagulation. Data was derived from administrative and insurance claims data. Pradaxa was found to be associated with a lower risk of ischemic stroke (HR, 0.8; 95% CI, 0.67 to 0.96), ICH (HR, 0.34; 95% CI, 0.26 to 0.46) and death (HR, 0.86; 95% CI, 0.77 to 0.96) vs warfarin. Risk for GI bleeding was higher for Pradaxa (HR, 1.28; 95% CI, 1.14 to 1.44) vs warfarin, and MI risk was similar (HR, 0.92; 95% CI, 0.78 to 1.08). Most results were similar to RE-LY; however, the MI risk was found to be similar between groups rather than increased for Pradaxa as discovered in RE-LY. Also important to note, an increased risk of GI bleeds associated with Pradaxa was similar to the RE-LY study but differs from data found in the Mini Sentinel analysis which found less risk of GI bleeds with new users of Pradaxa vs warfarin (*FDA Drug Safety Communication 2014*).
- In NVAF patients who require AF cardioversion, standard oral anticoagulant therapy generally consists of a warfarin-based regimen to prevent thrombosis. More recently, FXa inhibitors have been evaluated for this use. Caution should be exercised when interpreting results of these studies as both were underpowered to demonstrate statistically significant differences for efficacy and safety endpoints. Key results are as follows:
  - The X-VeRT trial randomized 1,504 patients with AF undergoing elective cardioversion to Xarelto dosed between 15 to 20 mg daily depending on renal function or a VKA in a 2:1 ratio. The primary endpoint (defined as a composite of stroke, transient ischemic attack, peripheral embolism, MI, and CV death) occurred in 0.5% of XARETO-treated patients vs 1% of VKA-treated patients. Additionally, the proportion of patients who had major bleeding were similar in the Xarelto and VKA treatment groups (0.6% vs 0.8%, respectively) (*Cappato et al 2014*).
  - The ENSURE-AF trial randomized 2,199 NVAF patients undergoing cardioversion to Savaysa 30 to 60 mg daily vs an enoxaparin/warfarin regimen. The primary efficacy endpoint (defined as a composite of stroke, systemic embolic event, MI, or CV mortality) occurred in 0.5% of Savaysa-treated patients vs 1% of enoxaparin/warfarin-treated patients. Additionally, the proportion of patients who had a first major or clinically relevant non-major bleeding occurrence were similar (1% for each group) (*Goette et al 2016*).

Triple anticoagulant therapy after cardiac procedures

- Some patients require triple anticoagulant therapy in cases of cardiac procedures, including PCI, which may be indicated in patients with AF with certain co-morbid diseases. There is limited evidence to guide appropriate treatment. Evidence has been controversial and often outcomes vary greatly according to the population studied requiring clinicians to balance the risk of thrombosis and ischemic stroke with that of potential bleeding. Studies have demonstrated that a $P2Y_{12}$ inhibitor plus aspirin are superior to warfarin in reducing the risk of thrombosis in patients undergoing placement of a first-generation stent, but found oral anticoagulation was superior to dual antiplatelet therapy (DAPT) in reducing the risk of ischemic stroke in patients with AF (*Connolly et al 2006, Cutlip et al 1999, Gibson et al 2016, Leon et al 1998*).
  - Prior trials examining the use of oral anticoagulants vs DAPT post-procedurally has yielded mixed results. The ACTIVE-W trial found DAPT was inferior to warfarin for the prevention of vascular events in patients with AF at high risk of stroke, especially in those already taking oral anticoagulation therapy; however, in the STARS trial, DAPT was superior to an oral anticoagulant for the prevention of thrombosis related to coronary stent insertion (*Connolly et al 2006, Cutlip et al 1999*). Most evidence with triple therapy has included warfarin and consists of small open-label (OL) RCTs or observational studies (*Dewilde et al 2013, Fiedler et al 2015*).

- Recent American Heart Association (AHA) guidance recommends an assessment of CHA_2DS_2-VASc risk score to estimate the thromboembolic risk and the HASBLED risk score to estimate the hemorrhagic risk. The AHA recommends including the patient in a shared decision regarding the selection of DAPT vs triple therapy as well as the duration of therapy post-procedurally. Although the AHA acknowledges that both European and Canadian guidelines suggest TSOACs over warfarin for triple therapy, this has been based on lower quality observational data and post-hoc analyses (*Raval et al 2017*). Current AHA guidance acknowledges that in spite of limited data, certain patients for whom it is difficult to reach and maintain therapeutic INR levels with warfarin may warrant the use of a TSOAC with DAPT (but not in combination with prasugrel or ticagrelor) after PCI (*Cannon et al 2016, Gao et al 2015, Gibson et al 2016, Hoshi et al 2017, Ravel et al 2017*).

- Studies are currently underway examining the benefits and risks of triple anticoagulant therapy. These studies, including the recently published PIONEER-AF-PCI trial and the ongoing RE-DUAL PCI, RT-AF, SAFE-A, and AUGUSTUS studies, will provide further insights into the use of a TSOAC with DAPT in patients undergoing PCI (*Cannon et al 2016, Gao et al 2015, Gibson et al 2016, Hoshi et al 2017, Ravel et al 2017*). A number of studies have been conducted with three of the TSOACs which included triple therapy anticoagulant regimens for the treatment of secondary ACS prevention; however, this indication has not been FDA-approved and the percentage of patients who had concomitant AF has not been well documented:
  - Eliquis and Pradaxa have been studied in patients after an ACS via the APPRAISE trials and REDEEM trials, respectively. Trial outcomes resulted in minimal to no clinical benefit; however, an increased risk of harm was observed as bleeding events (*Alexander et al 2009, Cornel et al 2015, Ogawa et al 2013, Oldgren et al 2011*).
  - Xarelto has been studied at doses of 2.5 mg or 5 mg twice daily vs placebo in 15,526 patients with recent ACS and followed for approximately two years via the DB, PC, ATLAS trial. ACS patients were also administered DAPT therapy with a low-dose aspirin or thienopyridine (either clopidogrel or ticlopidine). Xarelto 2.5 mg twice daily dosing not only significantly reduced the primary endpoint (defined as the composite of death from CV causes, MI, or stroke; P = 0.02), but unlike the 5 mg dosing, the 2.5 mg dose also reduced the rate of death from CV or any cause (P = 0.002 for both). This benefit, however, was tempered by an increased risk of non-coronary artery bypass grafting (CABG) thrombolysis in myocardial infarction (TIMI) major bleeding (P < 0.001) and ICH (P = 0.04) vs placebo (*Mega et al 2012*).
  - The recently conducted PIONEER-AF-PCI trial was a large, OL, randomized safety trial (N = 2,124) conducted in patients with NVAF undergoing PCI with stent placement and compared triple therapy strategies with Xarelto and warfarin. Patients were randomized to: (1) Xarelto 15 mg once daily plus clopidogrel 75 mg daily for 12 months, or (2) Xarelto 2.5 mg twice daily plus DAPT with a prespecified duration of 1, 6 or 12 months, or (3) warfarin plus DAPT with a prespecified duration of 1, 6 or 12 months. Patients administered Xarelto-based regimens had a lower risk of the primary safety endpoint of clinically significant bleeding (composite of major or minor TIMI bleeding or bleeding requiring medical attention) compared to warfarin (17.4% and 26.7%, respectively; P < 0.001). Clinically significant bleeding was driven by bleeding requiring medical attention. For the secondary efficacy endpoints, patients experienced no difference in major adverse CV events (defined as a composite of death from CV causes, MI, or stroke) or stent thrombosis compared to warfarin plus DAPT; however, caution should be exercised as the study was not powered for this outcome and clinical efficacy remains uncertain (*Gibson et al 2015, Gibson et al 2016*).

<u>VTE treatment</u>

- Six large, randomized controlled trials (RE-COVER, RE-COVER II, AMPLIFY, Hokusai-VTE, EINSTEIN-DVT and EINSTEIN-PE) evaluated the efficacy and safety of Pradaxa, Eliquis, Savaysa, and Xarelto vs warfarin, respectively, for the treatment of acute VTE (although Pradaxa and Savaysa trials had 5 to 10 days treatment with a parenteral anticoagulant prior to initiating treatment). Baseline populations for Pradaxa, Eliquis, Savaysa, and Xarelto trials varied greatly including the following characteristics (*Schulman et al 2009, Schulman et al 2009, Agnelli et al [a] 2013, Büller et al 2013, Bauersachs et al 2010, Büller et al 2012, Prins et al 2013*):
  - Patients aged ≥ 75 years ~10%, 14%, 13.5%, and 13 to 17%, respectively
  - Prior VTE ~22%, 16%, 18%, and 19 to 20%, respectively
  - Unprovoked VTE ~ 35%, 89.8%, 65.7%, and 62 to 64.5%, respectively
  - Cancer at baseline ~4.3%, 2.7%, 9.3%, and 5.2%, respectively
  - Duration of treatment: 6 months, 6 months, 3 to 12 months, and measures at 3, 6, and 12 months, respectively
  - TTR ~ 60%, 61%, 64%, and 58 to 63%, respectively
- The primary efficacy and safety endpoints also varied among trials. Important data include the following:

- For RE-COVER, recurrent VTE and related deaths occurred in 2.4% in the Pradaxa arm and 2.1% in the warfarin arm (P < 0.001 for non-inferiority). Major bleeding was similar (1.6% Pradaxa vs 1.9% warfarin), but more Pradaxa patients discontinued treatment due to adverse events (9%) compared to warfarin (6.8%; P < 0.05) (*Schulman et al 2009*).
- In RE-COVER II, symptomatic VTE or VTE- related deaths occurred in 2.3% of Pradaxa patients vs 2.2% of warfarin patients (P < 0.001 for non-inferiority). Major bleeding was similar; however, warfarin had significantly more overall bleeds in 22.1% of patients compared to 15.6% of Pradaxa patients (P < 0.05) (*Schulman et al 2014*).
- In AMPLIFY, non-inferiority was met for the primary outcome of recurrent symptomatic VTE or death related to VTE, which occurred in 2.3% of Eliquis patients vs 2.7% of conventional therapy patients (RR, 0.84; 95% CI, 0.6 to 1.18). Significantly more major bleeding was observed with conventional therapy (1.8%) compared to patients treated with Eliquis (0.6%) (*Agnelli et al [a], 2013*).
- In Hokusai-VTE, Savaysa was non-inferior to warfarin for the prevention of recurrent VTE after treatment with parenteral anticoagulants (3.2% with Savaysa vs 3.5% with warfarin after 12 months follow-up; HR, 0.89; 95% CI, 0.7 to 1.13; P < 0.001 for non-inferiority). Significantly lower rates of major or clinically relevant non-major bleeding were observed in 8.5% of SAYVASA patients compared to 10.3% of warfarin patients (P = 0.004), but major bleeding was similar (P = 0.35) (*Büller et al 2013*).
- The results from EINSTEIN-DVT demonstrated Xarelto to be non-inferior to standard therapy (2.1% for Xarelto vs 3% for enoxaparin/VKA; P < 0.001 for non-inferiority) for symptomatic recurrent VTE. Identical rates (8.1%) of major or non-major clinically relevant bleeding were shown. Net clinical benefit in terms of symptomatic recurrent VTE plus major bleeding favored Xarelto (reported in 2.9% Xarelto vs 4.2% enoxaparin/VKA patients; P = 0.03) (*Bauersachs et al 2010*).
- In EINSTEIN-PE, Xarelto was shown to be non-inferior to enoxaparin/VKA (2.1% Xarelto vs 1.8% enoxaparin/VKA; HR, 1.12; 95% CI, 0.75 to 1.68) for symptomatic recurrent VTE. The principal safety outcome, clinically relevant bleeding, occurred in 10.3% of Xarelto patients and 11.4% of standard therapy patients (HR, 0.9; 95% CI, 0.76 to 1.07; P = 0.23). Major bleeding was observed in 1.1% of Xarelto patients and 2.2% in the standard-therapy group (HR, 0.49; 95% CI, 0.31 to 0.79; P = 0.003). Net clinical benefit occurred in 3.4% of Xarelto patients and 4% of standard therapy patients (HR, 0.85; 95% CI, 0.63 to 1.14; P = 0.28) (*Büller et al 2012*).

Reduction in Recurrent VTE

- Four large randomized controlled trials (RE-MEDY, RE-SONATE, AMPLIFY-EXT, and EINSTEIN-EXT) were evaluated for the reduction in recurrent VTE and the basis for clinical efficacy and safety for Pradaxa, Eliquis, and Xarelto vs placebo, respectively (however, Pradaxa is the only agent compared to warfarin as observed in the RE-MEDY trial). Each trial was an extension of the acute VTE trials mentioned previously (*Agnelli et al [b] 2013, Bauersachs et al 2010, Schulman et al 2013*). The EINSTEIN CHOICE trial also evaluated the rate of recurrent VTE with long-term TSOAC treatment (*Weitz et al 2017*).
- The primary efficacy and safety endpoints also varied among trials. Important data include the following:
  - The RE-MEDY (comparing Pradaxa to warfarin) and RE-SONATE (comparing Pradaxa to placebo) trials had similar efficacy results with recurrent VTE reported in 1.8% of patients with Pradaxa vs 1.3% with warfarin (P = 0.01 for non-inferiority) in the RE-MEDY trial and 0.4% with Pradaxa vs 5.6% with placebo (P < 0.001) in the RE-SONATE trial. However, RE-MEDY displayed lower major bleeding in the Pradaxa group (0.9% with Pradaxa vs 1.8% with warfarin; HR, 0.52; 95%, 0.27 to 1.02) compared to that of the RE-COVER trials (*Schulman et al 2013*).
  - In AMPLIFY-EXT, extended treatment with Eliquis demonstrated superiority vs placebo in the reduction of the composite endpoint of symptomatic, recurrent VTE and death from any cause (8.8% for placebo vs 1.7% for each Eliquis 2.5 and 5 mg groups). Across the trial, the rates of major bleeding were low and comparable (0.5% for placebo vs 0.2% and 0.1% for Eliquis 2.5 and 5 mg, respectively) (*Agnelli et al [b] 2013*).
  - In the EINSTEIN-EXT, Xarelto was superior to placebo with respect to the primary efficacy endpoint of symptomatic recurrent VTE (1.3% vs 7.1%; HR, 0.18; 95% CI, 0.09 to 0.39; P < 0.001). Rates of major bleeding were similar (0.7% vs 0%; P = 0.11). The outcome of net clinical benefit was significantly in favor of Xarelto, with symptomatic recurrent VTE plus major bleeding reported in 2% of Xarelto patients vs 7.1% of placebo patients (P < 0.001) (*Bauersachs et al 2010*).
  - Recently, the EINSTEIN CHOICE trial (N = 3,365) evaluated the rates of recurrent VTE with a long duration of treatment with Xarelto 10 mg (N = 1,127), 20 mg (N = 1,107), or aspirin 100 mg (N = 1,131) once daily after 6 to 12 months of therapy. Patients in the Xarelto 10 and 20 mg groups had a significantly lower rate of recurrence of VTE compared to aspirin 100 mg (1.2 vs 1.5 vs 4.4%; P < 0.001 for both Xarelto groups). The rates of major bleeding were

similar between groups (0.4 vs 0.5 vs 0.3%, respectively). Of note, patients within the study were younger than a real world population; therefore, results may not be generalizable (*Weitz et al 2017*).

- Current guidelines recommend LMWH in patients who have recurrent VTE, including those currently stable on VKA or TSOAC therapy (*Kearon et al 2016*).

VTE prophylaxis for total knee (TKR) and/or hip (THR) replacement surgery

- Nine large randomized, double blinded (DB) trials (RE-NOVATE and RE-NOVATE II [hip], RECORD 1 and 2 [hip], RECORD 3 and 4 [knee], ADVANCE 1 and 2 [knee], and ADVANCE 3 [hip]) were the basis for clinical efficacy and safety for Pradaxa, Xarelto, and Eliquis vs enoxaparin, respectively in VTE prophylaxis for TKR or THR surgeries. Duration of treatment, dose strength, and frequency varied for each group among trials.
- When evaluating anticoagulation therapies for patients undergoing THR or TKR, asymptomatic DVT, detected by mandatory venography, is used as a surrogate endpoint. The American College of Chest Physicians (ACCP) guidelines find this outcome unsatisfactory due to the inability to weigh the risks and benefits of efficacy (knowledge of symptomatic events) compared to serious bleeding. The guidelines provide suggestions to estimate reductions in symptomatic thrombosis; however, this is contingent on available evidence. Many studies rely on asymptomatic DVT events to determine differences and are not powered to detect a difference in the frequency of symptomatic events, due to low occurrence rates (*Guyatt et al 2012*).
- Data from the THR trials found Xarelto and Eliquis to be superior to enoxaparin 40 mg once daily and Pradaxa to be non-inferior to enoxaparin 40 mg once daily when prescribed for orthopedic prophylaxis (*Eriksson et al 2008, Eriksson et al 2007 [a], Eriksson et al 2007 [b], Eriksson et al 2011, Kakkar et al 2008, Lassen et al 2010 [a], Lassen et al 2010 [b]*).
  - RE-NOVATE and RE-NOVATE II: The RE-NOVATE trial compared 150 and 220 mg of Pradaxa to enoxaparin 40 mg per day and the RE-NOVATE II trial compared 220 mg of Pradaxa to enoxaparin 40 mg per day in over 5,500 patients. In both trials, Pradaxa was as effective as enoxaparin in reducing the risk of VTE and mortality after THR surgery (P for non-inferiority < 0.001). The incidence of major bleeding did not differ significantly among groups (enoxaparin 0.9% to 1.6% vs Pradaxa 1.3% to 2%) (*Eriksson et al 2007 [a], Eriksson et al 2007 [b], Eriksson et al 2011*).
  - ADVANCE-3: Eliquis 2.5 mg twice daily was superior to enoxaparin in approximately 5,400 patients in reducing the risk of VTE and mortality after THR surgery (P < 0.001). The incidence of adjudicated major bleeding events were similar between groups (enoxaparin 0.8% vs Eliquis 0.7%) (*Lassen et al 2010 [b]*).
  - RECORD 1: Xarelto 10 mg once daily was superior to enoxaparin in approximately 5,600 patients for the combined endpoint of any DVT, nonfatal PE, or all-cause mortality up to day 42 for Xarelto and ranged from 1.1% to 2% compared to 3.7% to 9.3% for enoxaparin. Major VTE was decreased 0.2% to 0.6% with Xarelto compared with 2% to 5.1% with enoxaparin. The incidence of major bleeding was similar between groups (enoxaparin 0.1% vs Xarelto 0.3%; P = 0.18) (*Eriksson et al 2008, Kakkar et al 2008*).
- In patients undergoing a TKR, evidence demonstrates superiority of Xarelto and Eliquis when compared to enoxaparin 40 mg once daily. A TKR study, the ADVANCE-1 trial, evaluated Eliquis vs the US enoxaparin dose of 30 mg twice daily and failed to demonstrate non-inferiority of Eliquis (95% CI not to exceed 1.25) for the primary endpoint of total VTE or death (RR, 1.02; 95% CI, 0.78 to 1.32; P for non-inferiority = 0.06) (*Lassen et al 2009*). Xarelto has demonstrated superiority to enoxaparin for the primary efficacy endpoint (a composite of DVT, non-fatal PE, or death) in the RECORD 4 trial (*Turpie et al 2009*).
- Studies which have compared Xarelto to aspirin for the prevention of VTE after THR or TKR have demonstrated aspirin may be as effective; however, most trials are not evaluated past hospital discharge. The EPCATII trial, which was a DB RCT, evaluated use of Xarelto 10 mg once daily to aspirin 81 mg once daily in 3,424 patients (with 1,804 undergoing THR and 1,620 undergoing TKR). All patients were administered Xarelto 10 mg once daily until postoperative day 5 and then randomized to treatment for an additional 9 days after TKR or 30 days after THR. VTE occurred in 0.64% of patients treated with aspirin vs 0.70% of patients treated with Xarelto (difference, 0.06%; 95% CI, –0.55 to 0.66; P < 0.001 for non-inferiority; P = 0.84 for superiority). In addition, major bleeding complications occurred in 0.47% of patients treated with aspirin and 0.29% of patients treated with Xarelto (difference, 0.18%; 95% CI, –0.65 to 0.29; P = 0.42). The results also showed that clinically important bleeding occurred in 1.29% of patients treated with aspirin and in 0.99% of patients treated with Xarelto (difference, 0.30%; 95% CI, –1.07 to 0.47; P = 0.43). (*Anderson et al 2018*).
- It is important to note that guidelines favor LMWH over Arixtra, Eliquis, Pradaxa, Xarelto, or UFH (*AAOS 2011, Guyatt et al 2012*).

General VTE prophylaxis for the medically ill:

- Currently, Bevyxxa is the only oral anticoagulant specifically FDA-approved as prophylaxis in patients with restricted mobility from acute illness and other risk factors. The APEX trial was a randomized, DB trial which compared the safety and efficacy of an extended duration of Bevyxxa to a short duration of enoxaparin in patients who were hospitalized due to an acute illness and had risk factors for VTE. A total of 7,513 patients were randomized to Bevyxxa 160 mg orally on day 1, followed by 80 mg once daily for 35 to 42 days (and a subcutaneous placebo injection for 6 to 14 days) or to enoxaparin 40 mg administered subcutaneously once daily for 6 to 14 days (and an oral placebo tablet for 35 to 42 days). Patients with renal insufficiency received 50% of the dose for each medication. In the first cohort analyzed, patients with an elevated D-dimer level, the difference between Bevyxxa and enoxaparin on the primary composite of asymptomatic proximal DVT between day 32 and day 47, symptomatic proximal or DVT, symptomatic nonfatal PE, or death from VTE between day 1 and day 42 did not reach statistical significance (6.9 vs 8.5%, respectively; RR, 0.81; 95% CI, 0.65 to 1; P = 0.054). In patients with an elevated D-dimer level or an age ≥ 75 years, the composite endpoint was reached in 5.6 vs 7.1%, respectively (RR, 0.8; 95% CI, 0.66 to 0.98; P = 0.03), and in the overall population, it was reached in 5.3 vs 7%, respectively (RR, 0.76; 95% CI, 0.63 to 0.92; P = 0.006). However, because the first test did not reach statistical significance, these subsequent outcomes were considered exploratory. In the overall population, there was no significant difference in the incidence of major bleeding through day 7 after discontinuation of therapy (0.7 vs 0.6%, respectively) (*Cohen et al 2016*).
  - Additionally, Bevyxxa compared with enoxaparin significantly reduced the incidence of all cause strokes (0.54 vs 0.97%, respectively; P = 0.032), ischemic strokes (0.48 vs 0.91%, respectively; P = 0.026), and a composite of all cause stroke or transient ischemic attack (0.65 vs 1.1%, respectively; P = 0.034) through 77 days of follow up (*Gibson et al 2017*).
- For patients who are medically ill and at risk for a DVT or PE, two studies (ADOPT and MAGELLAN) have been conducted for Eliquis and Xarelto, respectively. Both TSOACs were compared to enoxaparin 40 mg daily for approximately 10 days; Eliquis was given as 2.5 mg twice daily for 30 days and Xarelto was given as 10 mg once daily for 35 days. The following efficacy and safety outcomes were reported in each trial:
  - ADOPT: Eliquis was demonstrated to be similar to enoxaparin for the primary endpoint of composite of total VTE and VTE-related death at 30 days (RR, 0.87; 95% CI, 0.62 to 1.23; P = 0.44) and at 90 days (RR, 1.06; 95% CI, 0.69 to 1.63; P = not reported). Enoxaparin treatment was associated with significantly less risk of bleeding compared to Eliquis (*Goldhaber et al 2011*).
    - MAGELLAN: Xarelto was demonstrated to be as effective as enoxaparin for the primary endpoint of asymptomatic proximal or symptomatic VTE at day 10 (RR, 0.97; 95% CI, 0.71 to 1.31; P = 0.003 for non-inferiority) and superior to enoxaparin at day 35 (RR, 0.77; 95% CI, 0.62 to 0.96; P = 0.02 for superiority). Enoxaparin treatment was associated with significantly less risk of bleeding compared to Xarelto (*Cohen et al 2013*).
    - The clinical relevance of asymptomatic VTE is unknown in the MAGELLAN trial. The ADOPT trial included a number of endpoints, including the composite of VTE, PE, symptomatic DVT, or asymptomatic proximal leg DVT, and it is not clear if any of the individual measures were significantly different.

Safety in renal insufficiency:

- One meta-analysis of ten randomized controlled trials examined patients with mild to moderate renal insufficiency and AF, acute DVT/PE, or extended treatment of VTE who were administered recommended doses of TSOACs (e.g., Eliquis, Pradaxa, or Xarelto). The analysis of key outcomes demonstrated that TSOACs were non-inferior and had improved bleeding compared to conventional anticoagulant treatment with LMWH, VKA, LMWH followed by VKA, or aspirin therapy (*Sardar et al 2014*).

CLINICAL GUIDELINES

- In terms of current reputable guidelines, the following has been recommended:
  - For the prevention of stroke and systemic embolism in patients with NVAF, guidelines generally recommend oral anticoagulation in patients with NVAF at intermediate to high risk of stroke, or in certain patients with ≥ 1 moderate risk factors for stroke or thrombosis. TSOACs are considered to be a reasonable option in patients with native aortic valve disease, tricuspid valve disease, or mitral regurgitation, and in AF with a CHA_2DS_2-VASc score ≥ 2. Warfarin is generally recommended over the TSOACs, particularly for prosthetic or bioprosthetic valve thrombosis. Expert consensus guidelines stipulate that continuous uninterrupted VKA therapy has demonstrated lower bleeding risks vs interrupted treatment with heparin bridging for certain procedures such as pacemaker implants or implantable

cardioverter defibrillators (ICD) in most NVAF patients. Reputable societies encourage decisions to be made based on patient characteristics and a risk/benefit analysis (*Anderson et al 2013, Bushnell et al 2014, Culebras et al 2014, Doherty et al 2017, Furie et al 2012, Guyatt et al 2012, January et al 2014, Kernan et al 2014, Nishimura et al 2017, Otto et al 2017, Ravel et al 2017, Smith et al 2017*).

- All TSOACs have demonstrated non-inferiority to conventional therapy for acute VTE. The ACCP guidelines recommend the TSOACs over warfarin for the first 3 months of therapy for non-cancer associated VTE. Warfarin is recommended over LMWH for long-term VTE therapy; however LMWH is preferred in patients with cancer (*Guyatt et al 2012, Kearon et al 2016*).
- For patients with recurrent VTE and currently administered anticoagulants, the ACCP guidelines recommend patients be switched to LMWH, at least temporarily, in lieu of warfarin and TSOACs. If a recurrent VTE occurs while a patient is taking long-term LMWH, then a dose increase of 1/4 or 1/3 is recommended (*Guyatt et al 2012, Kearon et al 2016*).
- For VTE prophylaxis in patients undergoing TKR or THR surgery, the AAOS does not recommend a specific medication (*AAOS 2011*). The ACCP does favor LMWH over Arixtra, Eliquis, Xarelto, or UFH (*Guyatt et al 2012*). If a TSOAC is prescribed, the treatment duration of Eliquis and Xarelto is a minimum of 10 to 14 days for a TKR (prescribing information recommends 12 days) and 35 days for a THR which is in agreement with the prescribing information.

SAFETY SUMMARY

- Contraindications:
  - All oral anticoagulants in class are contraindicated in active pathological bleeding.
  - Bevyxxa, Coumadin, Eliquis, Jantoven, Pradaxa and Xarelto also have contraindications in patients with a severe hypersensitivity to any component of the products.
  - Pradaxa has an additional contraindication in patients with mechanical prosthetic heart valves; additionally, the indication for Bevyxxa has a limitation of use in patients with prosthetic heart valves as this population has not been studied.
  - Coumadin and Jantoven are contraindicated in patients with hemorrhagic tendencies or blood dyscrasias, recent or contemplated surgery of the central nervous system (CNS) or eye, or traumatic surgery resulting in large open surfaces, threatened abortion, eclampsia, preeclampsia, unsupervised patients with conditions associated with potential high level of non-compliance, spinal puncture, other diagnostic or therapeutic procedures with the potential for uncontrollable bleeding, major regional or lumbar block anesthesia, malignant hypertension, or bleeding tendencies associated with active ulceration, overt bleeding of the GI, genitourinary, or respiratory tract, CNS hemorrhage, cerebral aneurysms, dissecting aorta, bacterial endocarditis, pericarditis, or pericardial effusions.
- A boxed warning exists for:
  - Pradaxa, Xarelto, Savaysa, and Eliquis with regards to the increased risk of thrombotic events when prematurely discontinuing therapy without adequate continuous anticoagulation. Bevyxxa, or treatment with the aforementioned agents, increases the risk of epidural or spinal hematoma which may cause long-term or permanent paralysis in patients receiving neuraxial anesthesia or undergoing spinal puncture. The optimal timing between the administration of Pradaxa, Savaysa, or Eliquis and neuraxial procedures is not known.
  - Savaysa should not be used in NVAF patients with CrCL > 95 mL/min. In trials, these patients had an increased rate of ischemic stroke with Savaysa 60 mg once daily compared to patients treated with warfarin.
  - Coumadin and Jantoven may cause major or fatal bleeding. Drugs, dietary changes, and other factors affect INR levels achieved with Coumadin or Jantoven therapy. Regular monitoring of INR in all patients is recommended.
- Warnings/Precautions:
  - Warnings and precautions for all agents within the oral anticoagulant class include an increased risk of serious or potentially fatal bleeding (including hemorrhage). Patients should be evaluated for signs and symptoms of blood loss or thrombotic events when treated with oral anticoagulants.
  - Additional warnings and precautions for the TSOACs (Eliquis, Pradaxa, Savaysa, and Xarelto) include a risk of thrombotic events (including stroke) after premature discontinuation, use is not recommended in patients with heart valves (ie, prosthetic, bioprosthetic, mechanical valves, or moderate to severe mitral stenosis), and an increased risk of long-term or permanent paralysis from an epidural or spinal hematoma when neuraxial anesthesia or spinal/epidural puncture is employed in patients treated with an antithrombotic agent.

- Eliquis and Xarelto have a warning and precaution that use is not recommended acutely as an alternative to unfractionated heparin in patients with PE who present with hemodynamic instability or receive thrombolysis or pulmonary embolectomy.
- Coumadin, Jantoven, and Xarelto have a warning and precaution in pregnant women due to the potential for obstetric hemorrhage. Xarelto may also cause emergent delivery. Coumadin and Jantoven are contraindicated during pregnancy; however, the benefits may outweigh the risks in pregnant patients with mechanical heart valves at high risk of thromboembolism.
- Bevyxxa and Xarelto have a warning and precaution of use in renal impairment. Xarelto has a warning and precaution of use in hepatic impairment; additionally, Bevyxxa is not recommended for use in these patients.
- An additional warning and precaution for Savaysa is reduced efficacy in NVAF patients with CrCL > 95 mL/min.
- Coumadin and Jantoven have a warning and precaution that fatal and serious calciphylaxis or calcium uremic arteriolopathy has been reported with use in patients with and without end stage renal disease. When calciphylaxis is diagnosed, warfarin should be discontinued and an alternate anticoagulant considered. In patients with altered glomerular integrity or a history of kidney disease, acute kidney injury may occur. Additional warnings and precautions include the potential for tissue necrosis or gangrene, systemic atheroemboli, cholesterol microemboli, possible limb ischemia, necrosis, and gangrene in patients with heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia with thrombosis syndrome (HITTS). Should any of these issues occur, Coumadin or Jantoven should be discontinued. Should HIT or HITTS occur, treatment with Coumadin or Jantoven may be considered after the platelet count has normalized.

- Adverse events:
  - The most common adverse reactions reported with these agents include bleeding (all agents), anemia (Savaysa), rash (Savaysa), abnormal liver function tests (Savaysa), and gastritis-like symptoms (Pradaxa).
- Drug interactions:
  - Bevyxxa and Pradaxa have a warning and precaution of concomitant use with P-gp inducers or inhibitors, and Xarelto has a warning and precaution of combined use with dual P-gp and strong CYP3A4 inhibitors or inducers. Generally use with these products should be avoided. Although not a warning and precaution, interactions between strong P-gp inhibitors or inducers, CYP3A4 inhibitors or inducers, and oral anticoagulants are noted within the Eliquis and Savaysa labeling.
  - Concomitant use with other drugs (ie, aspirin, platelet inhibitors, antithrombotic agents, fibrinolytic therapy, non-steroidal anti-inflammatory drugs [NSAIDs], selective serotonin reuptake inhibitors [SSRIs], and serotonin norepinephrine reuptake inhibitors [SNRIs]) that impair hemostasis increase the risk of bleeding.
  - Numerous drug and dietary interactions exist for warfarin.
- Additional safety considerations:
  - All oral anticoagulants in class are contraindicated in active pathological bleeding.
    - Two oral anticoagulants have reversal agents available for urgent situations. These include warfarin (Coumadin and Jantoven) and dabigatran (Pradaxa). Vitamin K functions as a reversal agent for warfarin, and idarucizumab (Praxbind) is a specific reversal agent for Pradaxa.
    - A specific reversal agent for Eliquis, Savaysa, and Xarelto is not available. Hemodialysis does not significantly contribute to clearance. The use of prothrombin complex concentrates (PCC), or other procoagulant reversal agents such as activated prothrombin complex concentrate (APCC) or recombinant FVIIa may be considered but has not been evaluated in studies.
      - Andexanet alfa is a reversal agent under clinical development. In August 2016, a CRL was issued by the FDA questioning manufacturing and clinical data. In August 2017, Portola Pharmaceuticals re-submitted the BLA addressing deficiencies noted in the CRL. The anticipated FDA decision date is May 4, 2018 (*Portola Pharmaceuticals press release 2018*).

DOSING AND ADMINISTRATION

- Table 3 outlines general dosing recommendations. Please refer to prescribing information for additional details regarding certain drug interactions, various special populations, converting to other anticoagulants, and guidance as it relates to surgical procedures.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Bevyxxa (betrixaban)	Capsule	Oral	Reduction in the risk of DVT and PE in hospitalized patients with acute medical illness with restricted mobility and other VTE risk factors: 160 mg as a single dose, followed by 80 mg once daily for 35 to 42 days.	Take with food. Half the dose for CrCL 15 to 29 mL/min or if taking concomitant P-gp inhibitors.
Eliquis (apixaban)	Tablet	Oral	Reduce the risk of stroke in NVAF: 5 mg twice daily. Prophylaxis of DVT following THR or TKR: TKR: 2.5 mg twice daily for 12 days; THR: 2.5 mg twice daily for 35 days. Note: First dose should be taken 12 to 24 hrs after surgery. Treatment of DVT and PE: 10 mg twice daily for 7 days, followed by 5 mg twice daily. Reduction in the risk of DVT and PE recurrence: 2.5 mg twice daily after at least 6 months of treatment for DVT or PE.	For patients unable to swallow whole tablets, 5 mg and 2.5 mg tabs may be crushed and are stable in water, D5W, apple juice or applesauce. May deliver through a nasogastric tube after mixed with D5W or water. Half the dose in NVAF patients with at least 2 of the following characteristics: (1) age ≥ 80 years, (2) body weight ≤ 60 kg, or (3) serum creatinine ≥ 1.5mg/dL.
Pradaxa (dabigatran)	Capsule	Oral	Reduce the risk of stroke in NVAF: 150 mg twice daily. Treatment of DVT and PE/Reduction in the risk of DVT and PE recurrence: 150 mg twice daily. Prophylaxis of VTE following THR: 110 mg on the first day, then 220 mg once daily for 28 to 35 days. Note: The initial dose should be taken 1 to 4 hrs after surgery.	Take with or without food. For NVAF, reduce dose for CrCL 15 to 30 mL/min or for CrCL 15 to 30 mL/min and concomitant use of P-gp inhibitors (only dronedarone or ketoconazole). Avoid concomitant use of P-gp inhibitors in patients with CrCL < 30 mL/min. For DVT/PE treatment, recurrence risk reduction, and VTE prophylaxis (THR), dosing recommendations only include patients with CrCL > 30 mL/min. Avoid concomitant use of P-gp inhibitors in patients with CrCL < 50 mL/min.
Savaysa (edoxaban)	Capsule	Oral	Reduce the risk of stroke in NVAF: 60 mg once daily. Treatment of DVT and PE: 60 mg once daily following 5 to 10 days of initial parenteral anticoagulant.	Take with or without food. For patients unable to swallow whole tablets, tabs may be crushed and are stable in water or applesauce. May deliver through a nasogastric tube after mixed with water. For NVAF, half the dose for CrCL 15 to 50 mL/min. Do not use for CrCL > 95 mL/min.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				For DVT/PE treatment, half the dose for CrCL 15 to 50 mL/min, weight ≤ 60 kg, or if taking concomitant P-gp inhibitors.
Xarelto (rivaroxaban)	Tablet, starter pack (tablet)	Oral	Prophylaxis of DVT following THR or TKR: TKR: 10 mg once daily for 12 days. THR: 10 mg once daily for 35 days. Note: The initial dose should be taken 6 to 10 hrs after surgery. Reduce the risk of stroke in NVAF: 20 mg once daily. Treatment of DVT and PE: 15 mg twice daily with food, for first 21 days. Then after 21 days, 20 mg once daily for remaining treatment. Reduction in the risk of recurrence of DVT and PE: 10 mg once daily.	The 10 mg, 15 mg and 20 mg tablets may be crushed and are stable in water or applesauce for up to 4 hours. For NVAF, reduce dose for CrCL 15 to 50 mL/min. Administer with the evening meal. Administer the 15 mg and 20 mg tablets with food; the 10 mg tablets can be taken with or without food.
Coumadin; Jantoven (warfarin)	Tablet	Oral	Prophylaxis and treatment of the thromboembolic complications associated with AF and/or cardiac valve replacement: Once daily; maintain an INR of 2 to 3 for NVAF and most bioprosthetic and mechanical heart valves, and an INR of 2.5 to 3.5 for tilting disk valves, bileaflet mechanical valves in the mitral position, or caged ball or caged disk valves. Prophylaxis and treatment of VTE and its extension, PE: Once daily; maintain an INR of 2 to 3 and treat for a minimum of 3 months and reassess the risk-benefit ratio of long-term treatment. Reduce the risk of death, recurrent MI and thromboembolic events such as stroke or systemic embolization after MI: Once daily; for high risk patients with MI, maintain an INR of 2 to 3 (moderate intensity) plus low-dose aspirin ≤ 100 mg/day for at least 3 months after MI.	An INR > 4 appears to provide no additional therapeutic benefit in most patients and is associated with a higher risk of bleeding. Long-term anticoagulation with warfarin is recommended in NVAF patients with certain risk factors. Dosing may be modified in patients with certain identified genotypes.

CONCLUSION

- Four TSOACs, Pradaxa, Xarelto, Savaysa, and Eliquis, are all indicated for the reduction of stroke and systemic embolism in NVAF and for the treatment of DVT and PE, otherwise known as events caused by a VTE. Pradaxa, Xarelto, and Eliquis are indicated for the reduction in the risk of recurrence of DVT and PE, and DVT and PE prophylaxis in patients undergoing THR. Xarelto and Eliquis are indicated for DVT and PE prophylaxis in patients undergoing TKR surgery. Warfarin has various indications, including prophylaxis and/or treatment of PE; prophylaxis and/or treatment of thromboembolic complications associated with AF and/or cardiac valve replacement; prophylaxis and/or treatment of venous thrombosis and its extension; and to reduce the risk of death, recurrent MI and thromboembolic events such as stroke or systemic embolization after MI. Bevyxxa is the only agent in class indicated for patients hospitalized for an

acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE.

- Warfarin has long-term efficacy and safety data and is generically available. Trial evidence and recommendations from current clinical guidelines support the use of warfarin for all FDA-approved indications.
- Therapy with warfarin is associated with challenges including a slow on- and offset of action, unpredictable variability in response, a narrow therapeutic window, frequent monitoring, and numerous food and drug interactions. In addition, maintenance of a therapeutic level of anticoagulation may be difficult for patients and requires a good understanding of the pharmacokinetic and pharmacodynamic properties of warfarin.
- The major advancement with the TSOACs is that they do not require routine laboratory monitoring; however, this may make it difficult for physicians to objectively assess adherence to therapy. In addition, their propensity for drug and dietary interactions is less than warfarin. There is uncertainty regarding how to manage bleeding or perioperative management in patients treated with TSOACs. There are no FDA-approved assays or calibration reagents to measure the effect of the TSOACs. However, partial thromboplastin time (PTT) and thrombin time (TT) can be useful for measuring the effects of Pradaxa (*Raval et al 2017*).
- Pradaxa is the first TSOAC with an available antidote, idarucizumab (*Praxbind prescribing information, 2015*). There are no specific antidotes for Bevyxxa, Eliquis, Savaysa, or Xarelto; however, andexanet alfa is in the pipeline (*Portola Pharmaceuticals press release 2018*).
- Warfarin, Bevyxxa, Savaysa, and Xarelto are approved for once-daily dosing, while Eliquis is administered twice-daily. Based on the indication, Pradaxa may be administered once or twice-daily. Bevyxxa, Eliquis, Pradaxa, Savaysa, and Xarelto require a dose adjustment in patients with renal impairment and are only available as branded products.
- No head-to-head studies have been conducted comparing the TSOACs. Also, there is a lack of long-term efficacy and safety data and limited real-world experience with the TSOACs.
- In terms of current available evidence, the following has been demonstrated:
  - For those TSOACs FDA-approved for the prevention of stroke and systemic embolism in patients with NVAF, all TSOACs have been found to be superior or non-inferior to warfarin in pivotal trials; however, clinical differences have not been clearly defined (*Connolly et al 2009, Connolly et al 2014, Giugliano et al 2013, Granger et al 2011, Patel et al 2011*).
  - Eliquis, Pradaxa, Savaysa, and Xarelto have demonstrated non-inferiority to conventional therapy for acute VTE. Xarelto (EINSTEIN-PE only) and Eliquis have also demonstrated significant reductions in major bleeds; however, Pradaxa and Savaysa have similar rates of major bleeding compared to that observed with conventional therapy. Due to the design of the trials, Savaysa and Pradaxa also require 5 to 10 days of parenteral anticoagulation prior to initiating treatment (*Agnelli et al [a] 2013, Bauersachs et al 2010, Büller et al 2013, Büller et al 2012, Prins et al 2013, Schulman et al 2009, Schulman et al 2014*).
  - For the reduction of risk recurrence of VTE as demonstrated in extended VTE trials, Pradaxa, Eliquis, and Xarelto have demonstrated superiority to placebo for recurrent VTE; however, bleeding rates were comparable. Pradaxa has demonstrated non-inferiority to warfarin with less risk of major or clinically relevant bleeding and had lower major bleeding rates than those rates observed in the RE-COVER trials (*Agnelli et al [b] 2013, Bauersachs et al 2010, Schulman et al 2013*).
  - For VTE prophylaxis in patients undergoing TKR or THR surgery, Xarelto has demonstrated superiority to enoxaparin doses in both THR and TKR studies. Eliquis was found to be superior for THR and when compared to enoxaparin 40 mg once daily for TKR; however, Eliquis failed to demonstrate non-inferiority to the US enoxaparin recommended dose of 30 mg twice daily for TKR (*Eriksson et al 2008, Kakkar et al 2008, Lassen et al 2009, Lassen et al 2010 [b], Turpie et al 2009*). The FDA has approved Pradaxa for VTE prophylaxis associated with THR surgery after non-inferiority was demonstrated compared to enoxaparin 40 mg once daily and bleeding rates were similar (*Eriksson et al 2007 [a], Eriksson et al 2007 [b], Eriksson et al 2011*).
  - In hospitalized patients with restricted mobility from acute illness and other VTE risk factors, the use of oral anticoagulants has demonstrated a likelihood to reduce VTE when administered prophylactically. Studies have been conducted with Bevyxxa, Eliquis, and Xarelto; however, only Bevyxxa is specifically FDA-approved for this indication. Eliquis and Xarelto have demonstrated non-inferiority or were similar to enoxaparin, but were also associated with an increased bleeding risk. Bevyxxa was associated with numerically fewer events of asymptomatic or symptomatic proximal DVT, non-fatal PE, or VTE-related death compared to enoxaparin, but no increased incidence of major bleeding (*Cohen et al 2013, Cohen et al 2016, Gibson et al 2017, Goldhaber et al 2011*).

- Reputable societies encourage decisions to be made based on indication, patient characteristics, and a risk/benefit analysis (*Anderson et al 2013, Bushnell et al 2014, Culebras et al 2014, Doherty et al 2017, Furie et al 2012, Guyatt et al 2012, January et al 2014, Kearon et al 2016, Kernan et al 2014, Nishimura et al 2017, Otto et al 2017, Ravel et al 2017, Smith et al 2017*).

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Publication Date: March 29, 2018

Therapeutic Class Overview
Alpha-Glucosidase Inhibitors

INTRODUCTION

- Diabetes mellitus affects more than 30.3 million people in the US. A total of 84.1 million American adults have prediabetes, with 88.4% of this population unaware that they have the disease (*Centers for Disease Control and Prevention [CDC] 2017*).
- Type 2 diabetes mellitus (T2DM), the most common form of diabetes, is characterized by elevated fasting and postprandial glucose concentrations (*American Diabetes Association [ADA] 2018[a]*). It is a chronic illness that requires continuing medical care and self-management to prevent acute complications and reduce the risk of long-term complications (*ADA 2018[b]*).
- Complications of T2DM include heart disease, stroke, vision loss, kidney disease, and amputations of toes, feet, or legs. It is the leading cause of kidney failure, lower-limb amputations, and adult-onset blindness and the seventh leading cause of death in the US (*CDC 2017*).
- In addition to dietary and lifestyle management, T2DM can be treated with a variety of oral and injectable antidiabetic medications. Many patients with T2DM will require combination therapy (*Garber et al 2018*).
- Classes of oral medications for the management of blood glucose levels in patients with T2DM may work by increasing insulin secretion, increasing sensitivity to insulin, decreasing the rate of carbohydrate absorption, and blocking glucose reabsorption by the kidney (*Inzucchi et al 2015*).
- Pharmacologic options for T2DM include sulfonylureas, biguanides, thiazolidinediones (TZDs), meglitinides, alpha-glucosidase inhibitors (AGIs), dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogs, amylin mimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, combination products, and insulin (*ADA 2018[b]*).
- AGIs delay the absorption of ingested carbohydrates, resulting in a smaller rise in postprandial glucose (PPG) levels. The effect of AGIs is typically additive when used in combination with medications from other pharmacological classes due to its different mechanism of action (G*lyset Prescribing information 2016, Precose Prescribing information 2015*).
- Medispan Class: Alpha-Glucosidase Inhibitors

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Glyset (miglitol)	✔
Precose (acarbose)	✔

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. Food and Drug Administration (FDA)-Approved Indications

Indication	Glyset (miglitol)	Precose (acarbose)
As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	✔	✔

(*Prescribing information: Glyset, 2016, Precose, 2015*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- AGIs have demonstrated efficacy in the management of T2DM when used as monotherapy and in combination with other antidiabetic agents. Most trials evaluated the addition of an AGI to one or more classes of antidiabetic agents.
- Both acarbose and miglitol have consistently shown beneficial effects on hemoglobin A1c (HbA1c) and PPG when added to the following therapies:
  - Metformin (*Halimi et al 2000, Van Gaal et al 2001, Wang et al 2013*)
  - Sulfonylureas (*Bayraktar et al 1996, Hsieh et al 2011, Lin et al 2003*)

- Insulin (*Hwu et al 2003, Nemeto et al 2011, Schnell et al 2007*)
- Combination sulfonylurea and metformin (*Lam et al 1998, Standl et al 2001*)

- However, clinical trial results have demonstrated inconsistent effects on fasting plasma glucose (FPG) (*Halimi et al 2000, Hsieh et al 2011, Hwu et al 2003, Lam et al 1998, Lin et al 2003, Standl et al 2001, Van Gaal et al 2001*).
- In addition, acarbose has been compared to other classes of antidiabetics in a number of trials. Bayraktar et al performed a small crossover study (N = 18) comparing acarbose 100 mg 3 times daily to metformin 500 mg 3 times daily in patients with T2DM inadequately controlled on maximal doses of a sulfonylurea. Results demonstrated that both treatments improved FPG, PPG, and HbA1c; acarbose lowered PPG to a greater extent than metformin ($p < 0.05$) (*Bayraktar et al 1996*). Two studies compared acarbose to a sulfonylurea in patients with T2DM without previous pharmacologic treatment. In these studies, acarbose was associated with smaller reductions in HbA1c and FPG compared to tolbutamide (*van de Laar et al 2004*) and glimepiride (*Feinbock et al 2003*). Acarbose 100 mg 3 times daily was compared to bedtime NPH insulin in a small crossover study of patients inadequately controlled with combination sulfonylurea and metformin. In this study, acarbose demonstrated reductions in FPG and PPG, but overall results were superior in the insulin-treated group (*Lopez-Alvarenga 1999*). When compared to vildagliptin (*Pan et al 2008*) and to repaglinide (*Derosa et al 2009*), acarbose demonstrated comparable effects on PPG and HbA1c, and superior effects on weight loss. A comparison of acarbose and saxagliptin in 488 Chinese patients uncontrolled on metformin alone found that saxagliptin was non-inferior to acarbose in glycemic control, but was associated with fewer gastrointestinal adverse events (*Du et al 2017*).
- Miglitol has also been compared to other classes of diabetes treatments in a small number of trials. Johnston et al compared two doses of miglitol to glyburide for the treatment of drug-naïve patients greater than 60 years of age with T2DM. In this study, glyburide had greater beneficial effects on HbA1c, but miglitol had greater beneficial effects on body weight and one-hour PPG levels (in the miglitol 50 mg group). The glyburide group also had a higher incidence of hypoglycemia (*Johnston et al 1998*). Another study compared miglitol to metformin and the combination of both for the treatment of patients with T2DM inadequately treated with diet. In this trial, improvement in HbA1c, FPG, and PPG were numerically greater with metformin compared to miglitol, and with combination treatment compared to metformin. P-values were not provided for comparison between the monotherapy arms, because the primary comparison for efficacy was between the metformin monotherapy and the combination therapy group (*Chiasson et al 2001*).
- The effects of acarbose on cardiovascular outcomes in patients with coronary heart disease and impaired glucose tolerance was evaluated in the ACE trial (*Holman et al 2017*). The primary endpoint for the trial was a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospital admission for unstable angina, and hospital admission for heart failure. The incidence of new onset diabetes was evaluated as a secondary endpoint. A total of 6522 Chinese patients were randomized 1:1 to acarbose or placebo. After a median follow up period of 5 years, there was no significant difference in the incidence of the primary endpoint (14% with acarbose vs 15% with placebo; hazard ratio [HR], 0.98; 95% confidence interval [CI], 0.86 to 1.11; $p = 0.73$). Fewer patients in the acarbose group developed diabetes (rate ratio [RR], 0.82; 95% CI, 0.71 to 0.94).
- A 2005 Cochrane review reported that acarbose has clear beneficial effects on glycemic control compared to placebo, but no clinically relevant effects on body weight or lipids. Authors noted that few data are available on the effects of AGIs on morbidity, mortality, or quality of life (*van de Laar et al 2005*). Acarbose has been compared to placebo for major cardiovascular events in 1,429 obese patients with impaired glucose tolerance tests over 3 years (*Chiasson et al 2003*). Acarbose was associated with a 2.5% absolute risk reduction and 49% relative risk reduction (HR, 0.51; 95% CI, 0.25 to 0.95; $p = 0.03$) in the development of any cardiovascular event. Fewer patients treated with acarbose (17%) developed diabetes compared to the placebo group (26%) (HR, 0.68; 95% CI, 0.54 to 0.85; $p = 0.001$) (*Chiasson et al 2002*).
- A systematic review of 136 trials showed that most oral agents including TZDs, metformin, and repaglinide improved glycemic control to the same degree as sulfonylureas, with an absolute decrease in HbA1c level of about 1% (moderate-to-high strength of evidence) (*Bolen et al 2007*). Nateglinide and AGIs have slightly weaker effects, on the basis of indirect comparisons of placebo-controlled trials (low strength of evidence).
- A network meta-analysis evaluating the efficacy of 12 oral agents calculated surface under the cumulative ranking curves (SUCRA) based on direct and indirect evidence from 15 trials (*Wang et al 2017*). The analysis concluded that the HbA1c and FPG SUCRA values were highest for liraglutide and lowest for acarbose, suggesting that acarbose is the least effective for glycemic control.

CLINICAL GUIDELINES

- **American Diabetes Association (ADA):** Standards of Medical Care in Diabetes (2018)

- When lifestyle efforts alone do not achieve or maintain glycemic goals, metformin (if not contraindicated and if tolerated) is the preferred initial pharmacological agent for T2DM.
- Initiation of insulin therapy (with or without additional agents) should be considered in patients with newly diagnosed T2DM who are markedly symptomatic and/or have blood glucose levels ≥ 300 mg/dL or HbA1c ≥ 10%.
- If noninsulin monotherapy at the maximum tolerated dose does not achieve or maintain the HbA1c target after 3 months, a second oral agent (eg, sulfonylurea, TZD, DPP-4 inhibitor, SGLT-2 inhibitor), a GLP-1 receptor agonist, or basal insulin should be added. For patients with atherosclerotic cardiovascular disease, a second agent with evidence of cardiovascular risk reduction should be considered instead.
- A patient-centered approach should be used to guide the choice of pharmacological agents. Considerations include efficacy, cost, potential adverse events, weight, comorbidities, hypoglycemia risk, and patient preferences.
- Advantages of AGIs include low risk for hypoglycemia and decreased postprandial glucose excursions, while disadvantages include modest efficacy, gastrointestinal side effects, and frequent dosing schedule. The guidelines do not recommend AGIs in their general recommendation treatment algorithm (*ADA 2018[b]*).

- **American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE):** Type 2 Diabetes Management Algorithm – Executive Summary (2018)
  - For patients with recent onset T2DM or mild hyperglycemia (HbA1c < 7.5%), monotherapy with metformin is preferred. Alternatives include GLP-1 receptor agonists, SGLT-2 inhibitors, DPP-4 inhibitors, and AGIs. Sulfonylureas, TZDs, and glinides may be used with caution.
  - For patients with a HbA1c ≥ 7.5%, metformin or another first-line agent with a second agent (eg, GLP-1 receptor agonist, SGLT2 inhibitor, DPP-4 inhibitor, colesevelam, bromocriptine quick release, or an AGI) should be initiated. TZD, basal insulin, or sulfonylurea/glinide should be used with caution.
  - AGIs have modest HbA1c -lowering effects and low risk for hypoglycemia. While clinical trials have suggested cardiovascular benefit in patients with impaired glucose tolerance and diabetes, side effects (eg, bloating, flatulence, diarrhea) have limited their use in the US. AGIs should be used with caution in patients with chronic kidney disease (*Garber et al 2018*).

SAFETY SUMMARY

- Contraindications:
  - Hypersensitivity to the drugs or any of their components
  - Diabetic ketoacidosis
  - Cirrhosis (acarbose only)
  - Chronic intestinal diseases associated with marked disorders of digestion or absorption, or with conditions that may deteriorate as a result of increased gas formation in the intestine
  - Inflammatory bowel disease, colonic ulceration, partial intestinal obstruction, or patients predisposed to intestinal obstruction
- Adverse Events:
  - The most common adverse events are gastrointestinal in nature, including flatulence, diarrhea, and abdominal pain/distention.
  - Acarbose has been associated with elevated serum transaminase levels.
  - Miglitol has been associated with skin rash.
- Drug Interactions:
  - Intestinal adsorbents (eg, charcoal) and digestive enzyme preparations containing carbohydrate-splitting enzymes (eg, amylase, pancreatin) may reduce the effect of AGIs and should not be taken concomitantly.
  - Miglitol reduces the bioavailability of ranitidine and propranolol.
  - Acarbose may reduce the bioavailability of digoxin; dose adjustment of digoxin may be necessary.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Glyset (miglitol)	Tablets	Oral	Three times daily at the start of each meal	Avoid use in CrCl < 25 mL/min Not recommended in nursing women

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Precose (acarbose)	Tablets	Oral	Three times daily at the start of each meal	Avoid use in SCr > 2 mg/dL Not recommended in nursing women

Abbreviations: CrCl = creatinine clearance; SCr = serum creatinine
See the current prescribing information for full details

CONCLUSION

- AGIs are one of several oral drug classes used for the treatment of T2DM. Both acarbose and miglitol have demonstrated benefits for reducing glucose parameters, particularly HbA1c and PPG levels. Effects on FPG were inconsistent across studies.
- Effects on HbA1c, in the range of 0.7 to 0.8%, are modest compared to other classes of antidiabetics.
- While AGIs are not associated with hypoglycemia when given as monotherapy, they can contribute to hypoglycemia when administered in combination with other agents used to treat T2DM.
- Both acarbose and miglitol are poorly tolerated due to GI effects such as abdominal pain, flatulence, and diarrhea.
- Available clinical guidelines are consistent in their recommendation to use metformin as first-line therapy for T2DM unless contraindicated (*ADA 2018[b], Garber et al 2018, Inzucchi et al 2015, Qaseem et al 2017*). AGIs are listed as one of several potential alternatives or add-on therapies; however, AGIs are not among the agents preferentially recommended in combination with metformin as dual or triple combination therapy for patients with T2DM.
- Both available AGIs require a frequent dosing schedule of 3 times daily at the start of each main meal.
- Acarbose and miglitol have not been directly compared to one another in a randomized trial, and few distinctions can be made between them. Acarbose has been studied in a larger number of clinical trials and is not significantly absorbed. In contrast, miglitol has been studied in a smaller number of trials, is absorbed systemically, and is eliminated renally.

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Publication Date: March 20, 2018

Therapeutic Class Overview
Incretin Mimetics & Amylinomimetics

INTRODUCTION

- Diabetes mellitus affects more than 30 million people in the United States (U.S.) (*Centers for Disease Control and Prevention [CDC] 2017*).
- Diabetes mellitus is defined as a group of metabolic disorders characterized by hyperglycemia that result from defects in the secretion and action of insulin (*American Diabetes Association [ADA] Diabetes Basics 2018*).
- The classification of diabetes includes 4 clinical classes: 1) type 1 diabetes mellitus (T1DM) which results from beta-cell (β-cell) destruction, usually leading to absolute insulin deficiency, 2) type 2 diabetes mellitus (T2DM) which results from a progressive insulin secretory defect on the background of insulin resistance, 3) other specific types of diabetes due to other causes, eg, genetic defects in β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced (such as in the treatment of human immunodeficiency virus/acquired immunodeficiency syndrome or after organ transplantation), and 4) gestational diabetes mellitus (GDM) (diabetes diagnosed during pregnancy that is not clearly overt diabetes) (*ADA 2018*).
- Insulin is the standard treatment for T1DM. Pharmacologic options for T2DM include sulfonylureas (SFUs), biguanides, thiazolidinediones (TZDs), meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, amylinomimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, combination products, and insulin.
- The GLP-1 receptor agonists (albiglutide, dulaglutide, exenatide, exenatide extended-release [ER], liraglutide, lixisenatide, and semaglutide) were developed to mimic the effects of endogenous GLP-1 and are Food and Drug Administration (FDA)-approved as adjunctive therapy to diet and exercise to improve glycemic control in adults with T2DM.
- Pramlintide is the only amylin analog, or amylinomimetic, in the class, and is FDA-approved as an adjunctive treatment with insulin in patients with T1DM or T2DM who have failed to achieve desired glucose control despite optimal insulin therapy. It is a synthetic analog of human amylin, a naturally occurring neuroendocrine hormone synthesized by pancreatic β-cells that contributes to glucose control during the post-prandial period.
- This review will focus on the GLP-1 receptor agonists and pramlintide and their respective FDA-approved indications for treatment of diabetes. Liraglutide (Saxenda) is also indicated as adjunctive therapy for chronic weight management; however, the use of liraglutide for this indication will not be included in this review.
- Medispan class: Endocrine and Metabolic Drugs; Incretin Mimetic Agents (GLP-1 Receptor Agonists) and Amylin Analogs

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Adlyxin (lixisenatide)	-
Bydureon (exenatide ER)	-
Bydureon BCise (exenatide ER)	-
Byetta (exenatide)	-
Ozempic (semaglutide)	-
Symlin (pramlintide)	-
Tanzeum (albiglutide)*	-
Trulicity (dulaglutide)	-
Victoza (liraglutide)	-

*On July 26, 2017, the manufacturer announced plans to discontinue the manufacturing and sale of Tanzeum by July 2018 due to business reasons (*Tanzeum Discontinuation FAQ 2017*).

(*DRUGS@FDA 2018*, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. FDA Approved Indications

Indication	Adlyxin (lixisenatide)	Byetta (exenatide)	Bydureon (exenatide ER)	Bydureon BCise (exenatide ER)	Ozempic (semaglutide)	Symlin (pramlintide)	Tanzeum (albiglutide)	Trulicity (dulaglutide)	Victoza (liraglutide)
T1DM, as an adjunctive treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.						✔			
T2DM, as an adjunctive treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.						✔			
Adjunct to diet and exercise to improve glycemic control in adults with T2DM.	✔	✔	✔	✔	✔		✔	✔	✔
Reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction [MI], or non-fatal stroke) in adults with T2DM and established cardiovascular disease									✔
Limitations of Use									
Not recommended as first-line therapy for patients inadequately controlled on diet and exercise because of the uncertain relevance of the rodent C-cell tumor findings to humans. Prescribe only to patients for whom the potential benefits are considered to outweigh the potential risk.			✔	✔	✔		✔	✔	
Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in these patients.	✔	✔	✔	✔	✔		✔	✔	
Not indicated in treatment of patients with T1DM or for treatment of patients with diabetic ketoacidosis. Not a substitute for insulin in these patients.	✔	✔	✔	✔	✔		✔	✔	✔
Has not been studied in patients with severe gastrointestinal (GI) disease, including severe gastroparesis. Not recommended in patients with pre-							✔	✔	

Indication	Adlyxin (lixisenatide)	Byetta (exenatide)	Bydureon (exenatide ER)	Bydureon BCise (exenatide ER)	Ozempic (semaglutide)	Symlin (pramlintide)	Tanzeum (albiglutide)	Trulicity (dulaglutide)	Victoza (liraglutide)
existing severe GI disease.									
Has not been studied in patients with gastroparesis. Not recommended in patients with gastroparesis.	✔								
Not studied in combination with prandial/short-acting insulin.	✔	✔					✔		✔
Use with insulin has not been studied and is not recommended.			✔	✔					

(Prescribing information: *Adlyxin 2016*, *Bydureon 2017, Bydureon BCise 2017, Byetta 2015, Ozempic 2017, Symlin 2016, Tanzeum 2017, Trulicity 2017, Victoza 2017*)

NOTE: Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Albiglutide

- The approval of albiglutide was based on 8 pivotal trials involving over 5000 patients as a part of the HARMONY phase 3 program (*Tanzeum FDA Medical Review 2014*, *Tanzeum Prescribing Information 2017*). The majority of the trials were multicenter (MC), randomized, double-blind (DB), placebo-controlled (PC) or active control (AC) studies in adult patients with inadequately controlled T2DM (HbA1c 7% to 10%); however, 3 trials were open-label (OL). The primary outcome in each trial was change in HbA1c from baseline at 26 to 104 weeks.
  - HARMONY 1 demonstrated that albiglutide 30 mg once weekly was superior to placebo in patients taking concurrent pioglitazone with or without metformin at 52 weeks, with a mean reduction in HbA1c of 0.8% (*Reusch et al 2014*).
  - HARMONY 2 compared both albiglutide 30 mg and 50 mg once weekly to placebo in patients treated with diet and exercise alone and found that both were superior to placebo at 52 weeks. The least squares mean difference from placebo in HbA1c was -0.84% with the 30 mg dose and -1.04% with the 50 mg dose (*Nauck et al 2016*).
  - HARMONY 3 demonstrated that albiglutide 30 mg to 50 mg once weekly was superior to placebo, sitagliptin 100 mg once daily, and glimepiride 2 to 4 mg daily in patients taking concurrent metformin at 2 years, with a mean reduction in HbA1c of 0.6% (*Ahrén et al 2014*).
  - HARMONY 4 was an OL trial comparing albiglutide (30 mg to 50 mg once weekly) to protocol-titrated insulin glargine in patients taking concurrent metformin with or without an SFU. In this study, albiglutide demonstrated noninferiority to insulin glargine in HbA1c improvement at 52 weeks (*Weissman et al 2014*).
  - HARMONY 5 compared albiglutide (30 mg to 50 mg once weekly) to placebo and pioglitazone (30 mg to 45 mg per day) in patients taking concurrent metformin and glimepiride. At week 52, albiglutide did not meet the pre-specified noninferiority margin compared to pioglitazone; however, it was superior to placebo and had a mean reduction in HbA1c of 0.6% (*Home et al 2015*).
  - HARMONY 6, another OL trial, demonstrated that albiglutide 30 mg to 50 mg once weekly was noninferior to insulin lispro 3 times daily in patients taking concurrent pioglitazone with or without metformin at 26 weeks, with a mean reduction in HbA1c of 0.8% (*Rosenstock et al 2014a*).
  - HARMONY 7 was an OL study comparing albiglutide 50 mg once weekly to liraglutide 1.8 mg daily in patients taking concomitant metformin, TZD, SFU, or a combination of the medications. At week 32, the mean model adjusted change in HbA1c was -0.78% with albiglutide and -0.99% with liraglutide. Albiglutide failed to meet noninferiority (p = 0.085) (*Pratley et al 2014*).

- HARMONY 8 demonstrated that albiglutide 30 mg to 50 mg was superior to sitagliptin 25 to 100 mg in patients with impaired renal function on concurrent agents or lifestyle treatment at 26 weeks, with a mean reduction in HbA1c of 0.8% compared to a reduction of 0.5% with sitagliptin (*Leiter et al 2014*).

Dulaglutide

- The approval of dulaglutide was based on 6 pivotal trials enrolling over 3,000 patients as a part of the AWARD phase 3 program. Trials evaluated the use of dulaglutide 0.75 mg and 1.5 mg strengths. The primary outcome in each trial was the change in HbA1c from baseline to 26 through 52 weeks.
  - AWARD-1 demonstrated that once weekly dulaglutide resulted in significantly larger improvements in HbA1c at 26 weeks compared to placebo and exenatide in patients taking maximally tolerated doses of metformin and pioglitazone (*Wysham et al 2014*).
  - AWARD-2 was an OL study that demonstrated superiority of dulaglutide 1.5 mg once weekly and noninferiority of dulaglutide 0.75 mg once weekly compared to daily insulin glargine in terms of HbA1c reduction from baseline to week 52 (*Giorgino et al 2015*).
  - AWARD-3 was a DB study that demonstrated superiority of dulaglutide 0.75 mg and 1.5 mg once weekly to metformin in patients inadequately treated with diet and exercise with or without submaximal dosing of at least 1 oral antidiabetic drug (OAD). At 26 weeks, changes from baseline HbA1c were 0.78%, 0.71%, and 0.56% for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and metformin, respectively (*Umpierrez et al 2014*).
  - AWARD-4 was an OL, 52-week, noninferiority study which found that dulaglutide once-weekly (both 1.5 mg and 0.75 mg strengths) in combination with insulin lispro resulted in significantly greater improvement in glycemic control than insulin glargine in combination with insulin lispro ($p = 0.005$ and $p = 0.015$ for dulaglutide 1.5 mg and 0.75 mg, respectively) (*Blonde et al 2015*).
  - AWARD-5 was a DB trial that compared placebo, once-weekly dulaglutide (0.75 mg and 1.5 mg), and sitagliptin 100 mg once daily in uncontrolled metformin-treated patients. At weeks 52 and 104, both dulaglutide strengths were superior to sitagliptin in terms of HbA1c reduction from baseline ($p < 0.001$ for all comparisons) (*Nauck et al 2014, Weinstock et al 2015*).
  - AWARD-6 was an OL trial which demonstrated that, in patients taking concurrent metformin, dulaglutide 1.5 mg once weekly was noninferior to liraglutide once daily in HbA1c reduction from baseline to week 26 (*Dungan et al 2014*).

Exenatide

- The efficacy of exenatide as add-on therapy to metformin alone, an SFU alone, or metformin in combination with an SFU was evaluated in 3 PC, 30-week, randomized controlled trials (RCTs). In all trials, there were significant decreases in HbA1c with exenatide compared to placebo ($p < 0.001$, $p < 0.002$, and $p < 0.0001$, respectively) (*Buse et al 2004, DeFronzo et al 2005, Kendall et al 2005*). Extensions of these 30-week trials demonstrated that the benefits of exenatide are sustained (*Blonde et al 2006, Buse et al 2007, Klonoff et al 2008, Ratner et al 2006, Riddle et al 2006*).
- A trial evaluating exenatide as add-on therapy in patients currently taking a TZD found that at week 16, exenatide significantly decreased HbA1c ($p < 0.001$), fasting plasma glucose (FPG) ($p < 0.001$), and body weight ($p < 0.001$) compared to placebo (*Zinman et al 2007*).
- When exenatide was compared to glyburide as add-on therapy to metformin, exenatide significantly decreased body weight and body mass index (BMI) ($p < 0.001$ for both), whereas the SFU caused significant increases in both ($p < 0.05$ for both). Both treatments significantly decreased HbA1c, FPG, and postprandial plasma glucose (PPG) (exenatide; $p < 0.001$ for all; glyburide; $p < 0.001$ for all). Only exenatide significantly improved insulin resistance ($p < 0.01$) and β-cell function ($p < 0.05$) (*Derosa et al 2010*).
- The EUREXA study compared the efficacy of exenatide and glimepiride as add-on therapy to metformin. Patients receiving exenatide exhibited greater reductions in HbA1c from baseline (-0.36%), compared to those receiving glimepiride (-0.21%; $p = 0.002$) (*Gallwitz et al 2012*).
- Several trials have compared exenatide to insulin therapy as add-on therapy to metformin and/or an SFU (*Bunck et al 2009, Bunck et al 2010, Davies et al 2009, Heine et al 2005, Nauck et al 2007, Secnik et al 2006*). Similar improvements in HbA1c between treatments were observed in 3 of the trials while mixed results were observed for decreases in FPG. Specifically, in 2 trials, insulin therapy was “superior” in decreasing FPG (p value not reported and $p < 0.0001$), while in another trial there was no difference between the 2 treatments ($p = 0.689$). Insulin therapy was associated with an increase in body weight compared to a decrease with exenatide (*Bunck et al 2009, Heine et al 2005, Nauck et al 2007*). Patient-reported health outcome measures demonstrated no differences between exenatide or insulin therapy; both achieved significant improvements from baseline. However, neither treatment improved Diabetes Treatment Flexibility Scores ($p = 0.93$ for both) (*Secnik et al 2006*).

- Exenatide once weekly was also compared to daily insulin glargine in diabetic patients inadequately controlled with OADs. Following 26 weeks of therapy, exenatide was found to be statistically noninferior to insulin glargine for the change in HbA1c from baseline to endpoint (*Inagaki et al 2012*).

Exenatide ER

- Approval of exenatide ER in the management of T2DM was based on the clinical evidence for safety and efficacy derived from the DURATION trials (1 through 5). Exenatide ER was added to existing antidiabetic regimens in 4 of the 5 trials (1, 2, 3, and 5). In contrast, DURATION-4 compared exenatide ER, metformin, pioglitazone, and sitagliptin all as monotherapy (*Bergenstal et al 2010, Blevins et al 2011, Diamant et al 2010, Drucker et al 2008, Russell-Jones et al 2012*).
  - Overall, exenatide ER as add-on therapy to existing antidiabetic regimens significantly decreased HbA1c compared to exenatide ($p < 0.005$), sitagliptin ($p < 0.0001$), pioglitazone ($p = 0.0165$), and insulin therapy ($p = 0.017$), with no increased risk of hypoglycemia. In terms of decreases in body weight, exenatide ER was superior compared to sitagliptin ($p = 0.0002$) and pioglitazone ($p < 0.0001$), and similar compared to exenatide ($p = 0.89$) (*Bergenstal et al 2010, Blevins et al 2011, Drucker et al 2008*).
  - As expected, GI-related adverse events (AEs) were reported more commonly with the incretin-based therapies. When compared to exenatide, exenatide ER was associated with lower incidences of nausea (14.0% vs 35.0%) and vomiting (4.7% vs 8.9%), and higher incidences of diarrhea (9.3% vs 4.1%) and injection site-related AEs (13% vs 10%) (*Blevins et al 2011*).
  - In the DURATION-4 trial, the decrease in HbA1c achieved with exenatide ER monotherapy was superior compared to sitagliptin ($p < 0.001$) and similar compared to metformin ($p = 0.62$) and pioglitazone ($p = 0.328$). Exenatide ER and metformin were similar in terms of associated decreases in body weight, with exenatide ER achieving superiority compared to sitagliptin and pioglitazone. Overall, exenatide ER was associated with more GI-related AEs, with the exception of diarrhea which occurred at the highest frequency in patients receiving metformin (*Diamant et al 2010*).
- In a post-hoc analysis of 4 clinical trials, patients were treated with weekly exenatide for 52 weeks. Patients had significant lowering of HbA1c, blood pressure and low density lipoprotein (LDL) levels without an increase in weight or hypoglycemia (*Bergenstal et al 2013*).
- The DURATION-6 trial compared HbA1c reductions between liraglutide once daily and exenatide once weekly in patients with T2DM previously treated with lifestyle modifications and oral agents. Both therapies resulted in improvements in glycemic control; however, greater reductions were noted with liraglutide (*Buse et al 2013*).
- Bydureon BCise is a new formulation of Bydureon that is administered via an autoinjector device. It was approved based on the results of two 28-week, OL, AC trials. In the DURATION-NEO-1 trial, Bydureon BCise 2 mg once weekly achieved a statistically significant HbA1c reduction vs Byetta 10 mcg twice daily ($p < 0.05$) in patients with T2DM inadequately controlled with diet and exercise alone or with a stable regimen of metformin, an SFU, a TZD, or a combination of any 2 of these agents. In the DURATION-NEO-2 trial, Bydureon BCise 2 mg once weekly achieved a statistically significant HbA1c reduction vs placebo ($p < 0.05$) in patients with T2DM on metformin. The difference vs sitagliptin was -0.28% (95% CI, -0.62% to -0.02%) (*Bydureon BCise Prescribing Information 2017, Gadde et al 2017, Wysham et al 2017*).

Liraglutide

- Approval of liraglutide in the management of T2DM was based on the clinical evidence for safety and efficacy derived from the LEAD trials (1 through 6). The LEAD trials evaluated liraglutide monotherapy (LEAD-3); add-on therapy to an SFU (LEAD-1), metformin (LEAD-2), metformin plus a TZD (LEAD-4), metformin plus an SFU (LEAD-5); and monotherapy head-to-head with exenatide (LEAD-6).
  - In LEAD-1, liraglutide was compared to placebo or rosiglitazone as add-on therapy to an SFU. After 26 weeks, liraglutide (0.6, 1.2, and 1.8 mg per day) significantly decreased HbA1c compared to placebo ($p < 0.0001$ for all), with only higher doses achieving superiority compared to rosiglitazone ($p < 0.001$ for both) (*Marre et al 2009*).
  - In LEAD-2, liraglutide was compared to placebo and an SFU as add-on therapy to metformin. Liraglutide significantly decreased HbA1c compared to placebo; however, similar decreases were observed with liraglutide compared to the SFU. Liraglutide was associated with significant decreases in body weight compared to placebo ($p < 0.01$) and the SFU ($p < 0.001$) (*Nauck et al 2009*). Results of an 18-month OL extension trial were consistent with the DB study (*Nauck et al 2013*).
  - In LEAD-3, liraglutide was compared to an SFU as monotherapy, and liraglutide was superior in decreasing HbA1c ($p = 0.0014$ and $p < 0.0001$ for liraglutide 1.2 mg and 1.8 mg, respectively). In addition, increases in body weight were reported with the SFU, while liraglutide significantly decreased body weight ($p = 0.027$) (*Garber et al 2009*). In a 1-

year extension trial, patients continuing liraglutide for a total of 2 years maintained significant improvements in HbA1c compared to the SFU (*Garber et al 2011*).
- In LEAD-4 and LEAD-5, liraglutide was compared to placebo as add-on therapy to metformin plus an SFU and to a TZD. LEAD-5 also had an OL arm of insulin therapy. Results achieved with liraglutide in terms of decreases in HbA1c, body weight, and FPG compared to placebo were similar to those observed in the other LEAD trials (*Russell-Jones et al 2009; Zinman et al 2009*). When compared to insulin therapy, decreases in HbA1c ($p = 0.0015$) and body weight ($p < 0.001$) and improvements in β-cell function ($p = 0.0019$) were significantly greater with liraglutide. It was noted that decreases in PPG were not different between the 2 treatments, and the likelihood of patients achieving FPG goals were also similar (*Russell-Jones et al 2009*).
- LEAD-6 was a head-to-head trial comparing liraglutide to exenatide as add-on therapy to existing antidiabetic treatment regimens. Liraglutide significantly decreased HbA1c compared to exenatide (1.12% vs 0.79%; $p < 0.0001$), and a significantly greater proportion of patients receiving liraglutide achieved HbA1c goals of < 7%. Significant decreases in FPG were also achieved with liraglutide ($p < 0.0001$); however, exenatide significantly decreased PPG after breakfast and dinner ($p < 0.0001$ and $p = 0.0005$) (*Buse et al 2009*). A 14-week, extension trial revealed that patients who were switched from exenatide to liraglutide achieved additional glycemic control and cardiometabolic benefits (*Buse et al 2010*).

Lixisenatide

- The approval of lixisenatide was based on several phase 3 trials as part of the GetGoal clinical trial program. Lixisenatide 20 mcg once daily was evaluated as monotherapy, in combination with OADs, and in combination with basal insulin (with or without OADs). Its efficacy was compared with placebo, exenatide, and insulin glulisine. The primary endpoint, the difference in change in HbA1c from baseline to trial end between the lixisenatide and comparator groups, was assessed at varying time points ranging between 12 and 26 weeks.
  - GetGoal-Mono found that lixisenatide 20 mcg once daily as monotherapy resulted in significantly larger improvements in HbA1c at 12 weeks compared to placebo in patients with T2DM inadequately controlled on diet and exercise ($p < 0.0001$) (*Fonseca et al 2012*).
  - GetGoal-F1 was a DB study which found that lixisenatide 20 mcg once daily as add-on therapy to metformin was superior vs placebo in terms of HbA1c reduction from baseline to week 24. The least squares mean change from baseline was -0.26% for the placebo group vs -0.72% for the lixisenatide group. The difference vs placebo was -0.46% ($p < 0.0001$) (*Adlyxin Prescribing Information 2016, Bolli et al 2014*).
  - GetGoal-M-Asia demonstrated superiority of lixisenatide 20 mcg once daily as add-on therapy to metformin with or without an SFU compared to placebo in terms of HbA1c reduction from baseline to week 24 (*Yu et al 2014*).
  - GetGoal-S was a 24-week, DB study which found that lixisenatide 20 mcg once daily in combination with an SFU with or without metformin resulted in significantly greater improvement in glycemic control than placebo; the difference from placebo in change in HbA1c was -0.58% ($p < 0.0001$) (*Adlyxin Prescribing Information 2016, Rosenstock et al 2014b*).
  - GetGoal-P was a 24-week, DB study which found that lixisenatide 20 mcg once daily in combination with pioglitazone or without metformin resulted in significantly greater improvement in glycemic control than placebo; the difference from placebo in change in HbA1c was -0.48% ($p < 0.0001$) (*Adlyxin Prescribing Information 2016, Pinget al 2013*).
  - In GetGoal-Duo 1, lixisenatide was compared to placebo as add-on therapy to basal insulin and metformin with or without a TZD. Treatment with lixisenatide resulted in a significant reduction in HbA1c at week 24 vs placebo (*Riddle et al 2013a*).
  - In GetGoal-L, lixisenatide was compared to placebo as add-on therapy to basal insulin with or without metformin while in Get-Goal-L-Asia, lixisenatide was compared to placebo as add-on therapy to basal insulin with or without an SFU. Both studies found that lixisenatide was superior to placebo in terms of HbA1c reduction from baseline to week 24 (*Riddle et al 2013b, Seino et al 2012*).
  - GetGoal-Duo 2 was a 26-week, OL trial that compared lixisenatide to insulin glulisine once daily or 3 times daily for intensification of optimized insulin glargine ± metformin in patients with T2DM uncontrolled on basal insulin ± OADs (ie, an SFU and/or a DPP-4 inhibitor, and/or a glinide). Lixisenatide was found to be noninferior to both insulin glulisine regimens in terms of HbA1c reduction from baseline to week 26. However, lixisenatide provided less HbA1c reduction than insulin glulisine 3 times daily and the difference was statistically significant; the least squares mean difference of lixisenatide vs insulin glulisine 3 times daily was 0.23 ($p = 0.0002$) (*Adlyxin Prescribing Information 2016, Rosenstock et al 2016*).
  - GetGoal-X was a 24-week, OL trial that evaluated lixisenatide vs exenatide twice daily as add-on therapy to metformin. Lixisenatide met the pre-specified noninferiority margin vs exenatide twice daily for the difference in

HbA1c reduction from baseline to week 24. However, lixisenatide provided less HbA1c reduction than exenatide and the difference was statistically significant; the least squares mean difference vs exenatide was 0.17% (p = 0.0175) (*Adlyxin Prescribing Information 2016, Rosenstock et al 2013*).
  - A meta-analysis (MA) of 76-week data from 5 trials in the GetGoal clinical trial program (GetGoal-M, GetGoal-F1, GetGoal-S, GetGoal-P, and GetGoal-L) supported the sustained efficacy and tolerability of lixisenatide (*Broglio et al 2017*).

Semaglutide

- The approval of semaglutide was based on several phase 3 trials as part of the SUSTAIN clinical trial program. Semaglutide was evaluated as monotherapy, in combination with OADs, and in combination with basal insulin. Its efficacy was compared with placebo, sitagliptin, exenatide ER, insulin glargine, and dulaglutide. The primary endpoint, the difference in change in HbA1c from baseline to trial end between the semaglutide and comparator groups, was assessed at varying time points ranging between 30 and 56 weeks.
  - SUSTAIN 1 was a 30-week, PC trial which found that semaglutide 0.5 mg and 1 mg weekly significantly improved HbA1c vs placebo (p < 0.0001) (*Sorli et al 2017)*.
  - SUSTAIN 2 was a 56-week, OL trial that compared semaglutide 0.5 mg and 1 mg weekly to sitagliptin 100 mg daily in patients on metformin and/or TZDs. Compared with sitagliptin, treatment with semaglutide resulted in statistically significant reductions in HbA1c from baseline to week 56. The mean change from baseline was -1.3% for semaglutide 0.5 mg, -1.5% for semaglutide 1 mg, and -0.7% for sitagliptin. The difference vs sitagliptin was -0.6% (p < 0.0001) for semaglutide 0.5 mg and -0.8% (p < 0.0001) for semaglutide 1 mg (*Ahrén et al 2017, Ozempic Prescribing Information 2017*).
  - SUSTAIN 3 was a 56-week, OL trial that compared semaglutide 1 mg to exenatide ER 2 mg once weekly. At week 56, mean change from baseline in HbA1c was -1.4% in the semaglutide group vs -0.9% in the exenatide ER group (difference: -0.5%, p < 0.0001) (*Ahmann et al 2018, Ozempic Prescribing Information 2017*).
  - SUSTAIN 4 was a 30-week OL, AC trial in patients on metformin with or without an SFU that compared semaglutide 0.5 mg and 1 mg to insulin glargine initiated at 10 units once daily. Compared with insulin glargine, treatment with semaglutide resulted in statistically significant reductions in HbA1c from baseline to week 30. The mean change from baseline was -1.2% for semaglutide 0.5 mg, -1.5% for semaglutide 1 mg, and -0.9% for insulin glargine. The difference vs insulin glargine was -0.3% (p < 0.0001) for semaglutide 0.5 mg and -0.6% (p < 0.0001) for semaglutide 1 mg (*Aroda et al 2017*, *Ozempic Prescribing Information 2017*).
  - SUSTAIN 5 was a 30-week, DB, PC trial in patients inadequately controlled with basal insulin, with or without metformin, which found that semaglutide 0.5 mg and 1 mg significantly reduced HbA1c vs placebo (p < 0.0001) (*Ozempic Prescribing Information 2017).*
  - SUSTAIN 7 was a 40-week, OL trial that compared semaglutide to dulaglutide once weekly in patients on metformin monotherapy. From a mean baseline HbA1c of 8.2%, semaglutide 0.5 mg achieved a statistically significant reduction of 1.5% vs a reduction of 1.1% with dulaglutide 0.75 mg at week 40, while semaglutide 1.0 mg achieved a statistically significant reduction of 1.8% vs a reduction of 1.4% with dulaglutide 1.5 mg (both p < 0.0001 for noninferiority and superiority) *(Pratley et al 2018).*

Cardiovascular (CV) outcomes

- Several RCTs designed to assess the impact of incretin-based therapy on CV outcomes are in progress, including trials for albiglutide (HARMONY Outcomes, results expected in March 2018) and dulaglutide (REWIND, results expected in July 2018) (*ClinicalTrials.gov [NCT01394952, NCT02465515] 2018)*.
- A MC, DB, PC, RCT (EXSCEL trial; N = 14,752) was conducted to evaluate the long-term effects of exenatide ER vs placebo, as added to usual care, on CV outcomes in patients with T2DM with or without previous CV disease. A total of 73.1% of patients had previous CV disease, and the median follow-up was 3.2 years. A primary composite outcome event (CV death, non-fatal MI, or non-fatal stroke) occurred in 11.4% of patients in the exenatide ER group vs 12.2% in the placebo group (hazard ratio [HR], 0.91; 95% confidence interval [CI], 0.83 to 1.00). Thus, exenatide ER was found to be noninferior to placebo with respect to safety (p < 0.001), but not superior to placebo with respect to efficacy (p = 0.06). The risk of death from any cause was 6.9% vs 7.9% in the exenatide ER and placebo groups, respectively (HR, 0.86; 95% CI, 0.77 to 0.97); the difference was not statistically significant on the basis of the hierarchical testing plan. The rates of death from CV causes, nonfatal MI, nonfatal stroke, and hospitalization for heart failure did not differ significantly between groups (*Holman et al 2017*).
- A MC, DB, PC, RCT (LEADER trial; N = 9340) was conducted to evaluate the long-term effects of liraglutide vs placebo on CV outcomes in patients with T2DM and high CV risk. The median follow-up was 3.8 years. It was found that the primary composite outcome (CV death, non-fatal MI, or non-fatal stroke) occurred in fewer patients in the liraglutide

group (13.0%) vs the placebo group (14.9%) (HR, 0.87; 95% CI, 0.78 to 0.97; p < 0.001 for noninferiority; p = 0.01 for superiority). Fewer patients died from CV causes in the liraglutide group (4.7%) vs the placebo group (6.0%) (HR, 0.78; 95% CI, 0.66 to 0.93; p = 0.007). The rate of death from any cause was lower in the liraglutide group (8.2%) vs the placebo group (9.6%) (HR, 0.85; 95% CI, 0.74 to 0.97; p = 0.02). The rates of nonfatal MI, nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group (*Marso et al 2016a*).
  - A prespecified secondary analysis found that the composite renal outcome (new-onset persistent macroalbumineria, persistent doubling of serum creatinine level, end-stage renal disease, and death due to renal disease) occurred in fewer patients in the liraglutide group vs the placebo group (5.7% vs 7.2%; HR, 0.78; 95% CI, 0.67 to 0.92; p = 0.003) (*Mann et al 2017*).
- A MC, DB, PC, RCT (ELIXA trial; N = 6068) evaluated the long-term effects of lixisenatide vs placebo on CV outcomes in patients with T2DM who had a recent acute coronary syndrome (ACS) event within 180 days of screening. The median follow-up was 25 months. It was found that the primary endpoint event (a composite of the first occurrence of any of the following: death from CV causes, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina) occurred in 13.4% of patients in the lixisenatide group and 13.2% in the placebo group (HR, 1.02; 95% CI, 0.89 to 1.17), which demonstrated noninferiority of lixisenatide to placebo (p < 0.001), but did not demonstrate superiority (p = 0.81). The rates of the individual CV components of the primary endpoint were similar between the lixisenatide and placebo groups (*Pfeffer et al 2015*).
- *Marso et al 2016b* conducted a MC, DB, PC, RCT (SUSTAIN 6 trial; N = 3297) to assess the noninferiority of semaglutide as compared to placebo in terms of CV safety in patients with T2DM, 83.0% of whom had CV disease. Patients were randomized to semaglutide 0.5 mg or 1.0 mg once weekly or placebo. The median observation time was 2.1 years. The primary composite outcome was the first occurrence of CV death, nonfatal MI, or nonfatal stroke. The noninferiority margin was 1.8 for the upper boundary of the 95% CI of the HR. A larger study is planned to validate the results (*Skydsgaard 2016*).
  - The primary composite outcome occurred in 6.6% of the semaglutide group vs 8.9% of the placebo group (HR: 0.74 [95%CI, 0.58 to 0.95]; p < 0.001 for noninferiority). Although a p value of 0.02 for superiority was calculated; testing for superiority was not prespecified. Nonfatal stroke occurred in 1.6% in the semaglutide group vs 2.7% in the placebo group (HR: 0.61 [95% CI, 0.38 to 0.99]; p = 0.04). Rates of nonfatal MI, CV death, and all-cause death were not statistically significantly different between groups.
  - Rates of new or worsening nephropathy were lower in the semaglutide group, but rates of retinopathy complications were significantly higher (3.0% for semaglutide vs 1.8% for placebo, HR: 1.76 [95% CI, 1.11 to 2.78]; p = 0.02).

Meta-analyses

- Meta-analyses and Cochrane Reviews evaluating GLP-1 receptor agonists have found that they lead to decreases in HbA1c of ~1%, with greater decreases in body weight and systolic blood pressure compared to placebo and other antidiabetic agents (*Wang et al 2013, Shyangdan et al 2011, Sun et al 2015*).
- A systematic review and mixed-treatment comparison analysis of GLP-1 receptor agonists found that there were no differences in efficacy within the short-acting (exenatide or lixisenatide) or long-acting (albiglutide, dulaglutide, exenatide ER, liraglutide) groups. However, dulaglutide, liraglutide, and exenatide ER were superior to exenatide and lixisenatide at lowering HbA1c and FPG. There were no clinically meaningful differences between agents in weight loss or hypoglycemia. Albiglutide had the lowest risk of nausea and diarrhea, while exenatide ER had the lowest risk of vomiting (*Htike et al 2016*).
- Meta-analyses have revealed that incretin-based therapies are not associated with an increased risk of pancreatitis and appear to reduce all-cause mortality, CV mortality, and the incidence of MI compared to placebo or other antidiabetic agents. However, treatment with GLP-1 receptor agonists was associated with a significant increase in the incidence of cholelithiasis (*Monami et al 2017a*, *Monami et al 2017b)*.
- A meta-analysis found that overall, GLP-1 receptor agonists did not appear to be associated with an increase in the incidence of retinopathy, and there was a reduction in the incidence of nephropathy vs comparators (*Dicembrini et al 2017*).

Pramlintide

- The safety and efficacy of pramlintide in patients with T1DM have been established in PC, RCTs when administered in addition to existing insulin regimens. In a 52-week, DB, MC, PC study, pramlintide significantly reduced HbA1c from baseline compared to placebo (-0.39% vs -0.12%; p = 0.0071) and was also associated with a significant weight loss compared to placebo (p < 0.001) (*Whitehouse et al 2002*). In a second 52-week study, patients experienced a significant reduction in HbA1c when receiving pramlintide 60 mcg 3 times daily (-0.41 vs -0.18%; p = 0.012) and pramlintide 60

mcg 4 times daily (-0.39 vs -0.18%; p = 0.013) at 26 weeks. Treatment with pramlintide 3 or 4 times daily continued to maintain reductions in HbA1c at 52 weeks compared to treatment with placebo (p = 0.011 and p = 0.001 for the 3- and 4 times daily dosing, respectively) (*Ratner et al 2004*).

- A systematic review and meta-analysis of 10 randomized, PC studies (N = 3297) evaluating the effect of pramlintide as adjunctive therapy to insulin in patients with T1DM found that, compared to placebo, pramlintide resulted in significant reductions in HbA1c (p < 0.001), total daily insulin dose (p = 0.024), mean mealtime insulin dose (p < 0.001), body weight (p < 0.001), and PPG (p = 0.002) (*Qiao et al 2017*).
- A systematic review and meta-analysis of 8 PC, RCTs assessed the effect of pramlintide in patients with T2DM and in obese patients without diabetes. Four T2DM studies (N = 930; 16 to 52 weeks duration) and 4 obesity studies (N = 686; 6 to 24 weeks duration) were included. Of the T2DM studies, 3 studies used meal-time placebo as the comparator while 1 study used rapid-acting insulin as the comparator. When endpoint data from all T2DM studies were combined, pramlintide was associated with a small but significant reduction in HbA1c (mean difference: -0.33% [95% CI, -0.51 to -0.14]; p = 0.0004). In the meta-analysis of the T2DM studies, patients on pramlintide were 1.52 times more likely to reach the HbA1c goal ≤ 7% than patients in the control group; however, this difference was not significant (p = 0.18). Pramlintide was associated with a significant change in body weight in patients with T2DM compared to the control group (-2.57 kg [95% CI, -3.44 to -1.70]; p < 0.00001) (*Singh-Franco et al 2011*).

CLINICAL GUIDELINES

- According to current clinical guidelines, metformin remains the cornerstone of most T2DM treatment regimens. The incretin mimetics are recommended as a potential second-line treatment option to be added to metformin in patients not achieving glycemic goals. Clinical guidelines note a lower rate of hypoglycemia, established efficacy and safety profile when used in combination with metformin, demonstrated effectiveness in reducing PPG, and the potential for weight loss as advantages associated with the incretin mimetics compared to other antidiabetic agents. No one incretin mimetic is recommended or preferred over another in the general treatment algorithm. The ADA guidelines recommend that lifestyle management and metformin should be initiated in patients with T2DM and established atherosclerotic CV disease; subsequent addition of an agent proven to reduce MACE and CV mortality (currently empagliflozin and liraglutide) is given a grade A recommendation, while consideration of canagliflozin to reduce MACE is given a grade C recommendation. Current clinical guidelines do not support the use of amylinomimetics in the management of T2DM. Among T1DM patients, the addition of pramlintide to first-line insulin therapy may be considered to enhance glycemic control and to assist with weight management (*ADA 2018; Garber et al 2018, Inzucchi et al 2015*).

SAFETY SUMMARY

- GLP-1 receptor agonists are contraindicated in patients with hypersensitivity to any component of the products. With the exception of exenatide and lixisenatide, they are also contraindicated in those with a personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome, type 2 (MEN 2).
- All GLP-1 receptor agonists, except exenatide and lixisenatide, carry a boxed warning for risk of thyroid C-cell tumors. Other safety risks include pancreatitis (including fatal and non-fatal hemorrhagic or necrotizing pancreatitis), serious hypersensitivity reactions, immunogenicity, serious hypoglycemia when used in combination with SFUs or insulin, and renal impairment. Liraglutide also has a warning for acute gallbladder disease. Semaglutide carries a warning for diabetic retinopathy complications due to the results of the SUSTAIN 6 trial, which found a higher rate of events in patients treated with semaglutide vs placebo; the absolute risk was larger among patients with a history of diabetic retinopathy at baseline compared to those without. Common AEs with these drugs include: nausea, diarrhea, vomiting, headache, and injection site reactions.
- Pramlintide is contraindicated in patients with hypersensitivity to any component of the drug and in those with hypoglycemia unawareness and confirmed gastroparesis. It has a boxed warning for increased risk of hypoglycemia, particularly in patients with T1DM. Common AEs include nausea, headache, anorexia, and vomiting; the incidence of nausea tends to be higher at the beginning of treatment and decreases with time in most patients. Gradual titration of the dose minimizes the incidence and severity of nausea
- Albiglutide, exenatide, and pramlintide are Pregnancy Category C. Dulaglutide, exenatide ER, liraglutide, semaglutide, and lixisenatide are uncategorized in accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR).
  - There are no adequate and well-controlled studies in pregnant women. These drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether these drugs are excreted in human milk.

- Due to the long washout period for albiglutide, discontinuation of the drug at least 1 month before a planned pregnancy should be considered.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Adlyxin (lixisenatide)	Injection	SC	Once daily	Inject in the abdomen, thigh, or upper arm. Administer within 1 hour before the first meal of the day, preferably the same meal each day.
Bydureon (exenatide ER)	Injection	SC	Once weekly	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food. Administer immediately after the powder is suspended.
Bydureon BCise (exenatide ER)	Injection	SC	Once weekly	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food. Administer immediately after the autoinjector is prepared.
Byetta (exenatide)	Injection	SC	Twice daily	Inject in the thigh, abdomen, or upper arm. Inject within 60 minutes prior to the morning and evening meals (or before the 2 main meals of the day, approximately 6 hours or more apart).
Ozempic (semaglutide)	Injection	SC	Once weekly	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food.
Symlin (pramlintide)	Injection	SC	Prior to major meals	Inject in the thigh or abdomen. Administer immediately prior to each major meal. Reduce mealtime insulin doses by 50%. Adjust insulin doses to optimize glycemic control once the target dose of pramlintide is achieved and nausea (if experienced) has subsided. The dose should be decreased if significant nausea persists.
Tanzeum (albiglutide)	Injection	SC	Once weekly	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food. Wait 15 minutes for the 30-mg pen and 30 minutes for the 50-mg pen after the lyophilized powder and diluent are mixed to ensure reconstitution.
Trulicity (dulaglutide)	Injection	SC	Once weekly	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food.
Victoza (liraglutide)	Injection	SC	Once daily	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food.

CONCLUSION

- The GLP-1 receptor agonists exenatide, exenatide ER, albiglutide, dulaglutide, liraglutide, lixisenatide, and semaglutide are incretin-based antidiabetic therapies that are FDA-approved as adjunctive therapy to diet and exercise in adult patients with T2DM. Additionally, liraglutide is indicated to reduce the risk of major adverse CV events in patients with established CV disease. Pramlintide is the only agent within the amylinomimetic medication class and is FDA-approved as adjunctive therapy in patients with T1DM or T2DM who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.
- The incretin mimetics are available as SC injections to be administered in the abdomen, thigh, or upper arm. Exenatide is administered twice daily (60 minutes prior to meals); liraglutide is administered once daily (independent of meals); and lixisenatide is administered once daily (1 hour prior to the first meal of the day). Exenatide ER, albiglutide, dulaglutide, and semaglutide are administered once weekly. Pramlintide is available as a SC injection to be administered immediately prior to each major meal.
- The incretin mimetics have been studied extensively in combination with, and in comparison to, a variety of antidiabetic therapies. The agents are significantly more effective than placebo in reducing HbA1c, FPG, PPG, and body weight. Efficacy data comparing treatment to an SFU, TZD, DPP-4 inhibitor or insulin is mixed, with the GLP-1 agonists achieving significantly greater or comparable benefits in glycemic outcomes.
- Several CV outcomes trials evaluating GLP-1 receptor agonists in patients with T2DM and high CV risk have been published. The LEADER trial demonstrated a statistically significant CV risk reduction with liraglutide vs placebo (*Marso et al 2016a*), whereas the ELIXA trial did not demonstrate a statistically significant difference between lixisenatide vs placebo (*Pfeffer et al 2015*) and the EXSCEL trial did not demonstrate a statistically significant difference between exenatide ER vs placebo (*Holman et al 2017*). Although the risk of MACE was lower with semaglutide vs. placebo in the SUSTAIN 6 trial, a superiority analysis was not prespecified (*Marso et al 2016b*). A larger CV outcome study is planned.
- Overall, the AE profiles of the GLP-1 receptor agonists are similar. With the exception of lixisenatide and exenatide, all of the agents have a boxed warning regarding the risk of thyroid C-cell tumors. Other warnings include increased risks of pancreatitis (including fatal and non-fatal hemorrhagic or necrotizing pancreatitis), serious hypersensitivity reactions, immunogenicity, serious hypoglycemia when used in combination with SFUs or insulin, and renal impairment. Liraglutide also has a warning for acute gallbladder disease, while semaglutide has a warning for diabetic retinopathy complications.
- According to current clinical guidelines, metformin remains the cornerstone of most T2DM treatment regimens. The incretin mimetics are recommended as a potential second-line treatment option to be added to metformin in patients not achieving glycemic goals. Clinical guidelines note a lower rate of hypoglycemia, established efficacy and safety profile when used in combination with metformin, demonstrated effectiveness in reducing PPG, and the potential for weight loss as advantages associated with the incretin mimetics compared to other antidiabetic agents. No one incretin mimetic is recommended or preferred over another in the general treatment algorithm; however, the ADA guidelines recommend that liraglutide and the SGLT2 inhibitors, empagliflozin and canagliflozin, should be considered in patients with long-standing suboptimally controlled T2DM and established atherosclerotic CV disease. Current clinical guidelines do not support the use of amylinomimetics in the management of T2DM. For T1DM, the addition of pramlintide to first-line insulin therapy may be considered to enhance glycemic control and to assist with weight management (*ADA 2018; Garber et al 2018, Inzucchi et al 2015*).

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Publication Date: March 19, 2018

Therapeutic Class Overview
Bone Density Regulators

INTRODUCTION

- Osteoporosis is the most common bone disease and is characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to bone fragility and consequent susceptibility to fracture (*Cosman et al 2014*). The National Osteoporosis Foundation (NOF) estimates that 10.2 million Americans have osteoporosis and more than 2 million osteoporosis-related fractures occur annually, with more than 70% of these occurring in women. Age is an important risk factor for bone loss; by age 60, half of white women have osteopenia or osteoporosis (*Camacho et al 2016*).
- According to the World Health Organization, osteoporosis is defined by a bone mineral density (BMD) at the hip or spine that is less than or equal to 2.5 standard deviations below the expected average for a healthy young person. Utilizing a reference population of young healthy individuals is common when measuring BMD and is known as a T-score (*World Health Organization 1994*).
- Fractures are the most clinically significant physical manifestation of postmenopausal osteoporosis, and low bone mass is the primary indicator of fracture risk (*Camacho et al 2016*). Osteoporotic fractures commonly occur in the wrist, spine, or hip, and can result in complications such as chronic pain, disability, depression, or even death (*Cosman et al 2014*).
- To decrease the risk of fractures, the general population should be advised to consume 1200 mg of calcium and 800 to 1000 mg of vitamin D per day from dietary sources or supplements. All individuals should also participate in regular weight-bearing and muscle-strengthening exercise to reduce the risk of falls and fractures. Strategies for preventing falls should be implemented when needed. Smoking cessation and avoidance of excessive alcohol intake are other initiatives to prevent osteoporosis (*Camacho et al 2016, Cosman et al 2014*).
- Bisphosphonates are used to prevent and treat postmenopausal osteoporosis, osteoporosis in men, glucocorticoid-induced osteoporosis, and Paget's disease. There are several bisphosphonates approved for treatment of Paget's disease and malignancy-induced bone conditions, but not for osteoporosis. These agents include Aredia (pamidronate), Didronel (etidronate), and Zometa (zoledronic acid), which will not be discussed in this review (*Micromedex 2.0 2018*).
- Other agents used to treat postmenopausal osteoporosis include calcitonin (Miacalcin), an estrogen agonist/antagonist (Evista), the parathyroid hormone analogs (Forteo and Tymlos), and receptor activator of nuclear factor K-B ligand inhibitor (Prolia). These agents also have other indications, such as: reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis; reduction in the risk of invasive breast cancer in postmenopausal women at high risk of invasive breast cancer; increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture; treatment of Paget's disease; treatment of hypercalcemia; treatment of glucocorticoid-induced osteoporosis at high risk of fracture; treatment of bone loss in men receiving androgen deprivation therapy for prostate cancer; and treatment of bone loss in women receiving adjuvant aromatase inhibitor therapy for breast cancer.
- Other agents in the estrogen agonist/antagonist class include Clomid or Serophene (clomiphene), tamoxifen, Fareston (toremifene), and Osphena (ospemifene). These agents have different indications, including: to induce ovulation in appropriately selected anovulatory women desiring pregnancy; the treatment and prevention of breast cancer; and treatment of women experiencing moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy due to menopause (*Micromedex 2.0 2018*). These agents are not approved for treatment of osteoporosis and will not be discussed in this review.
- Another agent in the receptor activator of nuclear factor K-B ligand inhibitor class is Xgeva (denosumab). It is approved to prevent skeletal-related events in patients with bone metastases from solid tumors, treat hypercalcemia of malignancy refractory to bisphosphonates, and treat adults with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity (*Micromedex 2.0 2018*). It will not be further discussed in this review. The Food and Drug Administration (FDA) has approved estrogen/hormone therapy for the prevention of osteoporosis and relief of vasomotor symptoms and vulvovaginal atrophy associated with menopause. The Women's Health Initiative (WHI) found that 5 years of hormone therapy in the form of Prempro (conjugated estrogen/medroxyprogesterone) reduced the risk of clinical vertebral fractures and hip fractures by 34% and other osteoporotic fractures by 23% (*Writing Group for the WHI 2002*). However, the study also reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis during 5 years of treatment. It is now recommended to use estrogen/hormone therapy in the lowest effective doses for the shortest duration necessary. Thus, these agents are not recommended for long-term prevention and will not be further discussed in this review.

- Medispan Class: Bone Density Regulators; Hormone Receptor Modulators

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Bisphosphonates	
Actonel (risedronate)	✔
Atelvia (risedronate, delayed release tablet)	✔
Binosto (alendronate, effervescent tablet)	-
Boniva (ibandronate)	✔
Fosamax* (alendronate)	✔
Fosamax Plus D (alendronate/cholecalciferol)	-
Reclast (zoledronic acid)	✔
Calcitonin	
Miacalcin† (calcitonin salmon synthetic)	✔ (nasal spray only)
Estrogen Agonist-Antagonist	
Evista (raloxifene)	✔
Parathyroid Hormone Analogs	
Forteo (teriparatide)	-
Tymlos (abaloparatide)	-
Receptor Activator of Nuclear Factor K-B Ligand Inhibitors	
Prolia (denosumab)	-

* Brand Fosamax oral solution is not currently marketed; however, a generic is available.
† Brand Miacalcin nasal spray is not currently marketed; however, a generic is available. Miacalcin injection is only available as a branded product.

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. FDA Approved Indications for Bisphosphonates

Indication	alendronate* (Binosto, Fosamax, Fosamax Plus D)	ibandronate* (Boniva)	risedronate* (Actonel, Atelvia)*	zoledronic acid* (Reclast)
Treatment of postmenopausal osteoporosis	✔	✔	✔	✔
Prevention of postmenopausal osteoporosis	✔ (Fosamax only)	✔ (tablets only)	✔ (Actonel only)	✔
Treatment to increase bone mass in men with osteoporosis	✔		✔ (Actonel only)	✔
Treatment of glucocorticoid-induced osteoporosis	✔ (Fosamax only)		✔ (Actonel only)	✔
Prevention of glucocorticoid-induced osteoporosis			✔ (Actonel only)	✔
Treatment of Paget's disease	✔ (Fosamax only)		✔ (Actonel only)	✔

* Limitations of use: The optimal duration of use has not been determined. The safety and effectiveness of Actonel, Reclast and Boniva for the treatment of osteoporosis are based on clinical data of 3 years duration. The safety and effectiveness of Atelvia for the treatment of osteoporosis are based on clinical data of 1 year duration. The safety and effectiveness of Binosto and Fosamax/Fosamax PLUS D for the treatment of osteoporosis are based on clinical data of four years duration. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis. Patients at low risk for fracture should be considered for drug discontinuation after 3 to 5 years of use. Patients who discontinue therapy should have their risk for fracture re-evaluated periodically.

(Prescribing information: Actonel 2015, Atelvia 2015, Binosto 2016, Boniva injection 2016, Boniva tablets 2016, Fosamax 2016, Fosamax Plus D 2016, Reclast 2017)

Table 3: FDA Approved Indications for Calcitonins, Estrogen Agonist-Antagonist, Parathyroid Hormone Analogs, and Receptor Activator of Nuclear Factor K-B Ligand Inhibitor

Indication	Evista (raloxifene)	Forteo (teriparatide)	Miacalcin (calcitonin)	Prolia (denosumab)	Tymlos (abaloparatide)
Treatment of postmenopausal osteoporosis in women greater than 5 years postmenopause			✔		
Treatment of postmenopausal osteoporosis	✔				
Treatment of postmenopausal osteoporosis at high risk of fracture		✔		✔	✔
Prevention of postmenopausal osteoporosis	✔				
Reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis	✔				
Reduction in the risk of invasive breast cancer in postmenopausal women at high risk of invasive breast cancer	✔				
Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture		✔			
Treatment of Paget's disease			✔ (injection only)		
Treatment of hypercalcemia			✔ (injection only)		
Treatment of glucocorticoid-induced osteoporosis at high risk of fracture		✔			
Treatment of bone loss in men receiving androgen deprivation therapy for prostate cancer				✔	
Treatment of bone loss in women receiving adjuvant aromatase inhibitor therapy for breast cancer				✔	
Treatment to increase bone mass in men with osteoporosis at high risk for fracture				✔	

(*Prescribing Information: Evista 2016, Forteo 2016, Miacalcin nasal spray 2017, Miacalcin injection 2017, Prolia 2017, Tymlos 2017*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Bisphosphonates

- Clinical trials for bisphosphonates included within this review evaluate their efficacy in increasing BMD and/or decreasing bone turnover markers (BTMs). Regardless of whether a patient is being treated for osteoporosis or has osteopenia and is receiving preventative treatment, the goal of therapy is to increase BMD and reduce the risk of fractures. Since both the treatment and prevention of osteoporosis focus on the same therapeutic outcomes, the data supporting the use of bisphosphonates for these indications has been summarized together.
- Head-to-head trials have resulted in conflicting data when comparing the efficacy one bisphosphonate agent to another.

- Data from trials specifically examining fractures indicate that bisphosphonates are efficacious and significantly lower the risk of developing fractures in both vertebral and nonvertebral areas, compared to placebo in both men and women (*Black et al 1996, Kanis et al 2005, Lyles et al 2007, Ringe et al 2009, Sawka et al 2005*). Some evidence suggests that alendronate results in greater increases of BMD when compared to risedronate (*Bonnick et al 2006, Reid et al 2006, Reid et al 2008*). In an observational study, treatment with risedronate resulted in a greater reduction in the risk of nonvertebral and hip fractures compared to alendronate (*Silverman et al 2007*). In a small randomized trial (N = 50), once weekly alendronate demonstrated similar efficacy to daily risedronate (*Sarioglu et al 2006*). Zoledronic acid and alendronate 70 mg weekly had comparable increases in lumbar BMD over 1 year in a
- study with postmenopausal women with osteoporosis and over 2 years in a study of men with osteoporosis (*McClung et al 2007, Orwoll et al 2010*). Ibandronate was shown to reduce vertebral fractures more than alendronate and risedronate in 1 trial; however, 2 other trials demonstrated similar efficacy with ibandronate vs alendronate (*Guanabens et al 2013, Harris et al 2009, Miller et al 2008[a]*).
- Clinical trials have also established the efficacy of alendronate, risedronate, and zoledronic acid in patients with glucocorticoid-induced osteoporosis (*Mok et al 2008, Okada et al 2008, Reid et al 2009*). Few trials compare the efficacy of the bisphosphonates for the treatment of Paget's disease and glucocorticoid-induced osteoporosis. One such trial demonstrated that zoledronic acid is more effective than risedronate for the treatment of Paget's disease (*Reid et al 2005*).
- Based on the available evidence, and due to a lack of conclusive head-to-head data, it is unknown whether one agent is more efficacious than another and should be considered first-line for the treatment and prevention of osteoporosis.

- In terms of safety, a meta-analysis measuring bisphosphonate gastrointestinal (GI) adverse events (AEs) concluded that patients treated with zoledronic acid had a higher probability of any GI AE and nausea. However, risedronate was associated with a greater incidence of serious GI AEs, and alendronate was associated with a greater incidence of upper GI and esophageal AEs. Ibandronate was not included in the analysis (*Tadrous et al 2014*).
- Alendronate effervescent tablets (Binosto) have been shown to be bioequivalent to alendronate tablets (Fosamax). Therefore, clinical efficacy for this product is taken from clinical trials conducted for alendronate 10 mg per day and 70 mg per week (*Binosto prescribing information 2016*).

Calcitonin

- There is a lack of substantial clinical trial data for calcitonin; the body of evidence is primarily comprised of small observational trials (*Cadarette et al 2008, Chestnut et al 2000, Cranney et al 2002[b], Downs et al 2000, Hwang et al 2006, Kanis et al 1974, Woodhouse et al 1977*).
- Injectable calcitonin has demonstrated beneficial effects in the treatment of Paget's disease. Calcitonin therapy resulted in bone and symptom relief, increased mobility, and decreased alkaline phosphate and other BTMs. In addition, calcitonin has been shown to cause disease regression in some patients (*Kanis et al 1974, Woodhouse et al 1977*).
- Nasal calcitonin achieved significant increases in BMD at the lumbar spine compared to placebo after 6 months of therapy, which was maintained for up to 2 years. Effects on BMD at the forearm and hip have produced mixed results with some trials demonstrating improvement, or preservation, and others demonstrating no improvement (*Chestnut et al 2000, Downs et al 2000*). Furthermore, a meta-analysis of 30 clinical trials demonstrated that calcitonin significantly decreased the risk of vertebral fractures compared to control (placebo or calcium and/or vitamin D); however, there was no significant difference in the risk for nonvertebral fractures (*Hwang et al 2006*).

Estrogen Agonist-Antagonist

- Several placebo-controlled trials have demonstrated that treatment with raloxifene in postmenopausal women with osteoporosis significantly increases BMD. In addition, raloxifene demonstrated beneficial effects on lipid profile parameters (*Eastell et al 2009, Ettinger et al 1999, Johnston et al 2000, Kung et al 2003, Siris et al 2005, Tanaka et al 2011*). In the MORE trial, raloxifene decreased the risk of vertebral fractures compared to placebo, with no observed difference in the rate of nonvertebral fractures (*Kung et al 2003*). There was also no difference in nonvertebral fracture rate during a 7 year follow-up of the MORE trial (*Siris et al 2005*). These data are supported by results of a meta-analysis of seven placebo-controlled trials, in which the reduction in the risk of vertebral fractures associated with raloxifene was inconsistent between 2 clinical trials, and neither trial demonstrated a reduction in the risk in nonvertebral fractures (*Eastell et al 2009*). When compared to bisphosphonate therapy, increases in BMD were significantly greater with alendronate compared to raloxifene (*Recker et al 2007*).

- In addition to evaluating the efficacy of raloxifene on bone, the MORE trial evaluated its efficacy in reducing the risk of invasive breast cancer in postmenopausal women with osteoporosis. As a secondary end point, raloxifene reduced the incidence of newly diagnosed invasive breast cancer compared to placebo (*Cummings et al 1999*). In addition, the CORE trial evaluated the efficacy of 4 additional years of raloxifene treatment on the incidence of invasive breast cancer, and over a total of 8 years, the incidence of invasive breast cancer and estrogen receptor-positive breast cancer was reduced by 66% and 76%, respectively, with raloxifene compared to placebo. In the placebo-controlled RUTH trial, raloxifene significantly reduced the risk of invasive breast cancer, as well as vertebral fractures, and did not significantly affect the risk of coronary heart disease. Raloxifene, however, was associated with a higher risk of venous thromboembolism and fatal stroke (*Barrett-Connor et al 2006*).
- Raloxifene has also been compared head-to-head with the antineoplastic agent tamoxifen in reducing the risk of invasive breast cancer. In the STAR trial, raloxifene was shown to be as effective as tamoxifen in reducing the risk of invasive and noninvasive breast cancer, with a lower risk of thromboembolic events and cataracts after a median of 3.9 years. The risk of other cancers, fractures, ischemic heart disease, and stroke was similar between the 2 treatments (*Vogel et al 2006*). However, in a trial with a median follow-up of 6.75 years, tamoxifen was shown to significantly reduce the risk of invasive breast cancer compared to raloxifene. At this time, raloxifene significantly reduced the risk of invasive uterine cancer, uterine hyperplasia, and thromboembolic events. There was no difference in mortality rate between raloxifene and tamoxifen at the end of 3.9 years (*Vogel et al 2010*).
- In terms of safety data, raloxifene was most commonly associated with hot flashes and leg cramps. Several clinical trials reported thromboembolic events (*Bachmann et al 2011, Barrett-Conner et al 2006, Cadarette et al 2008, Cranney et al 2002[a], Cummings et al 1999, Eastell et al 2009, Ensrud et al 2006, Ettinger et al 1999, Johnston et al 2000, Kung et al 2003, Martino et al 2004, Recker et al 2007, Siris et al 2005, Tanaka et al 2011, Vogel et al 2006, Vogel et al 2010*).

Parathyroid Hormone Analogs

- A 2 year, placebo-controlled trial (N = 437) evaluating teriparatide in increasing bone mass in men with primary or hypogonadal osteoporosis was terminated early when a long-term toxicology trial noted an increase in the incidence of osteosarcoma in rats receiving teriparatide. After a median duration of 11 months, teriparatide significantly increased BMD at the lumbar spine and femoral neck compared to placebo (*Orwoll et al 2003*). In a follow-up of this trial, no serious safety concerns with teriparatide were observed (*Kaufman et al 2005*). Teriparatide has been compared to the bisphosphonate alendronate for the treatment of men with primary or hypogonadal osteoporosis. Specifically, when compared to alendronate and the combination of teriparatide plus alendronate, teriparatide significantly increased BMD at the posteroanterior spine, lateral spine, and femoral neck (*Finkelstein et al 2003*).
- Teriparatide also significantly increased BMD at the lumbar spine and total hip compared to alendronate in patients with glucocorticoid-induced osteoporosis. Additionally, significantly fewer patients receiving teriparatide had a vertebral fracture after 36 months (*Langdahl et al 2009, Saag et al 2007, Saag et al 2009*). Teriparatide was also compared to risedronate in men with glucocorticoid-induced osteoporosis. At 18 months, teriparatide was more effective at increasing BMD at the lumbar spine than risedronate (*Gluer et al 2013*).
- Teriparatide has been most extensively evaluated for the treatment of osteoporosis in postmenopausal women (Body et al 2002, Cosman et al 2009, Cosman et al 2011, Eastell et al 2009, Hwang et al 2006, Kendler et al 2018, Lindsay et al 2004, McClung et al 2005, Minne et al 2008, Neer et al 2001, Obermayer-Pietsch et al 2008). The double-blind, double-dummy, multicenter, randomized, controlled VERO trial enrolled 1360 postmenopausal women with at least 2 moderate or 1 severe vertebral fracture and a BMD T score ≤ -1.50 (Kendler et al 2018). Patients were randomly assigned to receive 20 mcg of teriparatide once daily plus oral weekly placebo or 35 mg risedronate once weekly plus daily placebo injections for 24 months. The primary outcome was new radiographic vertebral fractures. Results revealed that new vertebral fractures occurred in 28 (5.4%) patients in the teriparatide group and 64 (12%) patients in the risedronate group (risk ratio, 0.44; 95% confidence interval [CI], 0.29 to 0.68; $p < 0.001$). Clinical fractures were also significantly reduced with teriparatide: 4.8% vs 9.8%; $p = 0.0009$). The EUROFORS trial was a prospective, 2 year trial in which all patients received teriparatide for the first year of treatment. After 12 months, patients were divided into 2 different substudies. In Substudy 1, for the second year of treatment, patients were randomized to teriparatide, the selective estrogen receptor modulator raloxifene, or no active treatment. In Substudy 2, all patients remained on teriparatide for the second year of treatment. After the first year of treatment, teriparatide significantly increased BMD at the lumbar spine, total hip, and femoral neck. The benefits of teriparatide appeared greater in antiresorptive treatment-naïve patients compared to treatment-experienced patients. Within Substudy 2, patients who continued teriparatide for a total of 2 years achieved significant increases in BMD after 24 months. Within Substudy 1, during the second year of

treatment, BMD at the lumbar spine, total hip, and femoral neck continued to increase significantly with teriparatide. BMD at the lumbar spine did not change in patients who were switched to raloxifene; however, BMD at the total hip and femoral neck significantly increased. Patients who were switched to no active treatment had a significant decrease in BMD at the lumbar spine, no change in BMD at the total hip, and a significantly increased BMD at the femoral neck (Eastell et al 2009, Minne et al 2008, Obermayer-Pietsch et al 2008). In addition to significant increases in BMD, placebo-controlled trials demonstrate that teriparatide significantly reduces the risk of vertebral and nonvertebral fractures (Body et al 2002, Lindsay et al 2004, Neer et al 2001). Data also suggest that teriparatide in combination with a bisphosphonate may result in significant increases in BMD compared to monotherapy with either teriparatide or a bisphosphonate (Cosman et al 2009, Cosman et al 2011). In another study of 12 months duration, combined teriparatide plus denosumab were compared to either treatment alone. Combination therapy was associated with significantly greater BMD increases at the posterior-anterior spine, femoral neck, and hip than either drug alone (Leder et al 2014, Tsai et al 2013).

- In terms of safety data, no clinically significant concerns related to teriparatide were observed; however, treatment was associated with a higher rate of hypercalcemia compared to placebo and bisphosphonate therapy. No cases of osteosarcoma were reported (*Body et al 2002, Cosman et al 2009, Cosman et al 2011, Eastell et al 2009, Finkelstein et al 2003, Finkelstein et al 2006, Hwang et al 2006, Kaufman et al 2005, Langdahl et al 2009, Lindsay et al 2004, McClung et al 2005, Minne et al 2008, Neer et al 2001, Obermayer-Pietsch et al 2008, Orwoll et al 2003, Saag et al 2007, Saag et al 2009*).
- The efficacy of abaloparatide was compared with teriparatide and placebo in the 18-month randomized controlled ACTIVE trial in 2463 postmenopausal women with osteoporosis. Treatment with abaloparatide resulted in a significant reduction in new morphometric vertebral and nonvertebral fractures vs placebo, while treatment with teriparatide also resulted in a significant reduction in new morphometric vertebral fractures vs placebo. For reduction in nonvertebral fractures, treatment with abaloparatide was not statistically different from teriparatide. The incidence of hypercalcemia was significantly lower with abaloparatide vs teriparatide (*Miller et al 2016*). The ACTIVExtend open-label extension trial evaluated 6 months of follow-up therapy with alendronate 70 mg once weekly in both the abaloparatide and placebo groups, and demonstrated that the treatment cycle with abaloparatide for 18 months followed by alendronate reduced new morphometric vertebral fractures by 87%, nonvertebral fractures by 52%, clinical fractures by 45%, and major osteoporotic fractures by 58% vs placebo and alendronate (*Cosman et al 2017*).

Receptor Activator of Nuclear Factor K-B Ligand Inhibitors

- The safety and efficacy of denosumab for the treatment of bone loss in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer were established in a 2 year, double-blind, placebo-controlled, randomized trial enrolling 252 women (*Ellis et al 2008*). Patients were randomized to subcutaneous denosumab every 6 months (n = 127) or placebo (n = 125) for a total of 4 doses; all patients received supplemental calcium and vitamin D. Overall, denosumab increased BMD at the lumbar spine at 12 and 24 months by 5.5% and 7.6%, respectively, compared to placebo ($p < 0.0001$ at both time points). BMD at the lumbar spine was significantly higher with denosumab compared to placebo after 12 months (4.8% vs -0.7%; treatment difference, 5.5%; 95% CI, 4.8 to 6.3; $p < 0.0001$). Furthermore, after 2 years, denosumab increased BMD at the lumbar spine (-1.4% placebo, +4.8% denosumab), total hip (-1.0% placebo, +3.8% denosumab), and femoral neck (-0.8% placebo, +2.8% denosumab).
- A double-blind, placebo-controlled, Phase 3 trial evaluated denosumab vs placebo in 3420 postmenopausal women with early hormone-receptor positive breast cancer receiving treatment with aromatase inhibitors (*Gnant et al 2015*). Women were randomized to denosumab 60 mg every 6 months or placebo. The primary outcome measure of time to first fracture was significantly delayed in the denosumab group compared to placebo (hazard ratio [HR], 0.50; 95% CI, 0.39 to 0.65; $p < 0.0001$). The incidence of AEs was similar in both treatment groups.
- When compared to placebo, denosumab significantly prolonged bone-metastasis-free survival (composite of time to first occurrence of bone metastasis and death from any cause) in men with non-metastatic prostate cancer (treatment difference, 4.2 months; HR, 0.85; 95% CI, 0.73 to 0.98; $p = 0.028$). There was no difference in overall survival observed between the 2 treatment groups. In this trial, BMD evaluations were not performed; however, it was noted that biochemical markers of bone turnover significantly decreased with denosumab compared to placebo ($p < 0.001$ for all). Of note, the FDA-approved dosing was not evaluated in this trial; denosumab was administered once monthly (*Smith et al 2012*). The ADAMO trial showed that denosumab therapy administered every 6 months continued to increase BMD in men with low BMD throughout the second year of treatment (*Langdahl et al 2015*).

- Of the available clinical trial data evaluating the safety and efficacy of denosumab in postmenopausal women with osteoporosis who are at high risk of fracture, only one placebo-controlled trial (the FREEDOM trial) demonstrated a reduction in the risk of fracture with denosumab. In this trial, after 36 months, there were significant reductions with denosumab compared to placebo in the incidence of new vertebral (2.3% vs 7.2%; relative risk [RR], 0.32; 95% CI, 0.26 to 0.41; p < 0.001), nonvertebral (6.5% vs 8%; RR, 0.80; 95% CI, 0.67 to 0.95; p = 0.01), and hip fractures (0.7% vs 1.29%; RR, 0.6; 95% CI, 0.31 to 0.97; p = 0.04) (*Cummings et al 2009*). A 3-year extension trial maintained patients randomized to denosumab on active treatment for a total of 6 years and crossed over the placebo patients to denosumab treatment for a total of 3 years. For patients on denosumab for 6 years, BTMs were maintained at lower than pretreatment levels and BMD continued to increase. Fracture incidence in the long-term group remained low and below the rates reported in the FREEDOM placebo group. For the cross-over group, data obtained were consistent with FREEDOM observations (ie, rapid and marked reduction in BTMs, large increases in BMD, low fracture rates, favorable benefit/risk profile) (*Bone et al 2013*). A 7-year extension of FREEDOM, for a total of 7 to 10 years of exposure to denosumab, further confirmed a low fracture incidence rate with low rates of AEs (*Bone et al 2017*). Additionally, BMD at the lumbar spine, total hip, femoral neck, and radius continued to increase, suggesting no plateau to BMD benefits with denosumab.
- A meta-analysis/systematic review of clinical trials of denosumab in osteopenic and osteoporotic postmenopausal women with low bone mass sought to evaluate the effect of denosumab on BTMs and BMD. In this analysis, AEs, including fracture risk, were also evaluated as secondary endpoints. Due to missing or unavailable data, it was not possible for the investigators to evaluate the efficacy of denosumab based on change in baseline BMD. Treatment with denosumab was associated with increased BMD at the lumbar spine and hip, as well as decreased BTMs. Regarding secondary outcomes, denosumab did not demonstrate a significant reduction in fracture risk (odds ratio [OR], 0.74; 95% CI, 0.33 to 0.64; p = 0.45) (*Anastaskilakis et al 2009*).
- The efficacy of denosumab for increasing BMD is also supported by 3 dose-ranging, placebo-controlled trials, as well as a head-to-head trial with the bisphosphonate, alendronate (*Brown et al 2009, Lewiecki et al 2007, McClung et al 2006, Miller et al 2008[b]*). The 3 dose-ranging trials demonstrated that 48 months of denosumab therapy significantly increased BMD at all measured skeletal sites (lumbar spine, total hip, and distal 1/3 radius) (p < 0.001), and achieved potent and sustained reductions of BTMs compared to placebo (*Cummings et al 2009*). In a small subset of patients who discontinued treatment with denosumab, subsequent decreases in BMD at measured skeletal sites were observed. When compared to alendronate, changes in BMD at the total hip were also significantly greater with denosumab at 12 months (3.5% vs 2.6%; p < 0.0001) (*Brown et al 2009*). In a second meta-analysis comparing denosumab to weekly alendronate, no difference in fracture risk was demonstrated (OR, 1.42; 95% CI, 0.84 to 2.40; p = 0.19); however, both treatments were associated with significantly increased BMD at distal radius, total hip, lumbar spine, and femoral neck after 6 months (*Lin et al 2012*). In a 12-month trial comparing denosumab to monthly ibandronate therapy, treatment with denosumab resulted in significantly greater BMD increases at the total hip, femoral neck, and lumbar spine compared with ibandronate (*Recknor et al 2013*).
- A systematic review and meta-analysis assessed the efficacy and safety of denosumab compared to other anti-osteoporosis agents (eg, bisphosphonates, teriparatide) in patients previously treated with other medications (*Fontalis et al 2018*). Results demonstrated the superiority of denosumab in augmenting BMD at all skeletal sites studied (treatment difference in total hip [primary outcome], 1.59%; 95% CI, 1.01 to 2.17) compared to controls, whereas the overall incidence of serious AEs was not increased (p = 0.42).
- In terms of safety data, no clinically significant concerns related to denosumab were observed; the safety profile of denosumab appears similar to that of bisphosphonates (*Anastaskilakis et al 2009, Brown et al 2009, Cummings et al 2009, Lewiecki et al 2007, Lin et al 2012, McClung et al 2006, Miller et al 2008[b], Smith et al 2012*).

Comparative Efficacy

- From the Agency for Healthcare Research and Quality (AHRQ) evaluation (*Crandall et al 2012*), the following conclusions were reached:
  - Calcitonin was excluded because the reviewers found that it should no longer be considered appropriate therapy for osteoporosis.
  - There is a high level of evidence from randomized controlled trials (RCTs) that alendronate, risedronate, ibandronate, zoledronic acid, denosumab, teriparatide, and raloxifene reduce the risk of vertebral fractures in postmenopausal women with osteoporosis.

- There is a high level of evidence from RCTs that alendronate, risedronate, zoledronic acid and denosumab reduce the risk of nonvertebral fractures in postmenopausal women with osteoporosis; there is moderate evidence that teriparatide reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis.
- There is a high level of evidence from RCTs that alendronate, risedronate, zoledronic acid, and denosumab reduce the risk of hip fractures in postmenopausal women with osteoporosis.
- There is insufficient evidence from head-to-head trials with bisphosphonates to support the superiority of one agent over the others for the prevention of fractures.
- The evidence is insufficient regarding the use of combination therapy or sequential use of osteoporosis therapies in relation to fracture outcomes.
- Evidence is insufficient regarding the effectiveness of therapies to prevent or treat osteoporosis in men.
- Evidence is insufficient regarding the effect of glucocorticoid treatment on response to therapies.
- About half of patients appeared to show persistence with osteoporosis treatment at 1 year.
- Adverse effects of concern identified from the report included the following:
  - A relationship between zoledronic acid and atrial fibrillation is unproven but still an area of active surveillance.
  - Evidence is high for an increased risk for venous thromboembolic events (eg, pulmonary embolism) and vasomotor symptoms (eg, hot flashes) with raloxifene therapy.
  - Evidence is insufficient regarding the risk of esophageal cancer with bisphosphonates.
  - Evidence is high regarding the risk for alendronate and mild upper GI events (acid reflux, esophageal irritation, nausea, vomiting, and heartburn).
  - Evidence is high that the prevention and treatment of osteoporosis with bisphosphonates remains a relatively minor contributor to the development of osteonecrosis of the jaw.
  - The risk remains low for atypical, low-trauma subtrochanteric fragility fractures of the femur with long-term use of bisphosphonates for prevention or treatment of osteoporosis compared with the numbers of osteoporotic fractures prevented by bisphosphonate therapy.
  - Evidence is high for rashes, injection site reactions, and infection with denosumab.

- There is a lack of substantial head-to-head data comparing calcitonin to other established osteoporosis treatments. In 2 clinical trials, bisphosphonate and parathyroid hormone analog therapy demonstrated significantly greater increases in BMD at the lumbar spine compared to nasal calcitonin-salmon (*Downs et al 2000, Hwang et al 2006*).
- A network meta-analysis found that zoledronic acid significantly increased BMD in lumbar spine and teriparatide decreased fracture rates in men with osteoporosis when compared to other agents such as alendronate, ibandronate, and risedronate (*Chen et al 2015*).
- A network meta-analysis performed indirect comparisons to determine the likelihood of each drug being the most preferable for various outcomes (*Yang et al 2016*). Among products included in this study, the most preferred agents for various outcomes were teriparatide in nonvertebral fractures; denosumab, zoledronic acid, and alendronate in hip fractures; teriparatide in wrist fractures; and raloxifene, alendronate, and denosumab for AEs.
- A systematic review and meta-analysis demonstrated teriparatide to be superior to alendronate in increasing lumbar spine BMD in patients with postmenopausal osteoporosis. The results of the meta-analysis showed no significant difference in the change from baseline in femoral neck BMD or incidence of vertebral and/or nonvertebral fractures between the 2 therapies (*Wang et al 2017[a]*).
- An Institute for Clinical and Economic Review (ICER) and California Technology Assessment Forum (CTAF) evidence report included a network meta-analysis of 3 RCTs to evaluate the comparative safety and efficacy of teriparatide, abaloparatide, and zoledronic acid for treatment of osteoporosis in postmenopausal women at high risk for fracture The analysis determined that teriparatide and abaloparatide were not significantly different from each other or zoledronic acid in reducing morphometric vertebral or nonvertebral fractures, and safety issues had little influence on the net benefit for each therapy compared to each other (*CTAF 2017*).
- A systematic review and meta-analysis demonstrated significantly lower risk of vertebral fractures with alendronate and risedronate in men with osteoporosis, but not with injectable calcitonin or denosumab vs controls. For bisphosphonates as a treatment category, meta-analyses demonstrated a significantly lower risk of vertebral fractures and possible nonvertebral fractures vs controls (*Nayak & Greenspan 2017*).
- A network meta-analysis identified parathyroid hormone therapy (teriparatide) and zoledronic acid as agents with the highest probability of satisfactory performance in preventing vertebral fractures in postmenopausal women in the final relative ranking of interventions among 10 osteoporosis agents, including oral bisphosphonates, denosumab, raloxifene, and strontium ranelate. For prevention of clinical vertebral fractures, zoledronic acid was determined to be the most

effective, with denosumab as a second option, when compared to placebo. There were no significant differences between therapies identified with respect to adverse effects (*Wang et al 2017[b]*).

CLINICAL GUIDELINES

- To prevent and/or treat osteoporosis in postmenopausal women and men, national guidelines recommend adequate calcium and vitamin D intake, weight bearing exercise, cessation of smoking, and limiting alcohol intake (*ACOG 2012 [reaffirmed in 2016], Adler et al 2016, Buckley et al 2017, Camacho et al 2016, Cosman et al 2014, Qaseem et al 2017, Watts et al 2012*).
- Within the various treatment guidelines for osteoporosis in men and women, there is general agreement that treatment is indicated for patients > 50 years of age who have experienced a hip or vertebral fracture or have a bone density T-score ≤ -2.5 (*Adler et al 2016, Camacho et al 2016, Cosman et al 2014, North American Menopause Society 2010, Qaseem et al 2017, Watts et al 2012*).
  - Bisphosphonates are generally considered first-line therapy. Clinical trials have not consistently shown one agent to be more effective than another.
  - While some national guidelines recommend denosumab as an alternative to bisphosphonates (*ACOG 2012*), the American Association of Clinical Endocrinologists (AACE) recommends denosumab as an optional first-line treatment in postmenopausal women (*Camacho et al 2016*).
  - Teriparatide is generally reserved for patients at high risk for fractures, or unable to tolerate or manage therapy with oral bisphosphonates (*ACOG 2012, Camacho et al 2016, Watts et al 2012*). Osteoporosis guidelines have yet to be updated to include abaloparatide, the most recently approved parathyroid hormone analog.
  - Although calcitonin and raloxifene are approved for osteoporosis, they are not considered first-line therapies due to AEs, less evidence of efficacy, and/or route of administration.

SAFETY SUMMARY

- **Contraindications**
  - Bisphosphonates
    - Abnormalities of the esophagus that delay esophageal emptying (eg, stricture or achalasia)
    - Inability to stand or sit upright for at least 30 minutes (at least 60 minutes for ibandronate)
    - Hypocalcemia
  - Alendronate oral solution
    - Patients at increased risk of aspiration
  - Raloxifene
    - Active or past history of venous thromboembolism
    - Pregnancy or nursing mothers
  - Denosumab
    - Hypocalcemia
    - Pregnancy or nursing mothers

- **Warnings/precautions**
  - Bisphosphonates
    - Caution should be used in patients with active GI problems (except zoledronic acid)
    - Reports of severe and occasionally incapacitating bone, joint, and/or muscle pain
    - Osteonecrosis of the jaw
    - Caution should be used in aspirin-sensitive patients (zoledronic acid)
    - Caution should be used in patients who must restrict sodium intake (alendronate effervescent tablets)
  - Raloxifene
    - **Boxed warning:** Increased risk of venous thromboembolism and death from stroke
    - Venous thromboembolism: increased risk of deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis
    - Discontinue 72 hours prior to and during prolonged immobilization
    - Death due to stroke
    - Should not be used for the primary or secondary prevention of cardiovascular disease
    - Not recommended in premenopausal women

- Caution should be used in patients with hepatic impairment
- Concomitant use with systemic estrogens is not recommended
- Hypertriglyceridemia

○ Parathyroid Hormone Analogs
- **Boxed warning:** Teriparatide and abaloparatide should not be used in patients at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, prior external beam or implant radiation involving the skeleton, and in pediatric and young adult patients with open epiphyses).
  - Cumulative lifetime use of parathyroid hormone analogs (abaloparatide and/or teriparatide) > 2 years not recommended
- Orthostatic hypotension
- Caution should be used in patients with active or recent urolithiasis
- Hypercalcemia

○ Calcitonin
- Potential increased risk of malignancies
- Circulating antibodies and abnormal urine sediment
- Nasal spray: Periodic nasal examinations with visualization of the nasal mucosa, turbinates, septum and mucosal blood vessel status recommended at beginning of treatment, periodically during the course of therapy, and at any time nasal symptoms occur

○ Denosumab
- Atypical, low-energy, or low trauma fractures of the femoral shaft
- Osteonecrosis of the jaw
- Severe musculoskeletal pain
- An increased risk for multiple vertebral fractures has been reported following discontinuation of denosumab
- Increased risk for serious infections in patients on concomitant immunosuppressant agents or with impaired immune systems

• **AEs**

○ Bisphosphonates
- The most common AEs are headache and GI effects such as abdominal pain, diarrhea, constipation, nausea, and dyspepsia.

○ Raloxifene
- The most common AEs (> 2%) include hot flashes, leg cramps, peripheral edema, flu syndrome, arthralgia, and sweating.

○ Teriparatide
- The most common AEs (> 10%) include nausea, arthralgia, and pain.

○ Abaloparatide
- The most common AEs (≥ 2%) include hypercalciuria, dizziness, nausea, headache, palpitations, fatigue, upper abdominal pain, and vertigo.

○ Calcitonin
- Nasal spray: The most common AEs (≥ 3%) include rhinitis, epistaxis and other nasal symptoms, back pain, arthralgia, and headache.
- Injection: The most common AEs include nausea with or without vomiting (10%), injection site inflammation (10%), and flushing of the face or hands (2 to 5%).

○ Denosumab
- The most common AEs (> 5%) include back pain, pain in extremity, hypercholesterolemia, musculoskeletal pain, and cystitis. Pancreatitis has also been reported in clinical trials.

• **Drug Interactions**

○ Bisphosphonates
- Calcium supplements, antacids, magnesium-based supplements or laxatives, and iron preparations interfere with absorption of oral bisphosphonates
- Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) increase GI AEs with oral bisphosphonates

○ Raloxifene

- Cholestyramine, warfarin, and highly protein-bound drugs
- Teriparatide
  - Hypercalcemia may predispose patients to digitalis toxicity; caution recommended in patients on digoxin
- Calcitonin
  - Concomitant use of calcitonin and lithium may lead to a reduction in plasma lithium concentrations

- **Risk Evaluation and Mitigation Strategy (REMS)**
  - Denosumab has a REMS program with the goal of mitigating the risks of hypocalcemia, osteonecrosis of the jaw, atypical femoral fractures, serious infections, and dermatologic reactions (*REMS Web site 2018*).
    - The REMS program includes a medication guide and a communication plan to healthcare providers who prescribe denosumab.

DOSING AND ADMINISTRATION

- Bisphosphonates
  - Oral bisphosphonates should be taken at least 30 minutes (60 minutes for ibandronate) before the first food or drink of the day and swallowed whole in an upright position and with a full glass of plain water. Patients should not lie down for 30 minutes (60 minutes for ibandronate) after ingestion.
    - Exception: Delayed-release risedronate should be taken immediately after breakfast
  - Supplemental calcium and vitamin D are recommended if dietary intake is inadequate; however, calcium supplements, antacids, magnesium-based supplements or laxatives, and iron preparations interfere with bisphosphonate absorption and should be administered at a different time of the day.
- Calcitonin
  - Unopened nasal spray bottle should be stored in the refrigerator. Once opened, it should be stored at room temperature and discarded after 35 days.
  - Injection should be stored in the refrigerator. If the volume of the injection exceeds 2 mL, intramuscular (IM) injection is preferable, and the total dose should be distributed across multiple injection sites.
- Parathyroid Hormone Analogs
  - Teriparatide prefilled pens should be refrigerated at all times and injected into the thigh or abdominal wall.
  - Abaloparatide prefilled pens should be refrigerated before use then stored at room temperature for up to 30 days after first use. The injection should be into the periumbilical region of abdomen at approximately the same time every day.
- Denosumab
  - Denosumab should be administered by a healthcare professional in the upper arm, upper thigh, or abdomen.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency
Bisphosphonates			
Actonel (risedronate)	Tablets	Oral	Once daily Once weekly Once monthly
Atelvia (risedronate)	Delayed release tablets	Oral	Once weekly
Binosto (alendronate)	Effervescent tablets	Oral	Once weekly
Boniva (ibandronate)	Tablets Injection	Oral IV	Once monthly (oral) Every 3 months (IV)
Fosamax (alendronate)	Tablets Solution	Oral	Once daily Once weekly
Fosamax Plus D (alendronate/ cholecalciferol)	Tablets	Oral	Once weekly
Reclast (zoledronic acid)	Injection	IV	Once a year (treatment) Once every 2 years (prevention)
Calcitonin			

Drug	Available Formulations	Route	Usual Recommended Frequency
Miacalcin (calcitonin-salmon synthetic)	Nasal solution Injection	Intranasal SQ, IM	Once daily (for osteoporosis and Paget's disease)
Estrogen Agonist-Antagonist			
Evista (raloxifene)	Tablets	Oral	Once daily
Parathyroid Hormone Analogs			
Forteo (teriparatide)	Injection	SQ	Once daily
Tymlos (abaloparatide)	Injection	SQ	Once daily
Receptor Activator of Nuclear Factor K-B Ligand Inhibitors			
Prolia (denosumab)	Injection	SQ	Every 6 months

Abbreviations: IM = intramuscular; IV = intravenous; SQ = sucutaneous

See the current prescribing information for full details

CONCLUSION

- Within the various treatment guidelines for osteoporosis in men and women, there is general agreement that treatment is indicated for patients > 50 years of age who have experienced a hip or vertebral fracture or have a bone density T-score ≤ -2.5 (*Adler et al 2016, Camacho et al 2016, Cosman et al 2014, North American Menopause Society 2010, Qaseem et al 2017, Watts et al 2012*). Bisphosphonates are generally considered first-line therapy, and clinical trials have not consistently shown one agent to be more effective than another.
- Data for hip, vertebral, and nonvertebral fractures is most robust for alendronate, risedronate, and zoledronic acid. Ibandronate has data to support reduced vertebral fractures (*Guanabens et al 2013, Harris et al 2009, Miller et al 2008[a]*).
- Patient preference and ease of administration should be considered in the selection of a bisphosphonate, as adherence may be a barrier to the treatment and prevention of osteoporosis. Atelvia (risedronate delayed release) and alendronate can be administered once weekly, while Actonel (risedronate) and ibandronate can be administered once a month. Additionally, zoledronic acid is an intravenous infusion given once a year for treatment or every other year for prevention. Atelvia (risedronate delayed release) can be taken immediately after eating or drinking while other oral bisphosphonates must be administered 30 to 60 minutes before the first food or drink of the day.
- The receptor activator of nuclear factor K-B ligand inhibitor, denosumab, has data for hip, vertebral, and nonvertebral fractures. It is a subcutaneous injection given every six months. Monitoring for infection is required with this agent. The AACE recommends denosumab as an optional first-line treatment for postmenopausal osteoporosis (*Camacho et al 2016*).
- Teriparatide is generally reserved for patients at high risk for fractures or those unable to tolerate or manage therapy with oral bisphosphonates (*ACOG 2012, Camacho et al 2016, Watts et al 2012*). Abaloparatide is the most recently approved parathyroid hormone analog and is not included in current osteoporosis guidelines. Both teriparatide and abaloparatide are administered via daily subcutaneous injection, and lifetime cumulative treatment duration should not exceed 2 years. The parathyroid hormone analogs have a boxed warning for osteosarcoma.
- Raloxifene has data for vertebral fracture reduction and is only approved for women. It may be an appropriate initial therapy for patients requiring drugs with spine-specific efficacy who are unable to tolerate bisphosphonates (*Camacho et al 2016*). Raloxifene is also used for breast cancer risk reduction, which is recommended for asymptomatic women ≥ 35 years of age who are at risk for breast cancer. There is an increased risk of thromboembolism and stroke with raloxifene.
- Calcitonin lacks sufficient evidence for fracture reduction in the treatment of osteoporosis.
- For the treatment of Paget's disease, risedronate, alendronate, calcitonin injection, and zoledronic acid all have efficacy data to support their use.
- For the treatment of glucocorticoid-induced osteoporosis, risedronate, teriparatide, alendronate, and zoledronic acid are all FDA-approved. Selection of an agent should be based on the patient's preference of administration. Teriparatide should be reserved for higher doses of steroids and longer lengths of treatment per the national guidelines (*Buckley et al 2017*).

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Publication Date: April 4, 2018

Therapeutic Class Overview
Ophthalmic Antihistamines

INTRODUCTION

- The ophthalmic antihistamines are Food and Drug Administration (FDA)-approved for the management of the signs and symptoms associated with allergic conjunctivitis and include Lastacaft (alcaftadine); Optivar (azelastine); Bepreve (bepotastine); Zerviate (cetirizine); Emadine (emedastine); Elestat (epinastine); the ketotifen-containing products (eg, Alaway and Zaditor); and the olopatadine-containing products Pataday, Patanol, and Pazeo *(Micromedex 2.0 2018)*.
- All products are available by prescription with the exception of ketotifen, which is available over-the-counter (OTC). Ketotifen is approved for the temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair, and dander.
- Conjunctivitis can be classified as noninfectious or infectious, and as acute, chronic, or recurrent. Types of noninfectious conjunctivitis are allergic, mechanical/irritative/toxic, immune-mediated, and neoplastic. Causes of infectious conjunctivitis are viruses and bacteria *(American Academy of Ophthalmology [AAO] 2013)*.
- Types of allergic conjunctivitis include atopic keratoconjunctivitis, simple allergic conjunctivitis, seasonal or perennial conjunctivitis, vernal conjunctivitis, and giant papillary conjunctivitis. Atopic keratoconjunctivitis is a severe, chronic, external ocular inflammation associated with atopic dermatitis. Vernal conjunctivitis is a severe form of allergic conjunctivitis that may involve the cornea *(American Optometric Association [AOA] 2007)*. None of the ophthalmic antihistamines are FDA-approved for the treatment of vernal conjunctivitis.
- Symptoms of allergic conjunctivitis include itching, tearing, mucoid discharge, chemosis, hyperemia, and redness. Most commonly, symptoms are present in both eyes, but they may also occur unilaterally *(AOA 2007)*.
- Most of these agents have been shown to have both histamine type 1 (H_1-antihistamine) and mast cell stabilizing properties *(AAO 2013, Hamrah et al 2017)*. The ophthalmic antihistamines reduce itching and redness through competitive binding with histamine receptor sites and by inhibiting the degranulation of mast cells, thus limiting the release of inflammatory mediators associated with the development of allergy symptoms *(Micromedex 2.0 2018)*.
- The ophthalmic antihistamines with mast cell-stabilizing properties are the agents of choice in treating seasonal and perennial allergic conjunctivitis as they address both the acute and chronic aspects of these conditions *(Hamrah et al 2017)*. While the onset of action is within minutes for most of these agents, patients with seasonal allergies may benefit from early therapy initiation (ie, at least 2 weeks before expected symptom onset) since control of inflammation and symptom resolution often takes some time *(Hamrah et al 2017)*.
- Medispan Therapeutic Class: Ophthalmics - Miscellaneous

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Alaway† (ketotifen), Zaditor† (ketotifen)	✔
Bepreve (bepotastine besilate ophthalmic solution) 1.5%	-
Elestat (epinastine HCl ophthalmic solution) 0.05%	✔
Emadine (emedastine difumarate ophthalmic solution) 0.05%	-
Lastacaft (alcaftadine ophthalmic solution) 0.25%	-
Optivar (azelastine HCl ophthalmic solution, 0.05%)	✔
Pataday (olopatadine HCl ophthalmic solution) 0.2%, Patanol (olopatadine HCl ophthalmic solution) 0.1%, Pazeo (olopatadine HCl ophthalmic solution) 0.7%	✔ ✔ -
Zerviate (cetirizine ophthalmic solution) 0.24%‡	-

Key: HCl = hydrochloride
† Products contain ketotifen 0.025% (equivalent to ketotifen fumarate 0.035%) and are available over-the-counter.
‡ Zerviate contains cetirizine 0.24% (equivalent to cetirizine hydrochloride 0.29%) and was approved in May 2017; however, the product has not yet launched.

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	**Alaway, Zaditor** (ketotifen)	**Bepreve** (bepotastine)	**Elestat** (epinastine)	**Emadine** (emedastine)	**Lastacaft** (alcaftadine)	**Optivar** (azelastine)	**Pataday, Patanol, Pazeo** (olopatadine)	**Zerviate** (cetirizine)
Prevention of ocular itching associated with allergic conjunctivitis			✔		✔			
Treatment of ocular itching associated with allergic conjunctivitis		✔				✔	✔ *	✔
Treatment of signs and symptoms of allergic conjunctivitis							✔ †	
Temporary relief of the signs and symptoms of allergic conjunctivitis				✔				
Temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair, and dander	✔							

* 0.2% and 0.7% strengths
† 0.1% strength

(Prescribing information: Alaway 2015, Bepreve 2018, Elestat 2011, Emadine 2009, Lastacaft 2015, Optivar 2008, Pataday 2010, Patanol 2007, Pazeo 2017, Zaditor 2015, Zerviate 2017)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Due to the rapid onset of action of the ophthalmic antihistamines, most trials used the conjunctival allergen challenge model to establish the relative efficacy of these formulations compared to placebo. The results of these trials demonstrated improvements in symptoms, especially for itching, in those treated with ophthalmic antihistamines and antihistamines/mast cell stabilizers compared to placebo. Clinical data supporting the FDA approval of cetirizine

ophthalmic solution were from 3 unpublished, placebo-controlled trials that showed improvement in ocular itching with cetirizine *(Nicox 2017)*.

- Several studies have been conducted to directly compare ophthalmic ketotifen and ophthalmic olopatadine. These studies have produced mixed results, generally demonstrating no difference between the agents. Results of some studies suggest that ophthalmic olopatadine may be preferred and better tolerated by patients *(Avunduk et al 2005, Berdy et al 2000, Borazan et al 2009, Ganz et al 2003, Leonardi et al 2004)*. There are limited head-to-head studies that compare the clinical efficacy of the other agents in this class to one another, and all are considered equally efficacious at improving ocular allergy symptoms. While some studies reported statistically significant differences in symptom scores, the overall clinical significance of these differences is not known, as many of these trials were conducted using single doses of study medication (in the conjunctival allergen challenge model) and generally enrolled a small number of patients. A Cochrane review of topical antihistamines for treatment of allergic conjunctivitis concluded that topical antihistamines and mast cell stabilizers reduce symptoms short-term. Data for the long-term use of topical antihistamines are lacking *(Castillo et al 2015)*.

CLINICAL GUIDELINES

- According to the AAO, mild allergic conjunctivitis may be treated with an OTC ophthalmic antihistamine/vasoconstrictor or a prescription ophthalmic antihistamine. Ophthalmic allergy preparations with dual antihistamine and mast cell stabilizing properties may be used for either acute or chronic disease, with no preference given to one agent over another. The use of ophthalmic vasoconstrictors should be limited due to their short duration of action and potential to cause rebound hyperemia and conjunctivitis medicamentosa. Ophthalmic mast cell stabilizers may be used if the condition is recurrent or persistent *(AAO 2013)*.

SAFETY SUMMARY

- Contact lens use: patients should not wear a contact lens if the eye is red; remove contact lenses prior to instilling this product, as the preservative, benzalkonium chloride, may be absorbed by soft contact lenses.
- Contamination of tip and solution: do not touch eyelids or surrounding areas with the dropper tip of the bottle.
- Products are for topical use only.
- Adverse events are primarily ocular in nature with burning/stinging upon instillation, ocular irritation, ocular pruritus, and redness. Systemic adverse events include mild taste upon instillation, headache, rhinitis, and potential hypersensitivity reactions.
- Due to the topical application of the ophthalmic antihistamines, drug interactions have not been reported.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Alaway, Zaditor (ketotifen)	Both: Ophthalmic solutions	Ophthalmic	Twice daily	Instill 1 drop into affected eye(s) twice daily, every 8 to 12 hours, no more than twice per day. For children ≥ 3 years of age, refer to adult dose; safety and effectiveness in children < 3 years of age have not been established. Not studied in pregnancy.
Bepreve (bepotastine)	Ophthalmic solution	Ophthalmic	Twice daily	Instill 1 drop into affected eye(s) twice daily. For children ≥ 2 years of age, refer to adult dose; safety and

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				effectiveness in children < 2 years of age have not been established. Pregnancy: Unclassified†
Elestat (epinastine)	Ophthalmic solution	Ophthalmic	Twice daily	Instill 1 drop in each eye twice daily. Treatment should be continued throughout the period of exposure (ie, until the pollen season is over or until exposure to the offending allergen is terminated), even when symptoms are absent. For children ≥ 2 years of age, refer to adult dose; safety and effectiveness in children < 2 years of age have not been established. Pregnancy Category C*
Emadine (emedastine)	Ophthalmic solution	Ophthalmic	Up to 4 times daily	Instill 1 drop into affected eye(s) up to 4 times daily. For children ≥ 3 years of age, refer to adult dose; safety and effectiveness in children < 3 years of age have not been established. Pregnancy Category B*
Lastacaft (alcaftadine)	Ophthalmic solution	Ophthalmic	Daily	Instill 1 drop in each eye once daily. If more than 1 topical ophthalmic medicinal product is being used, each one should be administered at least 5 minutes apart. For children ≥ 2 years of age, refer to adult dose; safety and effectiveness in children < 2 years of age have not been established. Pregnancy Category B*
Optivar (azelastine)	Ophthalmic solution	Ophthalmic	Twice daily	Instill 1 drop into affected eye(s) twice daily. For children ≥ 3 years of age, refer to adult dose; safety and effectiveness in children < 3

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				years of age have not been established. Pregnancy Category C*
Pataday, Patanol, Pazeo (olopatadine)	All: Ophthalmic solutions	Ophthalmic	Once or twice daily (varies by product)	Patanol 0.1%: Instill 1 drop into affected eye(s) twice daily at an interval of 6 to 8 hours. Pataday 0.2%, Pazeo 0.7%: Instill 1 drop in affected eye(s) once daily For children ≥ 2 (0.2%, 0.7%) and ≥ 3 (0.1%) years of age, refer to adult dose; safety and effectiveness in children < 3 years (0.1%) and < 2 years (0.2%, 0.7%) of age have not been established. Pregnancy Pataday, Patanol: Pregnancy Category C* Pazeo: Unclassified†
Zerviate (cetirizine)	Ophthalmic solution	Ophthalmic	Twice daily	Instill 1 drop into affected eye(s) twice daily. For children ≥ 2 years of age, refer to adult dose; safety and effectiveness in children < 2 years of age have not been established. Pregnancy: Unclassified†

†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women. Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

See the current prescribing information for full details

CONCLUSION

- The ophthalmic antihistamines are FDA-approved for the management of the signs and symptoms associated with allergic conjunctivitis, the most common form of ocular allergy.
- Few distinguishing characteristics exist among the available ophthalmic antihistamines, but alcaftadine and olopatadine 0.2% and 0.7% may be administered once daily, while the remaining agents in this class are administered 2 to 4 times daily. In addition, ophthalmic alcaftadine and ophthalmic emedastine are classified as pregnancy category B; other agents in this class are pregnancy category C or were not studied in pregnant patients *(Micromedex 2.0 2018)*. Currently, ophthalmic formulations of azelastine, epinastine, ketotifen, and olopatadine are available generically. Ophthalmic formulations of ketotifen are also available generically in OTC formulations. Due to the ophthalmic

administration of these agents, relatively few adverse reactions have been reported; the most common adverse reactions are ocular burning and stinging and headache.

- Several studies have been conducted to directly compare ophthalmic ketotifen and ophthalmic olopatadine. These studies have produced mixed results, generally demonstrating no difference between the agents. There are limited head-to-head studies that compare the clinical efficacy of the other agents in this class to one another, and all are considered equally efficacious at improving ocular allergy symptoms. While some studies reported statistically significant differences in symptom scores, the overall clinical significance of these differences is not known, as many of these trials were conducted using single doses of study medication (in the conjunctival allergen challenge model) and generally enrolled a small number of patients.

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- Zerviate prescribing information. Akorn, Inc. Lake Forest, IL. May 2017.

Publication Date: March 15, 2018

Therapeutic Class Overview
Ophthalmic Antibiotics and Combinations

INTRODUCTION

- Blepharitis is a chronic inflammatory condition of the eyelids, often presenting with the symptoms of eye irritation and redness. Overgrowth of normal bacterial flora plays a role in the pathophysiology of blepharitis, with the most common causative organisms including *Staphylococcus* species, *Corynebacterium* species, and *Propionibacterium acnes*. The mainstay of the treatment of blepharitis is patient education regarding eyelid hygiene as well as the use of ophthalmic antibiotics. Of note, blepharitis is a chronic condition without definitive cure; therefore, satisfactory results require a long-term commitment to treatment and appropriate expectations. Ophthalmic corticosteroids may also be used acutely to treat exacerbations (*American Academy of Ophthalmology [AAO] 2013*).
- Conjunctivitis occurs worldwide and affects all ages and social strata. This infection rarely causes permanent visual loss or structural damage, and mild cases may be self-limited, as many cases will resolve without treatment in immunocompetent individuals. The most common causative pathogens seen with bacterial conjunctivitis include *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis*. Use of ophthalmic antibiotics is associated with earlier clinical and microbiological remission when compared to placebo. The selection of an ophthalmic antibiotic is typically empirical, and the most convenient or least expensive ophthalmic antibiotic is typically effective for most cases of conjunctivitis (*AAO 2013; American Optometric Association [AOA] 2002*).
- Severe bacterial conjunctivitis is characterized by purulent discharge, pain, and marked eye inflammation. In these cases, cultures and slides for gram staining should be obtained, and the results of these laboratory tests should guide the choice of the antibiotic. Methicillin-resistant *S. aureus* has been isolated in patients with bacterial conjunctivitis with increasing frequency and may be resistant to many available ophthalmic antibiotics. In patients with conjunctivitis caused by *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, systemic antibiotic therapy is necessary, and while not necessary, ophthalmic antibiotics are also typically used (*AAO 2013; AOA 2002*).
- Bacterial keratitis is characterized by an inflammation of the cornea and rarely occurs in the normal eye due to the cornea's natural resistance to infection. However, several predisposing factors such as contact lens wear, trauma, corneal surgery, ocular surface disease, systemic disease, and immunosuppression may alter the defense mechanisms of the ocular surface and allow for infection of the cornea. Due to corneal scarring or topographic irregularity, many forms of this infection result in visual loss. Untreated or severe bacterial keratitis can result in corneal perforation and may develop into endophthalmitis and result in the loss of the eye. The most common causative organisms of bacterial keratitis include *Staphylococci* and gram-negative rods, of which the most frequent organisms identified are *Pseudomonas* species. Ophthalmic antibiotics are the preferred method of treatment in many cases, and antibiotic ointments may be useful at bedtime in less severe cases or as adjunctive therapy. In addition, broad-spectrum ophthalmic antibiotics are used initially as empiric treatment. In severe cases, patients should be followed daily until stabilization or clinical improvement is documented (*AAO 2013*).
- Though not Food and Drug Administration (FDA)-approved, ophthalmic antibiotics are routinely used to prevent postoperative infections after eye surgeries such as refractive surgeries and cataract removal, while ophthalmic corticosteroids may also be used to reduce inflammation associated with surgeries (*AAO 2016; AAO 2013; AOA 2004*).
- Medispan class: Ophthalmic Antibiotics, Ophthalmic Anti-infective Combinations, and Ophthalmic Sulfonamides.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Aminoglycosides	
Gentak (gentamicin) †	✔
Tobrex (tobramycin) †	✔ *
Macrolides	
Azasite (azithromycin)	-
erythromycin	✔
Other	
bacitracin	✔
Bleph-10 (sulfacetamide sodium) §	✔
Quinolones	
Besivance (besifloxacin)	-
Ciloxan (ciprofloxacin)	✔ *
levofloxacin	✔
Moxeza, Vigamox (moxifloxacin)	✔ ‖
Ocuflox (ofloxacin)	✔
Zymaxid (gatifloxacin)	✔
Combinations	
bacitracin/neomycin/polymyxin	✔
bacitracin/polymyxin	✔
Neosporin (gramicidin/neomycin/polymyxin)	✔
Polytrim (polymyxin/trimethoprim)	✔

*solution only
† Gentak is a branded generic of gentamicin ophthalmic ointment; Genoptic brand of gentamicin sulfate solution has been discontinued; generic is available. AK-tob brand of tobramycin has been discontinued.
§ Brand name Bleph-10 is available in solution only; generics are available for solution and ointment. Cetamide brand of sulfacetamide sodium has been discontinued.
‖Multiple generic versions of Vigamox are available.

(*Drugs@FDA, 2018; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2018; Drug Facts and Comparisons, 2018; Clinical Pharmacology, 2018*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Aminoglycosides		Macrolides		Other		Quinolones							Combinations			
	gentamicin	tobramycin	Azasite	erythromycin	bacitracin	sulfacetamide	ciprofloxacin	levofloxacin	ofloxacin	Besivance	Moxeza	Vigamox	Zymaxid	bacitracin/neomycin/polymyxin	bacitracin/polymyxin	gramicidin/neomycin/polymyxin	polymyxin/trimethoprim
Treatment of bacterial conjunctivitis			✔				✔	✔	✔	✔	✔	✔	✔				
Treatment of corneal ulcers							✔ †		✔								
Treatment of external infections of the eye and its adnexa caused by susceptible bacteria		✔												✔		✔	
Treatment of superficial ocular infections involving the conjunctiva and/or cornea				✔	✔										✔		
Prophylaxis of ophthalmia neonatorum due to *N. gonorrhoeae* or *C. trachomatis*				✔ §													
Treatment of ocular bacterial infections including conjunctivitis, keratitis, keratoconjunctivitis, corneal ulcers, blepharitis, blepharoconjunctivitis, acute meibomianitis, and dacryocystitis	✔																
Treatment of surface ocular infections, including acute bacterial conjunctivitis and blepharoconjunctivitis																	✔
Treatment of conjunctivitis and other superficial ocular infections						✔											
Adjunctive treatment with systemic treatment for trachoma						✔ †											

†solution only
§ The effectiveness of erythromycin in the prevention of ophthalmia caused by penicillinase-producing *N. gonorrhoeae* is not established.

(*Prescribing information: Azasite, 2017; bacitracin, 2013; bacitracin/neomycin/polymyxin, 2016; bacitracin/polymyxin, 2013; Besivance, 2018; Bleph-10, 2017; Ciloxan solution, 2017; Ciloxan ointment, 2017; erythromycin, 2017; Gentak, 2016; gentamicin, 2016; levofloxacin, 2017; Moxeza, 2017; Neosporin, 2016; Ocuflox, 2017; polymyxin/trimethoprim, 2018; Polytrim, 2004; sulfacetamide ointment, 2013; sulfacetamide solution, 2017; Tobrex ointment, 2018; Tobrex solution, 2018; Vigamox, 2017; Zymaxid, 2016*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Clinical trials have demonstrated that ophthalmic antibiotics are effective in treating and providing relief of bacterial conjunctivitis in pediatric and adult patients (*Abelson et al 2007; Abelson et al 2008; Bremond-Gignac et al 2014; Cochereau et al 2007; DeLeon et al 2012; Gross et al 1997; Hwang et al 2003; Karpecki et al 2009; Kernt et al 2005; McDonald et al, 2009; Schwab et al 2003; Sheikh et al 2012; Silver et al 2005; Silverstein et al 2011; Silverstein et al, 2012; Tauber et al 2011; Tepedino et al 2009; Williams et al 2012*). Several studies comparing ophthalmic antibiotics such as azithromycin, besifloxacin, levofloxacin, and moxifloxacin to placebo have concluded that these medications resulted in significantly higher clinical resolution rates at days 1 through 5 (*Abelson et al 2008; DeLeon et al 2012; Hwang et al 2003; Karpecki et al 2009; Silverstein et al 2011; Tauber et al 2011; Tepedino et al 2009*).
- In a trial, there was no difference in clinical cure rate between treatment with ophthalmic polymyxin B/trimethoprim and ophthalmic moxifloxacin (p = 0.59) (*Williams et al 2012*). In a 5-day trial, a higher percentage of patients receiving levofloxacin had microbial eradication at the final visit compared to patients receiving ofloxacin (p = 0.034); however, clinical cure rates were similar between the 2 treatments (p value not reported) (*Schwab 2003*).
- Most other studies have shown no significant difference between ophthalmic antibiotic treatments with regard to bacterial eradication, clinical resolution, clinical response, efficacy, microbial eradication, physician's judgment of resolution, severity rating, or symptom improvement (*Ableson et al 2007; Cochereau et al 2007, Gross et al 1997; McDonald et al 2009; Sanfilippo et al 2017; Silver et al 2005*). While no difference was found between ophthalmic formulations of azithromycin and tobramycin with regard to clinical resolution and bacterial eradication, ophthalmic azithromycin produced the same clinical outcome with 65% fewer drops (*Abelson et al 2007*). In all studies, most adverse events were mild with no significant difference seen with regard to the rate of adverse events. Common adverse events included burning, ocular discomfort, stinging, and tearing (*Abelson et al 2007; Cochereau et al 2007; Gross et al 1997; McDonald et al 2009; Schwab et al 2003; Silver et al 2005; Williams et al 2012*).
- A number of studies consisted of patients with multiple diagnoses such as blepharitis, blepharoconjunctivitis, bacterial conjunctivitis, keratoconjunctivitis, or symptoms of surface ocular infections. These studies found that the ophthalmic formulations of gentamicin, levofloxacin, ofloxacin, and tobramycin solution were efficacious in resolving or curing multiple ocular infections (*Gwon 1992 Sep; Gwon 1992 Dec; Kanda et al 2012*). No significant differences were observed in any study with regard to cure rates, decline in bacterial counts, bacterial eradication or reduction of bacteria, microbial improvement, or overall improvement. In one study, ophthalmic ofloxacin was shown to significantly decrease the cumulative summary score on days 3 through 5 in patients with conjunctival hyperemia, eyelid crusting or discharge, and positive bacterial culture when compared to ophthalmic tobramycin (p < 0.05); however, by day 11, there were no significant differences between the 2 treatments with regard to clinical, microbial, and overall improvement rates (*Gwon 1992 Sep*). In studies of patients with multiple diagnoses, the most commonly reported adverse events were similar between treatment groups. The most common adverse events included burning, mild discomfort, and stinging on instillation.
- In one study evaluating the treatment of ophthalmia neonatorum, conjunctivitis in newborn babies principally caused by *N. gonorrhoeae*, prophylaxis with ophthalmic erythromycin ointment was found to be most effective prior to the infant's second week of life. The efficacy of ophthalmic erythromycin prophylaxis from days 0 to 14 was statistically significant when compared to no prophylaxis; however, the efficacy was not significant from days 15 to 60 (14 vs 9%; p = 0.05 and 7 vs 8%; p = 0.92, respectively) (*Bell et al 1993*). In another study, ophthalmic erythromycin prophylaxis resulted in significantly fewer reports of conjunctival redness and tearing or serious or purulent discharge during the first 24 hours to 2 weeks of life when compared to no prophylaxis (18.4 vs 22.4%; p = 0.03) (*Ali et al 2007*).
- In a study involving patients undergoing cataract extraction by either manual extraction or phacoemulsification with intraocular lens implantation, ophthalmic tobramycin/dexamethasone was non-inferior to ophthalmic neomycin/polymyxin B/dexamethasone concerning inflammation scores at days 3, 8, 14, and 21. Inflammation scores in the ophthalmic tobramycin/dexamethasone group were significantly lower than scores seen in the ophthalmic neomycin/polymyxin B/gramicidin group at days 8, 14, and 21 (p < 0.05 for all), and scores in the ophthalmic

neomycin/polymyxin B/dexamethasone group were significantly lower than those seen in the ophthalmic neomycin/polymyxin B/gramicidin group at day 8 ($p < 0.05$) (*Notivol et al 2004*).

CLINICAL GUIDELINES

- Guidelines published by the AAO recommend that blepharitis be treated with ophthalmic bacitracin or ophthalmic erythromycin, and the guidelines note that macrolide antibiotics may have anti-inflammatory activity with regard to the treatment of blepharitis (*AAO 2013*).
- Guidelines state that keratitis should be treated with a broad-spectrum ophthalmic antibiotic that may be selected based on the isolated organism, and if no organism is identified, treatment with an ophthalmic fluoroquinolone is recommended. The AAO guideline also notes that fewer gram-positive cocci are resistant to ophthalmic gatifloxacin and moxifloxacin than other fluoroquinolones (*AAO 2013*).
- For the treatment of bacterial conjunctivitis, it is recommended that the least expensive or most convenient broad-spectrum antibiotic be selected for a 5- to 7-day course of treatment, if needed (*AAO 2013; AOA 2002*).

SAFETY SUMMARY

- Contraindication to use of these products is hypersensitivity to any component of the product.
- Warnings/precautions include the following: 1) do not wear contact lenses while infected; 2) prolonged use may result in overgrowth of non-susceptible organisms, including fungi; and 3) cutaneous sensitization may occur with products containing neomycin.
- The most frequent adverse effects were burning, stinging, and irritation upon instillation, redness, blurred vision, itching, swelling, tearing, eye pain, and photophobia. Non-ocular reactions can occur and include headache, pharyngitis, dizziness, and allergic reactions. Ciloxan (ciprofloxacin) had a reported incidence of 17% for white crystalline precipitates in corneal ulcer studies.
- These agents are minimally absorbed; therefore, drug interactions are not likely to occur.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Usual Recommended Frequency	Comments
Gentak (gentamicin)	Ophthalmic ointment: 0.3% Ophthalmic solution: 0.3%	**Ointment**: 2 or 3 times a day **Solution**: every 4 hours *Severe infections:* dosage may be increased to as much as every hour.	Safety and efficacy in neonates have not been established.
Tobrex (tobramycin)	Ophthalmic ointment: 0.3% Ophthalmic solution: 0.3%	**Ointment**: *Mild to moderate disease*: 2 or 3 times a day *Severe infections*: every 3 to 4 hours until improvement, following which treatment should be reduced prior to discontinuation. **Solution**: *Mild to moderate disease*: every 4 hours *Severe infections*: hourly until improvement, following which treatment should be reduced prior to discontinuation	Safety and efficacy have not been established in infants < 2 months of age.
Azasite (azithromycin)	Ophthalmic solution: 1%	Twice daily, 8 to 12 hours apart for the first 2 days, then once daily for the next 5 days	Safety and efficacy have not been established in children < 1 year of age
erythromycin	Ophthalmic ointment: 0.5%	**Superficial infections**: Apply directly to the infected structure up	For neonates: The ointment should not be flushed from the eye following instillation

Drug	Available Formulations	Usual Recommended Frequency	Comments
		to 6 times daily, depending on the severity of the infection. **Prophylaxis of neonatal gonococcal or chlamydial conjunctivitis:** apply into each lower conjunctival sac.	
bacitracin	Ophthalmic ointment: 500 units/gram	Apply directly into the conjunctival sac 1 to 3 times daily	No data in pediatric patients
Bleph-10 (sulfacetamide sodium)	Ophthalmic ointment: 10% Ophthalmic solution: 10%	**Ointment**: every 3 to 4 hours and at bedtime for 7 to 10 days **Solution**: every 2 to 3 hours for 7 to 10 days *Trachoma*: every 2 hours; must also use systemic administration	Safety and efficacy have not been established in infants < 2 months of age.
Besivance (besifloxacin)	Ophthalmic suspension: 0.6%	Three times daily, 4 to 12 hours apart for 7 days	Safety and efficacy have not been established in children < 1 year.
Ciloxan (ciprofloxacin)	Ophthalmic ointment: 0.3% Ophthalmic solution: 0.3%	**Corneal ulcers**: *Solution*: every 15 minutes for the first 6 hours, every 30 minutes for the remainder of the first day. Second day: every hour Third through 14th day: every 4 hours **Conjunctivitis**: *Ointment*: 3 times daily for first 2 days, then twice daily for the next 5 days *Solution*: every 2 hours while awake for 2 days, then every 4 hours while awake for next 5 days	**Ointment**: Safety and efficacy have not been established in children < 2 years of age. **Solution**: Safety and efficacy have been established in all ages.
levofloxacin	Ophthalmic solution: 0.5%	Every 2 hours while awake, up to 8 times per day on days 1 and 2, then every 4 hours while awake, up to 4 times per day for days 3 to 7	Safety and efficacy have not been established in children < 1 year of age
Moxeza, Vigamox (moxifloxacin)	Ophthalmic solution: 0.5% (Moxeza - twice daily formulation), 0.5% (Vigamox - 3 times daily formulation)	**Moxeza**: twice daily for 7 days **Vigamox**: 3 times daily for 7 days	**Moxeza**: Safety and efficacy have not been established in infants < 4 months of age. **Vigamox**: Safety and efficacy have been established in all ages.
Ocuflox (ofloxacin)	Ophthalmic solution: 0.3%	**Conjunctivitis**: every 2 to 4 hours days 1 and 2, then 4 times daily for days 3 through 7 **Corneal ulcers:** *Days 1 and 2*: every 30 minutes, while awake *Days 3 through 7 to 9*: hourly, while awake *Days 7 to 9 through treatment completion*: 4 times daily	Safety and efficacy have not been established in children < 1 year of age.

Drug	Available Formulations	Usual Recommended Frequency	Comments
Zymaxid (gatifloxacin)	Ophthalmic solution: 0.5%	Every 2 hours while awake up to 8 times on day 1, then 2 to 4 times per day while awake on days 2 through 7	Safety and efficacy have not been established in children < 1 year of age.
bacitracin/ neomycin/ polymyxin	Ophthalmic ointment: bacitracin zinc 400 units, neomycin 3.5 mg, polymyxin B sulfate 10,000 units	Every 3 or 4 hours for 7 to 10 days, depending on the severity of the infection	Safety and efficacy have not been established in pediatric patients
bacitracin/ polymyxin	Ophthalmic ointment: bacitracin zinc 500 units, polymyxin B sulfate 10,000 units	Every 3 or 4 hours for 7 to 10 days, depending on the severity of the infection	No data in pediatric patients
Neosporin (gramicidin/ neomycin/ polymyxin)	Ophthalmic solution: neomycin sulfate 1.75 mg, polymyxin B sulfate 10,000 units, gramicidin 0.025 mg	Every 4 hours for 7 to 10 days *Severe infections*: may increase to every hour	Safety and efficacy have not been established in pediatric patients.
Polytrim (polymyxin/ trimethoprim)	Ophthalmic solution: polymyxin B sulfate 10,000 units, trimethoprim 1 mg	*Mild to moderate infections*: Every 3 hours (maximum of 6 doses per day) for a period of 7 to 10 days	Safety and efficacy have not been established in iinfants < 2 months of age.

See the current prescribing information for full details

CONCLUSION

- Ophthalmic antibiotics are used to treat ophthalmic infections, including blepharitis, conjunctivitis, and keratitis as well as several others. Classes of ophthalmic antibiotics include aminoglycosides, macrolides, quinolones, and other miscellaneous and combination products. For all FDA-approved indications, a generic ophthalmic antibiotic is available.
- In comparative clinical trials, no one ophthalmic antibiotic has been shown to be more effective than another in bacterial eradication, clinical resolution, clinical response, or symptom improvement.
- In clinical studies, adverse events were mild with no significant difference seen with regard to the rate of adverse events. Common adverse events reported include burning, ocular discomfort, stinging, and tearing.
- Ophthalmic antibiotics are not intended to be used for prolonged periods of time in order to avoid overgrowth of non-susceptible organisms and reduce the risk of resistance. Should super-infection occur, the ophthalmic antibiotic should be discontinued, and an alternative therapy should be initiated.
- Guidelines published by the AAO recommend that blepharitis be treated with ophthalmic bacitracin or ophthalmic erythromycin, and the guidelines note that macrolide antibiotics may have anti-inflammatory activity with regard to the treatment of blepharitis (*AAO 2013*).
- Guidelines state that keratitis should be treated with a broad-spectrum ophthalmic antibiotic that may be selected based on the isolated organism, and if no organism is identified, treatment with an ophthalmic fluoroquinolone is recommended. The AAO guideline also notes that fewer gram-positive cocci are resistant to ophthalmic gatifloxacin and moxifloxacin than other fluoroquinolones (*AAO 2013*).
- For the treatment of bacterial conjunctivitis, it is recommended that the least expensive or most convenient broad-spectrum antibiotic be selected for a 5- to 7-day course of treatment, if needed (*AAO 2013; AOA 2002*).

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Publication Date: June 28, 2018

Therapeutic Class Overview
Ophthalmic Immunomodulators

INTRODUCTION

- Dry eye syndrome refers to a group of disorders of the tear film that are due to reduced tear production or excessive tear evaporation (*American Academy of Ophthalmology [AAO] Dry Eye Syndrome 2013*). The condition can be associated with discomfort and/or visual symptoms and may result in disease of the ocular surface. The ocular surface and tear-secreting glands are recognized to be responsible for the maintenance of tear production and to clear tears. Therefore, disease or dysfunction results in an unstable and poorly maintained tear film that causes ocular irritation symptoms and an epithelial disease known as keratoconjunctivitis sicca (KCS). Decreased tear secretion and clearance initiates an inflammatory response on the ocular surface which plays a role in the pathogenesis of KCS. Symptoms of KCS include, but are not limited to, dryness, discomfort, irritation/pain, foreign body sensation, and blurred vision (*AAO Dry Eye Syndrome 2013*).
- Rare complications of severe dry eyes include ocular surface keratinization; corneal scarring, thinning, or neovascularization; microbial or sterile corneal ulceration with possible perforation; and severe visual loss.
- Frequent instillation of ophthalmic medications, such as natural tears, may also cause dry eye symptoms by preventing the normal maintenance of the tear film. Other factors known to exacerbate symptoms of dry eye include environmental factors such as reduced humidity, air drafts, air conditioning, or heating. Associated systemic diseases include Sjögren's Syndrome, rosacea, and viral infection. Common drug induced causes of dry eye symptoms include systemic medications such as anticholinergics, antidepressants, antihistamines, diuretics, and systemic retinoids (*AAO Dry Eye Syndrome 2013*).
- Medispan Therapeutic Class: Ophthalmic Immunomodulators

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Restasis, Restasis Multidose (cyclosporine ophthalmic emulsion)	-
Xiidra (lifitegrast ophthalmic solution)	-

(*Drugs@FDA 2017, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Restasis, Restasis Multidose (cyclosporine ophthalmic emulsion)	Xiidra (lifitegrast ophthalmic solution)
To increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca*	✔	
Treatment of the signs and symptoms of dry eye disease		✔

*Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

(*Restasis prescribing information~~,~~ 2017; Restasis Multidose prescribing information 2017, Xiidra prescribing information 2017*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The pivotal trials for cyclosporine ophthalmic emulsion were 2 randomized, placebo-controlled trials that included 877 patients and an open-label, extension trial that included 412 patients (*Barber et al 2005, Sall et al 2000*). All patients were diagnosed with moderate-to-severe KCS and decreased tear production based on the Schirmer tear test. The combined results of the 2 placebo-controlled trials demonstrated that cyclosporine ophthalmic emulsion 0.05% and 0.1%

were associated with significant improvements from baseline in corneal staining, Schirmer tear test scores, Ocular Surface Disease Index (OSDI) scores, Subjective Facial Expression Rating Scale scores, and various dry eye related symptoms (*Sall et al, 2000*). Specifically compared to placebo, at 4 months, improvements in corneal staining were significant in both cyclosporine ophthalmic emulsion groups compared to placebo ($p \leq 0.044$), and at 6 months, only the cyclosporine ophthalmic emulsion 0.05% group demonstrated significance over placebo ($p = 0.008$). Additionally, at 6 months, improvements in Schirmer tear test scores were significantly greater for both cyclosporine ophthalmic emulsion groups compared to placebo ($p \leq 0.05$ for both) and from baseline scores (p values not reported). Improvements in OSDI and Subjective Facial Expression Rating Scale scores were significant compared to baseline for all treatment groups ($p < 0.001$), but there were no significant differences among these groups (p values not reported). Improvements in blurred vision were significantly greater in the cyclosporine ophthalmic emulsion 0.05% group than placebo at all follow-up visits ($p \leq 0.014$), and significant improvements were achieved at all time points within all treatment groups when compared to baseline for relief of dry eye symptoms including dryness ($p < 0.001$), sandy/gritty feeling ($p < 0.001$), and itching ($p \leq 0.038$). A Chinese, double-blind study used similar subjective ratings for dry eye symptoms and found that cyclosporine ophthalmic emulsion 0.05% improved measures over 8 weeks (*Chen et al 2010*).

- An open-label, extension trial was also conducted to determine the long-term safety of cyclosporine ophthalmic emulsion. After 3 consecutive 12-month periods, results demonstrated that cyclosporine ophthalmic emulsion was safe and well tolerated. Over 3 years, adverse events were found in 65.3% (269/412) of patients with ocular burning reported most commonly (12.1%). This trial also demonstrated sustained efficacy of cyclosporine ophthalmic emulsion over an extended period of time (*Barber et al 2005*).
- A trial comparing cyclosporine ophthalmic emulsion to punctal plugs or a combination of both demonstrated that both treatments improved the symptoms of dry eye, but punctal plugs achieved results more rapidly than cyclosporine ophthalmic emulsion (*Roberts et al 2007*).
- A systematic review of 18 RCTs examined the efficacy and safety of topical cyclosporine for treatment of dry eye disease. All cyclosporine formulations proved safe for the treatment of dry eye disease. Symptoms improved in 100% (9/9 RCTs), tear function improved in 72% (13/18 RCTs) and ocular surface damage was ameliorated in 53% (9/17 RCTs) (*Saccheti et al 2014*).
  - Statistical comparison of cyclosporine efficacy through a meta-analysis of data was not possible due to a lack of standardized criteria and comparable outcomes among studies.
- The safety and efficacy of lifitegrast ophthalmic solution for the treatment of dry eye disease were assessed in a total of 1181 patients (1067 of which received lifitegrast 5%) in four 12-week, randomized, multicenter, double-masked, vehicle-controlled studies (*Semba et al 2012, Sheppard et al 2014, Tauber et al 2015, Holland et al 2017*). The use of artificial tears was not allowed during the studies. The clinical trials evaluated various endpoints related to signs and symptoms of dry eye disease. However, the Food and Drug Administration (FDA) approval relied on an assessment of symptoms based on change from baseline in patient reported eye dryness score (EDS; 0 to 100 visual analogue [VAS] scale) and an assessment of signs based on the inferior corneal staining score (ICSS; 0 to 4 scale).
- A larger reduction in EDS favoring lifitegrast was observed in all studies at day 42 and day 84.
  - EDS was used as a primary symptom endpoint in 2 of the 4 studies (OPUS-2 and OPUS-3); the other 2 evaluated EDS as a secondary endpoint.
  - In OPUS-1, the primary symptom endpoint was the visual-related function subscale score of the Ocular Surface Disease Index (VR-OSDI) questionnaire. No difference between lifitegrast and placebo was seen in the mean change from baseline to day 84 ($p = 0.7894$) (*Sheppard et al 2014*).
- At day 84, a larger reduction in ICSS favoring lifitegrast was observed in 3 of the 4 studies (no statistically significant difference between lifitegrast and placebo was found in the OPUS-2 study).
- In a 1-year safety study (N = 331: 220 lifitegrast; 111 placebo), there were no serious ocular treatment-emergent adverse events (TEAEs). Overall, 53.6% of participants receiving lifitegrast experienced ≥ 1 ocular TEAE vs. 34.2% in the placebo group; most TEAEs were mild to moderate in severity, with burning, instillation site reaction, reduced visual acuity, dry eye, and dysgeusia reported most commonly (*Donnenfeld et al 2016*).
- Ocular comfort of lifitegrast was also assessed in OPUS-3 (n = 711). Drop comfort scores (0 = very comfortable, 10 = very uncomfortable) were assessed immediately after instillation and at 1, 2, and 3 minutes post-instillation. The results showed that drop comfort scores with lifitegrast improved within 3 minutes of instillation with scores approaching that of placebo (*Nichols et al 2018*).

CLINICAL GUIDELINES

- Clinical guidelines consider cyclosporine ophthalmic emulsion to be an appropriate therapy for patients with moderate dry eye syndrome, and also in the treatment of severe atopic KCS or for those patients with atopic KCS who have failed conventional therapy (*AAO Dry Eye Syndrome 2013*). However, depending on patient preference and physician experience, any of the recognized treatment options for dry eye syndrome may be used to treat the disease regardless of the severity rating. The guidelines have not yet been updated to include lifitegrast.

SAFETY SUMMARY

- Cyclosporine ophthalmic emulsion
  - Cyclosporine ophthalmic emulsion is contraindicated in patients with known or suspected hypersensitivity to any ingredient in the formulation.
  - Warnings include the risk of eye injury and contamination when administering the medication if the vial tip touches the eye or other surfaces and use with contact lenses. Cyclosporine ophthalmic emulsion should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted15 minutes following administration of cyclosporine ophthalmic emulsion.
  - Ocular burning is the most frequently reported adverse event. Other adverse events reported include ocular pain, conjunctival hyperemia, discharge, foreign body sensation, pruritus, stinging, visual disturbance (most often blurring).
- Lifitegrast ophthalmic solution
  - Lifitegrast ophthalmic solution is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation.
  - The most commonly reported adverse events reported in 5 to 25% of patients were instillation site irritation, dysgeusia, and reduced visual acuity.
  - Other adverse events reported in 1 to 5% of patients included blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus, and sinusitis.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Restasis, Restasis Multidose (cyclosporine ophthalmic emulsion)	Ophthalmic emulsion	opth	To increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca: Ophthalmic emulsion: instill 1 drop in each eye twice daily approximately 12 hours apart	Cyclosporine ophthalmic emulsion can be used concomitantly with artificial tears; however, patients should allow for a 15-minute interval between the products. To avoid contamination, care should be taken not to touch the bottle tip to the eye or other surfaces Restasis (single-dose vial): Discard vial immediately after use. Restasis Multidose is packaged in a multi-dose preservative-free 10 mL bottle containing 5.5 mL.
Xiidra (lifitegrast ophthalmic solution)	Ophthalmic solution	opth	Instill 1 drop twice daily (approximately 12 hours apart)	Contact lenses should be removed prior to the administration of lifitegrast and may be reinserted 15 minutes following administration. Discard the single-use container immediately after using in each eye.

CONCLUSION

- Restasis (cyclosporine ophthalmic emulsion) is the first ophthalmic emulsion FDA-approved to increase tear production in patients with KCS. Although the exact mechanism of action of this agent is unknown, it is assumed that it acts as a partial immunomodulator.
- Xiidra (lifitegrast ophthalmic solution) is the second prescription treatment to receive FDA-approval for treatment of dry eye disease. Lifitegrast is a novel small molecule integrin antagonist that inhibits T cell-mediated inflammation by blocking the binding of 2 important cell surface proteins (lymphocyte function-associated antigen 1 [LFA-1] and intercellular adhesion molecule 1 [ICAM-1]), thus lessening overall inflammatory responses. However, the exact mechanism of action of lifitegrast in dry eye disease is unknown.
- In clinical trials, cyclosporine ophthalmic emulsion demonstrated significant increases in tear production and decreases in dry eye symptoms compared to placebo and demonstrated safety for up to 3 years (*Sall et al 2000, Barber et al 2005, Roberts et al 2007*).
- Lifitegrast also demonstrated significant improvements in the signs and symptoms of dry eye disease compared with placebo in clinical trials. Lifitegrast was well tolerated with no unexpected adverse events in a 1-year safety exposure study (*Donnenfeld et al 2016, Holland et al 2017, Semba et al 2012, Sheppard et al 2014, Tauber et al 2015*).
- Clinical guidelines consider cyclosporine ophthalmic emulsion to be an appropriate therapy for patients with moderate to severe dry eye syndrome (*AAO Dry Eye Syndrome 2013, AOA Ocular Surface Disorders 2010*). Lifitegrast has not yet been incorporated into the guidelines.
- There are no comparative trials of cyclosporine ophthalmic emulsion and lifitegrast ophthalmic solution.

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Publication Date: 3/20/2018