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Governor

STATE OF NEVADA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
DIVISION OF HEALTH CARE FINANCING AND POLICY
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Director

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Administrator

NOTICE OF OPEN PUBLIC MEETING

The Division of Health Care Financing and Policy (DHCFP) Pharmacy and Therapeutics Committee will conduct a public meeting on **November 13, 2014**, beginning at **1:00 p.m.** at the following location:

JW Marriott Las Vegas Resort and Spa
Grand Ballroom A
221 N. Rampart Blvd
Las Vegas, NV 89145
702-869-7777

This meeting will be held only in Las Vegas, NV, there will be no teleconference to Carson City, NV.

Reasonable efforts will be made to assist and accommodate physically challenged persons desiring to attend the meeting. Please call Rita Mackie at: 775-684-3681 or email rmackie@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 5 minutes per individual, organization, or agency, but may be extended at the discretion of the Chairperson.

AGENDA

- I. CALL TO ORDER AND ROLL CALL
- II. PUBLIC COMMENT

No action may be taken on a matter raised under this item of the agenda until the matter itself has been specifically included on the agenda as an item upon which action can be taken.

- III. **FOR POSSIBLE ACTION:** Review and Approval of the June 26, 2014 Meeting Minutes

IV. STATUS UPDATE BY DHCFP

- A. Public Comment
- B. Program Updates

V. ANNUAL REVIEW - ESTABLISHED DRUG CLASSES

A. CENTRAL NERVOUS SYSTEM: ADHD/STIMULANTS

- 1. Public Comment
- 2. Drug Class Review Presentation – Catamaran
- 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 Catamaran and the Division of Health Care Financing and Policy
- 5. **For Possible Action:** Committee Discussion and Approval of Drugs for Inclusion on the PDL

B. ANTIBIOTICS: Cephalosporins 3rd Generation

- 1. Public Comment
- 2. Drug Class Review Presentation – Catamaran
- 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 Catamaran and the Division of Health Care Financing and Policy
- 5. **For Possible Action:** Committee Discussion and Approval of Drugs for Inclusion on the PDL

C. ANTICOAGULANTS: Injectable

- 1. Public Comment
- 2. Drug Class Review Presentation – Catamaran
- 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 Catamaran and the Division of Health Care Financing and Policy
- 5. **For Possible Action:** Committee Discussion and Approval of Drugs for Inclusion on the PDL

- D. ANTI-MIGRAINE AGENTS: Triptans
1. Public Comment
 2. Drug Class Review Presentation – Catamaran
 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 Catamaran and the Division of Health Care Financing and Policy
 5. **For Possible Action:** Committee Discussion and Approval of Drugs for Inclusion on the PDL
- E. BENIGN PROSTATIC HYPERPLASIA (BPH) AGENTS: 5-alpha-reductase Inhibitors
1. Public Comment
 2. Drug Class Review Presentation – Catamaran
 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 Catamaran and the Division of Health Care Financing and Policy
 5. **For Possible Action:** Committee Discussion and Approval of Drugs for Inclusion on the PDL
- F. CARDIOVASCULAR: Antihyperlipidemics, Triglyceride Lowering Agents
1. Public Comment
 2. Drug Class Review Presentation – Catamaran
 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 Catamaran and the Division of Health Care Financing and Policy
 5. **For Possible Action:** Committee Discussion and Approval of Drugs for Inclusion on the PDL
- G. DIABETIC AGENTS: DPP-4 Inhibitors and Combinations
1. Public Comment
 2. Drug Class Review Presentation – Catamaran
 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 Catamaran and the Division of Health Care Financing and Policy

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

H. ELECTROLYTE DEPLETERS

1. Public Comment
2. Drug Class Review Presentation – Catamaran
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 Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action:** Committee Discussion and Approval of Drugs for Inclusion on the PDL

I. OPHTHALMIC ANTIHISTAMINES

1. Public Comment
2. Drug Class Review Presentation – Catamaran
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 Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action:** Committee Discussion and Approval of Drugs for Inclusion on the PDL

J. PSORIASIS AGENTS: Topical

1. Public Comment
2. Drug Class Review Presentation – Catamaran
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 Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action:** Committee Discussion and Approval of Drugs for Inclusion on the PDL

K. BONE OSSIFICATION AGENTS: BISPHOSPHONATES

1. Public Comment
2. Drug Class Review Presentation – Catamaran
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 Catamaran and the Division of Health Care Financing and Policy
- 5. **For Possible Action:** Committee Discussion and Approval of Drugs for Inclusion on the PDL

L. ANTIDEPRESSANTS: SSRI

- 1. Public Comment
- 2. Drug Class Review Presentation – Catamaran
- 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 Catamaran and the Division of Health Care Financing and Policy
- 5. **For Possible Action:** Committee Discussion and Approval of Drugs for Inclusion on the PDL

M. ANTIDEPRESSANTS: OTHER

- 1. Public Comment
- 2. Drug Class Review Presentation – Catamaran
- 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 Catamaran and the Division of Health Care Financing and Policy
- 5. **For Possible Action:** Committee Discussion and Approval of Drugs for Inclusion on the PDL

VI. ANNUAL REVIEW - ESTABLISHED DRUG CLASSES BEING REVIEWED DUE TO THE RELEASE OF NEW DRUGS.

N. ANALGESICS: LONG ACTING NARCOTICS

- 1. Public Comment
- 2. Drug Class Review Presentation – Catamaran
- 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 Catamaran and the Division of Health Care Financing and Policy

5. **For Possible Action:** Committee Discussion and Approval of Drugs for Inclusion on the PDL
- O. Diabetic Agents: GLP-1
1. Public Comment
 2. Drug Class Review Presentation – Catamaran
 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 Catamaran and the Division of Health Care Financing and Policy
 5. **For Possible Action:** Committee Discussion and Approval of Drugs for Inclusion on the PDL
- P. DIABETIC AGENTS: INCRETIN MIMETICS
1. Public Comment
 2. Drug Class Review Presentation – Catamaran
 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 Catamaran and the Division of Health Care Financing and Policy
 5. **For Possible Action:** Committee Discussion and Approval of Drugs for Inclusion on the PDL
- Q. CARDIOVASCULAR: ANTIHYPERLIPIDEMICS, NIACIN AGENTS
1. Public Comment
 2. Drug Class Review Presentation – Catamaran
 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 Catamaran and the Division of Health Care Financing and Policy
 5. **For Possible Action:** Committee Discussion and Approval of Drugs for Inclusion on the PDL
- R. CENTRAL NERVOUS SYSTEM: Oral Anticonvulsants, Misc.
1. Public Comment
 2. Drug Class Review Presentation – Catamaran
 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 Catamaran and the Division of Health Care Financing and Policy
 5. **For Possible Action:** Committee Discussion and Approval of Drugs for Inclusion on the PDL
- S. ANDROGENIC AGENTS: Topical
1. Public Comment
 2. Drug Class Review Presentation – Catamaran
 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 Catamaran and the Division of Health Care Financing and Policy
 5. **For Possible Action:** Committee Discussion and Approval of Drugs for Inclusion on the PDL
- T. IMMUNOMODULATORS: Injectable
1. Public Comment
 2. Drug Class Review Presentation – Catamaran
 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 Catamaran and the Division of Health Care Financing and Policy
 5. **For Possible Action:** Committee Discussion and Approval of Drugs for Inclusion on the PDL
- U. PLATELET AGGREGATION INHIBITORS
1. Public Comment
 2. Drug Class Review Presentation – Catamaran
 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 Catamaran and the Division of Health Care Financing and Policy
 5. **For Possible Action:** Committee Discussion and Approval of Drugs for Inclusion on the PDL
- V. RESPIRATORY: INHALED ANTICHOLINERGIC AGENTS
1. Public Comment
 2. Drug Class Review Presentation – Catamaran
 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 Catamaran and the Division of Health Care Financing and Policy
- 5. **For Possible Action:** Committee Discussion and Approval of Drugs for Inclusion on the PDL

W. RESPIRATORY: LONG ACTING BETA ADRENERGICS

- 1. Public Comment
- 2. Drug Class Review Presentation – Catamaran
- 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 Catamaran and the Division of Health Care Financing and Policy
- 5. **For Possible Action:** Committee Discussion and Approval of Drugs for Inclusion on the PDL

X. ANTIVIRALS: Hepatitis C Ribavirins

- 1. Public Comment
- 2. Drug Class Review Presentation – Catamaran
- 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 Catamaran and the Division of Health Care Financing and Policy
- 5. **For Possible Action:** Committee Discussion and Approval of Drugs for Inclusion on the PDL

VII. ANNUAL REVIEW – DRUG CLASSES WITHOUT PROPOSED CHANGES

- A. Public Comment
- B. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by Catamaran and the Division of Health Care Financing and Policy without Changes
- C. **For Possible Action:** Committee Discussion and Action
 - 1. ACNE AGENTS: Topical, Retinoid Agents and Combinations
 - 2. ACNE AGENTS: Topical, Benzoyl Peroxide, Antibiotics and Combination Products
 - 3. ALZHEIMER'S AGENTS

4. ANALGESICS/ANESTHETICS: Topical
5. ANALGESICS: Tramadol and Related Drugs
6. ANAPHYLAXIS: Self-Injectable Epinephrine
7. ANTIBIOTICS: Cephalosporins 2nd Generation
8. ANTIBIOTICS: Macrolides
9. ANTIBIOTICS: Quinolones 2nd Generation
10. ANTIBIOTICS: Quinolones 3rd Generation
11. ANTICOAGULANTS: Oral
12. ANTIEMETICS: Oral, 5-HT₃s
13. ANTIFUNGALS: Onychomycosis Agents
14. ANTIHISTAMINES: 2nd Generation
15. ANTIHYPERURICEMICS: Xanthine Oxidase Inhibitors for Gout
16. ANTIPARKINSON'S AGENTS: Non-ergot Dopamine Agonists
17. ANTIPSYCHOTICS: Oral, Atypical
18. ANTIVIRAL AGENTS: Influenza
19. BENIGN PROSTATIC HYPERPLASIA (BPH) AGENTS: Alpha-blockers
20. CARDIOVASCULAR: ACE Inhibitors and Diuretic Combinations
21. CARDIOVASCULAR: Angiotensin II Receptor Blockers and Diuretic Combinations
22. CARDIOVASCULAR: Antihyperlipidemics, Bile Acid Sequestrants
23. CARDIOVASCULAR: Antihyperlipidemics, Cholesterol Absorption Inhibitors
24. CARDIOVASCULAR: Antihyperlipidemics, Statins and Statin Combinations
25. CARDIOVASCULAR: Beta blockers
26. CARDIOVASCULAR: Calcium Channel Blockers and Combinations
27. CARDIOVASCULAR: Direct Renin Inhibitors and Combinations
28. CENTRAL NERVOUS SYSTEM: Anticonvulsants, Barbiturates
29. CENTRAL NERVOUS SYSTEM: Anticonvulsants, Benzodiazepines
30. CENTRAL NERVOUS SYSTEM: Oral Anticonvulsants, Hydantoins
31. CENTRAL NERVOUS SYSTEM: Sedative Hypnotics
32. DIABETIC AGENTS: Biguanides
33. DIABETIC AGENTS: Insulin Products
34. DIABETIC AGENTS: Meglitinides and Combinations
35. DIABETIC AGENTS: Other Agents
36. DIABETIC AGENTS: Sulfonylureas
37. DIABETIC AGENTS: Thiazolidinediones
38. ERYTHROPOIESIS STIMULATING PROTEINS
39. FIBROMYALGIA AGENTS
40. GASTROINTESTINAL AGENTS: H₂RAs
41. GASTROINTESTINAL AGENTS: Pancreatic Enzymes
42. GASTROINTESTINAL AGENTS: PPIs
43. GASTROINTESTINAL AGENTS: Ulcerative Colitis
44. GROWTH HORMONE AGENTS

45. Antivirals: Hepatitis C Pegylated Interferons
46. Antivirals: Hepatitis C Polymerase Inhibitors
47. Antivirals: Hepatitis C Protease Inhibitors
48. HERPETIC ANTIVIRAL AGENTS
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50. IMMUNOMODULATORS: Topical
51. IMPETIGO AGENTS: Topical
52. LEUKOTRIENE MODIFIERS
53. MULTIPLE SCLEROSIS AGENTS: Injectable Disease Modifying
54. MULTIPLE SCLEROSIS AGENTS: Oral Disease Modifying (NEW)
55. MULTIPLE SCLEROSIS AGENTS: Specific Symptomatic Treatment
56. NASAL CALCITONINS
57. NEUROPATHIC PAIN AGENTS
58. OPHTHALMIC ANTIBIOTICS: Macrolides
59. OPHTHALMIC GLAUCOMA AGENTS
60. OPHTHALMIC GLAUCOMA AGENTS: PROSTAGLANDINS
61. OPHTHALMIC NON-STEROIDAL ANTI-INFLAMMATORY AGENTS
62. OPHTHALMIC QUINOLONES
63. OPHTHALMIC STEROIDS
64. OTIC FLUOROQUINOLONES
65. PEDICULOCIDES / SCABICIDES
66. PROGESTINS FOR CACHEXIA
67. PULMONARY ARTERIAL HYPERTENSION AGENTS: Inhaled Agents
68. PULMONARY ARTERIAL HYPERTENSION: Oral Agents
69. RESPIRATORY: ORAL COPD AGENTS
70. RESPIRATORY: Inhaled Corticosteroid/Beta- Adrenergic Combinations
71. RESPIRATORY: Inhaled Corticosteroids/Nebs
72. RESPIRATORY: Intranasal Rhinitis Agents
73. RESPIRATORY: Intranasal Steroid
74. RESPIRATORY: Short Acting Beta Adrenergics-Inhalers/Nebs
75. RESTLESS LEG SYNDROME AGENTS
76. SKELETAL MUSCLE RELAXANTS
77. URINARY TRACT ANTISPASMODICS

VIII. REPORT BY CATAMARAN ON NEW DRUGS TO MARKET, NEW GENERIC DRUGS TO MARKET, AND NEW LINE EXTENSIONS

- IX. REVIEW OF NEXT MEETING LOCATION, DATE, AND TIME
 - A. March 26, 2015
- X. PUBLIC COMMENT
- XI. ADJOURNMENT

This notice and agenda has been posted on or before 9:00 a.m. on the third working day before the meeting at the following locations:

Notice of this meeting will be available on or after the posting date of this Agenda at the DHCFP Web site (www.dhcfp.nv.gov)

Posting of the Agenda will be at the Nevada Medicaid Central offices in Carson City and Las Vegas; 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; Humboldt County 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 copy of the action items will be mailed to you or they may be reviewed Monday through Friday from 9:00 a.m. until 5:00 p.m., or at the meeting. Please call at least one day ahead for an appointment for document review. Written comments on the proposed changes may be sent to the DHCFP, 1100 E. William Street, Suite 102, Carson City, NV 89701.

All persons that have requested in writing to receive the Open Meeting Agenda have been duly notified by mail or e-mail.

Anyone presenting documents for consideration during the public comment portion of the meeting must provide sufficient copies for each member of the committee and the official record. Copies are to be distributed at the time of the meeting and should be provided at both meeting locations; DHCFP or its contractor will not distribute public comment information or materials prior to the public meeting.



Division of Health Care Financing and Policy
Nevada Medicaid Preferred Drug List

Effective September 1, 2014

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Prior Authorization is required for non-preferred agents.

Not all non-preferred products may be listed. New products within established class will default to non-preferred.

<http://medicaid.nv.gov/providers/rx/PDL.aspx>



Division of Health Care Financing and Policy
Nevada Medicaid Preferred Drug List

Effective September 1, 2014

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Prior Authorization is required for non-preferred agents.

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<http://medicaid.nv.gov/providers/rx/PDL.aspx>



Division of Health Care Financing and Policy
Nevada Medicaid Preferred Drug List

Effective September 1, 2014

PREFERRED AGENTS		NON-PREFERRED AGENTS	
ACNE AGENTS: TOPICAL, RETINOID AGENTS AND COMBINATIONS			
<i>Payable only for recipients up to age 21.</i>			
RETIN-A MICRO®(Pump and Tube)		ADAPALENE GEL AND CREAM	EPIDUO®
TAZORAC®		ATRALIN®	TRETINOIN
ZIANA®		AVITA®	TRETIN-X®
		DIFFERIN®	VELTIN®
ACNE AGENTS: TOPICAL, BENZOYL PEROXIDE, ANTIBIOTICS AND COMBINATION PRODUCTS			
<i>Payable only for recipients up to age 21.</i>			
AZELEX® 20% cream		ACANYA	
BENZACLIN®		DUAC CS®	
BENZOYL PEROXIDE (2.5, 5 and 10% only)		ERYTHROMYCIN	
CLINDAMYCIN		CLINDAMYCIN/BENZOYL PEROXIDE GEL	
ERYTHROMYCIN/BENZOYL PEROXIDE SODIUM		SODIUM SULFACETAMIDE/SULFUR	
SULFACETAMIDE			
ALZHEIMER'S AGENTS			
DONEPEZIL	NAMENDA® TABS	ARICEPT® 23mg	GALANTAMINE ER
DONEPEZIL ODT	NAMENDA® XR TABS	ARICEPT®	RAZADYNE®
EXELON® PATCH	RIVASTIGMINE CAPS	GALANTAMINE	RAZADYNE® ER
EXELON® SOLN			
ANALGESICS: LONG ACTING NARCOTICS			
FENTANYL PATCH (PA required)		AVINZA®	METHADOSE®
MORPHINE SULFATE SA TABS (generic MS Contin®)		BUTRANS®	MS CONTIN®
		DOLOPHINE®	NUCYNTA® ER
		DURAGESIC® PATCHES (PA required)	OPANA ER®
		EMBEDA®	ORAMORPH SR®
		EXALGO®	OXYCODONE SR
		KADIAN®	OXYCONTIN®
		METHADONE	OXYMORPHONE SR
ANALGESICS/ANESTHETICS: TOPICAL			
LIDOCAINE	LIDOCAINE VISCOUS	EMLA®	LIDAMANTLE®
LIDOCAINE HC	VOLTAREN® GEL	FLECTOR®	PENNSAID®
		LIDODERM®	
ANALGESICS: TRAMADOL AND RELATED DRUGS			
TRAMADOL		CONZIPR®	TRAMADOL ER
TRAMADOL/APAP		NUCYNTA®	ULTRACET®
		RYZOLT®	ULTRAM®
		RYBIX® ODT	ULTRAM® ER



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PREFERRED AGENTS		NON-PREFERRED AGENTS	
ANAPHYLAXIS: SELF-INJECTABLE EPINEPHRINE			
AUVI-Q	EPIPEN®	ADRENACLICK® QL	
EPINEPHRINE®	EPIPEN JR.®		
ANDROGENIC AGENTS: TOPICAL			
ANDROGEL®		AXIRON®	TESTIM®
ANDRODERM®		FORTESTA®	
ANTIBIOTICS: CEPHALOSPORINS 2ND GENERATION			
CEFACTOR CAPS and SUSP	CEFUROXIME TABS and SUSP	CEFTIN®	CECLOR CD®
CEFACTOR ER	CEFPROZIL SUSP	CECLOR®	CEFZIL
ANTIBIOTICS: CEPHALOSPORINS 3RD GENERATION			
CEFDINIR CAPS and SUSP		CEDAX® CAPS and SUSP	SPECTRACEF®
CEFPODOXIME TABS and SUSP		CEFDITOREN	VANTIN®
SUPRAX®		OMNICEF®	
ANTIBIOTICS: MACROLIDES			
AZITHROMYCIN TABS/SUSP	ERYTHROMYCIN STEARATE	BIAXIN®	
CLARITHROMYCIN TABS/SUSP		DIFICID®	
ERYTHROMYCIN BASE		ZITHROMAX®	
ERYTHROMYCIN ESTOLATE		ZMAX®	
ERYTHROMYCIN ETHYLSUCCINATE			
ANTIBIOTICS: QUINOLONES 2ND GENERATION			
CIPROFLOXACIN TABS		FLOXIN®	
CIPRO® SUSP		OFLOXACIN	
ANTIBIOTICS: QUINOLONES 3RD GENERATION			
AVELOX®	LEVOFLOXACIN	LEVAQUIN®	
AVELOX ABC PACK®			
ANTICOAGULANTS: INJECTABLE			
ARIXTRA®	LOVENOX®	ENOXAPARIN	INNOHEP®
FRAGMIN®		FONDAPARINUX	
ANTICOAGULANTS: ORAL			
COUMADIN®	PRADAXA®		
ELIQUIS®	WARFARIN		
JANTOVEN®	XARELTO®		
ANTIDEPRESSANTS: OTHER			
BUPROPION	MIRTAZAPINE	BRINTELLIX®	
BUPROPION SR	MIRTAZAPINE RAPID TABS	DULOXETINE	
BUPROPION XL	PRISTIQ®	FETZIMA®	
CYMBALTA®(PA not required for ICD-9 code 729.1 or 250.6)	SAVELLA® (Indicated only for Fibromyalgia) TRAZODONE	VIIBRYD®	

Prior Authorization is required for non-preferred agents.

Not all non-preferred products may be listed. New products within established class will default to non-preferred.

<http://medicaid.nv.gov/providers/rx/PDL.aspx>



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ANTIDEPRESSANTS: SSRIs			
CITALOPRAM	PEXEVA®	CELEXA®	PAXIL®
FLUOXETINE	SERTRALINE	ESCITALOPRAM	PROZAC®
PAROXETINE		FLUVOXAMINE QL	SARAFEM®
		LEXAPRO®	ZOLOFT®
		LUVOX®	
ANTIEMETICS: ORAL, 5-HT3s			
GRANISETRON		ANZEMET®	ZOFRAN®
ONDANSETRON		KYTRIL®	ZUPLENZ®
		SANCUSO®	
ANTIFUNGALS: ONYCHOMYCOSIS AGENTS			
<i>Prior authorization is required for all drugs in this class.</i>			
CICLOPIROX SOLN	TERBINAFINE TABS		
ANTI-HISTAMINES: 2ND GENERATION			
<i>A two week trial of one of these drugs is required before a non-preferred drug will be authorized.</i>			
CETIRIZINE D OTC	LORATADINE D OTC	ALLEGRA®	FEXOFENADINE
CETIRIZINE OTC	LORATADINE OTC	CLARITIN®	SEMPREX®
		CLARINEX®	XYZAL®
		DESLORATADINE	
ANTIHYPURICEMICS: XANTHINE OXIDASE INHIBITORS FOR GOUT			
ALLOPURINOL			
ANTI-MIGRAINE AGENTS: TRIPTANS			
RELPAK®		AMERGE®	MAXALT® MLT
SUMATRIPTAN NASAL SPRAY		AXERT®	NARATRIPTAN
SUMATRIPTAN INJECTION		FROVA®	SUMAVEL®
SUMATRIPTAN TABLET		IMITREX®	TREXIMET®
ZOMIG® ZMT		MAXALT® TABS	ZOMIG®
ANTIPARKINSON'S AGENTS: NON-ERGOT DOPAMINE AGONISTS			
PRAMIPEXOLE	ROPINIROLE ER	MIRAPEX®	REQUIP®
ROPINIROLE		MIRAPEX® ER	REQUIP XL®
		NEUPRO®	
ANTIPSYCHOTICS: ORAL, ATYPICAL			
ABILIFY®	QUETIAPINE	CLOZARIL®	RISPERDAL®
CLOZAPINE	RISPERIDONE	FAZACLO®	SEROQUEL®
FANAPT®	SAPHRIS®	GEODON®	ZYPREXA®
LATUDA®	SEROQUEL XR®	INVEGA®	
OLANZAPINE	ZIPRASIDONE		
ANTIVIRAL AGENTS: INFLUENZA			
AMANTADINE	RIMANTADINE		
TAMIFLU®	RELENZA®		

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BENIGN PROSTATIC HYPERPLASIA (BPH) AGENTS: ALPHA-BLOCKERS			
DOXAZOSIN TAMSULOSIN TERAZOSIN		ALFUZOSIN CARDURA® FLOMAX® MINIPRESS®	PAZOSIN RAPAFLO® UROXATRAL®
BENIGN PROSTATIC HYPERPLASIA (BPH) AGENTS: 5-ALPHA-REDUCTASE INHIBITORS			
AVODART® FINASTERIDE		PROSCAR®	
BONE OSSIFICATION AGENTS: BISPHOSPHONATES			
ALENDRONATE FOSAMAX PLUS D®		ACTONEL® ATELVIA® BONIVA® DIDRONEL®	ETIDRONATE IBANDRONATE SKELID®
CARDIOVASCULAR: ACE INHIBITORS AND DIURETIC COMBINATIONS			
BENAZEPRIL ENALAPRIL HCTZ BENAZEPRIL HCTZ EPANED® ‡ (NEW) CAPTOPRIL LISINOPRIL CAPTOPRIL HCTZ LISINOPRIL HCTZ ENALAPRIL RAMIPRIL ‡ PREFERRED FOR AGES 10 AND UNDER		ACCURETIC® EPANED® ‡ (NEW) FOSINOPRIL MAVIK® MOEXIPRIL ‡ NONPREFERRED FOR OVER 10 YEARS OLD	QUINAPRIL QUINARETIC® TRANDOLAPRIL UNIVASC®
CARDIOVASCULAR: ANGIOTENSIN II RECEPTOR BLOCKERS AND DIURETIC COMBINATIONS			
DIOVAN® LOSARTAN DIOVAN HCTZ® LOSARTAN HCTZ		ATACAND® AVAPRO® BENICAR® EDARBI® EDARBYCLOR®	EPROSARTAN IRBESARTAN MICARDIS® TELMISARTAN TEVETEN®
CARDIOVASCULAR: ANTIHYPERLIPIDEMICS, BILE ACID SEQUESTRANTS			
COLESTIPOL WELCHOL® CHOLESTYRAMINE		QUESTRAN®	
CARDIOVASCULAR: ANTIHYPERLIPIDEMICS, CHOLESTEROL ABSORPTION INHIBITORS			
ZETIA®			
CARDIOVASCULAR: ANTIHYPERLIPIDEMICS, NIACIN AGENTS			
NIASPAN® (Brand only) NIACIN ER (Generic Slo-Niacin®)		NIACOR®	



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CARDIOVASCULAR: ANTIHYPERLIPIDEMICS, STATINS AND STATIN COMBINATIONS			
ATORVASTATIN	LOVASTATIN	ADVICOR®	LIPTRUZET®
CRESTOR®	PRAVASTATIN	ALTOPREV®	LIVALO®
FLUVASTATIN	SIMVASTATIN	AMLODIPINE/ATORVASTATIN	MEVACOR®
		CADUET®	PRAVACHOL®
		LESCOL®	SIMCOR®
		LESCOL XL®	VYTORIN®
		LIPITOR®	ZOCOR®
CARDIOVASCULAR: ANTIHYPERLIPIDEMICS, TRIGLYCERIDE LOWERING AGENTS			
GEMFIBROZIL	TRILIPIX®		
TRICOR®			
CARDIOVASCULAR: BETA BLOCKERS			
ACEBUTOLOL	LABETALOL		
ATENOLOL	METOPROLOL (Regular Release)		
ATENOLOL/CHLORTH	NADOLOL		
BETAXOLOL	PINDOLOL		
BISOPROLOL	PROPRANOLOL		
BISOPROLOL/HCTZ	PROPRANOLOL/HCTZ		
BYSTOLIC®*	SOTALOL		
CARVEDILOL	TIMOLOL		
*Restricted to ICD-9 codes 490-496			
CARDIOVASCULAR: CALCIUM CHANNEL BLOCKERS AND COMBINATIONS			
AFEDITAB CR®	ISRADIPINE		
AMLODIPINE	LOTREL®		
CARTIA XT®	NICARDIPINE		
DILTIA XT®	NIFEDIAC CC		
DILTIAZEM ER	NIFEDICAL XL		
DILTIAZEM HCL	NIFEDIPINE ER		
DYNACIRC CR®	NISOLDIPINE ER		
EXFORGE®	TAZTIA XT®		
EXFORGE HCT®	VERAPAMIL		
FELODIPINE ER	VERAPAMIL ER		
CARDIOVASCULAR: DIRECT RENIN INHIBITORS AND COMBINATIONS			
TEKAMLO®	TEKTRUNA HCT®	AMTURNIDE®	
TEKTRUNA®	VALTRUNA®		



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CENTRAL NERVOUS SYSTEM: ADHD/STIMULANTS			
ADDERALL XR®	METHYLIN®	ADDERALL®	METADATE CD®
AMPHETAMINE SALT COMBO	METHYLIN ER®	AMPHETAMINE SALT COMBO XR	MODAFINIL
DEXMETHYLPHENIDATE	METHYLPHENIDATE	CONCERTA®	NUVIGIL®
DEXTROAMPHETAMINE SA	METHYLPHENIDATE ER	DAYTRANA®	METADATE ER®
DEXTROAMPHETAMINE TAB	METHYLPHENIDATE SOL	DESOXYN®	PROVIGIL®*
DEXTROSTAT®	QUILLIVANT® XR SUSP	DEXEDRINE®	PROCENTRA®
FOCALIN XR®	RITALIN LA®	FOCALIN®	RITALIN®
INTUNIV®	STRATTERA®	KAPVAY®	
	VYVANSE®		
		* (No PA required for ICD-9 codes 347.00, 347.01, 347.10, 347.11, 780.53 and 780.57)	
CENTRAL NERVOUS SYSTEM: ANTICONVULSANTS, BARBITURATES			
LUMINAL®	PHENOBARBITAL		
MEBARAL®	MYSOLINE®		
MEPHOBARBITAL	PRIMIDONE		
SOLFOTON®			
CENTRAL NERVOUS SYSTEM: ANTICONVULSANTS, BENZODIAZEPINES			
CLONAZEPAM	DIAZEPAM rectal soln	ONFI®	
CLORAZEPATE	KLONOPIN®		
DIASAT®	TRANXENE T-TAB®		
DIAZEPAM	VALIUM®		
CENTRAL NERVOUS SYSTEM: ORAL ANTICONVULSANTS, HYDANTOINS			
CEREBYX®	PEGANONE®		
DILANTIN®	PHENYTEK®		
ETHOTOIN	PHENYTOIN PRODUCTS		
FOSPHENYTOIN			



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CENTRAL NERVOUS SYSTEM: ORAL ANTICONVULSANTS, MISC.	
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BANZEL®	LAMICTAL®	APTIOM® (NEW)
CARBAMAZEPINE	LAMOTRIGINE	FYCOMPA®
CARBAMAZEPINE XR	LEVETIRACETAM	OXTELLAR XR®
CARBATROL ER®	LYRICA®	POTIGA®
CELONTIN®	NEURONTIN®	
DEPAKENE®	OXCARBAZEPINE	
DEPAKOTE ER®	SABRIL®	
DEPAKOTE®	STAVZOR® DR	
DIVALPROEX SODIUM	TEGRETOL®	
DIVALPROEX SODIUM ER	TEGRETOL XR®	
EPITOL®	TOPAMAX®	
ETHOSUXIMIDE	TOPIRAGEN®	
FELBATOL®	TOPIRAMATE	
GABAPENTIN	TRILEPTAL®	
GABITRIL®	VALPROATE ACID	
KEPPRA®	VIMPAT®	
KEPPRA XR®	ZARONTIN®	
LAMACTAL ODT®	ZONEGRAN®	
LAMACTAL XR®	ZONISAMIDE	

CENTRAL NERVOUS SYSTEM: SEDATIVE HYPNOTICS	
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ESTAZOLAM	TEMAZEPAM	AMBIEN®	SILENOR®
FLURAZEPAM	TRIAZOLAM	AMBIEN CR®	SOMNOTE®
ROZEREM® *	ZOLPIDEM	DORAL®	SONATA®
		EDLUAR®	ZALEPLON
		INTERMEZZO®	ZOLPIDEM CR
		LUNESTA®	ZOLPIMIST®

DIABETIC AGENTS: BIGUANIDES	
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FORTAMET®	GLUMETZA®
GLUCOPHAGE®	METFORMIN (Glucophage®)
GLUCOPHAGE XR®	RIOMET®
METFORMIN EXT-REL (Glucophage XR®)	

DIABETIC AGENTS: INSULIN PRODUCTS	
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All types, mixes and pens containing these insulins are preferred.	
APIDRA®	LEVEMIR®
HUMALOG®	NOVOLIN®
HUMULIN®	NOVOLOG®
LANTUS®	



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DIABETIC AGENTS: DPP-4 INHIBITORS AND COMBINATIONS			
JANUMET®	JUVISYNC®	JENTADUETO®	OSENI®
JANUMET XR®	KOMBIGLYZE XR®	KAZANO®	TRADJENTA®
JANUVIA®	ONGLYZA®	NESINA®	
DIABETIC AGENTS: INCRETIN MIMETICS			
BYDUREON®	VICTOZA®		
BYETTA®			
DIABETIC AGENTS: MEGLITINIDES AND COMBINATIONS			
NATEGLINIDE (Starlix®)	PRANDIN®		
PRANDIMET®	STARLIX®		
DIABETIC AGENTS: SGLT-2 INHIBITORS (NEW)			
INVOKANA®		FARXIGA® (NEW)	
DIABETIC AGENTS: OTHER AGENTS			
ACARBOSE (Precose®)	PRECOSE®		
GLYSET®	SYMLIN® (PA required)		
DIABETIC AGENTS: SULFONYLUREAS			
AMARYL®			
CHLORPROPAMIDE	GLUCOTROL XL®		
DIABETA®	GLYBURIDE (Diabeta®)		
GLIMEPIRIDE (Amaryl®)	GLYNASE®		
GLIPIZIDE (Glucotrol®)	METAGLIP®		
GLUCOTROL®	TOLAZAMIDE		
GLUCOVANCE®	TOLBUTAMIDE		
GLIPIZIDE EXT-REL (Glucotrol XL®)			
GLIPIZIDE/METFORMIN (Metaglip®)			
GLYBURIDE MICRONIZED (Glynase®)			
GLYBURIDE/METFORMIN (Glucovance®)			
DIABETIC AGENTS: THIAZOLIDINEDIONES			
ACTOPLUS MET XR®	AVANDARYL®		
ACTOS®	AVANDIA®		
ACTOPLUS MET®	DUETACT®		
AVANDAMET®			
ELECTROLYTE DEPLETERS			
CALCIUM ACETATE	RENAGEL®		
ELIPHOS®	REVELA®		
ERYTHROPOIESIS STIMULATING PROTEINS			

Prior authorization is required for all drugs in this class.

ARANESP®	PROCRT®	EPOGEN®	OMONTYS®
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PREFERRED AGENTS		NON-PREFERRED AGENTS	
FIBROMYALGIA AGENTS			
<i>No PA required for drugs in this class if ICD-9 code=729.1.</i>			
CYMBALTA®	SAVELLA®		
LYRICA®			
GASTROINTESTINAL AGENTS: H2RAs			
FAMOTIDINE	RANITIDINE SYRUP (PA not required for < 12 years)		
RANITIDINE			
GASTROINTESTINAL AGENTS: PANCREATIC ENZYMES			
CREON®		PANCREAZE®	ULTRESA®
ZENPEP®		PANCRELIPASE	VIKACE®
		PERTZE®	
GASTROINTESTINAL AGENTS: PPIs			
<i>Prior authorization is required for all drugs in this class.</i>			
NEXIUM® CAPSULES	PANTOPRAZOLE	ACIPHEX®	PREVACID®
NEXIUM® POWDER FOR SUSP*		DEXILANT®	PRILOSEC®
		LANSOPRAZOLE	PRILOSEC® OTC TABS
		OMEPRAZOLE OTC TABS	PROTONIX®
*for children ≤ 12 yrs.			
GASTROINTESTINAL AGENTS: ULCERATIVE COLITIS			
ASACOL®SUPP	PENTASA®	APRISO®	
CANASA®	SULFASALAZINE DR	ASACOL HD®	
DELZICOL®	SULFASALAZINE IR	LIALDA®	
MESALAMINE ENEMA SUSP			
GROWTH HORMONE AGENTS			
<i>Prior authorization is required for all drugs in this class.</i>			
GENOTROPIN®	NORDITROPIN®	HUMATROPE®	SEROSTIM®
		NUTROPIN AQ®	SOMAVERT®
		OMNITROPE®	TEV-TROPIN®
		NUTROPIN®	ZORBTIVE®
		SAIZEN®	
HEPATITIS C AGENTS - ANTIVIRALS: HEPATITIS C PEGYLATED INTERFERONS			
PEGASYS®			
PEGASYS® CONVENIENT PACK			
PEG-INTRON® and REDIPEN			
HEPATITIS C AGENTS - ANTIVIRALS: HEPATITIS C POLYMERASE INHIBITORS			
SOVALDI			
HEPATITIS C AGENTS - ANTIVIRALS: HEPATITIS C PROTEASE INHIBITORS			
INCIVEK®	OLYSIO®		
VICTRELIS®			



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HEPATITIS C AGENTS - ANTIVIRALS: HEPATITIS C RIBAVIRINS			
RIBAVIRIN		RIBASPHERE RIBAPAK	
HERPETIC ANTIVIRAL AGENTS			
ACYCLOVIR	VALCYCLOVIR		
FAMVIR®			
HERPETIC ANTIVIRAL AGENTS: TOPICAL			
ABREVA®	ZOVIRAX®, OINTMENT		
DENA VIR®			
IMMUNOMODULATORS: INJECTABLE			
<i>Prior authorization is required for all drugs in this class.</i>			
CIMZIA®	HUMIRA®	KINERET®	ORENCIA®
ENBREL®		SIMPONI®	STELARA®
IMMUNOMODULATORS: TOPICAL			
<i>Prior authorization is required for all drugs in this class.</i>			
ELIDEL®	PROTOPIC®		
IMPETIGO AGENTS: TOPICAL			
MUPIROCIN OINT		ALTABAX®	MUPIROCIN CREAM
		CENTANY®	
LEUKOTRIENE MODIFIERS			
MONTELUKAST	ZAFIRLUKAST	ACCOLATE®	SINGULAIR®
MULTIPLE SCLEROSIS AGENTS: INJECTABLE DISEASE MODIFYING			
<i>Trial of only one agent is required before moving to a non-preferred agent</i>			
AVONEX®	EXTAVIA®		
AVONEX® ADMIN PACK	REBIF®		
BETASERON®	TYSABRI®		
COPAXONE®			
MULTIPLE SCLEROSIS AGENTS: ORAL DISEASE MODIFYING			
<i>Trial of only one agent is required before moving to a non-preferred agent</i>			
AUBAGIO®	TECFIDERA®		
GILENYA®			
MULTIPLE SCLEROSIS AGENTS: SPECIFIC SYMPTOMATIC TREATMENT			
AMPYRA® (PA required)			
NASAL CALCITONINS			
MIACALCIN®			
NEUROPATHIC PAIN AGENTS			
CYMBALTA®	LYRICA®	GRALISE®	HORIZANT®
GABAPENTIN		LIDODERM®	



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OPHTHALMIC ANTIBIOTICS: MACROLIDES			
ERYTHROMYCIN OINTMENT			
OPHTHALMIC ANTIHISTAMINES			
ALAWAY®		BEPREVE®	OPTIVAR®
PATADAY®		ELESTAT®	PATANOL®
		EMADINE®	ZADITOR OTC®
		LASTACRAFT®	
OPHTHALMIC GLAUCOMA AGENTS			
ALPHAGAN P®	DORZOLAM	ALPHAGAN®	OCUPRESS®
AZOPT®	DORZOLAM / TIMOLOL	BETAGAN®	OPTIPRANOLOL®
BETAXOLOL	LEVOBUNOLOL	BETOPTIC®	TIMOPTIC®
BETOPTIC S®	METIPRANOLOL	COSOPT®	TIMOPTIC XE®
BRIMONIDINE	SIMBRINZA®	COSOPT PF®	TRUSOPT®
CARTEOLOL	TIMOLOL DROPS/ GEL SOLN		
COMBIGAN®			
OPHTHALMIC GLAUCOMA AGENTS: PROSTAGLANDINS			
LATANOPROST	TRAVATAN Z®	LUMIGAN®	
TRAVATAN®	ZIOPTAN®	XALATAN®	
OPHTHALMIC NON-STEROIDAL ANTI-INFLAMMATORY AGENTS			
ACULAR®	DICLOFENAC	ACUVAIL®	ILEVRO®
ACULAR LS®	FLURBIPROFEN	BROMDAY®	PROLENSA®
ACULAR PF®	NEVANAC®	BROMFENAC®	
OPHTHALMIC QUINOLONES			
BESIVANCE®	OFLOXACIN®	CILOXAN®	
CIPROFLOXACIN	VIGAMOX®	ZYMAXID®	
MOXEZA®			
OPHTHALMIC STEROIDS			
ALREX®	FLUOROMETHOLONE	FLAREX®	OMNIPRED®
DEXAMETHASONE	LOTEMAX®	FML®	PRED FORTE®
DUREZOL®	PREDNISOLONE	FML FORTE®	PRED MILD®
		MAXIDEX®	VEXOL®
OTIC FLUOROQUINOLONES			
CIPRODEX®	OFLOXIN		
PEDICULOCIDES / SCABICIDES			
NATROBA®	PERMETHRIN	EURAX®	OVIDE®
NIX®	RID®	LINDANE	ULESFIA®
	SKLICE®	MALATHION	

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PLATELET AGGREGATION INHIBITORS			
AGGRENOX®	CILOSTAZOL®	EFFIENT®	
ANAGRELIDE	CLOPIDOGREL	PLAVIX®	
ASPIRIN	DIPYRIDAMOLE		
BRILINTA®	TICLOPIDINE		
PROGESTINS FOR CACHEXIA			
MEGESTROL ACETATE, SUSP		MEGACE ES®	
PSORIASIS AGENTS: TOPICAL			
CALCIPOTRIENE SOLUTION	DOVONEX® CREAM		
PULMONARY ARTERIAL HYPERTENSION AGENTS: INHALED AGENTS			
VENTAVIS®	TYVASO®		
PULMONARY ARTERIAL HYPERTENSION: ORAL AGENTS			
ADCIRCA®	SILDENAFIL	ADEMPAS®	REVATIO®
LETAIRIS®	TRACLEER®	OPSUMIT®	
RESPIRATORY: ORAL COPD AGENTS			
DALIRESP®			
RESPIRATORY: INHALED ANTICHOLINERGIC AGENTS			
ATROVENT® HFA INHALER	IPRATROPIUM NEBS	COMBIVENT RESPIMAT®	TUDORZA®
IPRATROPIUM/ALBUTEROL NEBS	SPIRIVA®		
RESPIRATORY: INHALED CORTICOSTEROID/BETA-ADRENERGIC COMBINATIONS			
ADVAIR DISKUS®	DULERA®	BREO ELLIPTA®	
ADVAIR HFA®	SYMBICORT®		
RESPIRATORY: INHALED CORTICOSTEROIDS/NEBS			
ASMANEX®	PULMICORT FLEXHALER®	ALVESCO®	
BUDESONIDE NEBS*	PULMICORT RESPULES®*		
FLOVENT DISKUS®	QVAR®		
FLOVENT HFA®			
*No PA required if < 4 years old			
RESPIRATORY: INTRANASAL RHINITIS AGENTS			
ASTEPRO®	PATANASE®	AZELASTINE	
DYMISTA®			
RESPIRATORY: INTRANASAL STEROID			
FLUTICASONE	NASONEX®	BECONASE AQ®	QNASL®
		FLONASE®	RHINOCORT AQUA®
		FLUNISOLIDE	TRIAMCINOLONE ACETONIDE
		NASACORT AQ®	VERAMYST®
		OMNARIS®	ZETONNA®



Division of Health Care Financing and Policy
Nevada Medicaid Preferred Drug List

Effective September 1, 2014

PREFERRED AGENTS		NON-PREFERRED AGENTS	
RESPIRATORY: LONG ACTING BETA ADRENERGICS			
ARCAPTA NEOHALER®	SEREVENT DISKUS®	BROVANA®	
FORADIL®			
RESPIRATORY: SHORT ACTING BETA ADRENERGICS-INHALERS/NEBS			
ALBUTEROL NEB/SOLN	XOPENEX® HFA (PA req)	MAXAIR AUTOHALER®	
PROVENTIL® HFA	XOPENEX® Solution(PA req)	VENTOLIN HFA®	
PROAIR® HFA		LEVALBUTEROL	
RESTLESS LEG SYNDROME AGENTS			
PRAMIPEXOLE	ROPINIROLE	HORIZANT®	MIRAPEX® ER
REQUIP XL		MIRAPEX®	REQUIP
SKELETAL MUSCLE RELAXANTS			
BACLOFEN	METHOCARBAMOL/ASPIRIN		
CHLORZOXAZONE	ORPHENADRINE CITRATE		
CYCLOBENZAPRINE	ORPHENADRINE COMPOUND		
DANTROLENE	TIZANIDINE		
METHOCARBAMOL			
URINARY TRACT ANTISPASMODICS			
OXYBUTYNIN TABS/SYRUP/ER		DETROL®	GELNIQUE®
SANCTURA XR®		DETROL LA®	OXYTROL®
TOVIAZ®		DITROPAN XL®	SANCTURA®
VESICARE®		ENABLEX®	TOLTERODINE
		FLAVOXATE	TROSPIUM

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.]

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) 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

STATE OF NEVADA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
DIVISION OF HEALTH CARE FINANCING AND POLICY
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MICHAEL J. WILLDEN
Director

LAURIE SQUARTSOFF
Administrator

Nevada Medicaid Pharmacy and Therapeutics Committee Draft Meeting Minutes

The Division of Health Care Financing and Policy (DHCFP) Pharmacy and Therapeutics Committee conducted a public meeting on **June 26, 2014**, beginning at **1:00 p.m.** at the following location:

JW Marriott Las Vegas Resort and Spa

Grand Ballroom A

221 N. Rampart Blvd

Las Vegas, NV 89145

702-869-7777

Committee Members Present:

Michael Hautekeet, RPh; Mark Decerbo, Pharm.D.; David Fluit, RPh; Adam Zold, Pharm.D.; Evelyn Chu, Pharm.D.; Shamim Nagy, MD, Chairwoman, MD;

Committee Members Absent:

Weldon Havins, MD; Amir Qureshi, MD, Joseph Adashek, MD; Constance Kalinowski, MD

Others Present:

DHCFP: Gabriel Lither, Deputy Attorney General; Coleen Lawrence, Chief Program Services;

Catamaran: Carl Jeffery, PharmD; Kevin Whittington, RPh

HPES: Beth Slamowitz, Pharm.D.

Others: Sandy Sierawski, Pfizer; Bret Fergeson, Pfizer; Brooks Hubbard, BIPI; Marcus Laughlin, BI; Caroline Nguyen, AZ; Don Cleveland, AZ; Shane Hall, Purdue; Patrick Moty, Supenius; Sean McGarr, Forest; Phil Walsh, Sunovion; Greg Broutman, Sanovian; Marykay Queener, J&J; Charissa Anne, J&J; C.R. Kannon, MD; Michael Weingarten, J&J; Peter Berggren, J&J; Dana Confill, NNI; Kyle Peter, NNI; Kim Jacoby, Lundbeck; Soheyla Aziz, Eisai; Carinne Caopeland, Eisai; Scott Larson, BMS; Lori Howarth, Bayer; Lovel Robinson, Abbvie

AGENDA

I. CALL TO ORDER AND ROLL CALL

Meeting called to order at 1:00 PM.

Roll Call:

David Fluitt, RPh

Evelyn Chu, PharmD

Mike Hautekeet, RPh

Adam Zold, PharmD

Gabe Lither

Shamim Nagy, MD

Mark Decerbo, Pharm.D.

Coleen Lawrence, Chief Clinical Policy Team, Nevada Medicaid

Kevin Whittington, Catamaran

Carl Jeffery, Catamaran

II. PUBLIC COMMENT

None

III. **FOR POSSIBLE ACTION:** Review and Approval of the March 27, 2014 Meeting Minutes

Review and approve March 27, 2014 Meeting Minutes

Michael Hautekeet, RPh: Moved to accept meeting minutes.

Evelyn Chu, Pharm.D.: Second.

Board votes unanimous, Aye.

Minutes approved.

IV. STATUS UPDATE BY DHCFP

Coleen Lawrence: Provided updates on:

- Director, Mike Willden has been appointed Chief of Staff of Staff for Nevada. The previous administrator for the Division of Healthcare Services, Romaine Gilliland, will now serve as the Director.
- P&T annual review will be in November as required by statute.

V. ESTABLISHED DRUG CLASSES

A. CARDIOVASCULAR: ACE Inhibitors and Diuretic Combinations

Public Comment: None

Carl Jeffery – Catamaran: New Liquid product available – Enalapril - comes with a packet of Ora-Sweet that you mix together and then give to the patient. Comes in a powder, makes a solution when mixed with the Ora-Sweet. It comes all prepackaged and is ready to go. Other than that, I'm not going to get into the details about ace inhibitors. There's really no special studies done on just this one. Nothing that I'm aware of has changed with ace inhibitors recently. It's just another one that falls into the treatment. With the Enalapril, guidelines just recently came out. Current guidelines recommend the ace inhibitor. I think this may be a topic that we talk about in the future, but right now nothing that I'm aware of has really changed as far as the treatment guidelines, or new clinical information. It's really only going to be used for kids. I think what we want to avoid is it being used in nursing homes for the ease of the nursing staff that could easily crush a pill up and give it via a tube that way. So Catamaran would like to make the recommendation that the board consider these clinically and therapeutically equivalent.

David Fluitt, RPh: Motion to consider clinically and therapeutically equivalent.

Adam Zold, Pharm.D. : Second.

Board votes unanimously: Aye.

Motion approved.

Carl Jeffery: Our recommendation is to make the Epaned the new version of the liquid Enalapril as non-preferred. Our logic behind this is if a child does need this for some reason, it would be easily justified if medical necessity would be able to override the non-preferred criteria. This would also potentially limit it for use in the nursing home if it wasn't really necessary.

Michael Hautekeet, RPh: One of the problems I see in the pharmacy is that we have a lot of compounding prescriptions for Enalapril for children. Could we update your recommendation to accept it and put an age limit on it, to make it preferred for children under 4 or 5, because compounds are not covered by Medicaid, trying to get it through the doctors, we can't get ahold of the doctors.

Carl Jeffery: I mean it's up to the board's discussion I guess.

Adam Zold, Pharm.D. - Agrees with age limit.

Michael Hautekeet, RPh – Motions to add Epaned on the preferred list for ages of less than 5 years.

Adam Zold, Pharm.D.: Second.

Mark Decerbo, Pharm.D. – Do we have past precedent of setting age restrictions?

Carl Jeffery: We do. There are some other ones for example Xopenex is that way.

Further discussion question related to swallow studies where patients who have had strokes are unable to swallow medication.

Board member wanted to ensure that this medication will still be accessible to those patients.

Carl Jeffery: So basically, if Mike's motion is approved, how it would go is, if a prescription came in for the Epaned, for a child who is 5 or under, the claim would go through without any prior authorization. It would just go right through. If they were older than 5, it would stop for non-preferred. At that time, they would have to call. If it was somebody who had difficulty swallowing, they could call and make that medical justification of why they need this product over something else.

Michael Hautekeet, RPh: Amends motion to make Epaned preferred for 10 years old and younger.

Adam Zold, Pharm.D.: Second.

Board Votes unanimously: Aye.

Motion carried.

B. CENTRAL NERVOUS SYSTEM: Oral Anticonvulsants, Misc.

Public Comment:

Dr. Bratman: Epilepsy is a serious neurological condition characterized by unpredictable seizures, which vary in type and severity, and can be extremely disruptive, to the patient and the lives of their caregivers. There's a high degree of variability in the response rates to medications for this condition. In a seminal study by Quan and Brody, they showed that 53% of patients with epilepsy did not respond to their initial epilepsy medication. In addition to that, 36% of patients with epilepsy, seizures remained uncontrolled, despite being on more than two epilepsy medications. Therefore, today there is still definitely an unmet need in this class for epilepsy patients. On November 8th, 2013, the USFDA approved Aptiom for the use of adjunctive treatment of partial onset seizures. Aptiom, or the generic is recognized by the FDA as a new molecular entity, also a unique active ingredient, and structurally distinct from any other drug. The approval of Aptiom was supported by the results of three phase three randomized placebo control trials involving more than 1,400 patients. The patients in these studies

experienced partial onset seizures at baseline despite being on up to three concomitant epilepsy medications. In the pool of data analysis for Aptiom, on the 800 mg and 1200 mg doses, given once daily, demonstrated significant reductions in standardized seizure frequency vs. placebo over 12 weeks, which was the period studied in our trials. Also, at 1200 mg, 41% of patients experienced seizure reduction of 50% or more. The most common adverse reaction in patients taking Aptiom at doses of 800 or 1200 mg were dizziness somnolence, nausea, headache, diplopia, vomiting, fatigue, vertigo, ataxia, blurred vision, and tremor. These are all adverse events that were seen in 2% or more than placebo. The incidents of adverse events during titration were less frequent for those patients that began the initial dose at 400 mg as compared to those patients that started at 800 mg. Aptiom is available in 200, 400, 600, and 800 mg tablets which can be taken whole or crushed, with or without food. The recommended starting dose for safety reasons is, in most patients, 400 mg once daily. After one week, dose should be increased to 800 mg, once daily, which is the recommended maintenance dose. If patient needs additional therapy after one week at 800 mg, they can be increased to 1200mg, once daily. Lastly, Aptiom is not a scheduled medication.

Clinical Presentation:

Carl Jeffery: New anti-epileptic on the market – Aptiom, or eslicarbazepine, indicated for adjunctive therapy for partial onset seizures. Mechanism of action is not exactly known, but they think it has something to do with the inhibition of the voltage gate and sodium channels. Catamaran would like to make the suggestion that these are clinically and therapeutically equivalent.

Michael Hautekeet, RPh: Motion to consider class clinically and therapeutically equivalent.

Evelyn Chu, Pharm.D.: Second.

Board votes unanimously: Aye.

Motion carried.

Carl Jeffery: Catamaran would like to make the recommendation that Aptiom be considered non-preferred because it is not first line. It is adjunctive therapy. If there was no preferred drug list at all, there would still be two or three agents down the line before they got to this one. As the board looks at it, we can make this listed as non-preferred and that would maybe guide the therapy toward more first line therapy agents.

Questions:

Information for other agents in this class?

Carl Jeffery: We really don't have any new information for these other agents. The class is open if you see some other agents on there, but our hands are a little bit tied on this class because any agent that was available before June 30, 2010, we have to have preferred. The ones on the right side here are the ones that have come out afterward that we can make non-preferred. It just so happens that all of them are indicated for adjunctive therapy as well. That's why we've made that decision in the past. Just for consistency we can have this that way as well.

Adam Zold, Pharm.D.: Motion to accept recommendations for PDL making Aptiom non-preferred.
Michael Hautekeet, RPh: Second.
Board votes unanimously: Aye.
Motion carried.

VI. NEW DRUG CLASSES

A. DIABETIC AGENTS: Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors

Presenter:

Dr. Kannon: Dr. Chuck Kannon – Endocrinologist- works as the Director of Diabetes Center in the Redrach Medical Group at 5701 Charleston. 97% of his patients are people with diabetes. A sizable number of them, over 35-40% have some form of Medicaid plan or another. As challenging as it is, some days, at the end of the day, I feel like I'm at the epicenter of the unraveling diabetes tsunami that is sweeping this country. Las Vegas is a microcosm of that. Also I'm learning from my experience with our patients who are on Medicaid, that diabetes is not an equal opportunity villain. It seems to be those who are at the lower rungs of the economic ladder this disease is more capricious. To give you an example, when I used to work elsewhere, in silk stocking districts, the average referral of A1C was under 10. Now my average referral of a patient who comes to me with type 2 diabetes, who has Medicaid, is 12 or above. And you can keep wondering, for the obvious reasons. You can blame it on noncompliance. You can blame it on, yes, physician apathy. You can blame it on not having enough access to healthy food, and you can also blame it on lack of specialists. But the one thing you cannot blame it on is lack of access to diabetes medications. Thanks to this group, thanks to the wisdom and foresight, virtually every drug for treatment of type 2 is made available to our patients with type 2 diabetes and clearly, all of us our grateful for that. In the same realm, people keep asking, why do you have to have so many pills to treat one single disease? The reason for that is reasonably straight forward. Unlike type 1, where the entire problem is total and irrevocable loss of insulin, it's not that way for type 2s. It's got multiple ideologies. 8 to be exact. And we will call it, cleverly, the (garbled) of reasons why people get diabetes type 2. So we're looking for drugs that work in very many ways and hit the disease at multiple fronts. Towards that end, last year, this committee okayed the approval of making one of the first SGLT2 inhibitors available to people with diabetes sometime about a year ago. The first in its class, canagliflozin, or Invokana, was approved by this committee last year. I've now been using this in our patient population, for more than a year. As we all know, this drug works by making the kidney excrete excessive glucose. Remember, in old days, having glycosuria was bad news. This is exploiting the ability of the kidney to promote glycosuria. The nice thing about the mechanism is no matter what other treatment you are on, whatever pills you are on, whatever insulin you are on. When you are out of control, adding a drug that flushes away the glucose, it's almost like using the kidney to flush more. If you think glucose is a toxin, you're detoxing now with the use of this class of drugs. Invokana has caught on for almost a year and universally, the big advantage that we see is the weight loss. Everyone agrees today that the treatment of type 2 diabetes is just not lowering the glucose, in fact it's lowering the body weight. In fact there is even a clever term for this disorder now. It's no longer diabetes. It is Diabesity, indicating that unless you lose weight, no matter what else you do,

that's the core of the problem. And so far, from what I've seen, Invokana, as a SGLT2 inhibitor, effectively does that and brings down the A1C on all other treatments you can layer it on. The side effects are very few, but these are important to discuss, such as genital mycotic infection, volume depletion, and so on. It's a small price to pay for the big payload at the end of the road. I thank you for having introduced and made it available. We just hope that it will continue to be made available to our patients who are enormously benefiting by the largess of availability. Thank you much and if you have any questions I would be happy to answer them.

Dr. Wynn: Doctor Carolyn Wynn – Medical Science Liaison with AstraZeneca – Farxiga. Newly approved drug in the SGLT class for the treatment of diabetes. As he (the previous speaker) so eloquently described it is a selective SGLT2 inhibitor. Farxiga works in the kidney to remove glucose from the urine. It does this by blocking the SGLT2 transporter thus preventing the reabsorption of glucose back into the bloodstream. It is indicated for use with patients for treatment of diabetes, for those who are inadequately controlled through diet and exercise. It is not yet indicated for the treatment of type 1 diabetes or diabetic ketoacidosis. There are two doses available. There's a 5mg dose and a 10mg dose. The recommended starting dose of Farxiga is 5 mg once daily, taken in the morning, with or without food. In patients tolerating Farxiga 5 mg once daily, who require additional glycemic control, the dose can be increased to 10 mg once daily. This medicine is not recommended for patients with moderate renal impairment, which is defined as GFRs of less than 16 mls per minute. For this medication to be beneficial, your kidneys need to function properly. This is why there is a caveat regarding moderate renal impairment. There have been about 24 clinical trials for Farxiga in the past 10 years. (Phase 2 and Phase 3 trails)

Over 11,000 patients worldwide were studied. Over 6,000 patients were actually treated with Farxiga. These patients covered the range of Type 2 diabetes progression. This includes patients who were drug naïve, who failed oral agents, who are already on insulin, those who are elderly, history of cardiovascular disease, and that's just to name a few. We know that there are many therapeutics available for the treatment of diabetes and we studied Farxiga in various capacities with these agents as well. I'm not here to give you a data dump of all 24 clinical trials, but I do want to give you a brief overview of what these entailed. We studied these in a placebo controlled setting in monotherapy, as an add-on to Metformin, Sitagliptin, Pioglitazone, Sulfonylurea, as add-on to insulin. Those include dual agents as well as triple agents. Also had active comparative trials, or "head-to-head" trials. That was in comparison to Metformin XR as well as in comparison to Sulfonylurea which are standards of care. Additional studies, of course, you have to consider special populations. I've already mentioned looking at patients with mild to moderate renal impairment. We also had two dedicated hypertension studies for patients who had a background of ACE and ARMS which, again, are standard of care for patients with diabetes. Overall, these clinical studies proved that Farxiga is effective in reducing A1C, with additional benefits of weight, as well as blood pressure reduction. And just to mention, we have been a long time in the making with these clinical studies and they ranged from 12 weeks to 4 years. So we have long term extension data as well that also shows that the A1C as well as the glycemic effects of Farxiga are sustained. Equally as important, is for me to share the safety considerations. Some of them have already been mentioned, of course symptomatic hypotension may occur, especially in patients with potentially moderate renal impairment, elderly patients, those on loop diuretics, those are a little

more volatile. It's important to assess and correct that volume status before initiating this type of medication. In addition to that, we did note that there were an increased rate of genital mycotic infections. The symptoms were mild to moderate in intensity and patients usually responded to standard of care and rarely resulted in discontinuation. The last thing I wanted to point out is that we did see an imbalance in bladder cancer within our trials. And we do, within our label, recommended not to use in patients with active bladder cancer and caution the use for those with a history of bladder cancer because at this point in time, there isn't enough data. If you have any questions, I'd be happy to discuss further. AstraZeneca would appreciate your consideration to add Farxiga as the second drug in the SGLT2 class to the preferred drug list

Michael Hautekeet, RPh: In Invokana, if the GFR is less than 45 and for Farxiga it's less than 60. So that's pretty much the only difference between the two.

Dr. Wynn: There are a few differences in the label. I will briefly speak on our moderate renal impairment study which is in our label. In that study we did look at patients within that moderate renal impairment group of 30 – 60. Within that study, looking at placebo vs. moderate renal impairment, we saw in our patients with Farxiga, a decrease efficacy. We saw a -0.29% A1C decrease. Equally, we actually saw patients in our renal impairment group who were on placebo have improvement as well. Because of that, we saw a numerical difference but it wasn't statistically different. I think what we see, when we are looking at patients with moderate renal impairment, is that this drug works with the kidney. You need good kidneys for it to work at its best efficacy.

Mary Kay Queener – Clinical Pharmacist – Healthy Outcomes Group – Johnson and Johnson – Representing Invokana. Presented to board last year. Voice support for maintaining Invokana on the preferred list. Offer answers to any questions the board may have.

Vince Bera – Personal anecdote – diabetes and aspartame

About a year ago, I was rushed to the hospital as a diabetic, and the doctors told me I was fortunate to be alive. Why I wasn't in a diabetic coma was perplexing to them. I was on insulin 3 times a day and in the evening, I sure all of you professionals here from the pharmaceutical companies know what I'm talking about, fortunately, I'm no longer on any medication whatsoever. What I hear going on here is that you're trying to fix the problem that was created by the food industry, or certain chemical companies primarily aspartame. I see no one discussing aspartame and getting that out of our food cycle, or food chain rather. Aspartame has changed its name. It is in just about every product that requires some sort of sweetening and now we have all of these great pharmaceutical companies trying to fix the problem that aspartame has contributed to. I am no longer a diabetic. I did lose about 40 pounds in the process. What I can attribute some of my success to is probably colloidal silver. Knowing a little about that, I discovered that colloidal silver does destroy a lot of diseases that are oxygen dependent. As a result it eliminates a lot of inflammation in many organs of the body. That's my story. I think you should address those issues that pollute our food chain rather than approve more drugs, not that some of them are not successful. I'm sure that they are with all of the studies that they've done. I'm sure that they work on the problem, but you've got to fix the source of the problem first. Then maybe you won't need all of these great people working in their labs, creating something that may never be needed.

Carl Jeffery: So we've got a new agent in this class, and this has been beat to death here about the mechanism of action and how this stuff works. It's been covered a few times. I'm not going to go over it again. These agents are associated with weight loss and a lowering of blood pressure, so I think they have some benefits as well. I'd like to point out the indication for both of these new agents are the same in adjunctive with diet and exercise, so we're not just treating with the medication alone. Farxiga, and again, these studies along with some of the newer ones have been talked about before, so I'm not going to beat this into the ground too much, but again: Large studies, these are some pooled data done alone and in combination. We've seen some pretty good results in here. Anywhere between 0.6 and 1.5% reduction to A1C, when it's used alone, or up to a 2% when combined, and I think these studies were done with Metformin. As the doctor said before, they studied with Glimepiride, Pioglitazone, so there's all sorts of studies that they did that show that adjunctive therapies are successful too. Showing one study to be non-inferior to the Metformin at the 10mg dose, which I think is a pretty significant study there too. As far as, and I know Mr. Hautekeet you referred to the differences there are. There are no head-to-head studies with this with the new Farxiga. That would be wonderful to see that, but I don't see it happening in the foreseeable future. So at this time, we compare what we know about the Farxiga and the Invokana separately and look at those numbers and they're pretty similar. As you've seen before, there's really not that many differences. With that information Catamaran would like to recommend that these be considered clinically and therapeutically equivalent.

Michael Hautekeet, RPh: Motions to consider clinically and therapeutically equivalent.

David Fluitt, RPh: Second.

Board votes unanimously: Aye.

Motion carried.

Carl Jeffery: Catamaran would like to recommend that Farxiga be non-preferred, because the Invokana is already preferred. We broke these out into their own class, and so really, in order to add the step and get Farxiga and they try and for some reason they can't tolerate the Invokana, or if they have some medical reason why they need the Farxiga, which, I'm not sure what it would be, but it would still be available to those patients. Basically Invokana would be the first lane. Some of this has to do with the anticipation of and the outlook as new products in the class come out.

Michael Hautekeet, RPh: Last year, when we talked about Invokana, I was just placed on Invokana, maybe a few weeks before. So it has been now almost a year and I have seen the improvement of the A1C. My feeling is that Invokana is a good drug. I hate to have just one available because, again, one drug doesn't fit everybody. Even so Invokana and Farxiga may be similar on paper, but there are still chemical differences that could be beneficial to some patients where the Invokana doesn't quite work correctly. I would make the recommendation to have Farxiga in the preferred because two drugs are better than none. I've seen how they work. Excreting sugar, everyone used to be scared of it. When I was placed on that drug. Besides the diuresis effect, the drug has to be taken in the morning; don't take it at night. The sugar, it works good. I would make the motion to make both Invokana and Farxiga preferred.

No Second.

Need another motion.

David Fluitt, RPh: Motion to keep Farxiga as the non-preferred drug and keep Invokana as the preferred.

Mark Decerbo, Pharm.D.: Second.

Board votes: 5 Aye, 1 Nay.

Motion doesn't carry, no sixth vote.

This will be discussed by the end of the year. Motion that this drug will stay non-preferred.

When new products are introduced they are automatically moved into the non-preferred class. This was a proposal for a new class. Invokana wasn't put into this other class, this miscellaneous class. Our proposal was to make a new class with just these two agents. Now, since the motion didn't pass, does that mean this new class....?

Coleen Lawrence: It just means that it stays by itself. Farxiga will remain in the non-preferred status. Invokana will stay in the preferred status.

Michael Hautekeet, RPh: Motion to create a SGLT2 inhibitor class by itself separate from the miscellaneous.

David Fluitt, RPh: Seconded.

Board votes unanimously: Aye.

Motion carries.

Carl Jeffery: For the clarification of the board, this is what the new miscellaneous class is going to look like. There is no action to be taken on this.

B. IMMUNOMODULATORS: Oral

Withdrawn from the agenda.

Public Comment:

Coleen Lawrence: We've had a lot of comments come in about the different formularies between Medicaid paper service and the two managed care formularies come in. We've been reviewing them on the user service side of the house. One of the things we've been looking at is more on the cosmetic side of the formularies, on our side especially. As you all know I don't have a lot of control of the coverage is on the managed care side, but we do have control over what we do. One thing that we are going to do

is revamp what our drug list looks like, so we can move our side of the house. That's what we can do. We're going to go through a chain of what ours looks like. And what we're trying to do is shift some of our classes around, the titles, not the therapeutic alternatives that's been voted by the board, but the higher categories. And we're going to try to move toward what HPN and Amerigroup has used as their titles, so that way we can try to get a little more identical so that the look and feel will be the same.

VII. REPORT BY CATAMARAN ON NEW DRUGS TO MARKET, NEW GENERIC DRUGS TO MARKET, AND NEW LINE EXTENSIONS

Carl Jeffery: The Entyvio is a new drug for the ulcerative colitis that is currently available. This will be something brought up in one of our future classes. There's a new intranasal testosterone that will be of interest. That will be brought up at least by November. A lot of patent expiration dates that will affect our drug list that we will be talking about in either the September meeting, or the November meeting. Some of the big ones that I'd like to highlight here are the Copaxone. This brings in the whole bio-similar discussion of whether these are interchangeable with the brand, or how that's going to work. It will be interesting to see how this really plays out in the real world. Some of the big ones: Actinium and Nexium are some high utilization drugs that are going generic and are going to have some impact. Some big things coming down the pipeline that the FDA has given their initial nod to: Coming from Gilead for the treatment of Hep-C. It's a combination of Sovaldi and another protease inhibitor. This is a once a day treatment, a fixed dose combination. We'll see what the guidelines say with that one. That's another big one that is coming out. With that, Bristol Meyers Squibb is getting into the game as well. They've got two new Hep-C treatment agents. Right now, initially with the information we have is for the genotype 1s. As with the Sovaldi, we'll see if they get the additional genotypes, but that's how it's playing out right now. One more Hep-C agent here with AbbVie has another combination medication for the treatment of genotype 1 Hep-C. A lot of new players coming out. I think we've started to see just a little bit of warehousing again, so a little bit of a dip in the treatment of Hep-C with these. These are supposed to be available. The one from Gilead was supposed to be available in October 2014. These other ones just have the fourth quarter of 2014 listed. By the end of the year, these will be on the market, maybe not until the first of 2015. On the diabetes front, this is what I sort of alluded to before. We've got another SGLT2 product coming out from Lilly, a DPP4. It will be interesting to see how that one plays out on the market place. And then Purdue, the makers of Oxycontin, are working on a once daily, extended release, hydrocodone product that will probably make Zohydro obsolete. It's an abuse deterrent.

VIII. REVIEW OF NEXT MEETING LOCATION, DATE, AND TIME

September 25, 2014 at 1PM at the JW Marriott Las Vegas Resort and Spa.

IX. PUBLIC COMMENT

X. ADJOURNMENT

Meeting adjourned at 2:02 PM

Therapeutic Class Overview

Attention Deficit/Hyperactivity Disorder (ADHD) Agents and Stimulants

Therapeutic Class

- Overview/Summary:** Attention deficit/hyperactivity disorder (ADHD) is a common psychiatric disorder that is often diagnosed during childhood; however, children with ADHD may continue to manifest symptoms into adulthood.¹ The core symptoms of ADHD utilized in the diagnosis of the disorder include hyperactivity, impulsivity, and inattention. Untreated, or undertreated ADHD is associated with adverse sequelae, including delinquent behavior, antisocial personality traits, substance abuse and other comorbidities.² Several central nervous system agents are Food and Drug Administration (FDA)-approved for the treatment of ADHD, including the cerebral stimulants (amphetamines and methylphenidate derivatives), atomoxetine (Strattera[®]), clonidine extended-release (Kapvay[®]) and guanfacine extended-release (Intuniv[®]).³⁻²³ The cerebral stimulant agents are classified as Schedule II controlled substances due to their potential for abuse.^{3-11,14-21,23} Atomoxetine, clonidine extended-release and guanfacine extended-release are not classified as controlled substances.^{12,13,22} Clonidine and guanfacine, extended-release formulations, are approved as adjunctive therapy with stimulant medications as well as monotherapy.^{12,13,24} Some cerebral stimulant agents are indicated for the treatment of a variety of sleep disorders. Narcolepsy is a sleep disorder characterized by excessive daytime sleepiness and intermittent manifestations of rapid eye movement sleep during wakefulness. Obstructive sleep apnea (OSA) is a common chronic disorder that often requires lifelong care. Cardinal features of OSA include obstructive apneas, hypopneas, or respiratory effort related arousals; daytime symptoms attributable to disrupted sleep (e.g., sleepiness, fatigue, poor concentration); and signs of disturbed sleep (e.g., snoring, restlessness, or resuscitative snorts).^{25,26} Circadian rhythm sleep disorder consists of a persistent/recurrent pattern of sleep interruption. The shift work type occurs in individuals who work non-standard hours (e.g., night work, early morning work and rotating schedules) and is characterized by excessive sleepiness and/or insomnia.²⁵ Modafinil (Provigil[®]) and armodafinil (Nuvigil[®]) are both FDA-approved to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, OSA and shift work sleep disorder. These agents are classified as Schedule IV controlled substances because they have been shown to have been shown to produce psychoactive and euphoric effects similar to stimulants.^{27,28} Sodium oxybate (Xyrem[®]) is γ -hydroxybutyric acid, a known drug of abuse. It is approved for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. It is classified as a Schedule III controlled substance. However, non-medical uses of sodium oxybate are classified under Schedule I.²⁸ Several generic ADHD agents and stimulants are currently available. Specifically, at least one short-, intermediate-, and long-acting agent is available generically.²⁹

Table 1. Current Medications Available in the Therapeutic Class^{3-22, 26-28}

Generic (Trade Name)	Food and Drug Administration- Approved Indications	Dosage Form/Strength	Generic Availability
Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines			
Amphetamine/ dextroamphetamine salts (Adderall ^{®*} , Adderall XR ^{®*})	Treatment of ADHD	Capsule (Adderall XR [®]): 5 mg 10 mg 15 mg 20 mg 25 mg 30 mg Tablet (Adderall [®]): 5 mg	a

Generic (Trade Name)	Food and Drug Administration- Approved Indications	Dosage Form/Strength	Generic Availability
		7.5 mg 10 mg 12.5 mg 15 mg 20 mg 30 mg	
Dextroamphetamine (ProCentra [®] , Dexedrine Spansule ^{®*} , Zenzedi ^{®*})	Treatment of ADHD, narcolepsy	Solution (ProCentra [®]): 5 mg/5 mL Sustained-release capsule (Dexedrine Spansule [®]): 5 mg 10 mg 15 mg Tablet: 2.5 mg 5 mg 7.5 mg 10 mg	a
Lisdexamfetamine (Vyvanse [®])	Treatment of ADHD	Capsule: 20 mg 30 mg 40 mg 50 mg 60 mg 70 mg	-
Methamphetamine (Desoxyn ^{®*})	Exogenous obesity, treatment of ADHD	Tablet: 5 mg	a
Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous			
Armodafinil (Nuvigil [®])	Improve wakefulness in patients with excessive sleepiness associated with OSA and narcolepsy, improve wakefulness in patients with excessive sleepiness associated with shift work disorder	Tablet: 50 mg 150 mg 250 mg	-
Dexmethylphenidate (Focalin ^{®*} , Focalin XR [®])	Treatment of ADHD	Extended-release capsule: 5 mg 10 mg 15 mg 20 mg 25 mg 30 mg 35 mg 40 mg Tablet: 2.5 mg 5 mg	a

Generic (Trade Name)	Food and Drug Administration- Approved Indications	Dosage Form/Strength	Generic Availability
Methylphenidate (Concerta [®] , Daytrana [®] , Metadate CD [®] , Metadate ER [®] , Methylin [®] , Quillivant XR [®] , Ritalin [®] , Ritalin LA [®] , Ritalin SR [®])	Treatment of ADHD, narcolepsy	10 mg Chewable tablet (Methylin [®]): 2.5 mg 5 mg 10 mg Extended-release capsule (Metadate CD [®]): 10 mg 20 mg 30 mg 40 mg 50 mg 60 mg Extended-release capsule (Ritalin LA [®]): 10 mg 20 mg 30 mg 40 mg Extended-release suspension (Quillivant XR [®]): 25 mg/ 5 mL Extended-release tablet (Concerta [®]): 18 mg 27 mg 36 mg 54 mg Extended-release tablet (Metadate ER [®]): 20 mg Solution (Methylin [®]): 5 mg/5 mL 10 mg/5 mL Sustained-release tablet (Ritalin-SR [®]): 20 mg Tablet (Ritalin [®]): 5 mg 10 mg 20 mg Transdermal patch	a

Generic (Trade Name)	Food and Drug Administration- Approved Indications	Dosage Form/Strength	Generic Availability
		(Daytrana [®]): 10 mg/9 hours (1.1 mg/hour) 15 mg/9 hours (1.6 mg/hour) 20 mg/9 hours (2.2 mg/hour) 30 mg/9 hours (3.3 mg/hour)	
Modafinil (Provigil ^{®*})	Improve wakefulness in patients with excessive sleepiness associated with OSA and narcolepsy, improve wakefulness in patients with excessive sleepiness associated with shift work disorder	Tablet: 100 mg 200 mg	a
Central α-Agonists			
Clonidine extended-release (Kapvay [®])	Treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications	Extended-release tablet: 0.1 mg 0.2 mg	a
Guanfacine extended-release (Intuniv [®])	Treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications	Extended-release tablet: 1 mg 2 mg 3 mg 4 mg	-
Central Nervous System Agents-Miscellaneous			
Atomoxetine (Strattera [®])	Treatment of ADHD	Capsule: 10 mg 18 mg 25 mg 40 mg 60 mg 80 mg 100 mg	-
Sodium oxybate (Xyrem [®])	Treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy	Solution: 500 mg/mL (180 mL)	-

ADHD=attention deficit/hyperactivity disorder, OSA=obstructive sleep apnea

* Generic available in at least one dosage form or strength.

Evidence-based Medicine

- Data from several clinical trials demonstrate that the attention deficit/hyperactivity disorder (ADHD) agents and stimulants are effective in the treatment of ADHD, as measured by significant decreases in ADHD rating scale scores compared to placebo. Although comparative trials have been conducted, it is difficult to interpret the results of these trials due to design flaws (e.g., small population, short treatment duration, variable outcomes). Overall, there is insufficient evidence to suggest that one ADHD agent and stimulant is more efficacious than another for the treatment of ADHD.³⁸⁻¹²⁵
- The majority of efficacy data supporting the use of the ADHD agents and stimulants is derived from placebo-controlled trials. In addition, the majority of trials were conducted in the pediatric population. Limited data exists to demonstrate the efficacy of a variety of cerebral stimulants (amphetamine/

dextroamphetamine, dexamethylphenidate, and lisdexamfetamine) and atomoxetine in the adult population.^{43,51,68,93,94,109}

- Clonidine extended-release and guanfacine extended-release have been shown to improve ADHD symptoms scores both as monotherapy and as adjunctive therapy to psychostimulants. These agents are Food and Drug Administration (FDA)-approved for use in ADHD as monotherapy and as adjunctive treatment to stimulants.^{64,65,74-82}
- Armodafinil, modafinil and sodium oxybate have all been shown to be more effective compared to placebo in patients with narcolepsy, obstructive sleep apnea (OSA) and shift work disorder, as measured by significant improvements in sleepiness scale scores. In addition, sodium oxybate has been shown to significantly reduce the rate of inadvertent naps and cataplexy attacks compared to placebo. Similar to ADHD, there is insufficient evidence to suggest that one ADHD agent and stimulant is more efficacious than another for the treatment of sleep disorders.¹²⁶⁻¹⁵⁵

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - Guidelines recommend the use of Food and Drug Administration (FDA)-approved agents for initial pharmacologic treatment of attention deficit/hyperactivity disorder (ADHD), and preference of one agent over another is not stated.
 - Stimulant medications remain the most effective treatment option for most children with ADHD, and response to one stimulant dose not predict response to another. Other factors associated with treatment decisions include presence of comorbid conditions, patient/family preference, storage/administration issues at school, history and/or presence of substance abuse, pharmacokinetics, and anticipated adverse events.^{2,24,31-33}
 - With regard to the use of non stimulant medications in the treatment of ADHD, atomoxetine is recognized as a good option for patients with comorbid anxiety, sleep initiation disorder, substance abuse, or tics, or if initially preferred by parents and/or the physician.
 - Overall, atomoxetine, clonidine extended-release and guanfacine extended-release are effective in reducing ADHD core symptoms; however, these agents have a smaller evidence base compared to the cerebral stimulants.²⁴
 - Methylphenidate is recommended as first-line treatment of ADHD in adults, with atomoxetine and dexamphetamine recommended second line.³¹⁻³³
 - For the treatment of narcolepsy, obstructive sleep apnea (OSA), and shift work disorder, guidelines recommend the use of FDA-approved agents for the treatment of such sleep disorders, with modafinil recommended first-line for the treatment of narcolepsy.^{25,139-141}
 - Even though guidelines were published prior to FDA-approval of sodium oxybate, the agent is the only one to be recognized as being an effective option for the treatment of cataplexy due to narcolepsy. Armodafinil, was FDA-approved in 2007; however, its role is not defined within current clinical guidelines.^{25,34-36}
- Other Key Facts:
 - Armodafinil (Nuvigil[®]) is the longer half-life enantiomer of modafinil (Provigil[®]).
 - At least one short-, intermediate-, and long-acting stimulant is available generically.³⁰
 - Due to safety concerns and abuse potential, sodium oxybate (Xyrem[®]) is available only through restricted distribution, the Xyrem Success Program.

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C. Agents used for the treatment of Attention Deficit Disorder (ADD)/Attention Deficit Hyperactivity Disorder (ADHD)

Therapeutic Class: ADHD/ADD Agents

Last Reviewed by the DUR Board: January 24, 2008

Agents, both stimulants and non-stimulants used for the treatment of ADD/ADHD are subject to prior authorization for pediatric, adolescent, and adult clients that meet the criteria for coverage.

1. Coverage and Limitations

Approval for medications will be given at the therapeutics class level if the following criteria is met and documented:

a. General Criteria (Children and Adults)

1. Only one long-acting agent at a time may be used for the treatment of ADD/ADHD (applies to the entire ADD/ADHD/Stimulant Class); a 30-day transitional overlap in therapy will be allowed.
2. The following two criteria's must be met and documented in the recipient's medical record for adult and pediatric recipients.
 - a. The decision to medicate for ADD or ADHD must be based on problems that are persistent and sufficiently severe to cause functional impairment in one or more of the following social environments: school, home, work or with peers; and
 - b. Before treatment with pharmacological methods is instituted, other treatable causes have been ruled out.

b. Children (up to age 18 years)

In addition to the general criteria above, the following conditions apply and must be documented in the recipient's medical record.

1. Prescriptions for ADD/ADHD medications do not require prior authorizations for children five years of age, up to eighteen years of age, if the following conditions apply:
 - a. The medication is prescribed by a psychiatrist; and
 - b. One of the following ICD-9 codes is documented on the prescription: 314.0-314.9.

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2. In all other cases, prior authorization is required. The following is required for prior authorization.
 - a. An initial evaluation or examination has been done within the past 12 months by the treating physician, pediatrician, psychiatrist or neurologist documenting the developmental history, physical evaluation, medical history or a primary neurological diagnosis and all of the following:
 1. School information, Standardized Teachers Rating Scales testing reports such as Test of Variables of Attention (TOVA), achievement test, neuropsychological testing if indicated, Conner’s scale, speech and language evaluation;
 2. **Diagnosis** and symptoms of ADD or ADHD, presence or absence-child behavior checklist, development and context of symptoms and resulting impairment, including school, family and peers, **diagnostic** symptoms of possible alternate or comorbid psychiatric diagnosis, history of psychiatric, psychological pediatric or neurological treatment for ADD or ADHD; and
 3. Family history including diagnosis of ADD and ADHD, tic disorder, substance abuse disorder, conduct disorder, personality disorder and other anxiety disorders, past or present family stressors, crises, any abuse or neglect, interview with parent(s) or guardian(s).
 - c. Adults (18 years and above) In addition to the general criteria above, the following must be present and documented in the recipient’s medical record:
 1. An initial evaluation-complete psychiatric assessment, present and past, **diagnostic** symptoms of ADD or ADHD, history of development and context of symptoms and resulting past and present impairment, including academic achievement, learning disorder evaluation, and
 2. One of the following:
 - a. Medical history, medical or primary neurological diagnosis, identify medication(s) that could be causing symptoms (e.g. Phenobarbital, steroids), or;
 - b. History of other psychiatric disorder(s) and treatment, or;
 - c. **Diagnostic** symptoms of ADD and ADHD presence or absence, possible alternate comorbid psychiatric diagnosis (especially:

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personality disorder, mood disorder, depression or mania, anxiety disorder, dissociative disorder, tic disorder including Tourette’s disorder and substance abuse disorder); or

- d. Family history including diagnosis of ADD or ADHD, tic disorder, substance abuse disorder, conduct disorder, personality disorder, mood disorder and anxiety disorder, possible family stressors, any history of abuse or neglect.

- 3. Prior Authorization will be given for a one year time period.

Prior Authorization forms are available at:

<http://www.medicaid.nv.gov/providers/rx/rxforms.aspx>

Therapeutic Class Overview Third Generation Cephalosporins

Therapeutic Class

- Overview/Summary:** This review will focus on the oral third generation cephalosporins.¹⁻⁷ The cephalosporin family of antibiotics is part of a larger group known as β -lactam antibiotics. Agents within this group share the structural feature of a β -lactam ring. The β -lactam antibiotics are generally considered bactericidal and work by inactivating enzymes involved with bacterial cell wall synthesis.⁸ Cephalosporins cover a wide range of organisms and are frequently used antibacterial agents due to their spectrum of activity and ease of administration.⁹ Cephalosporins are grouped into generations, based on their spectrum of activity. The first generation cephalosporins are active against gram-positive aerobes but are inactive against penicillin-resistant pneumococci. They typically have poor activity against gram-negative organisms, though some strains of *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Shigella* may be susceptible. Second generation cephalosporins have greater activity against *Haemophilus influenzae* compared to the first generation cephalosporins and have enhanced activity against gram-negative bacteria in vitro. Third generation cephalosporins are active against streptococci, *Haemophilus influenzae* and *Moraxella catarrhalis* and are more active against gram-negative bacilli compared to first or second generation cephalosporins; however, they are not as active against susceptible strains of staphylococci compared to first generation cephalosporins. Among the orally available third generation cephalosporins, cefpodoxime proxetil and cefdinir have more activity against staphylococci compared to cefixime and ceftibuten, while ceftibuten is weakly active against pneumococci. Its spectrum of activity is similar to cefdinir and cefpodoxime.^{9,10} Fourth generation cephalosporins have enhanced activity against gram-negative bacteria compared to the first and second generation cephalosporins and have activity in vitro against gram-negative bacteria that are typically resistant to the third generation cephalosporins, including *Pseudomonas aeruginosa* and Enterobacteriaceae. In addition, they may be more active against gram-positive bacteria compared to some third generation cephalosporins. The only fourth generation cephalosporin is cefepime, which is only available parenterally. As a family, cephalosporins have poor activity against enterococci, *Listeria* and oxacillin-resistant staphylococci.^{9,10} The cephalosporins reach therapeutic levels in urine and in pleural, pericardial, peritoneal and synovial fluid. With the exception of cefuroxime, the first and second generation cephalosporins are not able to effectively penetrate the cerebrospinal fluid and therefore should not be used to treat central nervous system infections. Conversely, the third generation cephalosporins do effectively penetrate the cerebrospinal fluid.⁹ Clinical guidelines list third generation cephalosporins in different lines of therapy depending on type of infection, causative organisms and other patient specific factors.¹¹⁻²⁵

Table 1. Current Medications Available in the Class¹⁻⁷

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Cefdinir*	Acute exacerbations of chronic bronchitis (bacterial), acute maxillary sinusitis, community-acquired pneumonia, otitis media, pharyngitis and/or tonsillitis, uncomplicated skin and skin structure infections	Capsule: 300 mg Powder for oral suspension: 125 mg/5 mL 250 mg/5 mL	a
Cefditoren (Spectracef®)	Acute exacerbations of chronic bronchitis (bacterial), community-acquired pneumonia, pharyngitis and/or tonsillitis, uncomplicated skin and skin structure infections	Tablet: 200 mg 400 mg	a
Cefixime (Suprax®)	Acute exacerbations of chronic bronchitis (bacterial), otitis media, pharyngitis and/or	Powder for oral suspension:	-

	tonsillitis, uncomplicated gonorrhea (cervical/urethral), uncomplicated urinary tract infections	100 mg/5 mL 200 mg/5 mL Tablet: 400 mg	
Cefpodoxime*	Acute ano-rectal infections in women, acute exacerbations of chronic bronchitis (bacterial), acute maxillary sinusitis, community-acquired pneumonia, otitis media, pharyngitis and/or tonsillitis, uncomplicated skin and skin structure infections, uncomplicated gonorrhea (cervical/urethral), uncomplicated urinary tract infections	Powder for oral suspension: 50 mg/5 mL 100 mg/5 mL Tablet: 100 mg 200 mg	a
Ceftibuten (Cedax®*)	Acute ano-rectal infections in women, otitis media, pharyngitis and/or tonsillitis	Capsule: 400 mg Powder for oral suspension: 90 mg/5 mL 180 mg/5 mL	a

*Generic available in at least one dosage form or strength.

Evidence-based Medicine

- Studies evaluating the third generation cephalosporins for the treatment of acute exacerbations of chronic bronchitis have not consistently demonstrate significant differences in clinical response or eradication rate when compared to other cephalosporin agents.²⁶⁻³¹
- Verghese and colleagues compared cefixime and cephalexin in the treatment of hospitalized patients with exacerbations of chronic bronchitis and demonstrated significantly better clinical cure rates in patients treated with cefixime compared to cephalexin (70.8 vs 50.0%; $P < 0.05$). The incidence of diarrhea was higher in the cefixime group.³²
- In the treatment of gonorrhea, cefixime and cefpodoxime have generally demonstrated comparable efficacy in the rate of bacteriologic cure (>90%) in open-label and dose-response studies, while cefixime has been shown to have comparable efficacy when compared to ceftriaxone.³³⁻³⁷
- Asmar et al compared cefixime and cefpodoxime in the treatment of acute otitis media. By day 15, the a bacteriologic cure was reported in 83 and 81% of patients treated with cefpodoxime and cefixime, respectively ($P = 0.541$).³⁸
- Casey et al conducted a study of high dose amoxicillin/clavulanic acid (10 day regimen) compared with a standard cefdinir regimen (5 days) and found that the clinical cure rate was statistically greater in the amoxicillin/clavulanic acid group ($P = 0.001$).⁶⁶
- Other head-to-head studies of the third generation cephalosporins in the treatment of acute otitis media demonstrated no statistically significant differences in efficacy between the agents.⁶⁰⁻⁶⁵
- Third generation cephalosporins have demonstrated their efficacy in the treatment of bacterial infections of acute bronchitis, chancroid and genital tract infections.⁵⁸⁻⁶⁰
- Studies evaluating the use of the third generation cephalosporins for the treatment of pharyngitis and/or tonsillitis have failed to consistently demonstrate “superiority” of any third generation cephalosporins over penicillin or amoxicillin.³⁹⁻⁴⁶
- In the treatment of lower respiratory tract infections including community-acquired pneumonia, no cephalosporin consistently demonstrated significant differences when the third generation cephalosporins were compared with each other or with cephalosporins in other generations.⁴⁷⁻⁴⁹
- Studies evaluating the treatment of skin and soft tissue infections, sinusitis and urinary tract infections did not consistently demonstrate the “superiority” of any third generation cephalosporins when compared with in-class or with other cephalosporins in other generations.⁵⁰⁻⁵⁶

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - Treatment guidelines identify third generation cephalosporins as alternative empiric agents for the treatment of community-acquired pneumonia, and as treatment options for infections due to *Enterobacteriaceae*.¹¹⁻¹⁴
 - Third generation cephalosporins are considered alternative agents for the treatment of otitis media in patients with non-type 1 penicillin allergies and second-line agents for the treatment of sinusitis and pharyngitis due to penicillin and sulfamethoxazole/trimethoprim resistant bacteria or in patients with non-type 1 penicillin allergies.¹⁵⁻¹⁷
 - Cefixime is considered a second-line agent for the treatment of gonorrhea after ceftriaxone.²³
 - The Global Initiative for Chronic Obstructive Lung Disease recommends the use a second or third generation cephalosporin as an alternative to penicillin, ampicillin, amoxicillin, tetracycline or sulfamethoxazole/trimethoprim in patients with chronic obstructive pulmonary disease and mild exacerbations with no risk of a poor outcome.²⁴
 - For specific recommendations from current consensus guidelines, please refer to the full therapeutic class review.
- Other Key Facts:
 - Currently only cefixime (Suprax[®]) is only available as a branded agent. All other third generation cephalosporins are available generically in at least one dosage form or strength.
 - Only third generation cephalosporins that are available in an oral formulation are included within this review.

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Therapeutic Class Overview Injectable Anticoagulants

Therapeutic Class

- Overview/Summary:** The injectable anticoagulants include low molecular weight heparin (LMWH) agents (dalteparin [Fragmin[®]], enoxaparin [Lovenox[®]]) and factor Xa inhibitors (fondaparinux [Arixtra[®]]). In general, the injectable anticoagulants are Food and Drug Administration (FDA)-approved for prophylaxis and/or treatment of venous thromboembolism. Certain agents within the class are also approved for the treatment of acute ST-segment elevation myocardial infarction or for prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction. The specific FDA-approved indications of the injectable anticoagulants are outlined in Table 1.¹⁻³ The LMWH agents exert their effect by binding to antithrombin, an endogenous inhibitor of various activated clotting factors, including factor Xa and thrombin. LMWH is a smaller fragment of unfractionated heparin (UFH) formed by enzymatic or chemical depolymerization processes. The difference in the average size of LMWH (5,000 daltons) compared to UFH (3,000 to 30,000 daltons) contributes to the chief difference between the agents. LMWH primarily inhibits factor Xa and has 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 to occur while the LMWH molecules typically are not.^{4,5} Fondaparinux is a synthetic factor Xa inhibitor that was developed to have an increased affinity to antithrombin. Its specific anti-factor Xa activity is higher than that of the LMWH agents. 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.⁵ Currently, enoxaparin and fondaparinux are available generically.^{6,7}

Table 1. Current Medications Available in the Therapeutic Class¹⁻³

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Dalteparin (Fragmin [®])	Extended treatment of symptomatic venous thromboembolism (proximal deep vein thrombosis and/or pulmonary embolism) in patients with cancer*, prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction [†] , prophylaxis of deep vein thrombosis which may lead to pulmonary embolism in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness, in patients undergoing abdominal surgery who are at risk for thromboembolic complications and in patients undergoing hip fracture surgery	Injection: 2,500 IU/0.2 mL [‡] 5,000 IU/0.2 mL [‡] 7,500 IU/0.3 mL [‡] 10,000 IU/0.4 mL [‡] 10,000 IU/1 mL [§] 12,500 IU/0.5 mL [‡] 15,000 IU/0.6 mL [‡] 18,000 IU/0.72 mL [‡] 95,000 IU/3.8 mL 95,000 IU/9.5 mL	-
Enoxaparin (Lovenox [®])	Prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction [†] , prophylaxis of deep vein thrombosis which may lead to pulmonary embolism in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness, in patients undergoing abdominal surgery who are at risk for thromboembolic complications, in patients undergoing hip replacement surgery [#] , in patients undergoing knee replacement surgery, treatment of acute deep vein	Injection (100 mg/mL): 30 mg/0.3 mL [‡] 40 mg/0.4 mL [‡] 60 mg/0.6 mL [§] 80 mg/0.8 mL [§] 100 mg/1 mL [§] 300 mg/3 mL ^{‡‡} Injection (150 mg/mL): 120 mg/0.8 mL [§]	a

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	thrombosis**, treatment of acute ST-segment elevation myocardial infarction ^{††}	150 mg/1 mL [§]	
Fondaparinux (Arixtra [®])	Prophylaxis of deep vein thrombosis which may lead to pulmonary embolism in patients undergoing abdominal surgery who are at risk for thromboembolic complications, in patients undergoing hip fracture surgery ^{§§} , in patients undergoing hip replacement surgery, in patients undergoing knee replacement surgery, treatment of acute deep vein thrombosis , treatment of acute pulmonary embolism ^{¶¶}	Injection: 2.5 mg/0.5 mL [‡] 5 mg/0.4 mL [‡] 7.5 mg/0.6 mL [‡] 10 mg/0.8 mL [‡]	a

IU=international units

*In these patients therapy begins with the initial venous thromboembolism treatment and continues for six months.

†When concurrently administered with aspirin therapy.

‡Available as a single-dose prefilled syringe.

§Available as a single-dose graduated prefilled syringe.

|| Available as a multiple-dose vial. After first penetration of the rubber stopper, store the multiple-dose vials at room temperature for up to two weeks.

¶¶ Generic available in at least one dosage form and/or strength.

#During and following hospitalization.

**Indicated for inpatient treatment of acute deep vein thrombosis with or without pulmonary embolism, when administered in conjunction with warfarin, and for outpatient treatment of acute deep vein thrombosis without pulmonary embolism when administered in conjunction with warfarin.

††When administered concurrently with aspirin, enoxaparin has been shown to reduce the rate of the combined endpoint of recurrent myocardial infarction or death in patients with acute ST-segment elevation myocardial infarction receiving thrombolysis and being managed medically or with percutaneous coronary intervention.

‡‡Available as a multi-dose vial.

§§Including extended prophylaxis.

|| When administered in conjunction with warfarin.

¶¶ When administered in conjunction with warfarin when initial therapy is administered in the hospital.

***With or without pulmonary embolism when administered in conjunction with warfarin.

Evidence-based Medicine

- A Cochrane Review (16 randomized controlled trials) of cancer patients receiving initial treatment for venous thromboembolism (VTE), revealed that low molecular weight heparin (LMWH) agents may be “superior” to unfractionated heparin (UFH) due to an observed nonsignificant advantage of these agents for reducing the incidence of recurrent VTE. No difference between LMWH agents and fondaparinux was observed for this outcome, or for the incidence of major and minor bleeding events. No significant differences were observed between dalteparin and tinzaparin for the incidence of VTE or major bleeding. With regards to mortality, a significant difference between LMWH agents and UFH was observed, which favored LMWH agents.⁸
- Several placebo-controlled trials, meta-analyses, and systematic reviews evaluating the injectable anticoagulants in medical patients, immobilized patients, and in those undergoing an orthopedic surgery have been conducted and consistently demonstrate their safety and efficacy for VTE treatment and/or thromboprophylaxis.⁹⁻²²
- When the injectable anticoagulants are compared to other methods of thromboprophylaxis (e.g., heparin, UFH, warfarin), “superiority”, in terms of recurrent VTE and safety, is not always consistent.²³⁻⁴¹
- Although data comparing the safety and efficacy of the LMWH agents to fondaparinux have not consistently demonstrated significant “superiority” of one therapy in all comparisons, treatment with fondaparinux appears to be associated with a lower incidence of VTE and a comparable incidence of major bleeding compared to enoxaparin.⁴²⁻⁴⁵ However, in a meta-analysis, the incidence of VTE was significantly less and the incidence of major bleeding was significantly greater with fondaparinux compared to LMWH therapy (enoxaparin).⁴⁶ Another trial demonstrated no difference between fondaparinux and dalteparin for the incidence of VTE and bleeding.⁴⁷

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - For total hip or knee arthroplasty, irrespective of the concomitant use of an intermittent pneumatic compression device or length of treatment, a low molecular weight heparin (LMWH) is suggested in preference to other agents recommended as alternatives (fondaparinux, apixaban, dabigatran, rivaroxaban, low dose unfractionated heparin (UFH), vitamin K antagonist (VKA), or aspirin). Extended prophylaxis (up to 35 days) may be required in certain clinical situations.⁴⁸
 - For the prevention of venous thromboembolism (VTE) in acutely ill medical patients, LMWH agents, UFH, and fondaparinux are recommended, while LMWH agents and VKAs are recommended in patients with cancer.⁴⁸
 - For the treatment of an acute deep vein thrombosis (DVT) or pulmonary embolism (PE), initial anticoagulation with a LMWH agent or fondaparinux is recommended over UFH for at least five days (until the International Normalized Ratio is at least 2.0 or greater for 24 hours). A VKA should also be initiated on the first day of treatment and continued for a period of three months. Extended prophylaxis with a VKA may be required in certain clinical conditions.⁴⁸
 - § Because patients with cancer are at high risk, it is recommended that initial treatment of an acute DVT or PE with a LMWH agent continue for the first three to six months, followed by indefinite therapy with either a VKA or LMWH agent.
 - Injectable anticoagulants are recommended in the management of non-ST-elevation acute coronary syndromes and ST-elevation myocardial infarctions. Use of a specific agent over another is based on individual patient risk factors, as well as the timing and intensity of other planned management strategies.⁴⁹⁻⁵²
- Other Key Facts:
 - Enoxaparin and fondaparinux are available generically.

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Therapeutic Class Overview 5-HT₁ Receptor Agonists

Therapeutic Class

- Overview/Summary:** Migraine is a common disabling primary headache disorder that can present with or without aura. The International Headache Society describes migraine without aura as a clinical syndrome characterized by headache with specific features and associated symptoms. Migraine with aura is primarily characterized by the focal neurological symptoms that usually precede or accompany the headache.¹ Migraine without aura is further described as a recurrent headache disorder manifesting in attacks that can last four to 72 hours. Typical characteristics of these headaches are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia. Migraine with aura is also a recurrent headache disorder; however, it manifests in attacks of reversible focal neurological symptoms that usually develop gradually over five to 20 minutes and last for less than 60 minutes.¹ The serotonin (5-HT) 1 receptor agonists, commonly referred to as triptans, work in the management of migraine via the release of vasoactive peptides, promotion of vasoconstriction and blockade of pain pathways in the brainstem.² Triptans are Food and Drug Administration (FDA)-approved for the acute treatment of migraine with or without aura.³⁻¹³ There is a lack of consistent head-to-head data demonstrating “superiority” of any triptan, making it difficult to recommend the use of one over another.² Currently there are seven single-entity triptans available (Axert[®] [almotriptan], Relpax[®] [eletriptan], Frova[®] [frovatriptan], Amerge[®] [naratriptan], Maxalt[®] and Maxalt-MLT[®] [rizatriptan], Imitrex[®] [sumatriptan] and Zomig[®] and Zomig ZMT[®] [zolmitriptan]) and one combination product (Treximet[®] [sumatriptan/naproxen]). Sumatriptan/naproxen is a fixed-dose combination product containing a triptan and a nonsteroidal anti-inflammatory drug. The combination targets the multiple mechanisms of migraine pathology. Almotriptan is approved for use in children 12 years of age and older while rizatriptan is approved for use in children as young as six years of age.^{3,7} The triptans are available in several different dosage formulations, including orally disintegrating tablets, nasal sprays, subcutaneous injections and tablets. All triptans are currently available as an oral tablet. Naratriptan, rizatriptan and sumatriptan are currently available generically in various formulations.¹⁴

Table 1. Current Medications Available in the Class³⁻¹²

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Almotriptan (Axert [®])	Acute treatment of migraine attacks in adults with a history of migraine with or without aura and acute treatment of migraine headache pain in children 12 to 17 years of age with a history of migraine attacks with or without aura, and who have migraine attacks usually lasting four hours or more	Tablet: 6.25 mg 12.5 mg	-
Eletriptan (Relpax [®])	Acute treatment of migraine attacks with or without aura in adults	Tablet: 20 mg 40 mg	-
Frovatriptan (Frova [®])	Acute treatment of migraine attacks with or without aura in adults	Tablet: 2.5 mg	-
Naratriptan (Amerge ^{®*})	Acute treatment of migraine attacks with or without aura in adults	Tablet: 1 mg 2.5 mg	a
Rizatriptan (Maxalt ^{®*} , Maxalt-MLT ^{®*})	Acute treatment of migraine with or without aura in adults and in	Orally disintegrating	a

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
	pediatric patients six to 17 years of age	tablet: 5 mg 10 mg Tablet: 5 mg 10 mg	
Sumatriptan (Alsuma [®] , Imitrex ^{®*} , Sumavel DosePro [®])	Acute treatment of cluster headache episodes [†] , acute treatment of migraine attacks with or without aura in adults	Nasal spray: 5 mg 20 mg Subcutaneous injection: 4 mg/0.5 mL 6 mg/0.5 mL Tablet: 25 mg 50 mg 100 mg	a
Zolmitriptan (Zomig [®] , Zomig-ZMT [®])	Acute treatment of migraine attacks with or without aura in adults	Nasal spray: 2.5 mg 5 mg Orally disintegrating tablet: 2.5 mg 5 mg Tablet: 2.5 mg 5 mg	-
Combination Products			
Sumatriptan/naproxen (Treximet [®])	Acute treatment of migraine attacks with or without aura in adults	Tablet: 85/500 mg	-

*Generic available in at least one dosage form or strength.

† Subcutaneous injection only.

Evidence-based Medicine

- In general, clinical trial data consistently demonstrates the “superiority” of the triptans over placebo in achieving headache pain relief, freedom from pain at two hours, sustained pain-free response, reducing rescue medication use and improving migraine-associated symptoms such as nausea, photophobia and phonophobia.¹⁵⁻⁵³
- Clinical trial data also suggest the available triptans, when administered orally, range in comparative efficacy. Specifically, in a large meta-analysis, consisting of 53 controlled trials and over 24,000 patients, results demonstrated that while all triptans were effective and well tolerated, eletriptan (80 mg) and rizatriptan (10 mg) were “superior” to sumatriptan (100 mg) in terms of achievement of headache response at two hours, pain-free response at two hours and sustained pain-free response. Almotriptan (12.5 mg) demonstrated “superiority” over sumatriptan for pain-free response at two hours and sustained pain-free response. Of note, lower doses of eletriptan and rizatriptan in this analysis did not achieve the same results.¹⁵

- While there appears to be differences in the relative efficacies among the triptans, direct head-to-head trials do not consistently support the use of one over another, suggesting that individual variations in the response to different triptans exist.⁵⁴⁻⁶⁶
- Trials comparing different formulations of triptans measured patient preference as the primary endpoint.^{60,65-67}

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - The triptans are recommended for initial treatment of an acute migraine attack of moderate to severe severity, especially when “nonspecific” therapies have failed.⁶⁸⁻⁷¹
 - “Nonspecific” therapies, such as nonsteroidal anti-inflammatory drugs are recommended for initial treatment of acute migraine attacks of mild to moderate severity.⁶⁸⁻⁷¹
 - A non-oral route of administration is recommended for patients whose migraines present early with nausea or vomiting. Nausea should be treated with an antiemetic.⁶⁸⁻⁷¹
 - The subcutaneous sumatriptan injection and zolmitriptan nasal spray are recognized as potential treatment options for the acute management of cluster headaches.⁶⁸⁻⁷¹
- Other Key Facts:
 - Almotriptan is approved for use in children 12 years of age and older while rizatriptan is approved for use in children as young as six years of age.^{3,7}
 - The subcutaneous sumatriptan injection is also Food and Drug Administration-approved for the acute treatment of cluster headache episodes.⁸
 - The subcutaneous sumatriptan injection has the fastest onset of action, but there is no evidence to suggest that different oral triptan formulations have a faster onset of action than the others.⁷¹
 - Naratriptan, rizatriptan and sumatriptan are currently available generically in various formulations.¹⁴

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Therapeutic Class Overview

β -Agonists: Combination Products

Therapeutic Class

- Overview/Summary:** The agents approved for the treatment of signs and symptoms of benign prostatic hyperplasia will be the focus of this review. The α -adrenergic blockers including, alfuzosin, doxazosin, silodosin, tamsulosin, and terazosin, reduce smooth-muscle tone in the prostate and bladder neck decreasing lower urinary tract symptoms (LUTS) secondary to BPH. Alfuzosin, silodosin and tamsulosin are selective to the α -adrenergic receptors located in the prostate and therefore are only Food and Drug Administration (FDA) approved for BPH, whereas doxazosin and terazosin additionally inhibit α -adrenergic receptors found in the vascular smooth muscle and are additionally indicated for hypertension.¹⁻⁶ The 5- α reductase inhibitors, dutasteride and finasteride, are appropriate treatment options for LUTS associated with overall prostatic enlargement. They act by blocking the conversion of testosterone to dihydrotestosterone and in turn suppress the growth of the prostate.^{7,8} Jalyn[®] (dutasteride/tamsulosin) is a combination of both an α -adrenergic blocker and a 5- α reductase inhibitors.⁹ The final drug approved for use in BPH is the phosphodiesterase-5 inhibitor, tadalafil. The exact mechanism for reducing BPH symptoms is unknown.¹⁰ Note that even though doxazosin and terazosin are FDA-approved for use in the treatment of hypertension, tadalafil is FDA-approved for use in the treatment of erectile dysfunction and pulmonary arterial hypertension, and finasteride is FDA-approved for alopecia, they are not included in this review. Jalyn[®] (dutasteride/tamsulosin) is a combination of both an α -adrenergic blocker and a 5- α reductase inhibitors.⁹ The final drug approved for use in BPH is the phosphodiesterase-5 inhibitor, tadalafil. The exact mechanism for reducing BPH symptoms is unknown.¹⁰ Note that even though doxazosin and terazosin are FDA-approved for use in the treatment of hypertension, tadalafil is FDA-approved for use in the treatment of erectile dysfunction and pulmonary arterial hypertension and finasteride is FDA-approved for alopecia, they are not included in this review.

Clinical manifestations of BPH include LUTS (frequency of urination, nocturia, hesitancy, urgency, and weak urinary stream). The appearance and progression of symptoms is usually slow, over a couple of years, with a poor correlation between symptoms and the presence of an enlarged prostate on rectal exam.¹¹ Disease prevalence and the occurrence of symptoms are age dependent, with an initial onset of disease occurring patients greater than 50 years of age.¹¹ The American Urological Association (AUA) acknowledges that not all men with histological evidence of BPH will develop bothersome LUTS and not all patients with BPH and LUTS actually have prostate enlargement, one of the main features of symptomatic disease. Additionally, prostate enlargement may exist in the absence of LUTS.¹²

Table 1. Current Medications Available in the Therapeutic Class¹⁻¹⁰

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Alfuzosin hydrochloride (Uroxatral [®])	Treatment of signs and symptoms of benign prostatic hyperplasia	Tablet, extended release: 10 mg	a
Doxazosin mesylate (Cardura [®] , [†] Cardura XL [®])	Treatment of signs and symptoms of benign prostatic hyperplasia [#] ; treatment of hypertension [*]	Tablet, extended release: 4 mg 8 mg Tablet: 1 mg 2 mg 4 mg	a

		8 mg	
Dutasteride (Avodart [®])	Treatment of signs and symptoms of benign prostatic hyperplasia ^{†,‡}	Capsule: 0.5 mg	-
Finasteride (Proscar [®])	Treatment of signs and symptoms of benign prostatic hyperplasia ^{†,§}	Tablet: 5 mg	a
Silodosin (Rapaflo [®])	Treatment of signs and symptoms of benign prostatic hyperplasia	Capsule: 4 mg 8 mg	-
Tadalafil (Cialis [®] , Adcirca [®])	Treatment of signs and symptoms of benign prostatic hyperplasia, treatment of erectile dysfunction	Tablet: 2.5 5 10 [¶] 20 [¶]	-
Tamsulosin hydrochloride (Flomax [®])	Treatment of signs and symptoms of benign prostatic hyperplasia [†]	Capsule: 0.4 mg	-
Terazosin hydrochloride	Treatment of signs and symptoms of benign prostatic hyperplasia,	Capsule: 1 mg 2 mg 5 mg 10 mg	a
Combination Products			
Dutasteride/tamsulosin hydrochloride (Jalyn [®])	Treatment of signs and symptoms of benign prostatic hyperplasia [†] , treatment of hypertension	Capsule: 0.5 mg/0.4 mg	-

*Instant release formulation only.

†In men with an enlarged prostate, to improve symptoms, reduce the risk of acute urinary retention and reduce the risk of the need for BPH-related surgery.

‡To treat symptomatic BPH in men with an enlarged prostate in combination with tamsulosin.

§To reduce the risk of symptomatic progression of BPH in combination with doxazosin.

#Doxazosin indicated for both the urinary outflow obstruction and obstructive and irritative symptoms associated with BPH.

¶Generic available in at least one dosage form or strength.

Evidence-based Medicine

- FDA-approval of silodosin was based on two clinical trials where it was compared to placebo and demonstrated its efficacy in decreasing the International Prostate Symptom Score (IPSS) and improving general quality of life scores. In a pooled analysis of these two clinical trials, the mean change in total IPSS at baseline was -6.40 (±6.63) and -3.50 (±5.84) for the silodosin and placebo groups, respectively with an adjusted mean difference reported as -2.8 (P<0.0001). The maximum urinary flow rate (Q_{max}) at endpoint was 2.6 mL/second (standard deviation [SD]±4.43) in the silodosin group and 1.5 mL/ second (SD±4.36) in the placebo group; corresponding to an adjusted mean group difference of 1.0 mL/ second (P=0.0007).¹⁶
- The safety and efficacy of tadalafil for BPH has been evaluated in multiple studies. These studies. Tadalafil consistently showed significantly better improvement in IPSS compared to placebo.¹⁸⁻²⁵ One study evaluated men with BPH who had comorbid erectile dysfunction. Tadalafil was associated with statistically significant improvements in both international index of erectile function (IIEF) scores and total IPSS (P<0.001 for both).²⁵
- Studies comparing the α-adrenergic blocking agents to each. Although some trials have suggested superiority one agent over another, most studies, have tended toward non-inferiority within the α-blockers related to reducing IPSS.²⁶⁻⁴⁶
 - A Cochrane review has evaluated tamsulosin in comparison to other α-adrenergic blocking agents. It was concluded that tamsulosin was as effective as other α-adrenergic blockers in improving LUTS and urinary flow rates. Dizziness, rhinitis and abnormal ejaculation occurred

- significantly more frequently than placebo and withdrawal was reported more often with higher doses of tamsulosin. Additionally, terazosin use was associated with a higher rate of discontinuation than low dose tamsulosin.³⁷
- A second Cochrane review evaluated terazosin to other α blockers, finasteride alone or in combination with terazosin and placebo. Terazosin was comparable to tamsulosin in improving IPSS (40% vs 43%), and more effective than finasteride (38% vs 20%) or placebo (38% vs 17%) in improving American Urological Association Symptom Score (AUA-SS). Peak urinary flow rates were similar among α blockers and higher with terazosin (22%) over finasteride (15%) and placebo (11%).³⁸
 - A meta-analysis by Djavan et al of α -adrenergic blocking agents (alfuzosin, doxazosin, tamsulosin, and terazosin) in men with LUTS suggestive of benign prostatic obstruction did not identify any difference among agents in improving total urinary symptom scores or Q_{max} . However, alfuzosin and tamsulosin were better tolerated than doxazosin and terazosin.³⁹
 - Similar to the α -blocking agents, the 5- α reductase inhibitors have been compared to one another in a number of clinical trials, with mixed results. Dutasteride was shown to be non-inferior to finasteride for reducing prostate volume, post-void volume, and American Urological Association Symptom Score (AUA-SS).⁴⁷⁻⁵⁰
 - Head-to-head trials between 5- α reductase inhibitors and α blockers have also been conducted.⁵¹⁻⁶²
 - When compared to finasteride, tamsulosin showed comparable effect on urinary symptom scores at study end point (24 weeks and 1 year)^{51,52}, however a benefit was found with tamsulosin at earlier assessment (4 weeks) in both IPSS and Q_{max} .⁵¹
 - Tamsulosin in combination with dutasteride has been found to be associated with a greater benefit in IPSS and Q_{max} than each agent alone. As expected tamsulosin use resulted in a much lower decrease in prostate volume as compared to combination therapy (0.00%±0.84% and 26.90%±0.62%, respectively; $P<0.001$).⁵³
 - Four large, long-term trials comparing doxazosin, finasteride, each agent alone and in combination, and placebo.⁵⁸⁻⁶¹ Rates of nocturia were significantly reduced with monotherapy and combination treatment compared to placebo.⁵⁹
 - Men with moderate to enlarged prostate glands benefited most from combination therapy ($P<0.05$), however doxazosin therapy alone was as effective as combination therapy for decreasing the risk of progression in men without an enlarged prostate.⁶⁰
 - Doxazosin monotherapy and in combination with finasteride was associated with significantly greater improvements in Q_{max} and IPSS. Differences between finasteride alone and placebo did not reach statistical significance.⁶¹
 - Terazosin use alone and in combination with finasteride was associated with significantly greater reductions in symptom scores and greater increases in Q_{max} compared to finasteride monotherapy or placebo. Differences among combination therapy and terazosin monotherapy did not reach statistical significance, nor did difference between finasteride and placebo.⁶²
 - Studies have been conducted evaluating the safety and efficacy of combination therapy with two agents from different classes.⁶³⁻⁶⁶
 - A retrospective analysis showed that combination therapy with finasteride and an α -blocking agent significantly improved IPSS in patients with severe BPH symptoms, but was not statistically different from monotherapy in the same population.⁶³
 - A meta-analysis conducted by Gacci et al found that a phosphodiesterase-5 inhibitor and α blocker combination therapy significantly improved IPSS, IIEF score and Q_{max} compared to α blockers alone ($P<0.05$, $P<0.0001$ and $P<0.0001$, respectively).⁶⁴
 - Tadalafil 5 mg once daily coadministered with finasteride 5 mg for 12 weeks resulted in an IPSS total score improvement that was significantly better than finasteride/placebo ($P=0.001$).⁶⁶
 - A systematic review of alfuzosin studies showed a greater improvement in the primary outcome (IPSS) over placebo (weighted mean difference, -1.8 points; 95% confidence interval [CI], -2.49 to -1.11); however, when compared to other α -blockers (doxazosin, tamsulosin), doxazosin use was associated with the most favorable change from baseline IPSS. Alfuzosin alone and in combination with finasteride showed a greater improvement in LUTS compared to finasteride alone.

Key Points within the Medication Class

- According to Current Clinical Guidelines:^{12,13}
 - Watchful waiting is recommended for mild symptoms of BPH (AUA symptom score <78) and patients with moderate or severe symptoms (AUA symptom score ≥8) who are not bothered by their symptoms.^{12,13}
 - α blockers are considered first line; their rapid onset of action, good efficacy, and low rate and severity of adverse events, followed by a 5- α reductase inhibitor
 - § The older, less costly, generic α -blockers remain reasonable choices.
 - Guidelines were published when little data was available on tadalafil.
 - Combination therapy is an appropriate and effective treatment for patients with LUTS associated with demonstrable prostatic enlargement based on volume measurement, prostate specific antigen level as a proxy for volume, and/or enlargement on digital rectal exam.¹²
- Other Key Facts:
 - Alfuzosin, doxazosin, terazosin and finasteride are available generically in standard formulations. The doxazosin sustained-release tablet (Cardura XL[®]) is not currently available generically.
 - Finasteride (Propecia[®]) is also available as a 1 mg tablet for the treatment of alopecia. Tadalafil (Adcirca[®]) is available as a 20 mg tablet for the treatment of pulmonary hypertension.¹⁴
 - 5- α reductase inhibitors are pregnancy category X; women who are pregnant or who could be pregnant should avoid handling dutasteride and dutasteride/tamsulosin capsules along with crushed finasteride tablets.¹⁻¹⁰
 - Administration considerations:¹⁻¹⁰
 - § Alfuzosin, doxazosin extended-release, dutasteride, tamsulosin and dutasteride/tamsulosin should all be swallowed whole and not crushed, chewed, or cut.
 - § Doxazosin instant-release, finasteride, and tadalafil tablets may be crushed.
 - § Silodosin capsules can be opened and the power sprinkled on applesauce.
 - § Terazosin capsules can be dissolved in hot water (which may take five to 15 minutes) for administration through a feeding tube via an oral syringe if required.

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Therapeutic Class Overview Fibric Acid Derivatives

Therapeutic Class

- Overview/Summary:** The fibric acid derivatives are agonists of the peroxisome proliferator activated receptor α (PPAR α). Activation of PPAR α increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein CIII. The resulting decrease in triglycerides (TG) produces an alteration in the size and composition of low-density lipoprotein cholesterol (LDL-C) from small, dense particles to large buoyant particles. There is also an increase in the synthesis of high-density lipoprotein cholesterol (HDL-C), as well as apoprotein AI and AII.¹⁻¹⁰ The major action of this class of medications is to reduce TG. The fibric acid derivatives can decrease TG by 20 to 50% and increase HDL-C by 10 to 35%. They also lower LDL-C by 5 to 20%; however, in patients with hypertriglyceridemia, LDL-C may increase with the use of fibric acid derivatives.¹¹

Several fenofibrate products are currently available, including micronized and non-micronized formulations. The different fenofibrate formulations are not equivalent on a milligram-to-milligram basis. Micronized fenofibrate is more readily absorbed than non-micronized formulations, which allows for a lower daily dose. Fenofibrate (micronized and non-micronized formulations), fenofibric acid, and gemfibrozil are available generically in at least one dosage form and/or strength.¹² Fenofibrate and fenofibric acid are Food and Drug Administration (FDA)-approved for the adjunctive treatment of primary hypercholesterolemia or mixed dyslipidemias, as well as an adjunctive treatment for hypertriglyceridemia. Trilipix[®] has the additional indication of adjunct therapy to diet in combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal.⁹ Gemfibrozil is FDA-approved for the treatment of hypertriglyceridemia and to reduce the risk of developing coronary heart disease (CHD) in select patients.¹³ Gemfibrozil has demonstrated a reduction in the risk of fatal and nonfatal myocardial infarction (MI) for primary prevention, as well as a reduction in CHD death and nonfatal MI and stroke for secondary prevention. Clinical trial results demonstrating that the fibric acid derivatives, as a class, reduce CHD incidence is less robust than that with statin therapy.¹¹

Table 1. Current Medications Available in the Therapeutic Class¹⁻¹⁰

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Fenofibrate (Antara ^{®*} , Fenoglide [®] , Lipofen [®] , Lofibra ^{®*} , Tricor ^{®*} , Triglide [®])	Adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia. Adjunctive therapy to diet to reduce elevated LDL-C, total cholesterol, TG and apolipoprotein B, and to increase HDL-C in patients with primary hypercholesterolemia or mixed dyslipidemia.	Capsule: 50 mg (Lipofen [®]) 150 mg (Lipofen [®]) Capsule, Micronized: 30 mg (Antara [®]) 43 mg (Antara [®]) 67 mg (Lofibra [®]) 90 mg (Antara [®]) 130 mg (Antara [®]) 134 mg (Lofibra [®]) 200 mg (Lofibra [®]) Tablet: 40 mg (Fenoglide [®]) 48 mg (Tricor [®]) 50 mg (Triglide [®]) 54 (Lofibra [®]) 120 mg (Fenoglide [®]) 145 mg (Tricor [®])	a

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/ Strength	Generic Availability
		160 mg (Lofibra [®] , Triglide [®])	
Fenofibric acid (Fibricor ^{®*} , Trilipix ^{®†})	Adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fibricor [®]). [‡] Adjunctive therapy to diet to reduce elevated LDL-C, total cholesterol, TG and apolipoprotein B, and to increase HDL-C in patients with primary hypercholesterolemia or mixed dyslipidemia.	Delayed-release capsule: 45 mg (Trilipix [®]) 135 mg (Trilipix [®]) Tablet: 35 mg (Fibricor [®]) 105 mg (Fibricor [®])	a
Gemfibrozil (Lopid ^{®*})	Treatment of adult patients with very high elevations of serum TG levels who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them. Reducing the risk of developing CHD only in Type IIb patients without history of or symptoms of existing CHD who have had an adequate response to weight loss, dietary therapy, exercise and other pharmacologic agents and who have the following triad of lipid abnormalities: low HDL-C levels in addition to elevated LDL-C and elevated TG.	Tablet: 600 mg	a

CHD=coronary heart disease, HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, TG=triglycerides

*Generic is available in at least one dosage form and/or strength.

†Choline fenofibrate.

‡Indicated for therapy in patients with triglycerides ≥ 500 mg/dL.

Evidence-based Medicine

- In general, the fibric acid derivatives consistently demonstrate greater efficacy compared to placebo in the management of hypercholesterolemia and hypertriglyceridemia.¹⁴⁻¹⁸
- The addition of fibric acid derivatives to other well established lipid lowering agents has been shown to be safe and resulted in additional improvements in lipid profile compared to each drug given as monotherapy.¹⁶⁻²⁸
- The five year, placebo-controlled FIELD trial (N=9,975) demonstrated that fenofibrate did not significantly reduce the risk of the combined primary outcome of coronary events (CHD), death or nonfatal myocardial infarction (MI) in patients with type 2 diabetes. When individual endpoints were analyzed, fenofibrate significantly reduced nonfatal MI by 24% (hazard ratio [HR], 0.76; $P=0.010$), but a nonsignificant increase in CHD mortality (HR, 1.19; $P=0.22$) was observed.²⁹ Similar results were observed in the ACCORD trial (N=5,518) which evaluated the efficacy of fenofibrate on reducing the risk of major cardiovascular events in high risk type 2 diabetics.³⁰
- In the five year, Helsinki Heart Study (N=4,081), a primary prevention trial, gemfibrozil demonstrated a significant 34% ($P<0.02$) reduction in the incidence of cardiac events but demonstrated no effect on all-cause mortality.³¹ After 8.5 years of follow up, all-cause mortality was numerically higher with gemfibrozil, but the increase did not meet significance.³² In a secondary prevention component of the Helsinki Heart Study, there was no difference between gemfibrozil and placebo in the incidence of fatal and nonfatal MI and cardiac death.³³
- A meta-analysis of 10 randomized controlled trials (N=36,489) evaluated fibric acid derivatives for the primary and secondary prevention of cardiovascular events and demonstrated that treatment tended to increase all-cause mortality (odds ratio [OR], 1.07; $P=0.08$) and was associated with a significant increase in noncardiovascular mortality (OR, 1.16; $P=0.004$). No effect of fibric acid derivatives was observed for cardiovascular mortality (OR, 0.98; $P=0.68$). When the individual fibric acid derivatives

were analyzed, the odds of cardiovascular mortality were significantly lower with gemfibrozil (OR, 0.77; $P=0.05$).³⁴

- A second meta-analysis of 18 randomized controlled trials (N=45,058) demonstrated no effect on all-cause mortality (relative risk [RR], 1.00; $P=0.918$), cardiovascular mortality (RR, 0.97; $P=0.582$) or sudden death (RR, 0.89; $P=0.190$). An increased risk of noncardiovascular mortality was noted; however, this finding did not reach significance (RR, 1.10; $P=0.063$).³⁵
- Fenofibric acid was added to rosuvastatin in patients with chronic kidney disease and it was shown that there was a significantly greater decrease in median percent TGs compared to rosuvastatin alone after eight weeks ($P<0.001$) and 16 weeks ($P<0.001$) along with an increase in HDL-C over the same time periods ($P<0.001$).³⁶

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - Therapeutic lifestyle changes remain an essential modality in the management of patients with hypercholesterolemia.³⁷⁻⁴⁴
 - In general, hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are considered first line therapy for decreasing low density lipoprotein cholesterol (LDL-C) levels. If after six weeks, lipid goals are not achieved with statin monotherapy, a dosage increase or the addition of a bile acid sequestrant or nicotinic acid (niacin) should be considered.³⁷⁻⁴⁴
 - Due to increased muscle side effects including rhabdomyolysis, gemfibrozil is not recommended to be used in a combination with statins.⁴³
 - Fibric acid derivatives are typically reserved for the treatment of hypertriglyceridemia, to reduce the risk of pancreatitis, or for an isolated low high density lipoprotein cholesterol.^{37,40}
 - Fibric acid derivatives can be considered in patients with coronary heart disease who have low levels of LDL-C and atherogenic dyslipidemia, or in combination with a statin in patients who have elevated LDL-C and atherogenic dyslipidemia.³⁷
 - The National Institute for Health and Clinical Excellence (NICE) guidelines recommend non-routine use of fibrates if intolerant to statins as monotherapy and recommend against the use of niacin, bile acid sequestrants, and omega-3 fatty acids or any combination of a statins plus either a fibrate, niacin, bile acid sequestrants, or omega-3 fatty acids for primary or secondary prevention of coronary vascular disease due to lack of evidence.⁴⁴
- Other Key Facts:
 - Gemfibrozil (Lopid[®]) is the only fibric acid derivative approved for reducing the risk of developing coronary heart disease in select patients.¹⁰
 - Currently, all fibric acid derivatives are available generically in at least one dosage form and/or strength.¹²

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Therapeutic Class Review **Dipeptidyl Peptidase-4 (DPP-4) Inhibitors**

Therapeutic Class

- **Overview/Summary:** A significant advancement in the management of type 2 diabetes has been the development of incretin-based therapies. This novel therapeutic approach is important as type 2 diabetics have been shown to have an impaired incretin response.¹ Currently there are two classes of incretin-based therapies available; the dipeptidyl peptidase-4 (DPP-4) inhibitors and the glucagon-like peptide-1 receptor agonists, or incretin mimetics. The DPP-4 inhibitors include alogliptin, linagliptin, saxagliptin, and sitagliptin, which are all available as single-entity agents (alogliptin [Nesina[®]], linagliptin [Tradjenta[®]], saxagliptin [Onglyza[®]], and sitagliptin [Januvia[®]]) or in fixed-dose combination products (alogliptin/metformin [Kazano[®]], alogliptin/pioglitazone [Oseni[®]], linagliptin/metformin [Jentadueto[®]], saxagliptin/metformin [Kombiglyze ER[®]], sitagliptin/metformin [Janumet[®], Janumet XR[®]], and sitagliptin/simvastatin [Juvivync[®]]). The DPP-4 inhibitors are Food and Drug Administration-approved as adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes. Single-entity agents are available for use either as monotherapy or in combination with other antidiabetic agents. The fixed-dose combination products are available for use when treatment with both drug components is appropriate.²⁻¹²

The DPP-4 inhibitors reversibly block the enzyme DPP-4, which is responsible for the rapid degradation of endogenous incretin hormones. These hormones are produced by the gastrointestinal tract in response to meals and are involved in the regulation of insulin. The antidiabetic actions of endogenous incretin hormones include the enhancement of meal stimulated insulin secretion, decreased glucagon secretion, improvements in β cell function, and slowing of gastric emptying. Through their effect on these hormones, the DPP-4 inhibitors primarily target post-prandial glucose and have also been shown to decrease fasting plasma glucose.^{13,14} In general, the DPP-4 inhibitors are associated with a favorable side effect profile and also have a weight neutral effect compared to other antidiabetic agents commonly used in the management of type 2 diabetes. Compared to sulfonylureas, the risk of hypoglycemia associated with the DPP-4 inhibitors is low due to the glucose-dependent nature of incretin hormone activity. In addition, the DPP-4 inhibitors have not been associated with the same increased risk of cardiovascular disease that has been observed with the use of thiazolidinediones (TZDs). In addition, as mentioned earlier the DPP-4 inhibitors improve the function of β cells and although TZDs and metformin treat insulin resistance, these agents do not address the progressive decline in β cell function that is observed in patients with type 2 diabetes.¹³⁻¹⁵

The DPP-4 inhibitors are available as a fixed-dose combination product with metformin. Metformin, a biguanide, improves glucose tolerance in type 2 diabetics by lowering both basal and postprandial plasma glucose. Specifically, the actions of metformin result in decreased hepatic glucose production, decreased intestinal absorption of glucose, and improvement in insulin sensitivity via increased peripheral glucose uptake and utilization.^{3,5} Additionally, alogliptin is available in a fixed-dose combination with pioglitazone. Pioglitazone is a thiazolidinedione, an agonist for peroxisome proliferator-activated receptor-gamma (PPAR γ). PPAR receptors are found in adipose, skeletal muscle and liver tissue and activation of these receptors modulates transcription of insulin response genes that control glucose and lipid metabolism, providing an overall effect of increasing insulin sensitivity in muscle and adipose tissue while inhibiting hepatic gluconeogenesis.³ Sitagliptin is also available as a fixed-dose combination product with simvastatin. Simvastatin is a 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG CoA) inhibitor, and works to improve lipid profiles by inhibiting HMG CoA reductase, the enzyme that catalyzes the rate-limiting step in cholesterol biosynthesis.¹² It should be noted that in September 2013, Merck pharmaceuticals, the manufacturer the sitagliptin/simvastatin fixed-dose combination product issued a notice to voluntarily discontinue the manufacturing of this agent for business reasons. Patients currently receiving the agent were recommended to discuss alternative treatment options at their next physician appointment.¹ Overall, the DPP-4 inhibitors are significantly more effective compared to placebo in reducing glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose, and post-prandial glucose, with no major

effect on body weight. Combination therapy with a DPP-4 inhibitor and metformin consistently demonstrates improved benefits in glycemic control over monotherapy with either a DPP-4 inhibitor or metformin, limited within class head-to-head trials have been conducted.¹⁷⁻⁶⁴

Two meta-analyses revealed that DPP-4 inhibitors are not associated with an increased risk of cardiovascular events or cancer compared to placebo or other antidiabetic agents, respectively.^{38,62} However, a recent clinical trial suggested an increased risk of heart-failure with saxagliptin compared to placebo.³⁹ The Food and Drug Administration announced the intention of further reviewing the risk of cardiovascular outcomes with this agent.⁶⁵

With regards to the specific DPP-4 inhibitor agents, all single-entity agents are available for once-daily dosing. Three fixed-dose combination products contain metformin immediate-release (alogliptin/metformin [Kazano[®]], linagliptin/metformin [Jentadueto[®]] and sitagliptin/metformin [Janumet[®]]) which are available for twice-daily dosing. One other fixed-dose combination product (alogliptin/pioglitazone [Oseni[®]]) contains pioglitazone and is also dosed once daily. Two other fixed-dose combination products contain metformin extended-release (ER) (saxagliptin/metformin ER [Kombiglyze XR[®]] and sitagliptin/metformin ER [Janumet XR[®]]), and because of the metformin ER component, these products are available for once-daily dosing. The fixed-dose combination product combining sitagliptin and simvastatin (Juvissync[®]), a hydroxymethylglutaryl coenzyme A reductase inhibitor (statin), is also available for once-daily dosing. Single-entity linagliptin is the only agent within the class that does not require renal and hepatic dosing. The fixed-dose combination of alogliptin/pioglitazone [Oseni[®]] carries a boxed warning regarding the risk of use in patients with congestive heart failure as the TZD component may cause or exacerbate congestive heart failure in some patients. Furthermore, because of the metformin component in certain fixed-dose combination products, caution is recommended with both renal and hepatic dysfunction. In addition, these products all have a boxed warning regarding the risk of lactic acidosis due to metformin accumulation. The fixed-dose combination product of sitagliptin/simvastatin has a pregnancy category of X and is associated with several drug interactions due to the simvastatin component.²⁻¹² Currently, none of the DPP-4 inhibitors are available generically.

Table 1. Medications Included Within the Therapeutic Class Review²⁻¹²

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Alogliptin (Nesina [®])	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 6.25 mg 12.5 mg 25 mg	-
Linagliptin (Tradjenta [®])	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 5 mg	-
Saxagliptin (Onglyza [®])	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 2.5 mg 5 mg	-
Sitagliptin (Januvia [®])	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 25 mg 50 mg 100 mg	-
Combination Products			
Alogliptin/metformin (Kazano [®])	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet (alogliptin/metformin): 12.5/500 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		12.5/1000 mg	
Alogliptin/ pioglitazone (Oseni [®])	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet (alogliptin/ pioglitazone): 12.5/15 mg 12.5/30 mg 12.5/45 mg 25/15 mg 25/30 mg 25/45 mg	-
Linagliptin/ metformin (Jentaduet [®])	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes*	Tablet (linagliptin/ metformin): 2.5/500 mg 2.5/850 mg 2.5/1,000 mg	-
Saxagliptin/ metformin (Kombiglyze XR [®])	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes†	Tablet (saxagliptin/ metformin ER): 5/500 mg 2.5/1,000 mg 5/1,000 mg	-
Sitagliptin/ metformin (Janumet [®] , Janumet XR [®])	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes‡	Tablet (sitagliptin/ metformin): 50/500 mg 50/1,000 mg Tablet (sitagliptin/ metformin ER): 50/500 mg 50/1,000 mg 100/1,000 mg	-
Sitagliptin/ simvastatin (Juvissync [®])	Patients for whom treatment with both sitagliptin and simvastatin is appropriate§	Tablet (sitagliptin/ simvastatin): 100/10 mg 100/20 mg 100/40 mg	-

*When treatment with both linagliptin and metformin is appropriate.

†When treatment with both saxagliptin and metformin is appropriate.

‡When treatment with both sitagliptin and metformin or metformin extended-release is appropriate.

§Sitagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. Simvastatin is indicated as an adjunctive therapy to diet to reduce the risk of total mortality by reducing coronary heart disease deaths and reduce the risk of non-fatal myocardial infarction, stroke, and the need for revascularization procedures in patients at high risk of coronary events; reduce elevated total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), apolipoprotein B, triglycerides (TG) and increase high density lipoprotein cholesterol in patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia; reduce elevated TG in patients with hypertriglyceridemia and reduce TG and very low density lipoprotein cholesterol in patients with primary dysbetalipoproteinemia; and reduce TC and LDL-C in patients with primary homozygous familial hypercholesterolemia.

Evidence-based Medicine

- Clinical trials demonstrating the safety and efficacy of the dipeptidyl peptidase-4 (DPP-4) inhibitors in the management of type 2 diabetes are outlined in Table 4.¹⁷⁻⁶⁸ Of note, there have been minimal clinical efficacy or safety trials conducted with any of the DPP-4 inhibitor fixed-dose combination products; bioequivalence of these products with co-administration of the individual drug components has been demonstrated for all tablet strengths.⁶⁻¹² Available trials evaluating the fixed-dose

combination of sitagliptin/metformin support its efficacy and safety in the management of type 2 diabetes. Specifically, combination therapy was associated with significantly improved glycemic control compared to metformin monotherapy.⁵⁸

- In studies, alogliptin was associated with significant decreases in glycosylated hemoglobin (HbA_{1c}) from baseline as monotherapy compared to placebo. In addition, in studies with metformin or pioglitazone combination therapy with alogliptin, significant decreases in HbA_{1c} were observed and more patients' specific HbA_{1c} goals compared to the monotherapy comparator. As an add-on therapy in patients already being treated with metformin, pioglitazone, metformin/pioglitazone, glipizide or insulin therapy, the additions of alogliptin demonstrated significant improvements in HbA_{1c} from baseline compared to placebo.¹⁷⁻²⁴
- Overall, linagliptin is more effective compared to placebo in decreasing glycosylated hemoglobin and fasting plasma glucose (FPG) as monotherapy or as add-on therapy to other antidiabetic agents in type 2 diabetics not achieving glycemic goals. In addition, more patients achieved glycemic goals (HbA_{1c} <7.0%) with linagliptin compared to placebo.²⁵⁻²⁸ Combination therapy with linagliptin and pioglitazone has been shown to be more efficacious in terms of reducing HbA_{1c} compared to pioglitazone monotherapy.⁵⁴
- Similar results were achieved with saxagliptin when compared to placebo.³⁰⁻³⁷ In addition, combination therapy with saxagliptin and metformin was "superior" to monotherapy with either agent in observed reductions in HbA_{1c}, FPG, and post-prandial glucose (PPG), and a significantly greater proportion of patients achieved glycemic goals with combination therapy.^{56,57}
- Similar to the results of clinical trials evaluating other DPP-4 inhibitors, sitagliptin is consistently more efficacious in improving glycemic control compared to placebo, and combination therapy with sitagliptin and metformin is more efficacious than monotherapy with either agent.⁴¹⁻⁵²
- In a single head-to-head trial, saxagliptin demonstrated non-inferiority to sitagliptin in reducing HbA_{1c}. However, a significantly greater proportion of patients achieved an HbA_{1c} ≤6.5% and achieved significant reductions in FPG with sitagliptin compared to saxagliptin.⁵³ While the beneficial effects of the DPP-4 inhibitors in improving HbA_{1c}, FPG, and PPG compared to placebo are well established, observed improvements in body weight and β cell function with these agents are not consistent.^{17-64,66}
- In general, meta-analyses and systematic reviews evaluating incretin-based therapies, including the DPP-4 inhibitors, support the results observed in randomized-controlled trials evaluating these agents.^{38,54,63-68} Two meta-analyses revealed that DPP-4 inhibitors are not associated with an increased risk of cardiovascular events or cancer compared to placebo or other antidiabetic agents, respectively.^{38,62}

Key Points within the Medication Class

- According to Current Clinical Guidelines:⁷⁰⁻⁷⁵
 - According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone of most antidiabetic treatment regimens.
 - Additionally, patients with a high glycosylated hemoglobin (HbA_{1c}) will likely require combination or triple therapy in order to achieve glycemic goals.
 - At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered.
 - The dipeptidyl peptidase-4 (DPP-4) inhibitors are recommended as a potential second-line treatment option to be added in combination with metformin in patients not achieving glycemic goals.
 - Clinical guidelines note a lower rate of hypoglycemia and an established efficacy and safety profile when used in combination with metformin as advantages associated with the DPP-4 inhibitors compared to other classes of antidiabetic agents.
 - Patients who are not appropriate for initial therapy with metformin, may be initiated on another oral antidiabetic agent, such as a sulfonylurea/glinide, pioglitazone, or a DPP-4 inhibitor, and in occasional cases where weight loss is seen as an essential aspect of

therapy, initial therapy with an incretin mimetic may be useful. Among all current clinical guidelines, preference of one DPP-4 inhibitor over another is not stated.

• Other Key Facts:

- All single-entity agents are available for once-daily dosing.
- Single-entity linagliptin is the only agent within the class that does not require renal and hepatic dosing.
- The metformin component in certain fixed-dose combination products requires caution in patients with renal and hepatic dysfunction.
- Fixed-dose combination product of sitagliptin/simvastatin has a pregnancy category of X and is associated with several drug interactions due to the simvastatin component.
- The DPP-4 inhibitors are associated with low risk of hypoglycemia and is weight neutral when used as monotherapy.
- DPP-4 inhibitors improve the function of β cells in the pancreas.

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Therapeutic Class Review Phosphorus Depleters

Therapeutic Class

- Overview/Summary:** 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 (CaxP) product, is associated with an increased risk of vascular, valvular and other soft-tissue calcification in patients with CKD. The two principal modalities used to control serum phosphorus levels in patients with CKD include restricting dietary phosphorus intake and the administration of 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 different phosphorus binders that are currently available; however, the class can be divided into two subcategories: calcium- and non-calcium-containing products.¹⁻⁴ In general, calcium-containing phosphorus binders (Eliphos[®], PhosLo[®], Phoslyra[®]) are associated with higher serum calcium and lower serum parathyroid hormone levels compared to the non-calcium-containing products. Increased serum calcium levels leads to hypercalcemia and also increases the risk of vascular calcification and arterial disease in CKD patients.⁴ As a result, these products are typically avoided in CKD patients with hypercalcemia or severe vascular calcification.²⁻⁴ The available non-calcium-containing phosphorus binders include sevelamer, available in two salt forms (hydrochloride [Renagel[®]] and carbonate [Renvela[®]]), and lanthanum carbonate (Fosrenol[®]). These products are typically reserved for use in CKD patients with hypercalcemia, or as adjunct to a regimen supplying the maximum allotted dose of elemental calcium from calcium-containing phosphorus binders.¹⁻⁴ The sevelamer hydrochloride salt was the initial sevelamer formulation developed; however, because of the incidence of metabolic acidosis associated with its use, a new, buffered formulation was created. The newer, sevelamer carbonate formulation will most likely be thought of as the preferred formulation of sevelamer because it does not lower a patient's bicarbonate level and does not result in the development of metabolic acidosis. An advantage to the use of lanthanum carbonate is a decrease in the pill burden compared to other products.⁴

Table 1. Current Medications Available in the Class⁵⁻¹⁰

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Calcium acetate (Eliphos [®] *, PhosLo [®] *, Phoslyra [®])	Control hyperphosphatemia in end stage renal failure. Reduce Phosphate with End Stage renal disease (Phoslyra [®]).	Capsule: 667 mg Oral solution: 667 mg/5 mL Tablet: 667 mg	a
Lanthanum carbonate (Fosrenol [®])	Reduce phosphate with end stage renal disease.	Tablet, chewable: 250 mg 500 mg 750 mg 1,000 mg	-
Sevelamer carbonate (Renvela [®])	Control serum phosphorus in patients with chronic kidney disease on dialysis.	Powder for oral suspension: 0.8 g 2.4 g Tablet: 800 mg	a

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Sevelamer hydrochloride (Renagel®)	Control serum phosphorus in patients with chronic kidney disease on dialysis. [†]	Tablet: 400 mg 800 mg	-

*Generic available in at least one dosage form or strength.

† The safety and efficacy of sevelamer hydrochloride in chronic kidney disease patients who are not on dialysis have not been studied.

Evidence-based Medicine

- The available evidence supports the hypothesis that all of the phosphorus binders (or phosphorus depleters) are efficacious in controlling serum phosphorus levels.¹⁰⁻⁴⁸ In general, the true benefits of phosphorus lowering with respect to hard clinical outcomes have not been established, and most clinical trials evaluate surrogate endpoints. In addition, due to ethical concerns regarding a prolonged lack of appropriate treatment, most trials evaluating the newer phosphorus binders against placebo have been short term, with longer trials using calcium-containing binders as the comparator.¹
- No prospective trials have specifically examined the benefits of targeting different phosphorus levels to determine the effect on patient-level endpoints. Epidemiological data suggests that phosphorus levels above the normal range are associated with increased morbidity and mortality.¹
- The results of a recent Cochrane Systematic Review by Navaneethan and colleagues demonstrated that there was no statistically significant reduction in all-cause mortality when patients received sevelamer hydrochloride compared to those receiving calcium-based phosphate binders (relative risk, 0.73; 95% confidence interval, 0.46 to 1.16). No comparison of lanthanum carbonate to calcium-containing salts was made.⁴⁶
- Two meta-analysis have been published reviewing the clinical trials of the phosphate binders.^{47,48} Tonelli et al compared sevelamer products to any other therapy or placebo in patients with ESRD, on dialysis or who had had a kidney transplant. The pooled analysis showed that phosphate levels with sevelamer was similar or slightly higher than with calcium-based phosphate binders by 0.12 mmol/L (95% CI, 0.05 to 0.19). However, the overall weighted mean difference in serum calcium was significantly lower with sevelamer therapy (0.10 mmol/L; 95% CI, -0.12 to -0.07).⁴⁷ Jamal et al evaluated all-cause mortality and compared calcium-based phosphate binders to non-calcium phosphate binders in patients with chronic kidney disease. The results of this meta-analysis showed that patients randomly assigned to non-calcium-based phosphate binders had a statistically significant 22% reduction in all-cause mortality compared with those randomly assigned to calcium-based phosphate binders (RR,0.78; 95% CI, 0.61 to 0.98). When non-randomized trials were added to the pooled analysis, the reduction in all-cause mortality was 13% (RR,0.87; 0.77 to 0.97) in favor of non-calcium-based phosphate binders.⁴⁸

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - Currently available evidence supports the hypothesis that all of the phosphorus binders are efficacious in controlling serum phosphorus levels. Furthermore, it is generally accepted that no one product is effective and acceptable to every patient.^{2,3}
 - Although treatment guidelines recommend serum phosphorus levels to be maintained within or slightly above the normal range (depending on chronic kidney disease [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.
 - 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.¹
 - Combination therapy, with multiple binders, may also be an option in order to control serum phosphorus levels while minimizing the side effects associated with any specific binder.^{2,3}

- Phosphorus binders should be utilized in patients with CKD Stages 3 to 5D who cannot adequately maintain serum phosphorus levels within the normal range with dietary phosphorus restriction.¹⁻³
- Choice of product should take into account the Stage of CKD, the presence of other components of CKD-Mineral and Bone Disorder, concomitant therapies and adverse event profiles.¹

Other Key Facts:

- Currently, the calcium-containing products (Eliphos[®], PhosLo[®]) are available generically in tablet and capsule formulations along with sevelamer carbonate tablets.
- Calcium acetate (Phoslyra[®]) is available as an oral solution, and sevelamer carbonate (Renvela[®]) is available as oral powder for suspension.^{7,9}
- Lanthanum, and sevelamer carbonate/hydrochloride are contraindicated in patients with bowel obstruction, while calcium acetate is contraindicated in hypercalcemia⁵⁻¹⁰

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Therapeutic Class Overview Ophthalmic Antihistamines

Therapeutic Class

Overview/Summary:

All of the ophthalmic antihistamines listed in Table 1 are Food and Drug Administration (FDA)-approved for the prevention or treatment of the signs and symptoms of allergic conjunctivitis.¹⁻¹¹ Ketotifen (Alaway[®], Zaditor[®]) is also indicated for the temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair and dander.^{6,7} Allergic conjunctivitis is the most common form of ocular allergy. Itching manifests as the primary symptom; however, other common symptoms include ocular burning, chemosis, conjunctival and eyelid edema, hyperemia, photophobia and tearing.¹² Symptoms usually occur in both eyes, yet one eye may be affected more than the other.¹² Vernal conjunctivitis is a severe form of allergic conjunctivitis that may involve the cornea.¹² None of the ophthalmic antihistamines are FDA-approved for the treatment of vernal conjunctivitis. Following topical administration to the conjunctiva, ophthalmic antihistamines competitively bind histamine receptor sites to reduce itching and vasodilation.¹⁻¹¹ The ocular antihistamines are relatively selective for the histamine type 1 (H₁-antihistamine) receptor but may also inhibit the degranulation of mast cells, thereby limiting the release of inflammatory mediators such as histamine, eosinophil and neutrophil chemotactic factors.^{1-3,5-10} Emedastine (Emadine[®]) has only H₁-antihistamine activity.⁴ Ophthalmic antihistamines have demonstrated a faster onset of action compared to oral antihistamines and ophthalmic mast-cell stabilizers and they are all approved for use in children.¹⁻¹¹ The most common adverse events associated with these agents are ocular burning, stinging and headache.¹⁻¹¹ In general, drug interactions are limited due to low systemic bioavailability via the ocular route. The administration schedule for these products ranges from once daily to four times daily, with only alcaftadine (Lastacaft[®]) and olopatadine 0.2% (Pataday[®]) available for once daily use.^{1,9} Azelastine (Optivar[®]), epinastine (Elestat[®]) and ketotifen are available generically. Ketotifen is also available over-the-counter.¹⁵

Table 1. Current Medications Available in the Therapeutic Class¹⁻¹¹

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Alcaftadine (Lastacaft [®])	Allergic conjunctivitis [†]	Ophthalmic solution: 0.25% (3 mL)	-
Azelastine (Optivar [®])	Allergic conjunctivitis [†]	Ophthalmic solution: 0.05% (6 mL)	a
Bepotastine (Bepreve [®])	Allergic conjunctivitis [†]	Ophthalmic solution: 1.5% (5, 10 mL)	-
Emedastine (Emadine [®])	Allergic conjunctivitis [‡]	Ophthalmic solution: 0.05% (5 mL)	-
Epinastine (Elestat [®])	Allergic conjunctivitis [§]	Ophthalmic solution: 0.05% (5 mL)	a
Ketotifen (Alaway [®] , Zaditor [®])	Allergic conjunctivitis [§] , ocular itching	Ophthalmic solution: 0.025% (OTC, RX) (5, 10 mL)	a #
Olopatadine (Pataday [®] , Patanol [®])	Allergic conjunctivitis ^{†‡}	Ophthalmic solution: 0.1% (5 mL) 0.2% (2.5 mL)	-

OTC=over-the-count, RX=prescription

* Available generically in one dosage form or strength.

† For the treatment of ocular itching associated with allergic conjunctivitis.

‡ For the treatment of signs and symptoms of allergic conjunctivitis.

§ For the prevention of ocular itching associated with allergic conjunctivitis.

|| For the temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair and dander.

Product is also available over-the-counter in at least one dosage form or strength.

Evidence-based Medicine

- The ophthalmic antihistamines are significantly more effective compared to placebo for reducing the symptoms of allergic conjunctivitis including ocular itching and conjunctival redness.¹⁶⁻²⁰
- Limited head-to-head trials comparing olopatadine, azelastine and ketotifen have failed to consistently show the “superiority” of one ophthalmic antihistamine over another for the management of allergic conjunctivitis.²¹⁻²⁶
- A meta-analysis of four trials found that patients were 1.3 times more likely to perceive their treatment response as “good” with ophthalmic antihistamines compared to patients receiving pure ophthalmic mast-cell stabilizers; however, the difference was not statistically significant.²⁷
- The ophthalmic antihistamines have consistently demonstrated a greater improvement in allergy symptoms and/or patient comfort scores compared to ophthalmic mast-cell stabilizers and ocular vasoconstrictors; however, many of these trials were conducted using single doses of study medication (conjunctival allergen challenge model) in a small number of patients.²⁸⁻³⁸

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - Ophthalmic formulations of agents from the following classes are useful in treating allergic conjunctivitis: corticosteroids, vasoconstrictor/antihistamine combinations, antihistamines, nonsteroidal anti-inflammatories (NSAIDs), mast-cell stabilizers, antihistamine/mast-cell stabilizers and immunosuppressants.¹⁴
 - An over-the-counter (OTC) antihistamine/vasoconstrictor or second-generation topical histamine H₁-receptor antagonist is recommended for mild allergic conjunctivitis. No preference is given to any one OTC antihistamine/vasoconstrictor or antihistamine.³⁹
 - If the condition is frequently recurrent or persistent, use mast-cell stabilizers. No single mast-cell stabilizer is preferred over another.³⁹
 - Medications with antihistamine and mast-cell stabilizing properties may be utilized for either acute or chronic disease. No one antihistamine/mast-cell stabilizer is preferred over another.³⁹
 - If the symptoms are not adequately controlled, a brief course (one to two weeks) of low-potency topical corticosteroid may be added to the regimen. The lowest potency and frequency of corticosteroid administration that relieves the patient’s symptoms should be used because of the potential for adverse events with their protracted use (e.g., cataract formation and elevated intraocular pressure).^{14,39}
 - Ketorolac, a NSAID, is also Food and Drug Administration-approved for the treatment of allergic conjunctivitis.^{14,39}
- Other Key Facts:
 - Alcaftadine and emedastine are classified as pregnancy category B while the other agents in this class have a pregnancy category C rating.
 - Alcaftadine and olopatadine 0.2% are the only agents within the class that are approved for once daily use.
 - Ophthalmic formulations of azelastine, epinastine and ketotifen are available generically.
 - Ketotifen is also available over-the-counter.¹⁵

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Therapeutic Class Overview Topical Psoriasis Agents

Therapeutic Class

- Overview/Summary:** The focus of this review will be the topical agents used for the treatment of psoriasis.¹⁻⁹ These agents include the vitamin D analogs calcipotriene and calcitriol along with the retinoid tazarotene. Calcipotriene is also formulated with betamethasone in a combination product. Each of these medications are Food and Drug Administration (FDA) approved for the treatment of plaque psoriasis. Certain calcipotriene products also have the indication for treatment of scalp psoriasis. In addition to psoriasis, tazarotene is approved for the treatment of acne vulgaris, however its use for this indication will not be included in this review.¹⁻⁹ The exact mechanisms of action of the vitamin D analogs and topical retinoids is unknown. The vitamin D analogs are believed to involve the drug's ability to inhibit keratinocyte proliferation and stimulate keratinocyte differentiation.¹⁰ The activated tazarotene binds to all three members of the retinoic acid receptor (RAR) family: RAR α , RAR β , and RAR γ , but shows relative selectivity for RAR β , and RAR γ and may modify gene expression. The clinical significance of this is unknown.^{8,9}

Psoriasis is a common chronic skin disorder typically characterized by erythematous papules and plaques with a silver scale, although other presentations occur. Most cases are not severe enough to affect general health and are treated in the outpatient setting.¹⁰ The options for treatment are topical or systemic and depend on the severity of the disease. Mild-to-moderate disease can often be managed with topical agents, while patients with moderate-to-severe disease may need systemic therapy. Moderate-to-severe disease is usually considered to effect more than 5 to 10% of the body. Topical therapy help provide symptomatic relief, minimize required doses of systemic medications (if being used) and may also be psychologically cathartic for some patients.¹⁰ Treatment options for mild-to-moderate disease include topical corticosteroids, emollients, tar, topical retinoids and the vitamin D analogs. Most often, a combination of topical corticosteroids and either calcipotriene, calcitriol or tazarotene are prescribed.¹⁰ Many patients find that certain medications are very messy or difficult to apply. For scalp psoriasis, many patients prefer lotions, solutions, gels, foams, or sprays as vehicles as opposed to creams and ointments.¹⁰

Table 1. Medications Included Within the Therapeutic Class Review¹⁻⁹

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/ Strength	Generic Availability
Single-Entity Agents			
Calcipotriene (Calcitrene ^{®*} , Dovonex ^{®*} , Sorilux [®])	Treatment of plaque psoriasis (cream, ointment, foam) , Treatment of plaque psoriasis of the scalp (foam, solution)	Cream, Ointment, Solution: 0.005% Foam: 0.01%	a
Calcitriol (Vectical ^{®*})	Treatment of plaque psoriasis [†]	Ointment: 3 μ g/g	a
Tazarotene (Tazorac [®])	Treatment of plaque psoriasis [#] , Treatment acne vulgaris (0.1% cream/gel)	Cream: 0.05% 0.1% Gel: 0.05% 0.1%	-
Combination Products			
Calcipotriene/ betamethasone (Taclonex ^{®*} , Taclonex Scalp ^{®*})	Treatment of plaque psoriasis [‡] , treatment of plaque psoriasis of the scalp (suspension)	Ointment: 0.005%/0.064% Suspension: 0.005%/0.064%	a

*Generic is available in at least one dosage form or strength.

Evidence-based Medicine

- Clinical trials have consistently demonstrated the safety and efficacy of the topical psoriasis agents, calcipotriene, calcitriol and tazarotene either alone or in combination.¹⁴⁻⁵⁶
- Calcipotriene monotherapy is an effective and safe treatment for the management of psoriasis and studies have evaluated its effectiveness versus placebo, coal tar and betamethasone.¹⁴⁻¹⁹
 - Calcipotriene was also found to be safe and effective for the treatment of scalp psoriasis.²⁰⁻²²
- The combination of calcipotriene and betamethasone was more effective than placebo or monotherapy with either agent alone at treating the signs and symptoms of psoriasis.²³⁻³⁵
 - The efficacy combination calcipotriene and betamethasone was also seen when treating patients who had a diagnosis of scalp psoriasis.³⁷⁻⁴⁰
- Calcitriol has been shown to be an effective treatment option for patients with psoriasis.⁴¹⁻⁴⁵
- Tazarotene has been shown to be as effective as clobetasol and coal tar in several clinical trials.⁴⁶⁻⁴⁸
- There have been several head-to-head studies evaluating the safety and efficacy of these agents. When calcipotriene is compared to calcitriol as monotherapies or in combination with a corticosteroid, the results of trials regarding “superiority” are conflicting, but suggest that both agents are effective.⁵⁰⁻⁵³
 - One study found that calcitriol is better tolerated than the calcipotriene, with perilesional erythema ($P < 0.001$), perilesional edema ($P < 0.02$) and stinging/burning ($P < 0.001$) all less severe with calcitriol than with calcipotriol.⁵³
- Tazarotene plus mometasone was compared to calcipotriene monotherapy and was shown to be not significantly different in the percentage of patients achieving complete or almost complete clearance at any time during eight weeks of treatment.⁵⁴
 - Two other studies comparing calcipotriene to tazarotene were done and showed similar results.⁵⁵⁻⁵⁶

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - Potent corticosteroids are recommended as first-line treatment for mild/moderate plaque psoriasis they have well documented efficacy and well known safety profile.¹¹⁻¹²
 - For psoriasis not responsive to a potent steroid and treatment is required longer than four to eight weeks (depending on potency of steroid), topical vitamin D analogs, tazarotene and other agents such as coal tar can be used.
 - Special considerations need to be made depending on the location and severity of the disease. For areas of the face, flexures and genitals, which are highly sensitive to steroid atrophy, a short term of mild or moderate potency corticosteroids are recommended for a short period of time (two weeks maximum).¹¹
 - For moderate to severe plaque psoriasis requiring systemic therapy, topical agents can be used as an adjunctive therapy to help with the signs and symptoms of the disease.¹³
- Other Key Facts:
 - Tazarotene is currently the only agent with no generic available; although, calcipotriene foam (Sorilux[®]) is also only available as a branded medication.

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Therapeutic Class Overview Bisphosphonates

Therapeutic Class

- Overview/Summary:** Osteoporosis is the most common bone disease in humans and is characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to bone fragility and consequent susceptibility to fracture.¹ 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.² Utilizing a reference population of young healthy individuals is common when measuring BMD and is known as a T-score.¹ Fractures are the most clinically significant physical manifestation of postmenopausal osteoporosis and low bone mass is the primary indicator of fracture risk.³ Osteoporotic fractures commonly occur in the wrist, spine, or hip, and can result in complications such as chronic pain, disability, depression, or even death.¹ Osteoporosis and related fractures represent a significant public health and economic burden. The management of osteoporosis is intended to prevent initial or subsequent fractures by maximizing skeletal strength and/or minimizing skeletal trauma, as well as increase the patient's quality of life.³ The bisphosphonates are primarily Food and Drug Administration (FDA)-approved for the prevention and/or treatment of osteoporosis in postmenopausal women, in men, and in patients taking prolonged courses of glucocorticoids. Bisphosphonates inhibit osteoclast activity by binding to bone surfaces that are undergoing active bone resorption resulting in the impairment of the ability for osteoclasts to form the ruffled border, adhere to the bony surface, and produce the protons necessary to continue bone resorption.⁴⁻¹¹ In general, the bisphosphonates are available for oral once-daily, once-weekly, or once-monthly administration. Currently, alendronate (tablet), etidronate, and ibandronate (150 mg tablet) are the only bisphosphonates available generically. Current clinical guidelines recommend that all drugs FDA-approved for use in osteoporosis are appropriate treatment options, with the bisphosphonates having good quality evidence supporting their use for reducing the risk of vertebral, non-vertebral, and hip fractures. While not every guideline recommends a preferred medication and/or medication class, the bisphosphonates are generally recognized as first-line therapy for the prevention and treatment of osteoporosis, including postmenopausal and glucocorticoid-induced osteoporosis. At this time, evidence is insufficient to determine whether one bisphosphonates is "superior" to another.^{1,3,13-16} Bisphosphonates are the most widely used drugs for the management of Paget's disease.¹⁷

Table 1. Current Medications Available in Therapeutic Class⁴⁻¹¹

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Alendronate (Binosto [®]) Fosamax [®])	Prevention of osteoporosis in postmenopausal women (Fosamax [®]). Treatment of glucocorticoid-induced osteoporosis (Fosamax [®]). Treatment to increase bone mass in men with osteoporosis. Treatment of osteoporosis in postmenopausal women. Treatment of Paget's disease of bone (Fosamax [®]).	Effervescent tablet (Binosto [®]): 70 mg Solution (Fosamax [®]): 70 mg Tablet (Fosamax [®]): 5 mg 10 mg 35 mg 40 mg 70 mg	a (tablet)

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Etidronate (Didronel®)	Prevention and treatment of heterotopic ossification.* Treatment of Paget's disease of bone.	Tablet: 200 mg 400 mg	a
Ibandronate (Boniva®)	Prevention of osteoporosis in postmenopausal women (tablet). Treatment of osteoporosis in postmenopausal women.	Injection: Tablet: 150 mg	a
Risedronate (Actonel®, Atelvia®)	Prevention of glucocorticoid-induced osteoporosis (Actonel®). Prevention of osteoporosis in postmenopausal women (Actonel®). Treatment of glucocorticoid-induced osteoporosis (Actonel®). Treatment to increase bone mass in men with osteoporosis (Actonel®). Treatment of osteoporosis in postmenopausal women. Treatment of Paget's disease of bone (Actonel®).	Delayed-release tablet (Atelvia®): 35 mg Tablet (Actonel®): 5 mg 30 mg 35 mg 150 mg	a (tablet)
Bisphosphonates-Combination Products			
Alendronate/cholecalciferol (Fosamax Plus D®)	Treatment to increase bone mass in men with osteoporosis Treatment of osteoporosis in postmenopausal women	Tablet: 70 mg/2,800 IU 70 mg/5,600 IU	-

IU=international units

*Following total hip replacement or due to spinal cord injury.

Evidence-based Medicine

- Clinical trials have demonstrated safety and efficacy their respective Food and Drug Administration-approved indications.¹⁸⁻⁷⁶
- Head-to-head trials have not consistently demonstrated on one bisphosphonate to be more effective than another with regard to efficacy. Data from trials specifically examining fractures indicates that bisphosphonates are efficacious and significantly lower the risk, in both men and women, of developing fractures in both vertebral and non-vertebral areas, compared to placebo.^{16,22,29,33}
- Evidence suggests that alendronate results in greater increases on BMD when compared to risedronate. Trials also support that risedronate results in a greater reduction in the risk of non-vertebral and hip fractures when compared to alendronate.³⁵⁻³⁷
- There is data to support alendronate and risedronate having similar efficacy.^{20,42}
- Ibandronate has also been shown to reduce vertebral fractures more than alendronate and risedronate, in one trial, while another showed ibandronate to be similar in efficacy to alendronate. The included data also shows that alendronate and risedronate are effective in patients with glucocorticoid-induced osteoporosis.^{12-14,38,40}
- Risedronate delayed release once weekly was compared to risedronate instant release daily in a new trial and found to be non-inferior.⁷³
- Several recent studies suggest that higher doses with longer dosing intervals (monthly) increase adherence, without decreasing overall efficacy or increasing side effects.^{73,74}

- Few trials compare the efficacy of the bisphosphonates for the treatment of Paget's disease and glucocorticoid-induced osteoporosis. Three identified trials demonstrated that alendronate, risedronate, and tiludronate are more effective options than etidronate for the treatment of Paget's disease.^{64,67}
- Overall, the most common adverse events associated with bisphosphonates are related to the gastrointestinal tract.¹²⁻⁶⁸

Key Points within the Medication Class

- According to Current Clinical Guidelines:^{1,3,13-17}
 - All drugs Food and Drug Administration-approved for use in osteoporosis are recommended as appropriate treatment options.
 - While not every guideline recommends a preferred medication and/or medication class, the bisphosphonates are generally recognized as first-line therapy for the prevention and treatment of osteoporosis, including postmenopausal and glucocorticoid-induced osteoporosis.
 - At this time, evidence is insufficient to determine whether one bisphosphonate is "superior" to another.
 - Bisphosphonates have good quality evidence supporting their use for reducing the risk of vertebral, non-vertebral, and hip fractures.
- Other Key Facts:
 - Alendronate (tablet, solution), etidronate, and ibandronate (tablet, solution), and risedronate (150 mg tablet) are the bisphosphonates currently available generically.

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Therapeutic Class Overview

Selective Serotonin Reuptake Inhibitors

Therapeutic Class

- Overview/Summary:** Antidepressants are used in the management of a variety of psychiatric disorders including mood disorders, eating disorders, premenstrual dysphoric disorders and anxiety disorders. Anxiety disorders include generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, social anxiety disorder and posttraumatic stress disorder. A mood disorder is defined as a disturbance in mood that is severe enough to impair a person's social, academic or occupational functioning for a specific duration of time.¹ Major depressive disorder and dysthymic disorder are two examples of mood disorders. Some antidepressants have also been used in nonpsychiatric conditions, such as diabetic peripheral neuropathy and nocturnal enuresis in children.

Treatment for psychiatric disorders includes psychotherapy, pharmacotherapy or the combination of the two. The decision to implement psychotherapy is dependent upon patient willingness and severity of illness. Despite the variety of pharmacologic options available, all antidepressants appear to be equally efficacious for mood disorders. Therefore, initial treatment should depend on the individual's overall medical condition and current medication profile.² Pharmacology, tolerability and safety profiles differ among these classes and among individual agents. However, for all antidepressants, the Food and Drug Administration (FDA) requires manufacturers to include a black-box warning notifying prescribers of the potential for antidepressants to increase suicidal thoughts in children and adults.³

The antidepressants are categorized into six different American Hospital Formulary Service (AHFS) subclasses, including monoamine oxidase inhibitors (MAOIs), selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs), selective serotonin-reuptake inhibitors (SSRIs), serotonin modulators, tricyclic antidepressants (TCAs) and miscellaneous agents. The agents which make up these subclasses differ with respect to their FDA-approved indications, mechanism of action, pharmacokinetics, adverse events and drug interactions.

The SSRIs include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. These agents are believed to exert their effects through potentiating the serotonergic activity in the central nervous system.^{1-2,5-13} All but fluvoxamine are Food and Drug Administration (FDA)-approved for the treatment of major depressive disorder.¹⁻¹⁹

Table 1. Current Medications Available in the Therapeutic Class^{1-2,5-13}

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Citalopram (Celexa ^{®*})	Depression (includes major depressive disorder),	Solution: 10 mg/5 mL Tablet: 10 mg 20 mg 40 mg	a
Escitalopram (Lexapro ^{®*})	Depression (includes major depressive disorder), generalized anxiety disorder,	Solution: 5 mg/5 mL Tablet: 5 mg 10 mg	a

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Fluoxetine (Prozac [®] *, Prozac Weekly [®] *, Sarafem [®])	Bulimia nervosa, depression (includes major depressive disorder), obsessive-compulsive disorder, panic disorder, presmenstrual dysphoric disorder,	20 mg Capsule, immediate release: 10 mg 20 mg 40 mg Capsule, delayed release: 90 mg Solution: 20 mg/5 mL Tablet, immediate release: 10 mg 20 mg 60 mg	a
Fluvoxamine (Luvox [®] , Luvox CR)	Obsessive-compulsive disorder,	Capsule, extended release: 100 mg 150 mg Tablet: 25 mg 50 mg 100 mg	a
Paroxetine hydrochloride (Paxil [®] *, Paxil CR [®] *)	Depression (includes major depressive disorder), generalized anxiety disorder*, obsessive-compulsive disorder*, panic disorder, presmenstrual dysphoric disorder [†] , posttraumatic stress disorder*, social anxiety disorder	Suspension, oral: 10 mg/5 mL Tablet, immediate release: 10 mg 20 mg 30 mg 40 mg Tablet, sustained release: 12.5 mg 25 mg 37.5 mg	a
Paroxetine mesylate (Brisdelle [®] , Pexeva [®])	Depression (includes major depressive disorder), obsessive-compulsive disorder, panic disorder, vasomotor symptoms associated with menopause; (moderate to severe) [#]	Capsule, immediate- release: 7.5 mg Tablet: 10 mg 20 mg 30 mg 40 mg	-
Sertraline (Zoloft [®])	Depression (includes major depressive disorder), obsessive-compulsive disorder, panic disorder, presmenstrual dysphoric disorder, posttraumatic stress	Concentrate, oral: 20 mg/mL Tablet: 25 mg	a

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	disorder, social anxiety disorder	50 mg 100 mg	

*Instant release only

†Sustained release only

#Brisdelle® only; Brisdelle® is not indicated for the treatment of any psychiatric condition.

Evidence-based Medicine

- Clinical trials demonstrating the safety and efficacy of the serotonin and norepinephrine reuptake - inhibitors are outlined in Table 4.¹⁴⁻⁶⁹
- In one study which compared fluoxetine, imipramine and desipramine for duration of initial therapy, fluoxetine was taken for a longer period of time than desipramine or imipramine ($P < 0.001$ for either desipramine or imipramine).²⁰ Statistical comparisons between the two TCAs were not done but they were numerically similar. The difference in duration of therapy was due primarily to less tolerability of desipramine and imipramine. Only 9% of the patients switched from fluoxetine due to adverse events while 27% and 28% assigned to desipramine and imipramine respectively switched due to adverse events ($P < 0.001$ for both TCAs compared to fluoxetine).
- The overall length of antidepressant therapy (if the patient switched to another agent) was not different regardless of which agent was initiated first. In addition, response to medication as measured by the Hamilton Depression Rating Scale (HDRS) was equivalent.²¹
- One study comparing health care costs of fluoxetine versus imipramine and fluoxetine versus desipramine compared outpatient costs to primary care and to mental health. The authors found no difference in primary care visit cost in either comparison (fluoxetine versus desipramine; $P = 0.19$ and fluoxetine versus imipramine; $P = 0.98$). There was also no difference in mental health outpatient visit cost in either comparison group (fluoxetine versus desipramine; $P = 0.33$ and fluoxetine versus imipramine; $P = 0.73$).²³
- A meta-analysis evaluated venlafaxine compared to SSRIs in treatment of major depressive disorder. Using a random effect model showed that venlafaxine has statistically higher rates of achieving remission (odds ratio [OR], 1.13; 95% CI, 1.0 to 1.28; $P = 0.05$) and response (OR, 1.17; 95% CI, 1.03 to 1.34; $P = 0.02$). Subgroup analysis found that venlafaxine had a significantly better response rate than fluoxetine (OR, 1.28; 95% CI, 1.05 to 1.55; $P = 0.01$). There were no significant differences in response or remission between venlafaxine and other individual SSRIs. There was no significant difference in all cause discontinuation between venlafaxine and SSRIs (OR, 1.10; 95% CI, 0.97 to 1.25; $P = 0.15$). Venlafaxine had significantly higher discontinuation due to adverse events compared with SSRIs (OR, 1.41, 95% CI, 1.10-1.79, $P = 0.006$).³¹

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - National and international treatment guidelines for the treatment of depression state that selecting an agent should be driven by anticipated side effects, tolerability, patient preference, and quantity and quality of available clinical data, and that the effectiveness of antidepressants is usually comparable within and between medication classes.⁷⁰⁻⁷⁴
 - Guidelines also state that medications that can be considered first-line therapy for most patients include selective serotonin reuptake inhibitors (SSRIs), SNRIs, mirtazapine, or bupropion, while monoamine oxidase inhibitors (MAOIs) should be reserved for patients who are unresponsive to other available medications. These guidelines do not recommend one SSRI, SNRI or MAOI over another.⁷⁰⁻⁷¹
 - Antidepressants are recommended as first-line treatment for GAD, with the following agents considered treatment options: SSRIs, SNRIs, and nonsedating tricyclic antidepressants (TCAs).⁷⁵

- Other Key Facts:
 - Fluoxetine is the only agent within the class that carries indications for treating bulimia nervosa, while Brisdelle[®] (paroxetine mesylate) is the only SSRI that is FDA-approved for the treatment of vasomotor symptoms associated with menopause.
 - All of the SSRI products have a Black Box Warning regarding the potential for antidepressants to increase suicidal thoughts in children and young adults.¹⁻¹²

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Therapeutic Class Overview

Serotonin and Norepinephrine Reuptake Inhibitors

Therapeutic Class

- **Overview/Summary:** The antidepressants are approved to treat a variety of mental disorders, including anxiety disorders, depressive disorders, eating disorders (bulimia nervosa) and premenstrual dysphoric disorder.¹⁻² Anxiety disorders include agoraphobia, anxiety disorder due to another medical condition, generalized anxiety disorder, other specified anxiety disorder, panic disorder, selective mutism, separation anxiety disorder, social anxiety disorder or social phobia, specific phobia, substance/medication induced anxiety disorder and unspecified anxiety disorder.³⁻⁴ Some of the antidepressants are also approved to treat nonpsychiatric conditions, such as chronic musculoskeletal pain, diabetic peripheral neuropathy, fibromyalgia, insomnia, moderate to severe vasomotor symptoms associated with menopause, nocturnal enuresis and tobacco abuse.¹⁻²

The antidepressants are categorized into six different American Hospital Formulary Service (AHFS) subclasses, including monoamine oxidase inhibitors (MAOIs), selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs), selective serotonin-reuptake inhibitors (SSRIs), serotonin modulators, tricyclic antidepressants (TCAs) and miscellaneous agents. The agents which make up these subclasses differ with respect to their FDA-approved indications, mechanism of action, pharmacokinetics, adverse events and drug interactions.

The SNRIs include desvenlafaxine, duloxetine, levomilnacipran, milnacipran and venlafaxine. These agents are believed to exert their effects through potentiating the serotonergic and noradrenergic activity in the central nervous system.^{1-2,5-13} As a result, the SNRIs are used in the management of a variety of psychiatric disorders and all SNRIs are Food and Drug Administration (FDA)-approved for the treatment of major depressive disorder.^{1-2,5-13} The venlafaxine extended-release capsules are also indicated for the treatment of generalized anxiety disorder and panic disorder. Both extended-release formulations are also indicated for social anxiety disorder. In addition to major depressive disorder and generalized anxiety disorder, duloxetine is approved for the management of various pain syndromes including chronic musculoskeletal pain, fibromyalgia and neuropathic pain associated with diabetic peripheral neuropathy.^{1-2,11-13} Desvenlafaxine is the primary active metabolite of venlafaxine and is approved for once-daily dosing. Unlike venlafaxine, desvenlafaxine does not undergo metabolism through cytochrome P450 2D6, and is therefore safe to use with inhibitors of this isoenzyme.^{1-2,5-7} The adverse event profiles appear to be similar between the two agents.

Levomilnacipran is a new SNRI approved by the FDA for the treatment of major depressive disorder. Of note, levomilnacipran has shown to be twice as selective for norepinephrine as serotonin. In addition, levomilnacipran has demonstrated 10-fold higher selectivity for norepinephrine vs serotonin reuptake inhibition when compared to duloxetine, venlafaxine and desvenlafaxine.¹⁴⁻¹⁶ It is important to understand that despite the higher selectivity for norepinephrine reuptake inhibition, levomilnacipran has comparable binding potency at the norepinephrine reuptake pump to duloxetine, and a lower binding potency at the serotonin reuptake pump than duloxetine.¹⁷

Levomilnacipran is the more active enantiomer of milnacipran (Savella[®]), a medication FDA-approved for the treatment of fibromyalgia, a functionally impairing disease state. Levomilnacipran is approximately twice as potent for reuptake inhibition of norepinephrine compared to milnacipran, its racemic mixture.^{3,10}

Currently, venlafaxine is available generically in both immediate- and extended-release formulations, while desvenlafaxine and duloxetine are only available as branded products.^{5,6}

Table 1. Current Medications Available in the Therapeutic Class^{1-2,5-13}

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Desvenlafaxine succinate (desvenlafaxine ER, Pristiq [®] , Khedezla [®])	Treatment of major depressive disorder	Extended-release tablet: 50 mg 100 mg	-
Duloxetine (Cymbalta [®])	Management of chronic musculoskeletal pain*; management of fibromyalgia; management of neuropathic pain associated with diabetic peripheral neuropathy; treatment of generalized anxiety disorder; treatment of major depressive disorder	Delayed-release capsule: 20 mg 30 mg 60 mg	-
Levomilnacipran (Fetzima [®])	Treatment of major depressive disorder	Extended-release capsules: 20 mg 40 mg 80 mg 120 mg	-
Levomilnacipran (Fetzima [®])	Management of fibromyalgia	Tablet: 12.5 mg 25 mg 50 mg 100 mg	-
Venlafaxine (Effexor [®] , Effexor XR [®] , venlafaxine ER)	Treatment of generalized anxiety disorder (extended-release capsule); treatment of major depressive disorder (extended-release capsule, extended-release tablet, tablet); treatment of panic disorder, with or without agoraphobia (extended-release capsule); treatment of social anxiety disorder (extended-release capsule)	Extended-release capsule (Effexor XR [®]): 37.5 mg 75 mg 150 mg Extended-release tablet: 37.5 mg 75 mg 150 mg 225 mg Tablet: 25 mg 37.5 mg 50 mg 75 mg 100 mg	a

ER, XR=extended-release

*This has been established in studies of patients with chronic low back pain and chronic pain due to osteoarthritis.

Evidence-based Medicine

- Clinical trials demonstrating the safety and efficacy of the serotonin and norepinephrine reuptake inhibitors are outlined in Table 4.¹⁴⁻¹¹¹
- Desvenlafaxine, duloxetine and venlafaxine have been shown to be efficacious for the management of major depressive disorder, as measured by improvements in Hamilton Rating Scale for Depression-17 and Montgomery-Åsberg Depression Rating Scale scores, when compared to

placebo.^{14-33,38} Duloxetine and venlafaxine have also been shown to be comparable to other antidepressants for the treatment of major depressive disorder.⁴¹⁻⁷² A limited number of head-to-head trials comparing duloxetine and venlafaxine have yet to demonstrate that one of these agents is more efficacious than the other for the treatment of major depressive disorder.⁴²⁻⁴³ Trials comparing desvenlafaxine to an active comparator have not been conducted.

- Results from several clinical trials demonstrate the efficacy of duloxetine in reducing pain severity in adults with fibromyalgia when compared to placebo.⁷³⁻⁷⁷ In addition, results from several clinical trials demonstrate the efficacy of duloxetine in reducing pain severity in adults with fibromyalgia when compared to placebo.⁷⁸⁻⁸⁰
- Duloxetine is consistently more effective compared to placebo in alleviating pain, improving functional outcomes and improving quality of life in patients with diabetic peripheral neuropathic pain. Specifically, duloxetine is associated with significant improvements in Brief Pain Inventory, Clinician and Patient Global Impression of Improvement and Severity, Short Form-36 Health Survey and Euro Quality of Life assessment scores. Commonly reported adverse events in patients receiving duloxetine include nausea, somnolence, anorexia and dysuria.⁹⁷⁻¹⁰³

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - National and international treatment guidelines for the treatment of depression state that selecting an agent should be driven by anticipated side effects, tolerability, patient preference, and quantity and quality of available clinical data, and that the effectiveness of antidepressants is usually comparable within and between medication classes.¹¹²⁻¹¹⁵
 - Guidelines also state that medications that can be considered first-line therapy for most patients include selective serotonin reuptake inhibitors (SSRIs), SNRIs, mirtazapine, or bupropion, while monoamine oxidase inhibitors (MAOIs) should be reserved for patients who are unresponsive to other available medications. These guidelines do not recommend one SSRI, SNRI or MAOI over another.¹¹²⁻¹¹⁵
 - Antidepressants are recommended as first-line treatment for GAD, with the following agents considered treatment options: SSRIs, SNRIs, and nonsedating tricyclic antidepressants (TCAs).¹¹⁶⁻¹¹⁸
 - For the treatment of neuropathic pain, the SNRIs are recommended as initial therapy along with TCAs and anticonvulsants.¹²⁴⁻¹²⁸
- Other Key Facts:
 - Duloxetine (Cymbalta[®]) is the only agent within the class that carries indications for treating fibromyalgia, chronic musculoskeletal pain and painful diabetic neuropathy.
 - All of the SNRI products have a Black Box Warning regarding the potential for antidepressants to increase suicidal thoughts in children and young adults.¹⁻¹²

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Therapeutic Class Overview **Long-acting Opioids**

Therapeutic Class

- **Overview/Summary:** Pain is one of the most common and debilitating patient complaints, with persistent pain having the potential to lead to functional impairment, disability, psychological distress and sleep deprivation. Pain can be categorized as being either nociceptive or neuropathic, and the treatments for each are specific. Nociceptive pain is caused by damage to tissues and can further be divided into somatic (pain arising from injury to body tissues) and visceral pain (pain arising from the internal organs). Visceral pain is often described as poorly localized, deep, dull, and cramping. In contrast, neuropathic pain arises from abnormal neural activity secondary to disease, injury, or dysfunction of the nervous system.¹ Pharmacologic therapy should not be the sole focus of pain treatment; however, it is the most widely utilized option to manage chronic pain. Major pharmacologic categories used in the management of pain include nonopioid analgesics, tramadol, opioid analgesics, α -2 adrenergic agonists, antidepressants, anticonvulsants, muscle relaxants, N-methyl-d-aspartate receptor antagonists, and topical analgesics. Combining pharmacologic therapies may result in improved analgesia, and because lower doses of each agent can be used, patients may experience fewer treatment-emergent adverse events. Response to pharmacologic therapies will vary between individual patients, and currently no one approach has been demonstrated to be appropriate for all patients. Treatment decisions are largely based on the type of pain (e.g., neuropathic, nociceptive), comorbidities, concurrent medications, pharmacokinetic/pharmacodynamic properties of the agent and anticipated adverse events.²

As a class, opioid analgesics encompass a group of naturally occurring, semisynthetic, and synthetic drugs that stimulate opiate receptors and effectively relieve pain without producing loss of consciousness.³⁻²² These agents primarily produce intense analgesia via their agonist actions at mu receptors, which are found in large numbers within the central nervous system. The binding of these agents to mu receptors produces a variety of other effects including bradycardia, sedation, euphoria, physical dependence, and respiratory depression. Key safety concerns associated with the opioid analgesics include respiratory depression, and to a lesser degree, circulatory depression.^{2,23} The long-acting opioids are primarily utilized in the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time.³ Long-acting opioids are available in a variety of different dosage forms, and currently several agents are available generically.³

OxyContin[®] (oxycodone extended-release) has received increased attention regarding overuse, abuse, and diversion, but oxycodone itself does not appear to have a greater dependence or abuse liability compared to the other available opioids.²⁴ The Food and Drug Administration (FDA) approved a new OxyContin[®] formulation in April of 2010 that was designed to discourage misuse and abuse. The reformulated OxyContin[®] is intended to prevent the medication from being cut, broken, chewed, crushed, or dissolved to release more medication. The FDA states that the new formulation may result in less risk of overdose due to tampering, and will likely result in less abuse by snorting or injection, but the agent can still be abused or misused by ingesting larger than recommended doses. The manufacturer is required to conduct a postmarketing study evaluating the extent to which the new formulation reduces abuse and misuse.²⁵ Similarly, a new, crush-resistant formulation of Opana ER[®] (oxymorphone extended-release) was approved in December 2011; however, the manufacturer notes that it has not been established that the new formulation is less subject to misuse, abuse, diversion, overdose or addiction.²⁶

In October 2013, the FDA approved the first sole entity hydrocodone product in an extended-release formulation known as Zohydro ER[®] (hydrocodone) for the treatment of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate.^{20,25} The approval of Zohydro ER[®] (hydrocodone) was somewhat controversial for a

number of reasons. The advisory panel to the Food and Drug Administration (FDA) voted 11 to 2 against the approval of Zohydro ER[®] (hydrocodone), due in large part to growing concerns regarding opioid abuse and the product's lack of an abuse deterrent mechanism. Despite the advisory committee vote, Zohydro ER[®] (hydrocodone extended-release) was approved based on an FDA Division Director's rationale that the benefit-risk balance for Zohydro ER[®] (hydrocodone extended-release) and other non-abuse deterrent opioid analgesics is still favorable for patients requiring chronic opioid therapy. In addition, the case was made for having another alternative long-acting opioid for patients that cannot tolerate other options or who are on an opioid rotation.²⁷

Xartemis XR[®] (oxycodone/acetaminophen extended-release) differs from other long-acting pain medications in that it is indicated for the treatment of acute pain severe enough to require opioid treatment for which alternate treatments are inadequate or not tolerated.²¹ Xartemis XR[®] is formulated for a biphasic release, and each tablet includes an immediate-release layer and an extended-release layer. When two tablets are administered together, the immediate-release layers allow for 3.75 mg of oxycodone and 325 mg acetaminophen to be released. The extended-release layers swell in fluid, and gradually release the remaining 11.25 mg of oxycodone and 325 mg of acetaminophen.²⁸

Table 1. Current Medications Available in the Therapeutic Class⁴⁻²¹

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Buprenorphine (Butrans [®])	The management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time	Transdermal system: 5 µg/hour 10 µg/hour 20 µg/hour	-
Fentanyl (Duragesic ^{®*})	The management of persistent, moderate to severe chronic pain that requires continuous, around-the-clock opioid administration for an extended period of time, and cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids	Transdermal system: [‡] 12 µg/hour 25 µg/hour 50 µg/hour 75 µg/hour 100 µg/hour	a
Hydrocodone (Zohydro [®])	The management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	Extended release capsules: 10 mg 15 mg 20 mg 30 mg 40 mg 50 mg	-
Hydromorphone (Exalgo [®])	The management of moderate to severe pain in opioid tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time	Extended release tablets: [‡] 8 mg 12 mg 16 mg 32 mg	a
Methadone (Dolophine ^{®*} , Methadose ^{®*})	Treatment of moderate to severe pain not responsive to non-narcotic analgesics, for detoxification treatment of opioid addiction (heroin or other morphine-like drugs) and for maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in	Concentrate (sugar-free available): 10 mg/mL Dispersible tablet:	a

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	conjunction with appropriate social and medical services	40 mg Solution: 5 mg/5 mL 10 mg/5 mL Tablet: 5 mg 10 mg	
Morphine sulfate (Avinza [®] , Kadian [®] *, MS Contin [®] *, Oramorph SR [®])	For the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time (Avinza [®]), for the relief of moderate to severe pain requiring continuous, around the clock opioid therapy for an extended period of time (Kadian [®] and MS Contin [®]) and for the relief of pain in patients who require opioid analgesics for more than a few days (Oramorph SR [®])	Extended release capsules: 10 mg [§] 20 mg [§] 30 mg 45 mg 50 mg [§] 60 mg ^{+,¶} 75 mg 80 mg [§] 90 mg ^{+,} 100 mg ^{+,§} 120 mg ^{+,} 200 mg ^{+,§} Extended release tablets: 15 mg 30 mg 60 mg 100 mg [§] 200 mg [§] Tablet (Oramorph SR [®]) 15 mg 30 mg 60 mg 100 mg	a
Oxycodone (OxyContin [®] *)	For the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time	Extended release tablet: 10 mg 15 mg [#] 20 mg 30 mg [#] 40 mg 60 mg ^{+,#} 80 mg ⁺	a [†]
Oxymorphone (Opana [®] ER)	For the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time	Extended release tablet: 5 mg 7.5 mg 10 mg 15 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		20 mg 30 mg 40 mg	
Tapentadol (Nucynta ER®)	For the management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time and treatment of neuropathic pain associated with diabetic peripheral neuropathy in adults	Extended release tablet: 50 mg 100 mg 150 mg 200 mg 250 mg	-
Combination Products			
Morphine sulfate/ naltrexone	For the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time	Extended release capsule: 20 mg/0.8 mg 30 mg/1.2 mg 50 mg/2 mg 60 mg/2.4 mg 80 mg/3.2 mg 100 mg/4 mg [†]	-
Oxycodone/ acetaminophen	For the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate	Extended release tablet: 7.5 mg/325 mg	-

*Generic is available in at least one dosage form or strength.

†Generic availability is sporadic and does not include all strengths.

‡For use in opioid-tolerant patients only.

§Kadian® only.

|| Avinza® only.

¶ Avinza® 60 mg extended-release capsules are for use in opioid-tolerant patients only.

#OxyContin® only.

Evidence-based Medicine

- In one trial, treatment with the buprenorphine transdermal system significantly improved the average pain score over 24 hours at week 12 compared to treatment with buprenorphine 5 µg/hour (P<0.001 for both). In a second trial, treatment with either 10 or 20 µg/hour of buprenorphine transdermal system resulted in a treatment difference favoring buprenorphine (95% confidence interval [CI], -1.02 to -0.14; P=0.01) compared to placebo. Two other trials failed to show efficacy for buprenorphine transdermal system in patients with low back pain and osteoarthritis, respectively against oxycodone/acetaminophen and oxycodone immediate-release. In another trial, treatment with either buprenorphine transdermal system 20 µg/hour or oxycodone immediate-release was compared to treatment with buprenorphine transdermal system 5 µg/hour in patients with osteoarthritis. The decrease in the average pain score over the last 24 hours was greater in the buprenorphine transdermal system 20 µg/hour and oxycodone immediate-release treatment groups compared to the buprenorphine transdermal system 5 µg/hour group, however the difference was not significant (P values not reported).^{4,29}
- The effectiveness of fentanyl in relieving pain appears to be similar to that of morphine sulfate sustained-release for the treatment of cancer and noncancer pain, and chronic lower back pain. Compared to morphine sulfate sustained-release, fentanyl transdermal systems appear to be associated with less constipation.²⁹⁻³¹

- A trial comparing hydrocodone extended-release capsules to placebo in patients with moderate to severe chronic low back pain demonstrated hydrocodone extended-release had a lower mean change from baseline in pain intensity scores compared to placebo at 12 weeks ($P=0.008$). In addition, there was a significantly higher amount of treatment responders in the hydrocodone extended-release group compared to the placebo group ($P<0.001$) at the end of treatment, and subject global assessment of medication scores increased from baseline significantly in the hydrocodone-extended release group compared to placebo ($P<0.0001$).³²
- In one trial, hydromorphone extended-release demonstrated greater efficacy in the treatment of lower back pain with regard to reducing pain intensity ($P<0.001$) and pain scores ($P<0.01$) compared to placebo.³¹ In a noninferiority analysis of a hydromorphone extended-release compared to oxycodone extended-release, two agents provided similar pain relief in the management of osteoarthritic pain.³⁴
- Methadone has demonstrated a greater efficacy over placebo for the treatment of nonmalignant neuropathic pain and similar efficacy compared to slow-release morphine sulfate for the treatment of cancer pain.^{35,36}
- A trial comparing different long-acting formulations of morphine sulfate for the treatment of osteoarthritis pain demonstrated that both Avinza[®] (morphine sulfate extended-release) and MS Contin[®] (morphine sulfate controlled-release) significantly reduced pain from baseline ($P\leq 0.05$ for both). Both treatments also reduced overall arthritis pain intensity, and achieved comparable improvements in physical functioning and stiffness. Each treatment significantly improved certain sleep parameters compared to placebo.³⁷ In a crossover trial, morphine sulfate (MS Contin[®]) was compared to fentanyl transdermal systems, and more patients preferred fentanyl transdermal systems ($P<0.001$), and reported on average, lower pain intensity scores than morphine sulfate phase ($P<0.001$).³⁸
- Morphine/naltrexone has demonstrated significantly better pain control compared to placebo in patients with osteoarthritis pain.³⁹
- Oxycodone controlled-release has demonstrated significantly greater efficacy compared to placebo for the treatment of neuropathic pain and chronic refractory neck pain.⁴⁰⁻⁴² For the treatment of cancer pain, no significant differences were observed between oxycodone controlled-release and morphine sulfate controlled-release in reducing pain intensity. The average number of rescue doses used within a 24 hour period was significantly less with morphine sulfate controlled-release ($P=0.01$), and the incidence of nausea and sedation were similar between treatments.⁴³
- In one trial, oxycodone/acetaminophen extended-release demonstrated greater efficacy than placebo, as measured by summed pain intensity difference from baseline to 48 hours after surgery (114.9 vs 66.9, respectively, $P<0.001$).⁴⁴
- Oxymorphone extended-release has produced similar mean daily pain intensity scores compared to both morphine sulfate and oxycodone controlled-release for the treatment of chronic cancer pain.^{45,46} The average scheduled daily dose of study drug and average total daily dose decreased after patients crossed over to oxymorphone extended-release from morphine sulfate or oxycodone controlled-release. No significant changes were observed in visual analog pain scores, quality of life domains, or quality of sleep in any of the treatment groups.⁴⁷ In another trial, oxymorphone extended-release demonstrated greater efficacy for the relief of osteoarthritis pain compared to placebo.⁴⁸
- In a 12-week active comparator and placebo-controlled trial, significant pain relief was achieved with tapentadol extended-release compared to placebo (least squares mean difference, -0.7; 95% CI, -1.04 to -0.33) at week 12. The average pain intensity rating at endpoint with oxycodone controlled-release was reduced significantly compared to placebo for the overall maintenance period (least squares mean difference vs placebo, -0.3), but was not significantly lower at week 12 (least squares mean, -0.3; P values not reported).⁴⁹ In a, placebo-controlled and active comparator trial in adults with moderate to severe low back pain, improvements in average pain intensity scores occurred with tapentadol extended-release and oxycodone controlled-release relative to placebo ($P<0.001$).⁵⁰ Schwartz et al evaluated tapentadol extended-release among adults with painful diabetic peripheral neuropathy. The least squares mean change in average pain intensity at week 12 was 1.4 in the placebo group, indicating a worsening in pain intensity, and 0.0 in the tapentadol extended-release group, indicating no change in pain intensity, (least squares mean difference, -1.3; 95% CI, -1.70 to -0.92; $P<0.001$).⁵¹

- Methadone is the only long-acting narcotic that is Food and Drug Administration-approved for the management of opioid addiction; however, in one study slow-release morphine sulfate demonstrated noninferiority to methadone in terms of completion rate for the treatment of opioid addiction (51 vs 49%).⁵²

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - Patients with pain should be started on acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). If sufficient pain relief is not achieved, patients should be escalated to a “weak opioid” and then to a “strong opioid”, such as morphine.^{52,53}
 - Opioid selection, initial dosing, and titration should be individualized according to the patient’s health status, previous exposure to opioids, attainment of therapeutic goals, and predicted or observed harms. There is insufficient evidence to recommend short-acting vs long-acting opioids, or as needed vs around-the-clock dosing of opioids.⁵³
 - Patients with chronic persistent pain controlled by stable doses of short-acting opioids should be provided with round-the-clock extended-release or long-acting formulation opioids with provision of a ‘rescue dose’ to manage break-through or transient exacerbations of pain.⁵²
 - Opioids with rapid onset and short duration are preferred as rescue doses. The repeated need for rescue doses per day may indicate the necessity to adjust the baseline treatment.^{52,53}
 - In a patient who has not been exposed to opioids in the past, morphine is generally considered the standard starting drug of choice.⁵²
 - Pure agonists (such as codeine, fentanyl, oxycodone, and oxymorphone) are the most commonly used medications in the management of cancer pain. Opioid agonists with a short half-life are preferred and include fentanyl, hydromorphone, morphine, and oxycodone.⁵²
 - Meperidine, mixed agonist-antagonists, and placebos are not recommended for cancer patients. Meperidine is contraindicated for chronic pain especially in patients with impaired renal function or dehydration.⁵²
 - In patients who require relatively high doses of chronic opioid therapy, clinicians should evaluate for unique opioid-related adverse events, changes in health status, and adherence to the chronic opioid therapy treatment plan on an ongoing basis, and consider more frequent follow-up visits.^{52,53}
- Other Key Facts:
 - All of the long-acting opioids are classified as Schedule II controlled substances by the Food and Drug Administration (FDA), with the exception of buprenorphine transdermal systems which are a Schedule III controlled substance.⁴⁻²¹ Buprenorphine is a partial opiate agonist, and the transdermal system is the first and only seven-day transdermal opioid approved by the FDA.⁴
 - On July 9, 2012, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for all long-acting opioids. The program will require companies who manufacture long-acting opioids to make training regarding proper prescribing practices available for health care professionals who prescribe these agents, as well as distribute educational materials to both prescribers and patients on the safe use of these agents.⁵⁴
 - The new REMS program is part of the national prescription drug abuse plan announced by the Obama Administration in 2011 to combat prescription drug misuse and abuse.⁵⁴

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F. Duragesic® (fentanyl transdermal) Patches

Therapeutic Class: Analgesics, Narcotic

Last Reviewed by the DUR Board: July 30, 2009

Transdermal fentanyl, a narcotic agonist analgesic, is indicated in the management of chronic pain in patients requiring continuous opioid analgesia for pain that cannot be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics or PRN dosing with short-acting opioids. Transdermal fentanyl is subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the Social Security Act and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

Because serious or life-threatening hypoventilation could occur, fentanyl transdermal is contraindicated in management of acute or postoperative pain, mild or intermittent pain responsive to PRN or non-opioid therapy, or in doses exceeding 25 mcg/hr at the initiation of opioid therapy. Therefore, patients must meet the following two criteria in order to gain prior authorization approval:

- a. Patient cannot be managed by lesser means such as acetaminophen-opioid combinations, nonsteroidal analgesics, or PRN dosing with short-acting opioid.
- b. Patient requires continuous opioid administration.

In addition the following guideline applies:

- c. Do not authorize if on long-acting narcotics. If recipient is switching to fentanyl and has a prior authorization for a long-acting narcotic, discontinue the prior authorization for the long-acting narcotic and inform the prescriber.

2. Prior Authorizations

Prior approval will be given for a six month time period.

Prior Authorization forms are available at:

<http://www.medicaid.nv.gov/providers/rx/rxforms.aspx>

DIVISION OF HEALTH CARE FINANCING AND POLICY

MEDICAID SERVICES MANUAL

Q. Long-Acting Narcotics

Therapeutic Class: Analgesics, Narcotic

Last Reviewed by DUR Board: July 30, 2009

Long-Acting Narcotics are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the Social Security Act and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

Indications: Management of moderate-to-severe pain when continuous around-the-clock analgesic is needed for an extended period of time. Medications:

a. Oxycontin (including generic); MS Contin (including generic); Avinza; Kadian; Oramorph.

1. No prior authorization is required for diagnosis of terminal cancer.

b. Please Note: The use of Long – Acting Narcotics for acute/short term treatment of pain not within the quantity limits will not be approved.

Approval will be for a three month time limit.

2. Prior Authorization Guidelines:

The prior authorization must be initiated by the prescriber. The approved Payment Authorization Request (PAR) must be available if requested.

Prior Authorization forms are available at:

<http://www.medicaid.nv.gov/providers/rx/rxforms.aspx>

Therapeutic Class Overview

Sodium-glucose co-transporter 2 (SGLT2) Inhibitors

Therapeutic Class

- Overview/Summary:** Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a novel class of oral antidiabetic agents recently approved by the Food and Drug Association (FDA). The kidneys play a pivotal role in controlling plasma glucose concentration; reabsorbing nearly all plasma glucose in the proximal tubules and preventing glucose excretion in patients with normal glucose-tolerance. Approximately 90% of the filtered renal glucose is done in the early convoluted segment of the proximal tubule and is facilitated by the SGLT2 transporter. The remaining 10% of filtered glucose is reabsorbed in the distal straight segment of the proximal tube by the SGLT1 transporter. In diabetic patients, the SGLT transporter system is often overwhelmed and unable to reabsorb all filtered plasma glucose due to hyperglycemic conditions. Once this threshold capacity is reached and surpassed, excess glucose that is not reabsorbed is excreted into the urine. In addition, a chronic elevated plasma glucose concentration provides the stimulus that ultimately leads to increased SGLT2 expression by the renal proximal tubular cells, resulting in an undesirable increase in renal capacity and threshold to reabsorb filtered glucose in both type 1 and type 2 diabetic patients.^{1,2}

SGLT2 inhibitors improve glycemic control by producing glucosuria. This is accomplished by inhibiting SGLT2 and increasing urinary glucose excretion. The net effect is an increase excretion of glucose from the body and normalizing plasma glucose levels. At this time, it is unknown if this mechanism of action serves to reduce the kidney's threshold capacity to reabsorb glucose, thus causing glucose excretion at lower plasma concentrations, or if the mechanism of action serves to prevent reabsorption of glucose load at all plasma glucose concentrations. SGLT2 inhibitors also have beneficial nonglycemic effects, such as weight loss observed during clinical trials and small decreases in systolic and diastolic blood pressure.^{1,2}

Table 1. Current Medications Available in Therapeutic Class³

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single Agent Products			
Canagliflozin (Invokana [®])	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 100 mg 300 mg	-
Dapagliflozin (Farxiga [®])	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 5 mg 10 mg	-
Empagliflozin (Jardiance [®])	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 10 mg 25 mg	-
Combination Products			
Canagliflozin/metformin (Invokamet [®])	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes*	Tablet: 50/500 mg 50/1,000 mg 150/500 mg 150/1,000 mg	-

*For patients who are not adequately controlled on a regimen containing metformin or canagliflozin or in patients already being treated with both canagliflozin and metformin

Evidence-based Medicine

- Each agent has been studied as monotherapy and dual and triple therapy compared to placebo and active controls and combinations of placebo and active controls.
- As monotherapy, patients randomized to canagliflozin 100 or 300 mg daily compared to patients randomized to placebo had a statistically significant improvement in HbA_{1c}. Both doses also resulted in a greater proportion of patients achieving an HbA_{1c} <7.0%, significant reductions in fasting plasma

glucose (FPG) and post prandial glucose (PPG), and in percent body weight reduction compared to placebo. There were also small decreases from baseline in systolic blood pressure relative to placebo (P values not reported).⁷

- As monotherapy in treatment-naïve patients, dapagliflozin was evaluated in two placebo-controlled trials. The first trial included 274 patients randomized to treatment with 2.5, 5 and 10 mg or placebo. At week 24, treatment with dapagliflozin 5 and 10 mg resulted in significant improvements in HbA_{1c} compared to placebo (-0.6, -0.8, -0.9 vs -0.2%, respectively; P<0.05 for 5 and 10 mg comparisons). Change in FPG (-24.1 and -28.8 vs -4.1 mg/dL, respectively) from baseline was also significantly greater in the 5 and 10 mg groups compared to placebo (P<0.05 for both comparisons).⁹
- The safety and efficacy of empagliflozin monotherapy was evaluated in a double-blind, placebo-controlled study of patients with type 2 DM (N=986). At week 24, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA_{1c} (-0.7% and -0.8% vs 0.1%, respectively; P<0.0001 for both comparisons), FPG (-19 mg/dL and -25 mg/dL vs 12 mg/dL, respectively; P values not reported) and body weight (-2.8 kg and -3.2 kg vs -0.4 kg, respectively; P values not reported) compared with placebo.¹²
- Similar results were observed when comparing sodium glucose co-transport 2 agents in combination for the treatment of diabetes mellitus.¹⁴⁻²⁸

Key Points within the Medication Class

- According to Current Clinical Guidelines:²⁹⁻³⁴
 - Metformin remains the cornerstone of most antidiabetic treatment regimens.
 - Patients with a high glycosylated hemoglobin (HbA_{1c}) will likely require combination or triple therapy in order to achieve glycemic goals.
 - § Uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered.
 - § The role of sodium-glucose co-transporter 2 (SGLT2) inhibitors are addressed in only one treatment guideline and are recommended as a potential second-line treatment option to be added in combination with metformin in patients not achieving glycemic goals.³³
- Other Key Facts:
 - Currently, three single-entity agents, and one combination product in this drug class have been approved by the FDA and are commercially available in the United States. Canagliflozin (Invokana[®]), dapagliflozin (Farxiga[®]) and empagliflozin (Jardiance[®]).³⁻⁵
 - Canagliflozin is also formulated with metformin in a single tablet (Invokamet[®]).⁶
 - All single-entity products are dosed once daily, with the combination product being dosed twice a day.³⁻⁶
 - Other effects observed in trials include weight loss and small decreases in systolic and diastolic blood pressure.
 - Common adverse side effects associated with SGLT2 inhibitor use included increased incidence of female genital mycotic infections, urinary tract infection, and increased urination.

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Therapeutic Class Overview Incretin Mimetics

Therapeutic Class

- Overview/Summary:** The glucagon-like peptide-1 (GLP-1) receptor agonists, or incretin mimetics, are one of two incretin-based therapies currently available for the management of type 2 diabetes. Specifically, albiglutide (Tanzeum[®]), exenatide (Bydureon[®], Byetta[®]), and liraglutide (Victoza[®]) are Food and Drug Administration-approved as an adjunct therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes.¹⁻⁴ This medication class was developed to mimic the effects of endogenous GLP-1, a hormone that maintains glucose homeostasis through several different mechanisms. The incretin mimetics work by stimulating insulin secretion, inhibiting glucagon secretion, improving β cell responsiveness to glucose, delaying gastric emptying, and enhancing satiety. In addition, these agents increase insulin secretion from pancreatic β cells in the presence of elevated glucose concentrations. Therefore, due to the glucose-dependent manner in which the incretin mimetics work, the medication class is associated with a low risk of hypoglycemia compared to other antidiabetic agents.^{5,6} The incretin mimetics are most commonly associated with gastrointestinal-related adverse events, and all agents are associated with the risk of developing pancreatitis. Only albiglutide, exenatide extended-release, and liraglutide have boxed warnings regarding the risk of thyroid C-cell tumors. The incretin mimetics are available as subcutaneous injections. Albiglutide is administered once-weekly, exenatide (Byetta[®]) is administered twice-daily, liraglutide is administered once-daily, and exenatide extended release (Bydureon[®]) is administered once-weekly.¹⁻⁴ There are currently no generic incretin mimetics available.

Table 1. Current Medications Available in Therapeutic Class¹⁻⁴

Generic (Trade Name)	Food and Drug Administration Approved Indications*	Dosage Form/Strength	Generic Availability
Albiglutide (Tanzeum [®])	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Injection: 30 mg single-dose pen† 50 mg single-dose pen†	-
Exenatide (Bydureon [®] , Byetta [®])	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Extended-release injection (Bydureon [®]): 2 mg/vial‡ Injection (Byetta [®]): 250 μ g/mL§	-
Liraglutide (Victoza [®])	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Injection: 6 mg/mL	-

* Consider reducing the dosage of concomitantly administered insulin secretagogues (e.g., sulfonylureas) and/or insulin to reduce the risk of hypoglycemia.

† Supplied in cartons of one and four pens containing lyophilized powder for reconstitution (each unit contains one 29-gauge, 5-mm, thin wall needle).

‡ Supplied in cartons of four single-dose trays (one vial containing 2 mg exenatide [as a white to off-white powder], one pre-filled syringe [0.65 mL diluents], one vial connector, and two custom needles).

§ Supplied as a 5 μ g/dose pre-filled syringe (1.2 mL, 60 doses) and 10 μ g/dose pre-filled syringe (2.4 mL, 60 doses).

|| Supplied as 0.6 (30 doses), 1.2 (15 doses), and 1.8 mg (10 doses) pre-filled, multi-dose pens (3 mL) available in a package of two or three pens.

Evidence-based Medicine

- In general, the incretin mimetics have been evaluated in clinical trials as add-on therapy to treatment regimens of established antidiabetic agents. Data consistently demonstrate that incretin mimetics are associated with positive effects on glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose (FPG),

- post-prandial glucose (PPG), and body weight. In addition, glycemic goals were consistently achieved when an incretin mimetic was added to existing treatment regimens.⁷⁻⁴⁸
- When compared to other antidiabetic agents (metformin, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, insulin therapy), efficacy data are not consistent, with the incretin mimetics achieving superiority or comparable benefits in glycemic outcomes. However, in general, all incretin-based therapies, including the incretin mimetics, consistently demonstrate a beneficial effect on body weight compared to other antidiabetic agents.⁷⁻⁴⁸
 - Albiglutide was compared in a non-inferiority trial with liraglutide. Albiglutide effectively reduced HbA_{1c}; however, based upon the prespecified non-inferiority parameters, the criteria for non-inferiority of albiglutide were not met. The HbA_{1c} treatment goal of <7.0% was achieved by 42% of albiglutide-treated patients and 52% of liraglutide-treated patients (P=0.0023), while the goal of HbA_{1c} lower than 6.5% was achieved by 20% of albiglutide-treated patients and 28% of liraglutide-treated patients (P=0.0009).⁸
 - Few head-to-head clinical trials within the class have been conducted. Compared to exenatide, exenatide extended-release significantly decreased HbA_{1c}, and achieved similar decreases in body weight.^{23,29} In a single trial, liraglutide significantly decreased HbA_{1c} compared to exenatide. Furthermore, liraglutide significantly decreased FPG while exenatide significantly decreased PPG.³⁷
 - In a 26-week open-label trial, there was a significantly greater reduction from baseline in HbA_{1c} at 26 weeks for patients treated with liraglutide compared to exenatide extended-release (-0.21%; 95% confidence interval [CI], -0.08 to -0.33). In addition, significantly more patients receiving liraglutide achieved an HbA_{1c} <7.0% compared to patients treated with exenatide extended-release (60 vs 53%; P=0.0011). Reductions in bodyweight also favored treatment with liraglutide (-0.90 kg; 95% CI, -0.39 to -1.40).³⁰
 - Overall, safety data demonstrate that incretin mimetics are commonly associated with gastrointestinal-related adverse events.⁷⁻⁴⁸ Exenatide extended-release appears to be associated with less nausea and vomiting, but more constipation, diarrhea, and injection site-related adverse events compared to exenatide.^{23,29,31}

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - Type 2 diabetes:⁴⁹⁻⁵⁴
 - § Metformin remains the cornerstone to most antidiabetic treatment regimens.⁴⁹⁻⁵⁴
 - § Patients with high glycosylated hemoglobin will most likely require combination or triple therapy in order to achieve glycemic goals.⁴⁹⁻⁵⁴
 - § The incretin mimetics are recommended as a potential second-line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals.^{49,50}
 - A lower rate of hypoglycemia, established efficacy and safety profile when used in combination with metformin, demonstrated effectiveness in reducing post-prandial glucose, and the potential for weight loss are noted as advantages associated with the incretin mimetics compared to other classes of antidiabetic agents.^{49,50}
 - No one incretin mimetic is recommended or preferred over another.⁴⁹⁻⁵⁴
- Other Key Facts:
 - Albiglutide (Tanzeum[®]) is administered once-weekly (independent of meals).¹
 - Exenatide (Byetta[®]) is administered twice-daily (60 minutes prior to food).²
 - Exenatide extended-release (Bydureon[®]) is administered once weekly (independent of meals).³
 - § The extended effect was achieved by adding the biodegradable polymer poly D, L-lactic-co-glycolic acid to exenatide. As a result, microspheres are formed and after administered, continued infiltration of water into the microspheres causes them to swell and release exenatide in a slow predictable fashion.^{3,7}

- § Patients who administer exenatide extended-release will have a palpable subcutaneous nodule at the injection site that dissipates as the medication is released.^{3,7}
- Liraglutide (Victoza[®]) is administered once-daily (independent of meals).⁴
 - No generic incretin mimetics are available.

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DIVISION OF HEALTH CARE FINANCING AND POLICY

MEDICAID SERVICES MANUAL

LL. Byetta® (exenatide), Bydureon® (exenatide extended-release) and Victoza® (liraglutide)

Therapeutic Class: Incretin Mimetics

Last Reviewed by the DUR Board: July 26, 2012

Byetta® (exenatide), Bydureon® (exenatide extended-release) and Victoza® (liraglutide) are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the Social Security Act and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

Authorization will be given if the following criteria are met and documented:

- a. The recipient is 18 years of age or older;
- b. The recipient has a diagnosis of type 2 diabetes mellitus; and
- c. The recipient has failed to achieve glycemic control despite an appropriate trial with metformin and/or a sulfonylurea.

2. Prior Authorization Guidelines

- a. Prior authorization approval will be for one year.
- b. Prior Authorization forms are available at:
<http://www.medicaid.nv.gov/providers/rx/rxforms.aspx>

Therapeutic Class Overview Niacin Derivatives

Therapeutic Class

- Overview/Summary:** Niacin favorably affects all lipids and lipoproteins when given in pharmacological doses; however, the mechanism of action is not completely understood.¹⁻⁵ Niacin has several effects on lipid metabolism including inhibition of hepatic production of very low-density lipoprotein cholesterol, and consequently its metabolite low-density lipoprotein cholesterol. In addition, it decreases plasma concentrations of triglycerides (20 to 50%), very low-density lipoprotein remnants, and intermediate density lipoprotein. Administration of niacin also causes a shift in low-density lipoprotein composition from small, dense particles to larger, more buoyant particles. Lastly, niacin increases high density lipoprotein cholesterol (15 to 35%) both by reducing lipid transfer of cholesterol from high density lipoprotein cholesterol to very low-density lipoprotein cholesterol, and by delaying high density lipoprotein cholesterol clearance. Niacin can decrease low-density lipoprotein cholesterol by 5 to 25%.¹⁻⁵

There are over-the-counter niacin products that are currently available, and these products are labeled as dietary supplements. While these supplements are “generally recognized as safe”, the Food and Drug Administration (FDA) does not examine the efficacy and safety of these products or regulate the manufacturing process. The FDA has imposed statutory restrictions prohibiting manufacturers of dietary supplements from claiming that their products “treat, cure, or prevent any disease”. Without FDA regulation, the content of nicotinic acid in niacin products is not guaranteed.⁶

Table 1. Medications Included Within the Therapeutic Class Review⁴⁻¹²

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Niacin (Niacor [®] , Niaspan [®])	To reduce elevated total cholesterol, low-density lipoprotein cholesterol, apolipoprotein B and triglycerides, and to increase high density lipoprotein cholesterol in patients with primary hyperlipidemia and mixed dyslipidemia; In combination with simvastatin or lovastatin: to treat primary hyperlipidemia and mixed dyslipidemia when treatment with niacin, simvastatin, or lovastatin monotherapy is considered inadequate; To reduce the risk of recurrent nonfatal myocardial infarction in patients with a history of myocardial infarction and hyperlipidemia.; In combination with a bile acid binding resin: slows progression or promotes regression of atherosclerotic disease in patients with a history of coronary artery disease and hyperlipidemia and as an adjunct to diet to reduce elevated total cholesterol and low-density lipoprotein cholesterol in adult patients with primary hyperlipidemia; To reduce triglycerides in adult patients with severe hypertriglyceridemia; Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in those individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia; nicotinic acid, alone or in combination with a bile-acid binding resin, is indicated as an adjunct to diet for the reduction of elevated total and low-density lipoprotein cholesterol	Extended-release tablet (Niaspan [®]):* 500 mg 750 mg 1,000 mg Tablet (Niacor [®]):* 500 mg	a

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	<p>levels in patients with primary hypercholesterolemia (Types IIa and IIb), when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate; prior to initiating therapy with nicotinic acid, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile performed to measure total cholesterol, high density lipoprotein cholesterol, and triglycerides; Adjunctive therapy for the treatment of adult patients with very high serum triglyceride levels (Types IV and V hyperlipidemia) who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them; such patients typically have serum triglyceride levels over 2,000 mg/dL and have elevations of very low-density lipoprotein cholesterol as well as fasting chylomicrons (Type V hyperlipidemia); subjects who consistently have total serum or plasma triglycerides below 1,000 mg/dL are unlikely to develop pancreatitis; therapy with nicotinic acid may be considered for those subjects with triglyceride elevations between 1,000 and 2,000 mg/dL who have a history of pancreatitis or of recurrent abdominal pain typical of pancreatitis; some Type IV patients with triglycerides under 1,000 mg/dL may, through dietary or alcoholic indiscretion, convert to a Type V pattern with massive triglyceride elevations accompanying fasting chylomicronemia, but the influence of nicotinic acid therapy on the risk of pancreatitis in such situations has not been adequately studied; drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low-density lipoprotein; inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV, and V hyperlipoproteinemia</p>		

*Generic is available in at least one dosage form or strength.

Evidence-based Medicine

- Clinical trials have demonstrated the safety and efficacy of the niacin derivatives.⁷⁻³⁵
- In a trial comparing niacin extended-release and immediate-release formulations, doses $\geq 1,500$ mg/day of niacin extended-release decreased low-density lipoprotein cholesterol to a significantly greater extent ($P < 0.04$ or $P < 0.01$); however, at all doses niacin immediate-release significantly increased high-density lipoprotein cholesterol ($P < 0.04$ or $P < 0.01$). Reductions in triglycerides were similar between the two formulations, except for niacin immediate-release 1,000 mg/day which led to significantly greater reductions ($P = 0.009$).⁴

- Direct comparisons of niacin with other lipid modifying agents demonstrated that no one medication class is consistently more efficacious over another in achieving significant alterations in individual lipid parameters, and results support the use of the niacin as combination therapy with other lipid modifying agents.⁷⁻³⁵

Key Points within the Medication Class

- According to Current Clinical Guidelines:³⁶⁻⁴³
 - In general, therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia.
 - When low-density lipoprotein cholesterol (LDL-C) lowering is required, initial treatment with a statin, a bile acid sequestrant or niacin is recommended. However, in general, the statins are considered first line therapy for decreasing LDL-C levels, and are recommended in patients with established coronary heart disease or coronary heart disease equivalents.
 - In patients with an elevated triglyceride level (≥ 500 mg/dL) a fibric acid derivative or niacin should be initiated before LDL-C lowering therapy to prevent pancreatitis.
 - Omega-3-acid ethyl esters represent an alternative to fibric acid derivatives and niacin for the treatment of hypertriglyceridemia.
- Other Key Facts:
 - Prescription niacin is approved by the Food and Drug Administration (FDA) for the treatment of hypertriglyceridemia.
 - Prescription niacin is also approved for the treatment of primary hypercholesterolemia and mixed dyslipidemia.⁴⁻⁵
 - Niacin is available over-the-counter in immediate-release and sustained-release formulations.
 - Niacin is also available by prescription as immediate-release (Niacor[®]) and extended-release (Niaspan[®]) formulations.

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Therapeutic Class Overview Anticonvulsants

Therapeutic Class

Overview/Summary: The anticonvulsants are Food and Drug Administration (FDA)-approved for the prevention and/or treatment of various seizure disorders either as monotherapy or adjunctive therapy. Some anticonvulsants are also FDA-approved for the prevention of migraines, and management of bipolar disorders, fibromyalgia, neuropathic pain and other non-seizure related conditions. The specific FDA-approved indications for each of these agents are outlined in Table 1.¹⁻⁴⁷ Seizure disorders are classified into four major categories: partial seizures (seizures beginning locally), generalized seizures (bilaterally symmetrical and without local onset), unilateral seizures (seizures that are predominantly unilateral) and unclassified epileptic seizures (seizures that are unclassifiable because of incomplete data). Partial seizures are subdivided into those with elementary symptomatology, those with complex symptomatology, and those that are secondarily generalized. Partial seizures with elementary symptomatology include those with motor symptoms (e.g., Jacksonian seizures) or with autonomic symptoms. Partial seizures with complex symptomatology are also known as temporal lobe or psychomotor seizures. Generalized seizures include tonic-clonic (grand mal) seizures, absence (petit mal) seizures, myoclonic seizures and akinetic seizures. Two or more seizures that occur sequentially without full recovery of consciousness between the seizures or seizures that last more than 30 minutes are known as status epilepticus.⁴⁸

Pharmacologic management of epilepsy should be individualized, and focused on controlling seizures, avoiding treatment-related adverse events and maintaining or restoring quality of life.⁴⁹ Prior to 1990, six major antiepileptic drugs were available for the treatment of various forms of epilepsy, including carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone and valproic acid. Over the past decade, many new chemical entities have become available in the United States. The newer antiepileptic drugs have better adverse event and drug interaction profiles, and they do not require serum concentration monitoring.⁵⁰⁻⁵² All of the anticonvulsants are FDA-approved for the treatment of various seizure disorders; however, these agents are primarily utilized in the treatment of partial, or focal, seizures and generalized tonic-clonic seizures. Currently there are several generic anticonvulsants available, and at least one generic agent is available within each anticonvulsant subclass.¹

Table 1. Current Medications Available in Therapeutic Class¹⁻⁴⁷

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Barbiturates			
Phenobarbital	Anticonvulsant (tablet), emergency control of certain acute convulsive episodes (injection), long term anticonvulsant for the treatment of generalized tonic-clonic and cortical focal seizures (injection), treatment of generalized and partial seizures (elixir), hypnotic, for short term treatment of insomnia (injection), preanesthetic (injection), sedative	Elixir: 20 mg/5 mL Injection: 65 mg/mL 130 mg/mL Tablet: 15 mg 16.2 mg 30 mg 32.4 mg 60 mg 64.8 mg 97.2 mg 100 mg	√
Primidone (Mysoline®*)	Control of grand mal, psychomotor, and focal epileptic seizures, used alone or	Tablet: 50 mg	√

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	concomitantly with other anticonvulsants	250 mg	
Benzodiazepines			
Clobazam (Onfi [®])	Adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome in patients two years of age or older	Tablet: 5 mg 10 mg 20 mg	-
Clonazepam (Klonopin ^{®*})	Treatment of Lennox-Gastaut Syndrome (petit mal variant), akinetic, and myoclonic seizures, alone or as adjunct therapy, treatment of panic disorder, with or without agoraphobia	Orally disintegrating tablet: 0.125 mg 0.25 mg 0.5 mg 1 mg 2 mg Tablet: 0.5 mg 1 mg 2 mg	√
Diazepam (Diastat ^{®*})	Management of selected, refractory, patients with epilepsy, on stable regimens of antiepileptic drugs, who require intermittent use of diazepam to control bouts of increased seizure activity	Rectal gel: 2.5 mg 10 mg 20 mg	√
Hydantoins			
Ethotoin (Peganone [®])	Control of generalized tonic-clonic and complex partial seizures	Tablet: 250 mg	-
Phenytoin (Phenytek ^{®*} , Dilantin ^{®*})	Control of status epilepticus of the grand mal type (injection), control of generalized tonic-clonic and complex partial seizures (chewable tablet, extended-release capsule, suspension), prevention and treatment of seizures occurring during or following neurosurgery	Chewable tablet: 50 mg Extended-release capsule: 30 mg 100 mg 200 mg 300 mg Injection: 50 mg/mL Suspension: 125 mg/5 mL	√
Succinimides			
Ethosuximide (Zarontin ^{®*})	Control of absence epilepsy	Capsule: 250 mg Syrup: 250 mg/5 mL	√
Methsuximide (Celontin [®])	Control of absence seizures that are refractory to other drugs	Capsule: 300 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Anticonvulsants, Miscellaneous			
Carbamazepine (Carbatrol [®] *, Epitol [®] *, Equetro [®] , Tegretol [®] *, Tegretol XR [®] *)	Generalized tonic-clonic seizures, mixed seizure patterns, partial seizures with complex symptomatology, acute treatment of manic or mixed episodes associated with bipolar disorder (Equetro [®]), trigeminal neuralgia	Chewable tablet: 100 mg Extended-release capsule: 100 mg 200 mg 300 mg Extended-release tablet: 100 mg 200 mg 400 mg Suspension: 100 mg/5 mL Tablet: 200 mg	√
Divalproex (Depakote [®] *, Depakote ER [®] *)	Adjunctive therapy in patients with multiple seizure types, that include absence seizures (extended-release, delayed-release), monotherapy and adjunctive therapy of complex partial seizures and simple and complex absence seizures, acute treatment of the manic episodes associated with bipolar disorder (delayed-release), acute treatment of manic or mixed episodes associated with bipolar disorder (extended-release), prophylaxis of migraine headaches (extended-release, delayed-release)	Capsule (sprinkle): 125 mg Delayed-release tablet: 125 mg 250 mg 500 mg Extended-release tablet: 250 mg 500 mg	√
Eslicarbazepine (Aptiom [®])	Adjunctive treatment of partial-onset seizures	Tablet: 200 mg 400 mg 600 mg 800 mg	-
Ezogabine (Potiga [®])	Adjunctive therapy in the treatment of partial onset seizures	Tablet: 50 mg 200 mg 300 mg 400 mg	-
Felbamate (Felbatol [®] *)	Patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or liver failure is deemed acceptable in light of the benefits conferred by its use	Suspension: 600 mg/5 mL Tablet: 400 mg 600 mg	√

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Gabapentin (Neurontin ^{®*})	Adjunctive therapy in the treatment of partial seizures, postherpetic neuralgia	Capsule: 100 mg 300 mg 400 mg Solution: 250 mg/5 mL Tablet: 600 mg 800 mg	√
Lacosamide (Vimpat [®])	Adjunctive therapy in the treatment of partial seizures	Injection: 200 mg/20 mL Solution: 10 mg/mL Tablet: 50 mg 100 mg 150 mg 200 mg	-
Lamotrigine (Lamictal ^{®*} , Lamictal CD ^{®*} , Lamictal ODT [®] , Lamictal XR ^{®*})	Adjunctive therapy in the treatment of partial seizures, adjunctive therapy in the treatment of primary generalized tonic-clonic seizures, adjunctive therapy for seizures associated with Lennox–Gastaut syndrome (chewable and orally disintegrating tablets), monotherapy in patients with partial seizures who are receiving treatment with carbamazepine, phenobarbital, phenytoin, primidone, or valproate as the single antiepileptic drugs, maintenance treatment of bipolar disorder to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy (chewable and orally disintegrating tablets)	Chewable tablet: 2 mg 5 mg 25 mg Extended-release tablet: 25 mg 50 mg 100 mg 200 mg 250 mg 300 mg Orally disintegrating tablet: 25 mg 50 mg 100 mg 200 mg Tablet: 25 mg 50 mg 100 mg 150 mg 200 mg 250 mg	√

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Levetiracetam (Keppra [®] *, Keppra XR [®] *)	Adjunctive therapy in the treatment of myoclonic seizures in patients with juvenile myoclonic epilepsy (injection, tablets), adjunctive therapy in the treatment of partial seizures, adjunctive therapy in the treatment of primary generalized tonic-clonic seizures (injection, tablets),	Extended-release tablet: 500 mg 750 mg Injection: 500 mg/5 mL Solution: 100 mg/mL Tablet: 250 mg 500 mg 750 mg 1,000 mg	√
Oxcarbazepine (Oxtellar XR [®] , Trileptal [®] *)	Monotherapy and adjunctive therapy in the treatment of partial seizures	Extended-release tablet: 150 mg 300 mg 600 mg Suspension: 300 mg/5 mL Tablet: 150 mg 300 mg 600 mg	√
Perampanel (Fycompa [®])	Adjunctive therapy in the treatment of partial onset seizures [†]	Tablet: 2 mg 4 mg 6 mg 8 mg 10 mg 12 mg	-
Pregabalin (Lyrica [®])	Adjunctive therapy in the treatment of partial seizures, fibromyalgia, neuropathic pain associated with diabetic peripheral neuropathy, neuropathic pain associated with spinal cord injury, postherpetic neuralgia	Capsule: 25 mg 50 mg 75 mg 100 mg 150 mg 200 mg 225 mg 300 mg Solution: 20 mg/mL	-
Rufinamide (Banzel [®])	Adjunctive therapy for seizures associated with Lennox–Gastaut syndrome	Suspension: 40 mg/mL Tablet: 200 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Tiagabine (Gabitril ^{®*})	Adjunctive therapy in the treatment of partial seizures	400 mg Tablet: 2 mg 4 mg 12 mg 16 mg	√
Topiramate (Qudexy XR [®] , Topamax ^{®*} , Trokendi XR [®])	Adjunctive therapy in patients with partial onset or primary generalized tonic-clonic seizures, adjunctive therapy for seizures associated with Lennox–Gastaut syndrome, monotherapy (initial) in patients with partial onset or primary generalized tonic-clonic seizures, prophylaxis of migraine headaches	Capsule (sprinkle): 15 mg 25 mg Tablet: 25 mg 50 mg 100 mg 200 mg Extended-release capsule: 25 mg 50 mg 100 mg 150 mg 200 mg	√
Valproic acid (Depakene ^{®*} , Stavzor [®])	Adjunctive therapy in patients with multiple seizure types, that include absence seizures, monotherapy and adjunctive therapy of complex partial seizures and simple and complex absence seizures, acute treatment of the manic episodes associated with bipolar disorder (delayed-release), prophylaxis of migraine headaches (delayed-release)	Capsule: 250 mg Delayed-release capsule: 125 mg 250 mg 500 mg Solution: 250 mg/5 mL	√
Vigabatrin (Sabril [®])	Adjunctive therapy for adult patients with refractory complex partial seizures who have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss (tablet), monotherapy for pediatric patients (one month to two years of age) with infantile spasms for whom the potential benefits outweigh the potential risk of vision loss (solution)	Solution (powder): 500 mg Tablet: 500 mg	-
Zonisamide (Zonegran ^{®*})	Adjunctive therapy in the treatment of partial seizures	Capsule: 25 mg 50 mg 100 mg	√

*Generic available in at least one dosage form or strength.

†With or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

Evidence-based Medicine

- Hancock et al conducted a meta-analysis of 14 randomized controlled trials which included infants and children with infantile spasms. Treatment with vigabatrin was associated with a complete cessation of spasms in 7/20 (35%) patients compared to 2/20 (10%) patients treated with placebo. A >70% reduction in the number of spasms was reported in 40% of patients treated with vigabatrin compared to 15% of patients treated with placebo.⁵³
- Another meta-analysis by Hancock et al included trials that evaluated the safety and efficacy of felbamate, lamotrigine, rufinamide and topiramate in the treatment of Lennox-Gastaut Syndrome (LGS). While all of these agents demonstrated some efficacy, the optimum treatment of LGS remained uncertain as no single drug was highly efficacious. Felbamate, lamotrigine, rufinamide and topiramate may be helpful as add-on therapy.⁵⁴
- The results of a study by Ng et al demonstrated that the mean percent reduction in weekly drop seizures was 41.2% with clobazam 0.25 mg/kg/day (P=0.0120), 49.4% with clobazam 0.5 mg/kg/day (P=0.0015) and 68.3% with clobazam 1.0 mg/kg/day (P<0.0001) compared to 12.1% for placebo.⁵⁵
- In a study by Porter et al, treatment with ezogabine 600, 900 and 1,200 mg reduced the total monthly seizure frequency from baseline by 23, 29 and 35% compared to 13% with placebo (P<0.001 for all).⁵⁶ In a second study of patients with drug-resistant partial epilepsy, ezogabine 1,200 mg daily reduced the total monthly seizure frequency from baseline by 44.3% compared to 17.5% with placebo (P<0.001).⁵⁷
- Perampanel is approved as adjunctive therapy in patients with partial onset seizures. In one study perampanel 8 or 12 mg significantly reduced seizure frequency compared to placebo (P=0.0261 and P=0.0158 for 8 and 12 mg, respectively); however, there was no significant difference in the proportion of patients who achieved a seizure reduction >50% from baseline compared to the placebo group.⁵⁸ Similar results were reported in a second study (P<0.001 and P=0.011 for 8 and 12 mg, respectively); however, more patients treated with perampanel 8 or 12 mg had a reduced seizure frequency >50% from baseline compared to placebo (P=0.002 and P<0.001 for 8 and 12 mg, respectively).⁵⁹ In a third study, treatment with perampanel 4 or 8 mg significantly reduced seizure frequency compared to placebo (P=0.003 and P<0.001 for 4 mg and 8 mg, respectively). Moreover, a greater proportion of patients treated with perampanel 4 or 8 mg achieved a reduction in seizure frequency >50% from baseline compared to placebo (P=0.013 and P<0.001 for 4 and 8 mg, respectively).⁶⁰
- The most recent Food and Drug Administration-approved anticonvulsant, eslicarbazepine, was based on the results of three double-blind, multi-center, randomized, placebo-controlled trials. Each of these trials compared adjunctive treatment with eslicarbazepine to placebo in patients who were currently receiving one to three anti-epileptic drugs. In the first and second published trials, the investigators compared eslicarbazepine at a dose of 400, 800 and 1,200 mg once daily to placebo for 12 weeks.^{61,62} In a pooled analysis of the three studies (third trial has not been published), the primary endpoint of seizure frequency per four weeks was 7.7 in the placebo group (N=406) compared to 7.3 with eslicarbazepine 400 mg (N=185; P=0.8136), 6.1 with 800 mg (N=375; P=0.0001) and 5.7 with 1,200 mg (N=352; P<0.0001). The proportion of patients who achieved a seizure reduction of at least 50% from baseline was 20.9% in the placebo group compared to 22.2% with eslicarbazepine 400 mg, 32.3% with 800 mg and 40.9% with 1,200 mg.⁶¹⁻⁶³ A fourth double-blind, multi-center, randomized, placebo-controlled trial compared adjunctive treatment with eslicarbazepine to placebo in patients who were currently receiving one to two anti-epileptic drugs. Investigators compared eslicarbazepine at a dose of 800 and 1,200 mg once daily to placebo for 12 weeks. The primary endpoint of seizure frequency per four weeks was 7.3 in the placebo group (N=88) compared to 5.7 with eslicarbazepine 800 mg (N=85; P=0.048) and 5.5 with 1,200 mg (N=80; P=0.021). The proportion of patients who achieved a seizure reduction of at least 50% from baseline was 22.6% in the placebo group compared to 34.5% with eslicarbazepine 800 mg (P=0.106) and 37.7% with 1,200 mg (P=0.020).⁶⁴

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - The 2012 National Institute for Clinical Excellence guideline recommends carbamazepine and lamotrigine as first-line treatment of children, young people, and adults with newly diagnosed focal seizures (partial seizures). Levetiracetam, oxcarbazepine or sodium

- valproate should be offered if first-line therapies prove inadequate, and adjunctive therapy should be considered if a second well-tolerated antiepileptic also proves inadequate. Sodium valproate is recommended first-line for the treatment of children, young people, and adults with newly diagnosed generalized tonic-clonic focal seizures. Lamotrigine should be offered if sodium valproate proves inadequate, and carbamazepine and oxcarbazepine should be considered. Adjunctive therapy with clobazam, lamotrigine, levetiracetam, sodium valproate, or topiramate should be offered to all patients if first-line therapies are inadequate.⁴⁸
- o Vigabatrin (oral solution) is Food and Drug Administration (FDA)-approved for the management of infantile spasm. According to the 2012 American Academy of Neurology medical management of infantile spasms guideline, there is insufficient evidence to support the use of agents other than adrenocorticotrophic hormone and vigabatrin. Evidence suggests that adrenocorticotrophic hormone may be preferred over vigabatrin for short-term management.⁶⁵
 - o Clobazam, clonazepam, lamotrigine, rufinamide and topiramate are FDA-approved for the management of Lennox Gastaut Syndrome. Sodium valproate is recognized as first-line, with lamotrigine recommended as adjunctive therapy if needed.⁴⁸
 - o Treatment guidelines recommend valproate and carbamazepine as potential beneficial options for the management of adults with a manic or mixed bipolar episode. Lamotrigine, topiramate, or gabapentin are unlikely beneficial in this clinical situation and oxcarbazepine may be considered for treatment. With regard to bipolar depression in adults, lamotrigine should be considered as a potential first-line option, and patients who do not respond to initial monotherapy should receive combination therapy with lithium.⁶⁶⁻⁷⁰
 - o Divalproex, topiramate and valproic acid are FDA-approved for the prophylaxis of migraine headaches, and all should be offered for migraine prevention according to the 2012 guidelines from the American Academy of Neurology/American Headache Society. Furthermore, carbamazepine may be considered for migraine prevention as it is a possibly effective treatment, and lamotrigine is ineffective.⁷¹
 - o According to the American Academy of Neurology, anticonvulsants, antidepressants, opioids and other pharmacologic agents (capsaicin, isosorbide dinitrate spray, and lidocaine patch) are potential treatment options for painful diabetic neuropathy. If clinically appropriate, pregabalin should be offered for treatment. Gabapentin and sodium valproate are other anticonvulsants that should be considered for treatment.⁷²
 - o According to the American Academy of Neurology, first-line therapies for the management of postherpetic neuralgia include tricyclic antidepressants, gabapentin, pregabalin, opioids, and topical lidocaine. At this time the use of these therapies for long-term management remains uncertain.⁷³
 - o The use of anticonvulsants in the management of fibromyalgia is not addressed in the European League Against Rheumatism guidelines.⁷⁴
- Other Key Facts:
- o The majority of anticonvulsants are available in a generic formulation, and there is at least one generic agent available within each pharmacologic class.
 - o Clobazam was approved by the FDA in 2011; however, this agent has been available internationally for several years for the treatment of anxiety and epilepsy.
 - o Ezogabine has a unique mechanism of action in that it may act as an anticonvulsant by reducing excitability through the stabilization of neuronal potassium channels in an “open” position.³⁴
 - o Perampanel is a first-in-class anticonvulsant that works as a highly selective, non-competitive AMPA-type glutamate receptor antagonist.⁷⁵
 - o The most recently FDA-approved anticonvulsant, eslicarbazepine, provides for another treatment option for patients with partial-onset seizures.

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Therapeutic Class Overview Topical Androgens

Therapeutic Class

- Overview/Summary:** The topical testosterone products listed in Table 1 are approved by the Food and Drug Administration for testosterone replacement therapy in males with primary hypogonadism (congenital or acquired) or hypogonadotropic hypogonadism (congenital or acquired).¹⁻⁷ There are few differences between the topical testosterone products with the exception of formulation and site of administration. Androderm[®] is the only testosterone product available as a transdermal patch. AndroGel[®], Fortesta[®], Testim[®], and Vogelxo[®] are available in gel preparations, while Axiron[®] is formulated as a topical solution. These products are available as metered-dose pumps or single-use packets/tubes. Androderm[®] is applied at night, while the others are generally applied in the morning.¹⁻⁶ A higher incidence of skin pruritus is associated with the transdermal patch compared to the topical gels; however, the use of hydrocortisone cream, may reduce skin irritations that develop.¹ The topical testosterone product labeling includes a Black Box Warning regarding the risk of virilization of female sexual partners that has been reported with male use of topical testosterone gels and solution.¹⁻⁷ The occlusive backing film on Androderm[®] prevents the partner from coming in contact with the active material in the system, and therefore the warning is not included on this product.¹ Testim is the only topical testosterone product with a generic available.

Hypogonadism refers to a defect of the reproductive system resulting in a lack of gonad function.⁸⁻¹² Hypogonadism is classified based on the level of the defect within the reproductive axis. Primary hypogonadism results from a defect of the gonads and occurs when the serum testosterone concentration and/or sperm counts are below normal, and the serum luteinizing hormone (LH) and/or follicle-stimulating hormone (FSH) concentrations are above normal.¹² Secondary hypogonadism, known as hypogonadotropic hypogonadism, results from defects in the hypothalamus or pituitary. This occurs when the serum testosterone concentration and/or sperm counts are below normal, and the serum LH and/or FSH concentrations are normal or reduced.¹² Combined primary and secondary hypogonadism may occur and results in below-normal testosterone concentrations and variable LH and/or FSH concentrations, depending upon which clinical condition predominates.¹⁰ Male hypogonadism may manifest as testosterone deficiency with or without infertility. Clinical signs and symptoms depend primarily on the age at the onset of the condition. Postpubertal hypogonadism usually results in slowly evolving clinical manifestations that may include a progressive decrease in muscle mass, loss of libido, impotence, oligospermia or azoospermia, poor concentration, and an increase in the risk of osteoporosis and fractures.⁸⁻¹²

Table 1. Current Medications Available in the Therapeutic Class¹⁻⁶

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Testosterone (Androderm [®])	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Androderm [®] : 2 mg/day patch 4 mg/day patch	-
Testosterone (AndroGel [®])	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	AndroGel [®] 1%: Metered-dose pump: 12.5 mg testosterone/actuation Unit-dose packet: 50 mg testosterone/packet AndroGel [®] 1.62%: Metered-dose pump: 20.25 mg/actuation	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		Unit-dose packet: 20.25 mg/packet	
Testosterone (Axiron®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Axiron®: Metered-dose pump: 30 mg/actuation	-
Testosterone (Fortesta®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Fortesta®: Metered-dose pump: 10 mg/actuation	-
Testosterone (Testim®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Testim® 1%: Unit-dose tubes: 50 mg/tube)	a
Testosterone (Vogelxo®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Vogelxo®: Metered-dose pump: 12.5 mg/actuation Unit-dose packet: 50 mg/packet Unit-dose tube: 50 mg/tube	-

Evidence-based Medicine

- In one study comparing Testim® 50 and 100 mg, Androderm® and placebo, all treatments significantly increased serum testosterone and dihydrotestosterone (DHT) levels. All treatments increased lean body mass (LBM); however, the Testim® 100 mg group increased LBM significantly more compared to the Androderm® and placebo groups ($P < 0.05$ for all). Testim® and Androderm® significantly decreased fat mass compared to placebo. Only Testim® 100 mg produced significant improvements in sexual function. There were no significant differences among groups with regard to improving mood.¹³
- Compared to Androderm®, AndroGel® 100 mg significantly increased levels of testosterone and free testosterone compared to AndroGel® 50 mg and Androderm®. There were significant increases in serum DHT levels with both doses of AndroGel® compared to Androderm®. The discontinuation rate, mostly due to adverse skin reactions, was significantly greater with Androderm®.¹⁴
- In a study comparing AndroGel® and Androderm®, the average serum testosterone levels increased most with AndroGel® 100 mg (P values not reported). A decrease in percent body fat and total fat mass occurred in all treatment groups; however, this was only significant for AndroGel®. All treatment groups experienced significant improvements in sexual function. AndroGel® treatment significantly increased prostate specific antigen levels. Skin irritation at the application site was more frequent in the Androderm® group compared to AndroGel® 100 mg and 50 mg groups.¹⁵
- The results from a study by Grober et al demonstrated the efficacy of changing from one testosterone gel preparation to another after suboptimal response (N=370). Among men switching from AndroGel® to Testim®, 69, 58 and 65% experienced improvements in libido, erectile function and energy levels, respectively. The rates of improvement for these parameters for men switching from Testim® to AndroGel® were 46, 39 and 46%, respectively.¹⁶
- In an open-label study, Axiron® topical solution applied to the axilla provided a serum testosterone level in the normal range for 84.1% of patients after 120 days of treatment.¹⁷ Results from a second open-

label study reported that 76.2% of men achieved a mean serum testosterone level within the normal physiologic range following 35 days of treatment with Fortesta[®].¹⁸

- A meta-analysis of 16 studies evaluating testosterone supplementation for the diagnosis or erectile dysfunction was conducted by Jain et al. The overall response rate was 57% ± 2.3% (203 of 356 cases). Among the studies with stratified results, 75 of 117 (64% ± 4%) men with a primary etiology responded and 53 of 120 (44% ± 2.9%) men with a secondary etiology responded, which was determined to be statistically significant ($P < 0.001$).¹⁹
- In an open label extension study Kaufman et al evaluated efficacy of testosterone 1.62% gel up to one year of therapy.²⁵ Results from the study show that testosterone 1.62% is effective in replacement therapy with 78% (95% CI, 70.0% to 84.6%) and 87.0% (95% CI, 66.4% to 97.2%) of the different dosing regimens reaching therapeutic levels of testosterone. This study also showed that >50% men require doses larger than the traditional starting dose, which is in agreement with previous data.²⁰
- Blick et al evaluated the use of testosterone replacement therapy in human immunodeficiency virus infection/acquired immune deficiency syndrome (HIV/AIDS). In this prospective cohort study the effects of replacement therapy with testosterone 1% (Testim[®]) were evaluated in HIV/AIDS patients. During the twelve month study, but non-HIV/AIDS patients and HIV/AIDS cohorts had significant increases in total testosterone and free testosterone to within normal limits along with increased sexual function and improved and decreased antidepressant use. Body composition profiles improved significantly in men without HIV/AIDS ($P \leq 0.05$) and remained stable in men with HIV/AIDS during the twelve months of follow-up.²¹

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - Intramuscular and topical testosterone preparations are generally recommended for the management of hypogonadism in adult male patients.⁹⁻¹¹
 - The oral alkylated androgens are not recommended due to poor androgen effects, adverse lipid changes, and hepatic side effects, but may be considered when other agents are not suitable.^{9,11}
 - The selection of testosterone replacement therapy should be a joint decision between the patient and physician and should be made after consideration of patient preferences, the pharmacokinetic profiles of the respective agents, treatment burden and cost.^{9,11}
 - The short-acting preparations may be preferred over long-acting depot preparations when initiating treatment in patients with late-onset hypogonadism due to the potential development of an adverse event that may require rapid discontinuation of testosterone replacement therapy. Treatment guidelines do not recommend one topical preparation over another.⁹⁻¹¹
- Other Key Facts:
 - There are no generic topical testosterone products available.

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DIVISION OF HEALTH CARE FINANCING AND POLICY

MEDICAID SERVICES MANUAL

DD. Androgel®, Androderm®, Testim® (Testosterone gel and transdermal system)

Therapeutic Class: Androgenic Agents

Last Reviewed by the DUR Board: July 22, 2010

Topical Androgens are subject to prior authorization.

1. Coverage and Limitations

Recipients must meet all of the criteria for coverage:

2. Criteria for approval

a. Recipient is a male;

b. Use is for the FDA Approved Indication:

Primary (congenital or acquired) or secondary (congenital or acquired) hypogonadism with ICD-9 diagnosis code of 257.2;

c. The patient has two morning pre-treatment testosterone levels below the lower limit of the normal testosterone reference range of the individual laboratory used;

d. The patient does not have breast or prostate cancer, a palpable prostate nodule or induration, prostate-specific antigen greater than 4 ng/ml or severe lower urinary symptoms with an International Prostate Symptom Score (IPSS) > 19;

e. The patient does not have a hematocrit > 50%;

f. The patient does not have untreated severe obstructive sleep apnea; and

g. The patient does not have uncontrolled or poorly controlled heart failure.

3. Prior Authorization Guidelines

Prior authorization approval will be for up to one year.

Prior Authorization forms are available at:

<http://www.medicaid.nv.gov/providers/rx/rxforms.aspx>

Length of authorization: one year.

Therapeutic Class Overview Immunomodulators

Therapeutic Class

- Overview/Summary:** This review encompasses immunomodulator agents used in immune-mediated inflammatory diseases. These agents include interleukin (IL) receptor antagonists (anakinra, tocilizumab), tumor necrosis factor (TNF)-blocking agents (adalimumab, certolizumab, etanercept, golimumab, and infliximab), T-cell activation inhibitor (abatacept), a janus kinase inhibitor (tofacitinib) and an integrin receptor antagonist (vedolizumab). These agents interfere with inflammatory pathways through slightly different mechanisms and are indicated in rheumatoid arthritis, psoriatic arthritis, psoriasis, ankylosing spondylitis, ulcerative colitis, Crohn's disease and neonatal-onset multisystem inflammatory disease.¹⁻¹⁴

Generally, current consensus guidelines support the use of the TNF-blockers with respect to their Food and Drug Administration (FDA)-approved indications and no one agent is preferred over another.¹⁵⁻³² As more recent guidelines are published, the recommendations for use of TNF-blockers earlier in therapy is becoming a more common occurrence.^{23,24,27} Because the immunomodulators are biologic agents made from living organisms and are extremely difficult to duplicate, congress has struggled to create regulations to approve generic versions of these agents. Currently, none of the agents in this class are available generically; however, the recently upheld Patient Protection and Affordable Care provides a legal framework for regulatory approval of biosimilar drugs.³³

Table 1. Current Medications Available in the Therapeutic Class³⁻¹⁴

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Abatacept (Orencia [®])	Monotherapy or concomitantly with disease modifying antirheumatic drugs other than tumor necrosis factor antagonists for moderately to severely active rheumatoid arthritis in adults; monotherapy or concomitantly with methotrexate for moderately to severely active polyarticular juvenile idiopathic arthritis in pediatric patients six years of age and older	Prefilled syringe: 125 mg/mL Single use vial: 250 mg	-
Adalimumab (Humira [®])	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 rheumatoid arthritis; reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (in pediatric patients four years of age and older; reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis; reducing signs and symptoms in adult patients with active ankylosing spondylitis; reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy; reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab; inducing and sustaining clinical remission in adult patients	Prefilled pen: 40 mg/0.8 mL Prefilled syringe: 20 mg/0.4 mL 40 mg/0.8 mL Single use vial: 40 mg/0.8 mL	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine; treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate		
Anakinra (Kineret®)	Reduction in signs and symptoms and slowing the progression of structural damage in moderately to severely active rheumatoid arthritis, in patients 18 years of age or older who have failed one or more disease modifying antirheumatic drugs; treatment of neonatal-onset multisystem inflammatory disease	Prefilled syringe: 100 mg/0.67 mL	-
Certolizumab (Cimzia®)	Reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy; treatment of adults with moderately to severely active rheumatoid arthritis; treatment of adults with active psoriatic arthritis; treatment of adults with active ankylosing spondylitis	Prefilled syringe: 200 mg/mL Vial (powder for injection): 200 mg	-
Etanercept (Enbrel®)	Monotherapy or in combination with methotrexate in reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis; reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients ages two and older; reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and as monotherapy in improving physical function in patients with psoriatic arthritis or in combination with methotrexate in patients who do not respond adequately to methotrexate alone; reducing signs and symptoms in patients with active ankylosing spondylitis; treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy	Prefilled "SureClick" autoinjector: 50 mg/mL Prefilled syringes: 25 mg/0.5 mL 50 mg/mL Vial (powder for injection): 25 mg	-
Golimumab (Simponi®, Simponi Aria®)	Treatment of adult patients with moderately to severely active rheumatoid arthritis in combination with methotrexate (Simponi® and Simponi Aria®); treatment of adult patients with active psoriatic arthritis alone or in combination with methotrexate (Simponi® only); treatment of adult patients with active ankylosing spondylitis (Simponi® only); treatment of moderately to severely active ulcerative colitis who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosalicylates, oral corticosteroids, azathioprine, or 6-	Prefilled "SmartJect" autoinjector: 50 mg/0.5 mL, 100 mg/mL Prefilled syringe: 50 mg/0.5 mL 100 mg/mL Single use	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	mercaptopurine (Simponi [®] only)	vial*: 50 mg/4 mL	
Infliximab (Remicade [®])	Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy; reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy; reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy; reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely ulcerative colitis who have had an inadequate response to conventional therapy; in combination with methotrexate to reduce signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis; reducing signs and symptoms in patients with active ankylosing spondylitis; reducing signs and symptoms of active psoriatic arthritis, inhibiting the progression of structural damage, and improving physical function; treatment of adult patients with chronic severe plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate	Single use vial: 100 mg	-
Tocilizumab (Actemra [®])	Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more disease modifying anti-rheumatic drugs; patients two years of age and older with active polyarticular juvenile idiopathic arthritis; patients two years of age and older with active systemic juvenile idiopathic arthritis	Prefilled syringe : 162 mg/0.9 mL Single use vial: 80 mg/4 mL 200 mg/10 mL 400 mg/20 mL	-
Tofacitinib (Xeljanz [®])	Monotherapy or concomitantly with nonbiologic disease modifying antirheumatic drugs for moderately to severely active rheumatoid arthritis in adults who have had an inadequate response or intolerance to methotrexate	Tablet: 5 mg	-
Ustekinumab (Stelara [®])	Treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy Treatment of adult patients (18 years or older) with active psoriatic arthritis alone or in combination with methotrexate.	Prefilled syringe: 45 mg/0.5 mL 90 mg/mL Single use vial: 45 mg/0.5 mL 90 mg/mL	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Vedolizumab (Entyvio [®])	Treatment of adult patients (18 years or older) with moderately to severely active Crohn's disease who have had an inadequate response with, were intolerant to or demonstrated dependence on corticosteroids; treatment of adult patients (18 years or older) with moderately to severely active ulcerative colitis who had an inadequate response with, lost response to or were intolerant to a tumor necrosis factor antagonist or immunomodulator or who had demonstrated dependence on corticosteroids	Single use vial: 300 mg/20 mL	-

*Only indicated for use in patients with rheumatoid arthritis.

Evidence-based Medicine

- The immunomodulators have been shown to be effective for their respective Food and Drug Administration (FDA)-approved indications, particularly in conditions where patients were unresponsive or refractory to traditional disease modifying antirheumatic drugs (DMARDs). Most research with these agents and FDA-approved indications (with the exception of ustekinumab) are for rheumatoid arthritis. In these trials, the immunomodulator were compared directly to placebo or traditional DMARD medications, either as monotherapy or in combination with a traditional DMARD. Consistently, immunomodulators have shown greater improvement in symptoms over the comparator.³⁸⁻¹²⁸
- Recently anakinra was FDA-approved for neonatal-onset multisystem inflammatory disease, the only agent FDA-approved for this indication. The approval was based on the results of a single trial demonstrating sustained improvements in affected patients over 60 months.¹²⁸
- To date, the majority of trials conducted have been placebo-controlled, with very few trials directly comparing two immunomodulators head-to-head for any of the FDA-approved indications. Those that have been conducted, most have shown comparable results.³⁸⁻¹²⁸ In one trial in rheumatoid arthritis patients who were either intolerant or were not candidates for methotrexate treatment, significantly greater improvements were observed in patients treated with tocilizumab compared to adalimumab.¹¹¹ In another trial in rheumatoid arthritis patients with inadequate response to methotrexate, similar responses were observed in patients treated with abatacept and adalimumab.^{112,113} The inclusion of adalimumab arm in one phase 3 trial of tofacitinib allowed establishing relative safety and efficacy of tofacitinib; however, formal noninferiority comparison was not performed.¹¹⁵ The few direct head-to-head trials available prevent clearly determining superiority of one agent over another.
- Generally, current consensus guidelines support the use of the tumor necrosis factor-blockers with respect to their FDA-approved indications and no one agent is preferred over another.¹⁵⁻³² As more recent guidelines are published, the recommendations for use tumor necrosis factor-blockers earlier in therapy is becoming a more common occurrence.^{23,24,27} The adverse event profiles are similar across the class; however, routes of administration and dosing frequency may vary. Currently, adalimumab and infliximab have the most FDA-approved indications among the agents in the class; however, several other agents have recently gained additional indications.

Key Points within the Medication Class

- According to Current Clinical Guidelines:¹⁵⁻³²
 - Support the use of the immunomodulators with respect to their Food and Drug Administration (FDA)-approved indications.
 - In general, no one agent is preferred over another; however, given the paucity of clinical experience and long-term safety data, the use of tofacitinib for rheumatoid arthritis is recommended primarily after biological treatment has failed.¹⁵

- Other Key Facts:
 - None of the immunomodulators included in this review are available generically.
 - Dosing frequency and route of administration vary between products.
 - § Currently none of the agents available may be administered via oral route.
 - § Infliximab and vedolizumab are administered intravenously and are the only agents in the class that are not available for subcutaneous administration. A loading- dose of abatacept is recommended to be administered intravenously, but can be given subcutaneously if the patient is not able to received intravenous infusion.
 - § Anakinra is administered subcutaneously, but requires more frequent daily administration.
 - Intravenous formulation of golimumab and subcutaneous formulation of tocilizumab are only indicated in the treatment of rheumatoid arthritis.
 - Anakinra is the only FDA-approved agent for neonatal-onset multisystem inflammatory disease.

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L. Immunomodulator Drugs

Therapeutic Class: Immunomodulators

Last Reviewed by the DUR Board: **January 23, 2014**

Actemra® (tocilizumab)	Cimzia® (certolizumab pegol)
Amevive® (alefacept)	Kineret® (anakinra)
Enbrel® (etanercept)	Orencia® (abatacept)
Humira® (adalimumab)	Remicade® (infliximab)
Simponi® (golimumab)	Stelara® (ustekinumab)
Simponi® ARIA™ (golimumab)	Xeljanz® (tofacitinib)

Immunomodulator **Drugs** are subject to prior authorization **and quantity limitations based on the Application of Standards in Section 1927 of the Social Security Act (SSA) and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.**

1. Coverage and Limitations

Approval will be given if the following criteria are met and documented:

a. Rheumatoid Arthritis (RA):

1. **The recipient has a diagnosis of moderately to severely active RA; and**
2. **The recipient has had a rheumatology consultation, including the date of the visit; and**
3. **The recipient has had a negative tuberculin test; and**
4. **The recipient does not have an active infection or a history of recurring infections; and**
5. **The recipient has had RA for \leq six months (early RA) and has high disease activity; and an inadequate or adverse reaction of a disease modifying antirheumatic drug (DMARD) (methotrexate, hydroxychloroquine, leflunomide, minocycline and sulfasalazine); or**
6. **The recipient has had RA for \geq six months (intermediate or long-term disease duration) and has moderate disease activity and has an inadequate response to a DMARD (methotrexate, hydroxychloroquine, leflunomide, minocycline or sulfasalazine); or**
7. **The recipient has had RA for \geq six months (intermediate or long-term disease duration) and has high disease activity.**

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b. Psoriatic Arthritis:

1. The recipient has a diagnosis of moderate or severe psoriatic arthritis; and
2. The recipient has had a rheumatology consultation including the date of the visit or a dermatology consultation including the date of the visit; and
3. The recipient had an inadequate response to any one nonsteroidal anti-inflammatory drug (NSAID) or a contraindication to treatment with an NSAID or to any one of the following DMARDs (methotrexate, leflunomide, cyclosporine or sulfasalazine); and
4. The recipient has had a negative tuberculin test; and
5. The recipient does not have active infection or a history of recurring infections.

c. Ankylosing Spondylitis:

1. The recipient has a diagnosis of ankylosing spondylitis; and
2. The recipient has had an inadequate response to NSAIDs; and
3. The recipient has had an inadequate response to any one of the DMARDs (methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, minocycline); and
4. The recipient has had a negative tuberculin test; and
5. The recipient does not have an active infection or a history of recurring infections.

d. Juvenile Rheumatoid Arthritis/Juvenile Idiopathic Arthritis:

1. The recipient has a diagnosis of moderately or severely active juvenile RA; and
2. The recipient is at least two years of age; and
3. The recipient has at least five swollen joints; and
4. The recipient has three or more joints with limitation of motion and pain, tenderness or both; and
5. The recipient has had an inadequate response to one DMARD; and

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6. **The recipient has had a negative tuberculin test;** and
 7. **The recipient** does not have an active infection or a history of recurring infections.
- e. Plaque Psoriasis:
1. **The recipient has a diagnosis of chronic, moderate to severe plaque psoriasis;** and
 2. **The agent is** prescribed by a dermatologist; and
 3. **The recipient has failed to adequately respond to a topical agent;** and
 4. **The recipient has failed to adequately respond to at least one oral treatment;** and
 5. **The recipient has had a negative tuberculin test;** and
 6. **The recipient** does not have an active infection or a history of recurring infections.
- f. Crohn's Disease:
1. **The recipient has a diagnosis of moderate to severe Crohn's Disease;** and
 2. **The recipient has failed to adequately respond to conventional therapy (e.g. sulfasalazine, mesalamine, antibiotics, corticosteroids, azathioprine, 6-mercaptopurine, leflunomide);** or
 3. **The recipient has fistulizing Crohn's disease;** and
 4. **The recipient has a negative tuberculin test;** and
 5. **The recipient** does not have an active infection or a history of recurring infections.
- g. Ulcerative Colitis:
1. **The recipient has a diagnosis of moderate to severe ulcerative colitis;** and
 2. **The recipient has failed to adequately respond to one or more of the following standard therapies:**
 - a. Corticosteroids;

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- b. 5-aminosalicylic acid agents;
 - c. Immunosuppressants; and/or
 - d. Thiopurines; and
- 3. The recipient has a negative tuberculin test; and
 - 4. The recipient does not have an active infection or history of recurring infections.
- 2. Approval will not be given for the use of more than one biologic at a time (combination therapy).
 - 3. Prior Authorization Guidelines

Prior Authorization forms are available at:
<http://www.medicaid.nv.gov/providers/rx/rxforms.aspx>

Prior authorization approval will be for one year.

Therapeutic Class Overview Platelet Inhibitors

Therapeutic Class

- Overview/Summary:** Platelet inhibitors play a major role in the management of cardiovascular, cerebrovascular, and peripheral vascular diseases. The agents in the class are Food and Drug Administration (FDA)-approved for a variety of indications including treatment and/or prevention of acute coronary syndromes, stroke/transient ischemic attack, and thrombocytopenia. The platelet inhibitors are also indicated to prevent thrombosis in patients undergoing cardiovascular procedures and/or surgery. The platelet inhibitors exert their pharmacologic effects through several different mechanisms of action.¹⁻⁸ The newest platelet inhibitor to be FDA-approved is vorapaxar (Zontivity[®]), which is indicated for the reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction (MI) or with peripheral arterial disease (PAD).⁷ Vorapaxar (Zontivity[®]), is the first in a new class of antiplatelet agents called protease-activated receptor-1 (PAR-1) antagonists. It is a competitive and selective antagonist of PAR-1, the major thrombin receptor on human platelets. It works by inhibiting thrombin-induced platelet aggregation and thus blood clot formation. In addition, vorapaxar is not a prodrug and does not require enzymatic conversion to become pharmacologically active, and is not subject to potential drug interactions associated with the other agents.⁷ Vorapaxar is available for once-daily dosing in combination with other antiplatelet agents (either clopidogrel and/or aspirin). Clopidogrel and prasugrel are administered once-daily, while ticagrelor is dosed twice daily.^{2,4,5}

Table 1. Current Medications Available in the Therapeutic Class¹⁻⁸

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/ Strength	Generic Availability
Single-Entity Agents			
Anagrelide (Agrylin ^{®*})	Treatment of thrombocytopenia associated with myeloproliferative disorders [†]	Capsule: 0.5 mg 1 mg	a
Clopidogrel (Plavix ^{®*})	Recent myocardial infarction, recent stroke, or established peripheral arterial disease, reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome [‡]	Tablet: 75 mg 300 mg	a
Dipyridamole (Persantine ^{®*})	Prevention of postoperative thromboembolic complications of cardiac valve replacement [§]	Tablet: 25 mg 50 mg 75 mg	a
Prasugrel (Effient [®])	Reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome who are being managed with percutaneous coronary intervention	Tablet: 5 mg 10 mg	-
Ticagrelor (Brilinta [®])	Reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome	Tablet: 90 mg	-
Ticlopidine (Ticlid ^{®*})	Reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation [#] , reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke	Tablet: 250 mg	a
Vorapaxar (Zontivity [®])	Reduce the risk of thrombotic cardiovascular events in patients with a history of myocardial infarction or with peripheral arterial disease:	Tablet: 2.08 mg	-

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/ Strength	Generic Availability
	Tablet: 2.08 mg QD in combination with other antiplatelet agents (clopidogrel and/or aspirin)		
Combination-Products			
Aspirin/ extended-release dipyridamole (Aggrenox®)	Reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis	Capsule: 25/200 mg	-

*Generic available in at least one dosage form or strength.

†To reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms including thrombohemorrhagic events.

‡For patients with non-ST-segment elevation acute coronary syndrome, including patients who are to be managed medically and those who are to be managed with coronary revascularization, and for patients with ST-elevation myocardial infarction.

§As adjunct to coumarin anticoagulants.

|| Patients who are to be managed with percutaneous coronary intervention as follows: patients with unstable angina or non-ST-elevation myocardial infarction and patients with ST-elevation myocardial infarction when managed with primary or delayed percutaneous intervention.

¶Patients with unstable angina, non-ST-elevation myocardial infarction, or ST-elevation myocardial infarction.

#As adjunct to aspirin.

Evidence-based Medicine

- Clopidogrel, Food and Drug Administration-approved in 1997, has been the principle platelet inhibitor for several years as the clinical data supporting its use is well established.¹⁰⁻¹⁵
- The RAPID Primary PCI study compared prasugrel to ticagrelor in patients who had a ST-Segment elevation myocardial infarction (STEMI) who were to undergo percutaneous coronary intervention (PCI). Prasugrel was noninferior as compared with ticagrelor in terms of residual platelet reactivity two hours after the loading dose (P=0.207).¹⁰⁹
- Approval of prasugrel for use in acute coronary syndromes (ACS) was based on the clinical evidence for safety and efficacy derived from the TRITON-TIMI 38 study (N=13,608). Within the study, prasugrel was significantly more effective compared to clopidogrel in reducing ischemic events in patients with ACS who underwent percutaneous coronary intervention. Prasugrel did not demonstrate a mortality benefit and a significantly higher rate of major, minor, life-threatening, and fatal bleeding events was observed with prasugrel.¹⁶
 - Of note, a benefit with prasugrel was not observed in certain patient subgroups within TRITON-TIMI 38, specifically those who were ≥75 years of age, those weighing <60 kg, and those with a past history of stroke or transient ischemic attack.
- The approval of ticagrelor for use in ACS was based on the clinical evidence for safety and efficacy derived from the PLATO study. Within the trial, hospitalized patients with documented ACS, with or without ST-elevation, were randomized to either ticagrelor or clopidogrel (N=18,624). After 12 months of treatment, ticagrelor was significantly more effective compared to clopidogrel in reducing the primary composite endpoint of cardiovascular death, myocardial infarction, or stroke; without increasing the risk of major bleeding. Ticagrelor demonstrated a mortality benefit compared to clopidogrel.¹⁷
 - There was no difference in quality of life scores between the clopidogrel group and the ticagrelor group in hospitalized patients with ACS.⁷⁶
- Brener et al evaluated prasugrel-treated patients to clopidogrel-treated patients with STEMI. The prasugrel group had higher rates of procedural success (P=0.03), TIMI 3 flow (P=0.06), and lower corrected TIMI frame counts (P=0.008).⁷⁷
- Approval of vorapaxar was based on the results of the TRA2°P-TIMI 50 trial. The composite of cardiovascular death, MI, stroke, and urgent coronary revascularization (UCR) in post-MI or PAD patients without a history of stroke or transient ischemic attack (TIA) the vorapaxar group showed a significant 17% relative risk reduction over the three years of the study (HR, 0.83; 95%CI, 0.76 to 0.90; P<0.001).⁷⁸
 - Patients who had a previous stroke were removed from the study after 24 month follow-up assessments. Among the patients with a history of stroke, the rate of intracranial hemorrhage

in the vorapaxar group higher ($P < 0.001$), without a history of stroke and was significantly increased as compared with the group without a prior stroke ($P = 0.049$).⁷⁸

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - Use of the platelet inhibitors, as monotherapy or combination therapy, is based on the specific clinical indication and the patient's risk for thromboembolic events.²⁴⁻⁴⁰
 - Antiplatelet therapy (aspirin plus extended-release [ER] dipyridamole or clopidogrel > aspirin) is recommended for long-term secondary prevention in patients with an acute ischemic stroke who are not receiving thrombolysis. Combination aspirin plus dipyridamole ER is recommended over aspirin, and clopidogrel is suggested over aspirin. Dual antiplatelet therapy should be used with caution and is favored in patients who have had a recent acute myocardial infarction, other ACS, or recently placed coronary stent.^{24,25}
 - According to the 2012 guideline on Antithrombotic Therapy and Prevention of Thrombosis by the American College of Chest Physicians, dual therapy aspirin with clopidogrel or ticagrelor or prasugrel monotherapy is recommended in the first year following ACS in patients regardless of PCI status.²⁴
 - § The guideline recommends ticagrelor plus low-dose aspirin over clopidogrel plus low-dose aspirin in patients post-ACS independent of whether PCI has been conducted.²⁴
 - The 2013 guidelines for managing patients with STEMI by American College of Cardiology Foundation and American Heart Association recommend clopidogrel, prasugrel or ticagrelor for one year following PCI, without recommendation for one antiplatelet drug over another.²⁸
 - The 2011 European Society of Cardiology guideline for the management of ACS in patients presenting without persisting ST-elevation recommends ticagrelor first-line in patients at moderate to high risk of ischemic events, regardless of treatment strategy and including those pretreated with clopidogrel.²⁷
 - § If coronary anatomy is known and PCI is planned, prasugrel is recommended.
 - § Clopidogrel is recommended in patients who cannot receive prasugrel or ticagrelor.
 - The 2011 American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions guideline for percutaneous intervention recommends clopidogrel, prasugrel, and ticagrelor as treatment options.²⁸
 - § Treatment with all agents should be continued for at least one year.
- Other Key Facts:
 - Anagrelide, dipyridamole, and ticlopidine are available generically.

References

1. Agrylin[®] [package insert]. Wayne (PA): Shire US, Inc.; 2014 Feb.
2. Plavix[®] [package insert]. Bridgewater (NJ): Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership; 2013 Sep.
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OO. Platelet Inhibitors

Therapeutic Class: Platelet Inhibitors

Last Reviewed by the DUR Board: January 23, 2014

Brilinta® (ticagrelor) and Effient® (prasugrel) are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the Social Security Act and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

Authorization will be given if the following criteria are met and documented:

a. Brilinta® (ticagrelor)

1. The recipient has a diagnosis of Acute Coronary Syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction or ST elevation myocardial infarction; and
2. The recipient does not have an active pathological bleed or history of intracranial hemorrhage; and
3. The recipient will be receiving concomitant treatment with aspirin in a dose of <100 mg/daily; and
4. The recipient has been started and stabilized on the requested medication; or
5. The recipient has experienced an adverse event with or has an allergy or contraindication to clopidogrel; or
6. Another clinically appropriate rationale is provided for why clopidogrel cannot be used.

c. Effient® (prasugrel)

1. The recipient has a diagnosis of ACS (unstable angina, non-ST elevation myocardial infarction or ST elevation myocardial infarction); and
2. The recipient does not have an active pathological bleed or history of transient ischemic attack or cerebral vascular accident (CVA); and
3. The recipient will be receiving concomitant treatment with aspirin in a dose of <100 mg/daily; and

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4. The recipient has a history of percutaneous coronary intervention; and
5. The recipient has been started and stabilized on the requested medication; or
6. The recipient has experienced an adverse event with or has an allergy or contraindication to clopidogrel; or
7. Another clinically appropriate rationale is provided for why clopidogrel cannot be used.

2. Prior Authorization Guidelines

- a. Prior authorization approval will be for one year.
- b. Prior Authorization forms are available at:
<http://www.medicaid.nv.gov/providers/rx/rxforms.aspx>

Therapeutic Class Overview **Inhaled Antimuscarinics**

Therapeutic Class

Overview/Summary: The inhaled antimuscarinics (anticholinergics) are a class of bronchodilators primarily used in the management of chronic obstructive pulmonary disease (COPD), a condition characterized by progressive airflow restrictions that are not fully reversible.¹⁻³ Symptoms associated with COPD typically include dyspnea, cough, sputum production, wheezing and chest tightness. Specifically, inhaled antimuscarinics work via the inhibition of acetylcholine at parasympathetic sites in bronchial smooth muscle causing bronchodilation. Meaningful increases in lung function can be achieved with the use of inhaled antimuscarinics in patients with COPD.¹⁻³ The available single-entity inhaled antimuscarinics include aclidinium (Tudorza[®] Pressair), ipratropium (Atrovent[®], Atrovent[®] HFA) and tiotropium (Spiriva[®] HandiHaler).⁴⁻¹⁰ Ipratropium, a short-acting bronchodilator, has a duration of action of six to eight hours and requires administration four times daily. Aclidinium and tiotropium are both considered long-acting bronchodilators. Aclidinium is dosed twice daily, while tiotropium has a duration of action of greater than 24 hours and therefore, is administered once daily. Ipratropium is available as a metered dose aerosol inhaler for oral inhalation as well as a solution for nebulization. Both aclidinium and tiotropium are available as dry powder inhalers for oral inhalation.⁴⁻¹⁰ The combination products include ipratropium/albuterol, which is available as an inhaler (Combivent Respimat[®]) and solution for nebulization (DuoNeb[®]), and umeclidinium/vilanterol (Anoro Ellipta[®]), which is available as a powder inhaler for oral inhalation. Aclidinium, ipratropium, tiotropium and umeclidinium/vilanterol are Food and Drug Administration (FDA)-approved for the maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. Tiotropium is the only inhaled antimuscarinic that is FDA-approved for reducing exacerbations associated with COPD. Ipratropium/albuterol is indicated for the treatment of bronchospasms associated with COPD in patients who require more than one bronchodilator. The ipratropium (Atrovent[®]) and ipratropium/albuterol solutions for nebulization are the only inhaled antimuscarinic products that are currently available generically.¹¹⁻¹²

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, inhaled bronchodilators are preferred for the management of COPD. Regular use of long-acting β_2 -agonists or short- or long-acting anticholinergics improves health status and long-acting anticholinergics reduce the rate of COPD exacerbations and improve the effectiveness of pulmonary rehabilitation. The choice of agent should be based on availability and individual response in terms of symptom relief and side effects. The GOLD guidelines emphasize that the use of long-acting bronchodilators is more effective and convenient than the use of short-acting bronchodilators.¹

Table 1. Current Medications Available in Therapeutic Class⁴⁻¹⁰

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agents			
Aclidinium (Tudorza [®])	Long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema	Powder for oral inhalation: 400 µg	-
Ipratropium (Atrovent ^{®*} , Atrovent HFA [®])	Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema	Aerosol for oral inhalation (Atrovent HFA [®]): 17 µg (200 actuations/unit) Solution for nebulization (Atrovent ^{®*}): 500 µg (0.02%)	a
Tiotropium (Spiriva [®])	Long-term, once-daily, maintenance treatment of bronchospasm associated	Powder for oral inhalation:	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; reduce exacerbations in chronic obstructive pulmonary disease patients	18 µg	
Combination Products			
Ipratropium/ albuterol (Combivent [®] , DuoNeb ^{®*})	Patients with chronic obstructive pulmonary disease on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator†; treatment of bronchospasm associated with chronic obstructive pulmonary disease in patients requiring more than one bronchodilator‡	Aerosol for oral inhalation (Combivent [®]): 21/120 µg [#] (200 metered inhalations) Inhalation spray (inhaler) (Combivent Respimat [®]): 20/100 µg [#] (120 actuations) Solution for nebulization (DuoNeb ^{®*}): 0.5/3.0 mg (3 mL vials)	a
Umeclidinium/ vilanterol (Anoro Ellipta [®])	Long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and/or emphysema	Powder for oral inhalation: 62.5/25 µg	-

* Generic available in at least one dosage form or strength.

† Combivent Respimat[®].

‡ DuoNeb[®].

#Delivering 103 µg of albuterol (90 µg albuterol base) and 18 µg of ipratropium.

Evidence-based Medicine

- The inhaled antimuscarinics have demonstrated to improve lung function and/or exercise tolerance in patients with chronic obstructive pulmonary disease (COPD).¹⁶⁻⁶³
- In general, the inhaled antimuscarinics have been demonstrated to improve lung function and exercise tolerance in patients with COPD. Few head-to-head trials have noted significant differences in improvements in lung function favoring tiotropium over ipratropium.³¹⁻³²
- In a large study of current or former smokers with COPD (N=828), patients were randomized to receive aclidinium 200 or 400 µg twice daily or placebo over 24 weeks. The mean change from baseline in trough forced expiratory volume in one second (FEV₁), the primary endpoint, was significantly higher in patients treated with aclidinium 200 or 400 µg compared to patients randomized to receive placebo (99±22 and 128±22 mL, respectively; P<0.0001).¹⁶
- In a 12-week study by Kerwin et al, patients randomized to receive aclidinium 200 or 400 µg twice daily experienced a statistically significant increase from baseline in trough FEV₁ compared to patients in the placebo group (86 and 124 mL, respectively; P<0.0001 for both).¹⁷ Significant improvements persisted through 52 weeks in an extension study.¹⁸
- Singh and colleagues conducted a small, five-way crossover study evaluating 100, 200 and 400 µg of aclidinium, formoterol 12 µg or placebo. Following seven days of treatment, the change from baseline in FEV₁ area under the curve over 12 hours (FEV₁ area under the curve [AUC]₀₋₁₂) was 154 mL in the aclidinium 100 µg group, 176 mL in the aclidinium 200 µg group, 208 mL in the aclidinium 400 µg group and 210 mL for the formoterol 12 µg group compared to placebo (P<0.0001 for all compared to placebo). The difference in FEV₁ AUC₀₋₁₂ between the aclidinium 400 µg and formoterol 12 µg treatment groups was not statistically significant (P value not reported).⁴²

- There is inconsistent data regarding a clinical advantage of tiotropium over other long-acting bronchodilators, although in one trial, tiotropium significantly increased the time to first exacerbation by 42 days compared to salmeterol (187 vs 145 days; $P < 0.001$).⁵⁰
- When tiotropium is used in combination with a bronchodilator from a different pharmacologic class, a significant clinical advantage is demonstrated.⁵⁴⁻⁵⁵
- In comparison to other short-acting bronchodilators, ipratropium does not appear to offer any significant advantages. In a systematic review, there was no statistically significant difference in short-term FEV₁ changes (up to 90 minutes post dose) between individuals receiving ipratropium compared to a β_2 -adrenergic agonist (P value not reported).⁴²
- As with tiotropium, improved outcomes are achieved when ipratropium is used in combination with other bronchodilators.⁴³⁻⁴⁴ Furthermore, ipratropium/albuterol has consistently demonstrated statistically significant improvements in FEV₁ and forced vital capacity in clinical studies when compared to either agent alone.³⁴⁻³⁸
- The ipratropium/albuterol (Combivent Respimat[®]) inhaler has demonstrated improvements in FEV₁ that are equivalent to the aerosol metered dose inhaler.³⁹
- Umeclidinium/vilanterol 62.5/25 μg once daily was compared to placebo and the single agents, umeclidinium 62.5 μg once daily and vilanterol 25 μg once daily. The primary endpoint of trough FEV₁ on treatment day 169 was significantly improved in all treatment groups compared to placebo ($P < 0.001$ for all). In addition, umeclidinium/vilanterol treated patients also had significant improvements compared to monotherapy with umeclidinium and vilanterol (0.052 L; $P = 0.004$ and 0.095 L; $P < 0.001$ respectively).⁶³

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - The Global Initiative for Chronic Obstructive Lung Disease guidelines state that inhaled bronchodilators are preferred for the management of chronic obstructive pulmonary disease (COPD). Regular use of long-acting β_2 -agonists or short- or long-acting anticholinergics improves health status and long-acting anticholinergics reduce the rate of COPD exacerbations and improve the effectiveness of pulmonary rehabilitation. The choice of agent should be based on availability and individual response in terms of symptom relief and side effects. The use of long-acting bronchodilators is more effective and convenient than short-acting bronchodilators.
 - The National Institute for Clinical Excellence states that short-acting bronchodilators should be the initial empiric treatment for the relief of breathlessness and exercise limitation while long-acting bronchodilators should be used in patients who remain symptomatic with use of short-acting agents. Once-daily long-acting antimuscarinic agents are preferred compared to four-times-daily short-acting antimuscarinic agents in patients with stable COPD who remain symptomatic despite use of short-acting agents and in whom the decision has been made to begin regular maintenance therapy with an antimuscarinic.²
- Other Key Facts:
 - Acclidinium (Tudorza[®]), approved in July 2012, is the newest inhaled antimuscarinic agent to be approved by the Food and Drug Administration (FDA).⁴
 - Tiotropium (Spiriva[®]) is the only agent within the class that is FDA-approved to reduce the risk of COPD exacerbations.⁶
 - By January 1, 2014, the Combivent[®] aerosol meter dose inhaler will be discontinued, and the recently- approved Combivent Respimat[®] will be the only one of these two products available.¹²

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Therapeutic Class Overview

β_2 -Agonists Single Entity Agents

Therapeutic Class

- Overview/Summary:** Respiratory β_2 -agonists are primarily used to treat reversible airway disease. Their Food and Drug Administration (FDA)-approved indications include asthma, chronic obstructive pulmonary disease, exercise-induced asthma/bronchospasm, and/or and reversible bronchospasm. Respiratory β_2 -agonists act preferentially on the β_2 -adrenergic receptors. Activation of these receptors on airway smooth muscle leads to the activation of adenylyl cyclase and an increase in intracellular cyclic-3',5'-adenosine monophosphate (cyclic AMP). The increase in cyclic AMP leads to activation of protein kinase A and the inhibition of myosin phosphorylation resulting in lower intracellular ionic calcium and smooth muscle relaxation. Increased cyclic AMP levels also inhibit the release of mediators from mast cells in the airways.¹⁻²⁰ The β_2 -agonists can be divided into two categories: short-acting and long-acting. The short-acting respiratory β_2 -agonists consist of albuterol, levalbuterol, metaproterenol, pirbuterol and terbutaline. The long-acting β_2 -agonists include extended release albuterol, arformoterol, formoterol, indacaterol and salmeterol. Respiratory β_2 -agonists elicit a similar biologic response in patients suffering from reversible airway disease, but differ in their dosing requirements, pharmacokinetic parameters and potential adverse events.¹⁻²⁰ As a result of the Clean Air Act and the Montreal Protocol on Substances that Deplete the Ozone Layer, the FDA made the decision to end production, marketing and sale of all albuterol metered dose inhalers (MDIs) containing chlorofluorocarbons (CFCs) as their propellant by December 31, 2008. These inhalers were replaced by MDIs which use hydrofluoroalkanes (HFAs). There is no difference in the safety or efficacy of the HFA inhalers compared to the CFC inhalers; however, there may small differences in taste and/or feel with the HFA inhalers. The deadline for removal of the pirbuterol (Maxair[®]) CFC inhaler is December 31, 2013.²¹

Table 1. Current Medications Available in the Therapeutic Class¹⁻²⁰

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Short-Acting β_2-agonists			
Albuterol (AccuNeb ^{®*} , ProAir HFA [®] , Proventil HFA [®] , Ventolin HFA [®] , Vospire ER ^{®*})	Relief of bronchospasm in patients with asthma (inhalation solution, oral formulations only), treatment or prevention of bronchospasm in patients with reversible obstructive airway disease (meter dose inhaler), prevention of exercise-induced bronchospasm (meter dose inhaler only)	Meter dose aerosol inhaler (HFA): 120 μ g albuterol sulfate (60 or 200 inhalations) Solution for nebulization: 0.63 mg 1.25 mg 2.5 mg 0.5% concentrated solution (3 mL unit dose vials) Sustained-release tablet: 4 mg 8 mg Syrup: 2 mg/5 mL	a

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		Tablet: 2 mg 4 mg	
Levalbuterol (Xopenex [®] *, Xopenex HFA [®])	Treatment or prevention of bronchospasm in patients with reversible obstructive airway disease	Meter dose aerosol inhaler (HFA): 59 μ g (80 or 200 inhalations) Solution for nebulization: 0.31 mg 0.63 mg 1.25 mg (3 mL vials)	a
Metaproterenol*	Prevention and treatment of asthma and reversible bronchospasm, which may occur in association with bronchitis and emphysema	Syrup: 10 mg/5 mL Tablet: 10 mg 20 mg	a
Pirbuterol (Maxair Autohaler [®])	Treatment or prevention of bronchospasm in patients with reversible obstructive airway disease	Breath activated aerosol inhaler: 200 μ g (80 or 400 inhalations)	-
Terbutaline* (Brethine [®])	Prevention and treatment of asthma and reversible bronchospasm, which may occur in association with bronchitis and emphysema	Injection: 1 mg/mL (2 mL vial) Tablet: 2.5 mg 5 mg	a
Long-Acting β_2-agonists			
Arformoterol (Brovana [®])	Long-term, twice daily, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema	Solution for nebulization: 15 μ g (2 mL)	-
Formoterol (Foradil [®] , Perforomist [®])	Treatment of asthma and prevention of bronchospasm as concomitant therapy with a long-term asthma control medication in patients with reversible obstructive airways disease, including patients with nocturnal symptoms (dry powder inhaler only), long-term, twice daily, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema, prevention of exercise-induced bronchospasm (dry powder inhaler only)	Capsule for inhalation: 12 μ g Solution for nebulization: 20 μ g/2 mL	-
Indacaterol (Arcapta Neohaler [®])	The long term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema	Capsule for inhalation: 75 μ g	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Salmeterol (Serevent Diskus [®])	Treatment of asthma and prevention of bronchospasm as concomitant therapy with a long-term asthma control medication in patients with reversible obstructive airways disease, including patients with nocturnal symptoms, long-term, twice daily, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema, prevention of exercise-induced bronchospasm	Dry powder inhaler: 50 μ g (28 or 60 inhalations)	-

COPD=chronic obstructive pulmonary disease, ER=extended release, HFA=hydrofluoroalkanes

*Generic available in at least one dosage form or strength.

Evidence-based Medicine

- Clinical trials have demonstrated the efficacy of short-acting and long-acting β_2 -agonists (SABAs and LABAs) in providing relief from asthma exacerbations, chronic obstructive pulmonary disease (COPD) exacerbations and exercise induced asthma (EIA).²²⁻⁷⁹
- In clinical trials that comparing albuterol to levalbuterol, inconsistent results have been reported and have not consistently demonstrated improved outcomes with levalbuterol compared to albuterol. Moreover, studies have shown no significant differences between the two agents in the peak change in forced expiratory volume in one second (FEV₁) or the number and incidence of adverse events.²²⁻³²
- Salmeterol and formoterol have been found to improve FEV₁ in patients with mild to moderate asthma who require persistent use of SABAs. In a meta-analysis by Salpeter et al, 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.³³
- A recent systematic review concluded that in patients with COPD, there was no difference in rate of mild exacerbation between patients treated with an ICS or LABA (odds ratio, 1.63; 95% confidence interval [CI], 0.49 to 5.39) or in the rate of moderate or severe COPD exacerbations (relative risk, 0.96; 95% CI, 0.89 to 1.02).³⁴
- Overall, data from published clinical trials demonstrate that treatment with indacaterol consistently results in significantly higher mean trough FEV₁ 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.³⁵⁻⁴⁴

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - Short-acting β_2 -agonists are recommended for patients in all stages of asthma, for symptomatic relief of reversible airway disease and for exercise-induced bronchospasm.^{80,81}
 - Short-acting β_2 -agonists should be used on an as-needed or "rescue" basis.^{80,81}
 - In the chronic management of asthma, the long-acting β_2 -agonists should be used as add-on therapy in patients not adequately controlled on an inhaled corticosteroid.^{80,81}
 - Long-acting β_2 -agonists should not be used as monotherapy for the long-term control of asthma.^{80,81}
 - Long-acting β_2 -agonists can be used for exercise-induced bronchospasm and provide a longer period of coverage compared to short acting β_2 -agonists.^{80,81}
 - Long-acting β_2 -agonists have a role in the treatment of chronic obstructive pulmonary disease (COPD), for patients who remain symptomatic even with current treatment with short-acting bronchodilators.^{80,81}
 - Long-acting β_2 -agonists can be added to other COPD treatment regimens, including an anticholinergic agent, in efforts to decrease exacerbations.^{82,83}

- Other Key Facts:
 - The role of the short- and long-acting respiratory β_2 -agonists in the treatment of asthma and COPD has been well established.
 - Studies have failed to consistently demonstrate significant differences between products.
 - Albuterol oral solution, oral tablets, and solution for nebulization, levalbuterol solution for nebulization, metaproterenol oral solution and oral tablets, and terbutaline oral tablets and solution for injection are available generically.
 - There are currently three branded albuterol hydrofluoroalkanes (HFA) inhalers; however, no generic equivalents are available.
 - None of the long-acting respiratory β_2 -agonists are currently available generically.

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RxOutlook®

Focus: Biosimilars

biosimilars

NUMBER OF DRUGS IN DEVELOPMENT: ~ 110

MARKET VALUE & OUTLOOK: The biosimilars market is expected to reach \$35 billion globally by 2020. By 2020, biologic medications worth an estimated \$81 billion globally are expected to experience patent expiry. The cost of developing a biosimilar is estimated to be between \$75 and \$250 million. Biosimilars are expected to have a 20 to 30 percent discount compared to innovator products (Allied Market Research, 2014; Lucio et al, 2013).

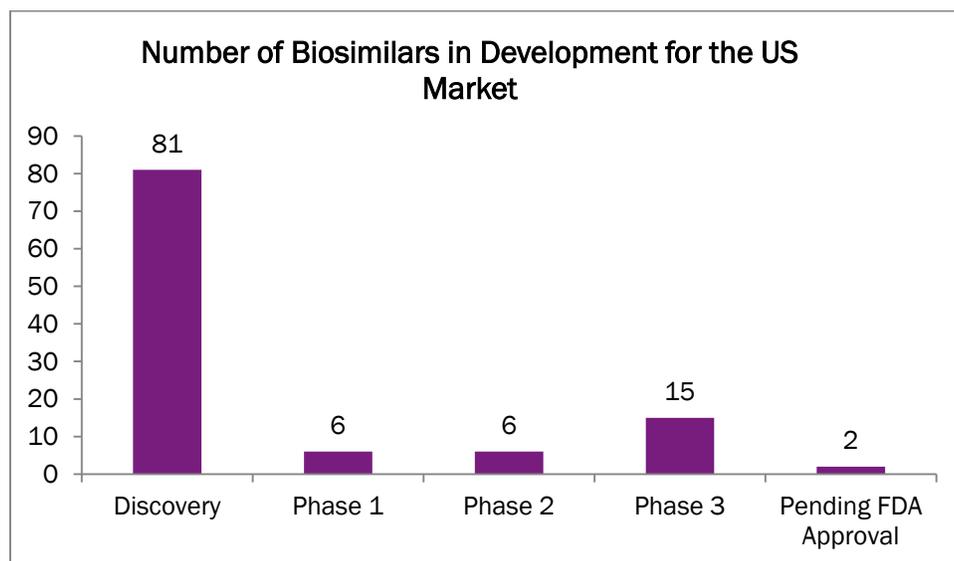
CURRENT BIOSIMILARS MARKET BASKET: No agent has yet been approved through the biosimilar pathway.

EMERGING THERAPIES: All biologic products with expiring patents are targets for biosimilar development.

UPCOMING PATENT EXPIRATIONS: See Biosimilars in Development for the US Market table.

For more information, requests for additional copies, or for questions regarding plan benefit changes, contact your Catamaran Account Manager.

pipeline snapshot



what is a biosimilar?

- ▶ The Food and Drug Administration (FDA) defines a biosimilar as “a biological product that is highly similar to a US-licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product” (FDA, 2011).
- ▶ Another definition is “a biosimilar can be simply defined as a copy of a therapeutic protein not developed by the original manufacturer and approved through some abbreviated regulatory process” (Lucio et al, 2013).
- ▶ When comparing a biosimilar and the original reference product, the formulation and the delivery device/container may be different. A biosimilar may apply for fewer than all routes of administration and indications for which the reference product is licensed. The strength of the biosimilar and the reference product must be the same (FDA, 2012[a]).
- ▶ Biologics differ from small-molecule drugs. Small-molecule drugs are relatively uncomplicated in structure, their molecular weights are small, and they are synthesized through predictable processes. The generic version of a small-molecule drug contains the identical active ingredient contained in the reference innovator product. Biologics are proteins derived from living sources, their molecular weights are much larger, their manufacturing steps are often proprietary and contain

complex processes, and they have the ability to produce immunogenicity. A biosimilar may be a slightly different molecule, but it will exert a similar effect (Lucio et al, 2013).

guidance for biosimilars

- A biosimilar pathway was created through the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). Under the BPCI Act, a sponsor may seek approval of a “biosimilar” product under new section 351(k) of the Public Health Service (PHS) Act (FDA, 2011).
- The BPCI Act is modeled after the Drug Price Competition and Patent Term Restoration Act of 1984 (i.e., the ‘Hatch-Waxman’ Act) which provides for abbreviated approval pathways for generic drugs to avoid unnecessary duplication of human and animal testing (FDA, 2011). However, it should be noted there is no way to make identical copies of biologics due to the complex make-up of the molecules.
- The biosimilar 351(k) pathway requires clinical studies whereas the traditional generic pathway, via an abbreviated new drug application (ANDA), does not require clinical studies, just demonstration of bioequivalence.
- To help implement the BPCI Act, the FDA has released a number of guidance documents. These documents are outlined in the table below.
- Additionally, the FDA will be developing two more draft guidances to be released prior to the end of 2014: (1) Considerations in Demonstrating Interchangeability to a Reference Product and (2) Labeling for Biosimilar Biological Products.

GUIDANCE DOCUMENTS	
Name of Document	Description
Guidance for Industry on Biosimilars: Q & As Regarding Implementation of the BPCI Act of 2009 (Click here for access to the full document)	This guidance is meant to provide answers to common questions from manufacturers interested in developing proposed biosimilar products. The guidance is broken into three parts: (1) Biosimilarity or Interchangeability; (2) Provisions Related to Requirement to Submit a BLA for a “Biological Product”; and (3) Exclusivity.
Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (Click here for access to the full document)	This guidance gives an overview of FDA’s approach to determining biosimilarity. The FDA recommends that manufacturers consider a stepwise approach in their development of a biosimilar product. The FDA will consider the totality of evidence for the demonstration of biosimilarity.
Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (Click here for access to the full document)	This guidance provides recommendations to manufacturers on the scientific and technical information of the chemistry, manufacturing, and controls (CMC) section of a marketing application for a proposed biosimilar product. It provides guidance on analytical studies that may be relevant for assessing whether the proposed biosimilar protein product and a reference product are highly similar.
Guidance for Industry: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (Click here for access to the full document)	This guidance is meant to help manufacturers design clinical pharmacology studies to support their application for a biosimilar agent. The FDA will review the clinical trials submitted and make one of four assessments: (1) Not similar: further development is not recommended unless changes to the manufacturing process are made; (2) Similar: further information is needed to determine if the product is highly similar to the reference product; (3) Highly similar: the proposed biosimilar product meets the statutory standard for analytical similarity; or (4) Highly similar with fingerprint-like similarity: the proposed biosimilar product meets the statutory standard for analytical similarity based on integrated, multi-parameter approaches that are extremely sensitive in identifying analytical differences.
Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act (Click here for access to the full document)	This guidance is intended to assist manufacturers who are developing biological products, manufacturers of biologic license applications (BLAs), and other interested parties in providing information that will help the FDA determine the date of first licensure for a reference product. The reference product exclusivity period is the time period when the FDA may first accept an application for a biosimilar (four years after the date of first licensure of the reference product) to when the FDA may make the product effective (12 years after the reference product was first licensed). An additional six-month period will be added to both the 4- and 12-year periods if pediatric studies are conducted.

GUIDANCE DOCUMENTS

Name of Document	Description
Guidance for Industry: Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants (Click here for access to the full document)	This guidance is intended to assist manufacturers in generating and submitting a meeting request and the associated meeting package to the FDA for biosimilar biological products intended to be submitted under 351(k) of the Public Health Service (PHS) Act.
Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations (Click here for access to the full document)	This book lists biological products, including any biosimilar and interchangeable biological products licensed by FDA under the PHS Act. The list includes the date a biological product was licensed and whether the FDA evaluated the biological product for reference product exclusivity. The Purple Book will also enable a user to see whether a biological has been determined by the FDA to be biosimilar to or interchangeable with a reference biological product. Biosimilar and interchangeable biological products will be listed under the reference product to which biosimilarity or interchangeability was demonstrated.

Primary informational sources: FDA, 2012[a]; FDA, 2012[b]; FDA, 2012[c]; FDA, 2013; FDA, 2014[a]; FDA, 2014[b]; FDA, 2014[c]

unanswered questions about biosimilars

- It is still unknown how biosimilars will be named. In September 2013, The Generic Pharmaceutical Association (GPhA) filed a Citizen’s Petition with the FDA. The GPhA feels all biosimilars should share the same international non-proprietary name (INN) as the biologic products to which they refer. They feel there are no clinically meaningful differences that require a unique name (GPhA, 2013). The World Health Organization (WHO) INN Expert Group states the following, “There should be no change in policy and no distinctive INN designation introduced to indicate a biosimilar product” (WHO, 2006). The WHO has recently revised their 2006 statement with a draft document in 2014 (WHO, 2014). The WHO had asked for comments by September 19, 2014. In this draft, the WHO is now proposing that a Biologic Qualifier (BQ) be assigned to each biological product in addition to the assigned INN. The BQ will provide a unique identification code distinct from the INN for all biological substances that are assigned INNs. The BQ would uniquely identify directly or indirectly the manufacturer and manufacturing site of the active substance in a biological product. The individual regulatory authority would voluntarily elect to adopt the BQ. The United States Pharmacopeial Convention (USP) supports the WHO’s proposed BQ and feels it is essential that the BQ not be part of the INN. The USP also supports the BQ being applied to all biologics (USP, 2014).
- In contrast, Pharmaceutical Research and Manufacturers of America (PhRMA) feels each biologic product should have a unique name with the use of common stems to indicate relatedness between products (PhRMA, 2010). Additionally, a number of physician organizations and individual physicians have sent a letter to the FDA commissioner recommending unique names for biosimilars. This group feels that unique names will allow better tracking of adverse events and also alert physicians to approved uses for the biosimilar (MM&M, 2014).
- The FDA has stated they will be releasing draft guidance on the naming of biosimilars in 2014.
- It is unknown how interchangeability between biosimilars and their referenced biologic should be demonstrated. The BPCI Act states that a biosimilar should have “the same clinical effect in any given patient” (FDA, 2011). No scientific, regulatory or medical guidelines currently exist to give direction on how to demonstrate this. The BPCI Act does give the FDA the authority to make these determinations. Draft guidelines are due from the FDA before the end of this year.
- Even though federal guidance for biosimilar development is not clearly defined and no product has been approved through the 351(k) biosimilar pathway, several states have enacted their own biosimilar laws. These states include Delaware, Florida, Indiana, Massachusetts, North Dakota, Oregon, Utah, and Virginia. Three states, Illinois, Michigan and Pennsylvania, have pending legislation. The state laws center around the following: (1) Requirements for pharmacists to notify patients and/or prescribers upon dispensing an interchangeable biosimilar in a specified amount of time; (2) Record-keeping requirements for pharmacists and prescribers for a specified amount of time; and (3) Maintaining a list of interchangeable biosimilar drugs (Pharmaceutical Care Management Association [PCMA], 2014). Further information about individual state laws may be found at the following links: [FDA Law Blog: The Biosimilars State Legislation Scorecard](#); [Indiana](#); [Delaware](#); and [Massachusetts](#).
- Pharmacy and Therapeutics (P&T) Committees will need to determine how they will evaluate biosimilars. Many factors will need to be evaluated such as: (1) efficacy, including clinical data and range of indications; (2) manufacturing capabilities/processes; (3) safety, including across all indications and long-term data; (4) interchangeability; and (5) immunogenicity.

emerging biosimilars

- ▶ On July 24, 2014, Sandoz announced its Biologic License Application (BLA) for the biosimilar, filgrastim, had been accepted by the FDA. The BLA is the first to be filed through the biosimilar pathway that was created through the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). The reference product is NEUPOGEN by Amgen (Sandoz, 2014).
- ▶ On August 8, 2014, Celltrion announced its BLA for the biosimilar, infliximab, had been filed with the FDA through the BCPI Act. The reference product is REMICADE by Janssen. The biosimilar infliximab known as REMSIMA has been approved in other countries (Celltrion, 2014).
- ▶ Insulin and growth hormones are not included as biosimilars. The originator products were filed through the NDA pathway; therefore, any similar product is required to be filed through the NDA 505 pathway.
- ▶ The U.S. pharmaceutical pipeline for biosimilars includes approximately 110 products in various stages of clinical development (i.e., discovery phase through those pending approval with the FDA) (Thomson Cortellis, 2014; BioMedTracker, 2014).
- ▶ The table below outlines biosimilar products that have been submitted to the FDA or are in Phase 3 clinical trials.

BIOSIMILARS IN DEVELOPMENT FOR THE US MARKET

Product Name (generic name)	Company(ies) Developing Biosimilar	Reference Biologic (Originator Company)	Key Patent Expiration(s)	Status
ZARZIO (filgrastim)	Sandoz/Novartis	NEUPOGEN (Amgen)	All patents are expired	<ul style="list-style-type: none"> • Sandoz submitted a biosimilar BLA with reference product, NEUPOGEN, in July 2014 • FDA accepted the BLA on 07/24/2014 • Prescription Drug User Fee Act (PDUFA) date: 05/08/2015 to 06/09/2015
REMSIMA (infliximab)	Celltrion; Hospira	REMICADE (Janssen)	09/04/2018	<ul style="list-style-type: none"> • Celltrion submitted a biosimilar BLA with reference product, REMICADE, in August 2014 • Based on a standard 10-month review period, approval may be seen in Q3 2015 • Celltrion has filed a patent challenge; current patent doesn't expire until the end of 2018
RETACRIT (epoetin alfa)	Hospira	EPOGEN (Johnson & Johnson)	2014; 05/26/2015	<ul style="list-style-type: none"> • Hospira is conducting Phase 3 trials • Hospira is expected to file with the FDA sometime between 09/01/2014 and 04/30/2015
BINOCRIT (epoetin alfa)	Sandoz/Novartis	PROCRIPT (Johnson & Johnson)	2014; 05/26/2015	<ul style="list-style-type: none"> • Sandoz/Novartis is conducting Phase 3 trials • Sandoz' Phase 3 trial is called ACCESS; enrollment to be completed by May 2014
BEMFOLA (follicle-stimulating hormone)	Finox Biotech	GONAL-F (EMD Serono)	Unknown	<ul style="list-style-type: none"> • Finox Biotech is conducting Phase 3 trials • Finox' Phase 3 trial is expected to be completed in March 2016
(follicle-stimulating hormone)	Actavis/Amgen	GONAL-F (EMD Serono)	Unknown	<ul style="list-style-type: none"> • Actavis/Amgen is conducting Phase 3 trials
CHS-0214 (etanercept)	Coherus	ENBREL (Amgen)	11/22/2028	<ul style="list-style-type: none"> • Coherus is conducting Phase 3 trials • Coherus is expecting FDA approval and launch sometime in 2016
GP-2015 (etanercept)	Sandoz	ENBREL (Amgen)	11/22/2028	<ul style="list-style-type: none"> • Sandoz is conducting Phase 3 trials • Sandoz has announced they will seek approval under the biosimilar pathway with plans to launch in 2016
GP-2017 (adalimumab)	Sandoz	HUMIRA (AbbVie)	12/31/2016	<ul style="list-style-type: none"> • Sandoz' Phase 3 trial is called ADACCESS; expected to be completed in December 2015

BIOSIMILARS IN DEVELOPMENT FOR THE US MARKET

Product Name (generic name)	Company(ies) Developing Biosimilar	Reference Biologic (Originator Company)	Key Patent Expiration(s)	Status
CHS-1420 (adalimumab)	Coherus	HUMIRA (AbbVie)	12/31/2016	<ul style="list-style-type: none"> Coherus expects to start Phase 3 trials in H1 2015; Coherus expects to file a BLA in 2016
ABP-501 (adalimumab)	Amgen	HUMIRA (AbbVie)	12/31/2016	<ul style="list-style-type: none"> Amgen is conducting Phase 3 trials in rheumatoid arthritis Amgen announced ABP-501 met the primary endpoint of Psoriasis Area and Severity Index (PASI) percent improvement from baseline to week 16 of treatment in patients with moderate-to-severe plaque psoriasis. This Phase 3 trial was conducted in Canada
ABP-215 (bevacizumab)	Actavis/Amgen	AVASTIN (Genentech)	07/04/2019	<ul style="list-style-type: none"> Actavis/Amgen is conducting Phase 3 trials
BI-695500 (rituximab)	Boehringer Ingelheim	RITUXAN (Genentech/Biogen)	2016; 02/18/2017; 04/19/2018; 05/04/2020	<ul style="list-style-type: none"> Boehringer Ingelheim is conducting Phase 3 trials Boehringer's Phase 3 trial is expected to be completed in April 2015
GP-2013 (rituximab)	Sandoz	RITUXAN (Genentech/Biogen)	2016; 02/18/2017; 04/19/2018; 05/04/2020	<ul style="list-style-type: none"> Sandoz is conducting Phase 3 trials
PF-05280014 (trastuzumab)	Pfizer	HERCEPTIN (Roche)	06/18/2019	<ul style="list-style-type: none"> Pfizer's Phase 3 trial is called REFLECTIONS; expected to be completed in October 2017
ABP-980 (trastuzumab)	Actavis/Amgen/Aurobindo	HERCEPTIN (Roche)	06/18/2019	<ul style="list-style-type: none"> Actavis/Amgen/Aurobindo is conducting Phase 3 trials
LA-EP2006 (pegfilgrastim)	Sandoz	NEULASTA (Amgen)	10/15/2015	<ul style="list-style-type: none"> Sandoz completed two Phase 3 trials by April 2014

Primary informational sources: Amgen, 2014; BioMedTracker, 2014; Catamaran RxOutlook Brand Pipeline Database, 2014; Catamaran RxOutlook Generic Pipeline Database, 2014; FDA Orange Book, 2014; IPD Analytics, 2014; Lucio et al, 2013; Thomson Cortellis, 2014.

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Recap: a monthly summary of pharmaceutical pipeline news, events, and trends

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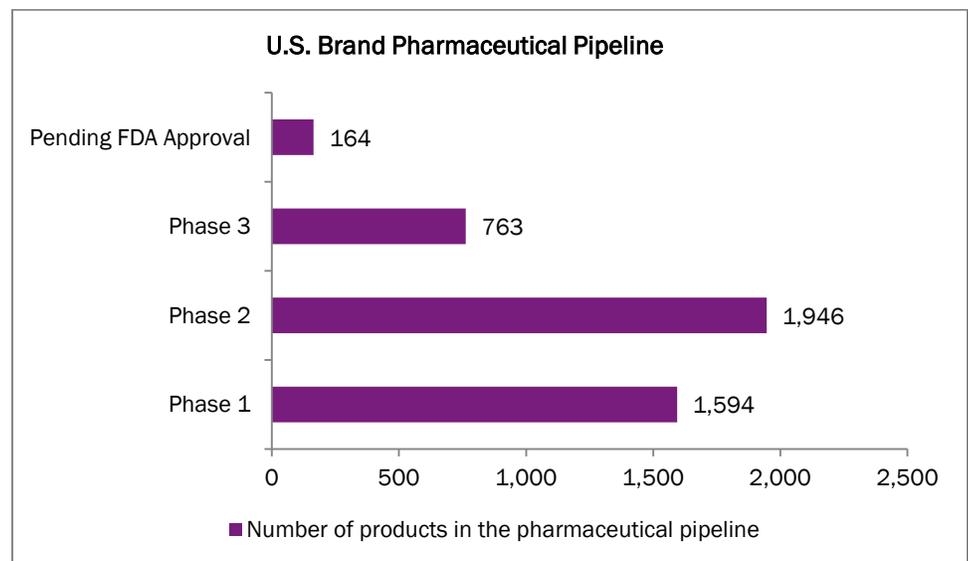
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References & Resources: pg. 17

For more information, requests for additional copies, or for questions regarding plan benefit changes, contact your Catamaran Account Manager.

brand pipeline snapshot

- As of September 30, 2014, there are approximately 4,467 products either pending FDA approval or in phase 1, 2, or 3 of clinical development within the United States.



select pipeline & trend headlines

- [Novartis' new heart failure medicine LCZ696 cut cardiovascular deaths by 20% vs. ACE-inhibitor in landmark PARADIGM-HF trial](#)
- [Achillion Achieves 100 Percent Sustained Virologic Response Rate \(SVR4\) From an Eight Week Phase 2 Trial Evaluating a Ribavirin-Free Regimen of ACH-3102 and Sofosbuvir for Genotype 1 HCV \("Proxy Study"\)](#)
- [Medical Marketing and Media \(MM&M\) – Therapeutic Focus 2014: Women's Health](#)
- [Acura Pharmaceuticals Provides Update on FDA Discussions Surrounding Development of Aversion Hydrocodone With Acetaminophen Tablet](#)
- [Sanofi and Regeneron Announce Presentation of Detailed Positive Results from Four Pivotal Alirocumab Trials at ESC Congress 2014](#)
- [Teva's Reslizumab Delivers Clinically and Statistically Significant Reduction in Asthma Exacerbations in Two Pivotal Phase III Studies](#)
- [Thomson Reuters Lifesciences Connect: Lysosomal Storage Disease: an Example of a Lucrative Ultra-Orphan Market](#)
- [Mallinckrodt Pharmaceutical's MNK-155, an Extended-Release Hydrocodone/Acetaminophen Combination, Shows Efficacy in Phase 3 Acute Pain Trial](#)

- ▶ [Lilly's Basal Insulin Peglispro Demonstrated AbA1C Superiority against LANTUS in Phase III Trials in Patients with Type 1 Diabetes](#)
- ▶ [First-Line Combination of Ambrisentan and Tadalafil Reduces Risk of Clinical Failure Compared to Monotherapy in Pulmonary Arterial Hypertension Outcomes Study](#)
- ▶ [Thomson Reuters Annual Pharmaceutical Factbook Projects Industry's Sales Will Reach \\$1 Trillion in 2014](#)
- ▶ [Decision Resources: The Psoriatic Arthritis Market Will Reach More than \\$3.5 Billion in 2023, Owing to Continued Uptake of Biologics and Penetration of Premium-Priced Orals](#)
- ▶ [Boehringer Ingelheim Presents Pivotal Phase III Data for the Investigational Fixed-Dose Combination of Tiotropium + Olodaterol in COPD](#)
- ▶ [Pharmaceutical Research and Manufacturers of America \(PhRMA\): 44 Medicines and Vaccines Being Developed For Those Living With HIV/AIDS](#)
- ▶ [FDA Drug Information Update- FDA publishes Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations](#)
- ▶ [Generic Pharmaceutical Savings Reach Highest-Ever Watermark of \\$239 Billion in 2013](#)
- ▶ [Merck Announces Data from Pivotal Phase 3 Fracture Outcomes Study for Odanacatib, an Investigational Oral, Once-Weekly Treatment for Osteoporosis](#)
- ▶ [Lilly Announces CYRAMZA™ Phase III Second-Line Colorectal Cancer Trial Meets Primary Endpoint of Overall Survival](#)
- ▶ [Amarin Provides Update on ANCHOR Trial SPA Agreement Rescission Appeal](#)
- ▶ [Merck Discontinues Clinical Development Program of Tecemotide as a Monotherapy in Stage III Non-Small Cell Lung Cancer](#)
- ▶ [FirstWord Lists: The curious case of disappearing HCV drugs](#) (may require free registration to access)
- ▶ [Reuters: Gilead to raise price for new hepatitis C drug above \\$84,000 ; FiercePharma: Balky payers, beware: Gilead eyes \\$95K-or-so price for Sovaldi combo pill](#)
- ▶ [Acura Pharmaceuticals Submits Formal Dispute Resolution Request With FDA Regarding Hydrocodone Bitartrate With Acetaminophen Tablets](#)
- ▶ [Mylan Commences Phase III Clinical Trials for its Generic Version of ADVAIR DISKUS and Insulin Analog to LANTUS](#)
- ▶ [UCERIS \(budesonide\) 2mg Rectal Foam for the Induction of Remission of Mild-to-Moderate Distal Ulcerative Colitis Granted Tentative Approval by FDA](#)
- ▶ [Detailed Results from Biogen Idec and AbbVie's Pivotal Phase 3 Decide Study Further Define the Efficacy and Safety Profile of ZINBRYTA \(Daclizumab High-Yield Process\)](#)
- ▶ [Altarum Center for Sustainable Health Spending: Health Sector Economic Indicators Briefs - Growth in Health Spending Exceeds 4%, Driven by Prescription Drugs](#)
- ▶ [Decision Resources: The Majority of Surveyed Gastroenterologists Agree that Biologics Should be Prescribed to More Patients in the Crohn's Disease and Ulcerative Colitis Treatment Paradigm](#)
- ▶ [Elusys Announces Results From Three Phase 3 Safety Studies Of Its Anthrax Anti-Toxin, Obiltoximab \(ETI-204\), In Adult Volunteers And Completion Of Its Phase 3 Clinical Development Program](#)
- ▶ [IMS Institute for Healthcare Informatics: IMS Health Identifies Ten Harbingers of Disruptive Change Forcing Adjustment to Healthcare Systems and Business Models](#)
- ▶ [OPKO's Second RAYALDEE Phase 3 Trial Meets Primary Endpoints](#)
- ▶ [EvaluatePharma: Biologics and orphan diseases spark huge increases in US drug prices](#) (may require free registration to access)
- ▶ [FDA Receives Paragraph IV Notice Letter for KUVAN \(sapropterin dihydrochloride\) Tablets](#)
- ▶ [Amarin Reaffirms Its Mission to Improve Patient Care With Commitment to Completing REDUCE-IT Cardiovascular Outcomes Study](#)

upcoming FDA approvals

Product Name (generic name) Company(ies)	Therapeutic Class	Route of Administration	Product Type	Potential Uses(s)	Anticipated FDA Approval Date (PDUFA)
EMBEDA (morphine sulfate ER / naltrexone) Pfizer	Analgesics & Anesthetics	Oral	Label Expansion	Label Update to Include Information from Abuse-Deterrent Studies (For the Management of Moderate-to-Severe Pain when a Continuous, Around-the-Clock Opioid Analgesic is Needed for an Extended Period of Time)	2014-Oct

Product Name (generic name) Company(ies)	Therapeutic Class	Route of Administration	Product Type	Potential Uses(s)	Anticipated FDA Approval Date (PDUFA)
HARVONI (sofosbuvir / ledipasvir) Gilead Sciences	Antiinfective Agents	Oral	New Molecular Entity; New Combination	Once-Daily, Fixed-Dosed Combination for Treatment of Chronic Hepatitis C Virus Genotype 1 Infection (HCV GT1) in Adults	2014-Oct 10
(recombinant porcine factor VIII) Baxter; Ipsen	Hematological Agents	Intravenous	New Formulation	Acquired Hemophilia A	2014-Oct 10
LYMPHOSEEK (technetium Tc 99m tilmanocept) Navidea	Diagnostic Products	Intravenous	New Indication	Expanded Label to Support Broader and More Flexible Use in Imaging and Lymphatic Mapping Procedures, including Lymphoscintigraphy and Other Optimization Capabilities	2014-Oct 16
SAXENDA (liraglutide) Novo Nordisk	ADHD / Antinarcotic / Antiobesity / Anorexic Agents	Subcutaneous	New Formulation; New Indication	Adjunct to a Reduced-Calorie Diet and Increased Physical Activity for Chronic Weight Management in Adults with Obesity, or who are Overweight with Comorbidities	2014-Oct 20
XIAFLEX (collagenase clostridium histolyticum) Auxilium; Pfizer	Assorted Classes	Intradermal	Label Expansion	Dupuytren's Contracture with Palpable Cords (Multi-Cord)	2014-Oct 20
AR-05 Arbor	Cardiovascular Agents	Unknown	New Formulation	Cardiovascular Disorders	2014-Oct 23
EYLEA (afibercept) Regeneron; Bayer	Ophthalmic Agents	Intraocular	New Indication	Macular Edema following Branch Retinal Vein Occlusion (BRVO)	2014-Oct 23
NATPARA (recombinant human parathyroid hormone (PTH) 1-84) NPS	Endocrine & Metabolic Drugs	Subcutaneous	New Formulation	Hypoparathyroidism	2014-Oct 24
CARBELLA (carbamazepine) Lundbeck; Ligand	Neuromuscular Drugs	Intravenous	New Formulation	As Replacement Therapy in Adults who are on a Stable Maintenance Oral Dose of Carbamazepine to Control Certain Seizure Types, when Oral Carbamazepine Administration is Temporarily not Feasible	2014-Oct 24 to Oct 31
XIGDUO XR (dapagliflozin / metformin ER) AstraZeneca	Endocrine & Metabolic Drugs	Oral	New Combination	Type 2 Diabetes Mellitus (DM)	2014-Oct 29
(hydrocodone bitartrate ER) Purdue	Analgesics & Anesthetics	Oral	New Formulation	Once Daily, Single-Entity, Extended-Release, Abuse-Deterrent Formulation for Chronic Pain Treatment	2014-Oct 30
ENVARUSUS (tacrolimus (improved tablet formulation)) Veloxis	Assorted Classes	Oral	New Formulation	Once Daily Formulation for Prevention of Organ Rejection in Adult Kidney Transplant Patients	2014-Oct 31
FLUZONE QIV (influenza vaccine) Sanofi	Vaccines	Intradermal	New Formulation	Prevention of Influenza Virus Infection	2014-Q4
(human papilloma virus vaccine) Merck	Vaccines	Intramuscular	New Formulation	Prevention of Genital Warts & Cervical Cancer Caused by Human Papillomavirus (HPV) Infection	2014-Q4 (Nov-Dec)
(palonosetron / netupitant) Helsinn; Eisai	Gastrointestinal Agents	Oral	New Combination; New Molecular Entity	Prevention of Acute and Delayed Chemotherapy-Induced Nausea and Vomiting (CINV) Following Both Highly and Moderately Emetogenic Chemotherapy	2014-Q4
(bortezomib) InnoPharma	Antineoplastics & Adjunctive Therapies	Intravenous	New Formulation	Modified Formulation for Multiple Myeloma	2014-Q4
SIGNIFOR (pasireotide) Novartis	Endocrine & Metabolic Drugs	Subcutaneous	New Indication	Acromegaly	2014-H2

Product Name (generic name) Company(ies)	Therapeutic Class	Route of Administration	Product Type	Potential Uses(s)	Anticipated FDA Approval Date (PDUFA)
(amphetamine polistirex) Neos Therapeutics	ADHD / Antinarcotic / Antiobesity / Anorexic Agents	Oral	New Formulation	Attention Deficit Hyperactivity Disorder (ADHD)	2014-H2
MISODEL (misoprostol) Ferring	Genitourinary Products	Vaginal	New Formulation	Decreasing Time to Vaginal Delivery in Women with an Unfavorable Cervix When Used in Sequential Regimen with Oxytocin Augmentation, if Needed	2014-H2
LONQUEX (lipegfilgrastim) BioGeneriX / Teva	Hematological Agents	Subcutaneous	New Formulation	Chemotherapy-Induced Neutropenia	2014-H2
LECETTE (desogestrel / ethinyl estradiol) Teva	Endocrine & Metabolic Drugs	Oral	New Formulation	Prevention of Pregnancy	2014-H2
SINGULAIR ALLERGY (montelukast) MSD Consumer Care (Merck)	Respiratory Agents	Oral	Rx to OTC	For Use in Adults 18 Years of Age and Older for Temporary Relief of Symptoms Due to Hay Fever or Other Upper Respiratory Allergies Including: Nasal Congestion, Runny Nose, Itchy, Watery Eyes, Sneezing, and Itching of the Nose	2014-H2
GeNOSyl MVG-2000 (nitric oxide delivery system) GeNO	Respiratory Agents	Inhalation	New Formulation	Hypoxic Respiratory Failure in Neonate	2014-H2
OCTAPLEX (human prothrombin complex concentrate) Octapharma	Hematological Agents	Intravenous	New Formulation	Urgent Reversal of Vitamin K Antagonist Anticoagulant Treatment in Adults who Require Urgent Surgery or Invasive Procedures	2014-H2
TEV-TROPIN (somatropin) Teva	Endocrine & Metabolic Drugs	Subcutaneous	New Formulation	10 mg Needle-Free Formulation for Growth Hormone Deficiency	2014-H2
BIO-HEP-B (hepatitis B vaccine) SciVac	Vaccines	Injection	New Formulation	Treatment and Prevention of Hepatitis B Virus (HBV) Infection	2014-H2
KALBITOR (ecallantide) Dyax	Hematological Agents	Subcutaneous	New Formulation	Concentrated Formulation for Single Injection for Hereditary Angioedema (HAE)	2014-H2
ZUBSOLV (buprenorphine / naloxone) Orexis	Misc. Psychotherapeutic & Neurological Agents	Sublingual	New Formulation	Additional Dosages for Maintenance Treatment of Opioid Dependence	2014-H2
VASCEPA (icosapent ethyl) Amarin	Cardiovascular Agents	Oral	New Indication	Concomitant Use with an HMG-CoA Reductase Inhibitor to Reduce Triglycerides, Non-HDL Cholesterol, ApoB, LDL Cholesterol, Total Cholesterol, and VLDL Cholesterol in Adults with Mixed Dyslipidemia and Coronary Heart Disease (CHD) or a CHD Risk Equivalent	2014-H2

upcoming patent expirations/generic launches

Trade Name (generic name) Company(ies)	Therapeutic Use(s)	Estimated U.S. Sales	Anticipated Generic Availability	Anticipated Generic Launch Type	Comments
EXFORGE (amlodipine besylate/valsartan) Novartis	Hypertension	\$263 million	October 2014	Exclusive	Par received FDA approval of generic EXFORGE on March 28, 2013. Par announced shipment on 09/30/2014.

Trade Name (generic name) Company(ies)	Therapeutic Use(s)	Estimated U.S. Sales	Anticipated Generic Availability	Anticipated Generic Launch Type	Comments
EXFORGE HCT (amlodipine besylate/valsartan/ hydrochlorothiazide) Novartis	Hypertension	\$93 million	October 2014	Exclusive	Teva received FDA approval of generic EXFORGE HCT on September 25, 2012.
ANDRODERM (testosterone) Actavis	Replacement Therapy in Males with Deficiency of Endogenous Testosterone	\$84 million	October 2014	Unknown	None
ADVICOR (niacin/lovastatin) AbbVie	Hyperlipidemia	\$42 million	H2 2014	Exclusive	Teva has a settlement agreement allowing launch any time after September 20, 2013. It is unknown when or if Teva will launch its generic. Other generics are not expected to launch until March 2018.
ASACOL 400 mg Tablets (mesalamine) Warner Chilcott	Ulcerative Colitis	\$460 million	H2 2014	Exclusive with Authorized Generic	Generic availability applies to ASACOL 400 mg tablets. Brand name ASACOL 400 mg tablet has been discontinued; Actavis/Warner Chilcott has released DELZICOL 400 mg that contains the same amount of mesalamine in a delayed-release capsule. Zydus will have an opportunity to launch generic ASACOL HD 800 mg in November 2015.
VALCYTE (valganciclovir hydrochloride) Roche	Cytomegalovirus (CMV) Disease and Infection; CMV Retinitis	\$195 million	H2 2014	Exclusive	Ranbaxy's generic VALCYTE was originally expected to launch in September 2013. Ranbaxy's manufacturing facility is under review by the FDA; it is unknown when the generic will receive approval by the FDA. A Citizen's Petition was filed on June 5, 2014 asking the FDA to forfeit Ranbaxy's exclusivity and approve other generics.
VIRACEPT (nelfinavir mesylate) ViiV Healthcare	Human Immunodeficiency Virus (HIV) Infection	\$51 million	H2 2014	Unknown	None
ORAPRED ODT (prednisolone sodium phosphate) Shionogi Pharma	Asthma; Atopic Dermatitis; Allergic Rhinitis	\$33 million	H2 2014	Exclusive	Mylan received FDA approval of generic ORAPRED ODT on April 10, 2013. Settlement agreement allows launch after April 1, 2014.
OXYCONTIN (oxycodone hydrochloride extended-release) Purdue	Moderate to Severe Pain	\$2.5 billion	H2 2014	Competitive	Purdue reached settlement agreements with Actavis, Impax, Par and Sandoz. Actavis may launch its generic OXYCONTIN (new abuse-deterrent formulation) any time after receiving FDA approval. Impax may launch its generic OXYCONTIN as early as 2016. Par and Sandoz's settlement agreement terms have not been disclosed.
INVEGA (paliperidone extended- release) Janssen	Schizophrenia; Schizoaffective Disorder	\$424 million	H2 2014	Competitive	None
TRAVATAN Z (travoprost) Alcon	Glaucoma; Ocular Hypertension	\$485 million	H2 2014	Exclusive	Alcon reached a settlement agreement with Par; terms have not been disclosed.
VIVELLE-DOT (estradiol transdermal patch) Novartis	Symptoms Associated with Menopause	\$240 million	H2 2014	Exclusive with Authorized Generic	None
FOSRENOL (lanthanum carbonate) Shire	Hyperphosphatemia Associated with Chronic Kidney Disease	\$95 million	H2 2014	Competitive	None

Trade Name (generic name) Company(ies)	Therapeutic Use(s)	Estimated U.S. Sales	Anticipated Generic Availability	Anticipated Generic Launch Type	Comments
NASONEX (mometasone furoate) Schering/Merck	Seasonal & Perennial Allergic Rhinitis; Nasal Polyps	\$1.2 billion	H2 2014	Exclusive	An "at risk" launch is possible at any time if the FDA grants effective approval to Apotex's generic NASONEX product.
LUMIGAN (bimatoprost) Allergan	Glaucoma; Ocular Hypertension	\$367 million	H2 2014	Unknown	Generic availability applies to LUMIGAN 0.03%; generic availability of LUMIGAN 0.01% is anticipated on June 13, 2027 pending the outcome of ongoing patent litigation.
NEXIUM (esomeprazole magnesium) AstraZeneca	Gastroesophageal Reflux Disease; Ulcers; Hypersecretory Conditions; <i>H. pylori</i> Eradication	\$6.1 billion	H2 2014	Exclusive	Generic availability applies to the oral formulations (capsules, granules); Ranbaxy has to acquire raw materials from another company; therefore, launch of its generic NEXIUM may be delayed. Some industry executives are projecting a delay in the launch of generic NEXIUM until June/July 2015. A Citizen's Petition was filed on June 5, 2014 asking the FDA to forfeit Ranbaxy's exclusivity and approve other generics. Sun launched generic NEXIUM IV in January 2014. Another salt form, esomeprazole strontium, by Amneal was approved by the FDA on August 8, 2013. This is not A-rated to NEXIUM. Amneal launched brand name esomeprazole strontium in December 2013 and an authorized generic by the same name in January 2014. Pfizer launched an over-the-counter NEXIUM 20 mg, NEXIUM 24HR, on May 27, 2014.
ACTONEL (risedronate sodium) Actavis	Osteoporosis Prophylaxis & Treatment; Paget's Disease	\$1 billion	H2 2014	Exclusive	Mylan, Sun and Apotex announced launch of their generic ACTONEL 150 mg on June 11, 2014; Actavis announced launch of their authorized generic ACTONEL 150 mg on June 18, 2014. Generics also anticipated for ACTONEL 5 mg, 30 mg, and 35mg. Generics also anticipated for ACTONEL WITH CALCIUM; however, the brand product has been discontinued per the FDA web site. Sales figure includes ACTONEL/ATELVIA.

recent FDA product filings/acceptances

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Route of Administration	Potential Use(s)	Anticipated FDA Approval Date (PDUFA)
SOMATULINE DEPOT (lanreotide) Ipsen	New Indication	Endocrine & Metabolic Drugs	Subcutaneous	Treatment of Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)	2015-Early Q1 (priority review)
(eluxadoline) Furix/ Actavis	New Molecular Entity	Gastrointestinal Agents	Oral	Treatment of Diarrhea and Abdominal Pain in Men and Women with Diarrhea- Predominant Irritable Bowel Syndrome (IBS-D)	2015-Q2 (priority review)
(ceftazidime / avibactam) Actavis	New Molecular Entity; New Combination	Antiinfective Agents	Intravenous	Intra-Abdominal Infections; Urinary Tract Infections	2015-Q1 (priority review)
(isavuconazole) Astellas ; Basilea	New Molecular Entity	Antiinfective Agents	Intravenous; Oral	Treatment of Invasive Aspergillosis and Invasive Mucormycosis	2015-Mar 8 (priority review)
(rolapitant) Opko ; Tesaro	New Molecular Entity	Gastrointestinal Agents	Oral	Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV)	2015-Sep 8
TUZISTRA XR (cough/cold therapy extended-release) Vernalis ; Tris	New Formulation	Respiratory Agents	Oral	Extended-Release Formulation (with different ingredients; research code CCP-01) for the Treatment of Cough & Cold	2015-Apr 30 (standard review)

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Route of Administration	Potential Use(s)	Anticipated FDA Approval Date (PDUFA)
VYVANSE (lisdexamfetamine dimesylate) Shire	New Indication	ADHD / Antinarcotic / Antiobesity / Anorexic Agents	Oral	Treatment for Adults with Binge Eating Disorder (BED)	2015-Feb (priority review)
XIFAXAN (rifaximin) Salix	New Indication	Antiinfective Agents	Oral	Treatment of Irritable Bowel Syndrome with Diarrhea (IBS-D)	2015-Feb 28 (class 2 resubmission)
RYTARY (carbidopa / levodopa extended-release) Impax	New Formulation	Neuromuscular Drugs	Oral	Parkinson's Disease (PD)	2015-Jan 9 (PDUFA extended by 3 months)
(blinatumomab) Amgen	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Intravenous	Philadelphia-Negative (Ph-) Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukemia (ALL)	2015-Mar 22 (if priority review)
(brexpiprazole) Otsuka; Lundbeck	New Molecular Entity	CNS Drugs	Oral	Schizophrenia; Adjunctive Therapy for Major Depressive Disorder (MDD)	2015-Jul 11 (standard review)
OPDIVO (nivolumab) Bristol Myers Squibb	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Intravenous	Advanced Melanoma	2015-Mar 30 (priority review)

products receiving FDA complete response letters (CRL) or refuse-to-file (RTF) letters

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Route of Administration	Potential Use(s)	Comments
<i>None Noted</i>					

FDA/CDC advisory committee (AdCom) meeting announcements / outcomes

Trade Name (generic name) Company(ies)	Therapeutic Class	Route of Administration	Potential Use(s)	FDA Advisory Committee Meeting Date	Comments
(nebivolol / valsartan) Actavis	Cardiovascular Agents	Oral	Fixed-Dose Combination Tablet for Hypertension	09/09/2014	Actavis confirmed that the FDA's Cardiovascular and Renal Drugs Advisory Committee (CRDAC) voted to recommend against approval of Actavis' New Drug Application (NDA) for the fixed-dose combination of nebivolol and valsartan for the treatment of hypertension. The committee vote was six to four recommending against approval.
SAXENDA (liraglutide) Novo Nordisk	Endocrine & Metabolic Drugs	Subcutaneous	Adjunct to a Reduced-Calorie Diet and Increased Physical Activity for Chronic Weight Management in Adults with Obesity, or who are Overweight with Comorbidities	09/11/2014	The FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted 14 to 1 in support of approval of liraglutide for use in adults with a body mass index (BMI) of at least 30 kilograms per square meter, or a BMI of at least 27 kilograms per square meter in those with at least one weight-related health issue.
NATPARA (rhPTH [1-84]) NPS	Endocrine & Metabolic Drugs	Subcutaneous	Hypoparathyroidism	09/12/2014	The FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted 8 to 5 that the available data support the approval of NATPARA (rhPTH [1-84]) for the long-term treatment of Hypoparathyroidism, a rare endocrine disorder characterized by insufficient levels of parathyroid hormone (PTH).

Trade Name (generic name) Company(ies)	Therapeutic Class	Route of Administration	Potential Use(s)	FDA Advisory Committee Meeting Date	Comments
REXTORO (testosterone undecanoate) Clarus Therapeutics	Endocrine & Metabolic Drugs	Oral	Testosterone Replacement Therapy in Males for Conditions Associated with a Deficiency or Absence of Endogenous Testosterone: Primary Hypogonadism (Congenital or Acquired) and Hypogonadotropic Hypogonadism (Congenital or Acquired)	09/18/2014	The FDA's Bone, Reproductive and Urologic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee voted 18-3 that the overall benefit/risk profile of REXTORO (testosterone undecanoate) was not acceptable to support approval for testosterone replacement therapy. The panel also voted 12-8 with one abstention that there was not sufficient evidence that REXTORO is effective.
Testosterone Replacement Therapies Various	Endocrine & Metabolic Drugs	Various	Testosterone Replacement Therapy in Males for Conditions Associated with a Deficiency or Absence of Endogenous Testosterone: Primary Hypogonadism (Congenital or Acquired) and Hypogonadotropic Hypogonadism (Congenital or Acquired)	09/18/2014	The FDA's Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee voted 20-1 that the current indication for testosterone treatment should be revised, calling for the indication to be narrowed with most favoring limiting use to patients with true primary or secondary hypogonadism. The committees noted that there is little evidence to suggest that testosterone therapies are effective for treating low levels of the hormone caused by aging. Twenty members of the panel voted in favor of requiring further sponsor study to assess a potential cardiovascular risk with use of testosterone therapy with the majority (16) calling for the further study most specifically in the age-related hypogonadism population and 4 members saying such a study should be conducted regardless of the indication.
SAVAYSA (edoxaban) Daiichi Sankyo	Hematological Agents	Oral	Reduction in Risk of Stroke and Systemic Embolic Events (SEE) in Non-Valvular Atrial Fibrillation (NVAF); Treatment of Deep Vein Thrombosis (DVT); Prevention of Symptomatic Recurrence of Venous Thromboembolism (VTE)	10/30/2014	The FDA's Cardiovascular and Renal Drugs Advisory Committee will discuss new drug application (NDA) 206316, edoxaban tablets, submitted by Daiichi Sankyo, Inc., for the prevention of stroke and systemic embolism (blood clots other than in the head) in patients with nonvalvular atrial fibrillation (A Fib; abnormally rapid and chaotic contractions of the atria, the upper chambers of the heart).

products receiving special FDA review designations or statuses

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Current Development Status	Route of Administration	FDA Designation or Status Awarded	Use(s) Receiving Designation / Status
WCK-771 Wockhardt	New Molecular Entity	Antiinfective Agents	Phase 2	Intravenous	Qualified Infectious Disease Product (QIDP)	Hospital Acquired Pneumonia (HAP); Bacterial Infections including MRSA and Sepsis
WCK-2349 Wockhardt	New Molecular Entity	Antiinfective Agents	Phase 2	Oral	Qualified Infectious Disease Product (QIDP)	Bacterial Infections including MRSA, Gram Negative and Anaerobic Infections
NUPLAZID (pimavanserin) Acadia	New Molecular Entity	CNS Drugs	Phase 3	Oral	Breakthrough Therapy	Parkinson's Disease (PD) Psychosis

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Current Development Status	Route of Administration	FDA Designation or Status Awarded	Use(s) Receiving Designation / Status
(motolimod); VTX-2337 VentiRx	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Phase 2	Injection	Fast Track	Treatment of Women with Ovarian Cancer whose Disease has Progressed on or Recurred After Platinum-Based Chemotherapy
(relebactam); MK-7655 Merck	New Molecular Entity	Antiinfective Agents	Phase 2	Intravenous	Qualified Infectious Disease Product (QIDP); Fast Track	Treatment of Complicated Urinary Tract Infections, Complicated Intra-abdominal Infections and Hospital-Acquired Bacterial Pneumonia/Ventilator-Associated Bacterial Pneumonia
Debio-1450 Debiopharm	New Molecular Entity	Antiinfective Agents	Phase 1	Intravenous	Qualified Infectious Disease Product (QIDP)	Treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSI)
PULMAQUIN (ciprofloxacin dual release) Aradigm	New Formulation; New Indication	Antiinfective Agents	Phase 3	Inhalation	Fast Track	Non-Cystic Fibrosis Bronchiectasis (BE) Patients with Chronic Lung Infections with Pseudomonas aeruginosa
PBT-2 Prana Biotechnology	New Molecular Entity	Misc. Psychotherapeutic & Neurological Agents	Phase 2	Oral	Orphan Drug	Huntington's Disease (HD)
VERMOX (mebendazole) Janssen	New Indication	Antiinfective Agents	Previously Marketed Product (now discontinued)	Oral	Orphan Drug	Treatment of Single or Mixed Gastrointestinal Infestations by Trichuris trichiura (Whipworm), Ascaris lumbricoides (Large Roundworm), and Ancylostoma duodenale and Nectar americanus (Hookworm)
(inBreath airway transplant system) Harvard Apparatus Regenerative Technology	Device	Medical Devices	Unknown	Unknown	Orphan Drug	To Restore the Structure and/or Function of the Trachea Subsequent to Tracheal Damage Due to Cancer, Injury or Infection
(6-((3S,4S)-4-Methyl-1-pyrimidin-2-ylmethyl-pyrrolidin-3-yl-1-(tetrahydro-pyran-4-yl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one)); PF-04447943 Pfizer	New Molecular Entity	Hematological Agents	Discovery	Oral	Orphan Drug	Treatment of Sickle Cell Disease
(Adenoassociated virus vector (AAV) carrying a modified AAV serotype 2 backbone and coding sequence of human thymidine phosphorylase preceded by a human thyroxine-binding globulin promoter) Columbia University Medical Center	Biologic	Endocrine & Metabolic Disorders	Unknown	Unknown	Orphan Drug	For the Treatment of Mitochondrial Neurogastrointestinal Encephalomyopathy (MNGIE)
(N-(2-(2-dimethylaminoethyl-methylamino)-4-methoxy-5-[[4-(1-methylindol-3-yl)pyrimidin-2-yl]amino]phenyl)prop-2-enamide mesylate salt); AZD-9291 AstraZeneca	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Phase 2	Oral	Orphan Drug	Treatment of Epidermal Growth Factor Receptor Mutation-Positive Non-Small Cell Lung Cancer

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Current Development Status	Route of Administration	FDA Designation or Status Awarded	Use(s) Receiving Designation / Status
ZELBORAF (vemurafenib) Genentech/Roche	New Indication	Antineoplastics & Adjunctive Therapies	Marketed Product; Phase 2	Oral	Orphan Drug	Treatment of Patients with Non-Small Cell Lung Cancer (NSCLC) with BRAF V600E Mutation
(Adenovirus serotype-5 (Ad5) vector that contains a modified non-oncogenic fused early 6 (E6) and early 7 (E7) gene of the human papillomavirus (HPV); (Ad5 [E1-, E2b-]-E6/E7)) Etubics	Biologic	Antineoplastics & Adjunctive Therapies	Discovery	Injection	Orphan Drug	Treatment of Human Papillomavirus (HPV)-Associated Head and Neck Squamous Cell Carcinoma (HNSCC)
(mitomycin and sterile hydrogel composed of poloxamer 407, hydroxypropyl methyl cellulose and polyethylene glycol 400) TheraCoat	New Formulation	Antineoplastics & Adjunctive Therapies	Unknown	Unknown	Orphan Drug	Treatment of Upper Tract Urothelial Cell Cancers (Transitional Cell Carcinoma of the Renal Pelvis and Ureter)
IMBRUVICA (ibrutinib) Pharmacyclis; Janssen	New Indication	Antineoplastics & Adjunctive Therapies	Marketed Product; Phase 3	Oral	Orphan Drug	Treatment of Follicular Lymphoma
((3S)-1-azabicyclo[2.2.2]oct-3-yl {2-[2-(4-fluorophenyl)-1,3-thiazol-4-yl]propan-2-yl}carbamate) Genzyme	New Molecular Entity	Hematological Agents	Unknown	Unknown	Orphan Drug	Treatment of Gaucher Disease
LYNOVEX (cysteamine) NovaBiotics	New Formulation; New Indication	Respiratory Agents	Discovery	Inhalation	Orphan Drug	Treatment of Cystic Fibrosis
LEGALON SIL (silibinin-C-2',3'-dihydrogensuccinate, disodium salt) Rottapharm	New Molecular Entity	Antidotes	Discovery	Intravenous	Orphan Drug	Treatment of Amatoxin Poisoning, which Includes the Prevention and Treatment of Amatoxin-Induced Hepatic Failure
(humanized monoclonal antibodies hu1B7 and hu11E6); SYN-005 Synthetic Biologics	New Molecular Entity	Antiinfective Agents	Discovery	Injection	Orphan Drug	Treatment of Bordetella Pertussis
EYLEA (afibercept) Regeneron	New Indication	Ophthalmic Agents	Phase 3	Intravitreal	Breakthrough Therapy	Treatment of Diabetic Retinopathy in Patients with Diabetic Macular Edema (DME)
LYMPHOSEEK (technetium Tc 99m tilmanocept injection) Navidea Biopharmaceuticals	New Indication	Diagnostics	Marketed Product	Intravenous	Orphan Drug	For Use in Sentinel Lymph Node Detection with a Hand-Held Gamma-Counter, with Scintigraphic Imaging, in Patients with Cancer of the Head and Neck
MEDI-3902 MedImmune/AstraZeneca	New Molecular Entity	Antiinfective Agents	Discovery	Injection	Fast Track	Prevention of Nosocomial Pneumonia caused by Pseudomonas aeruginosa (P. aeruginosa)
(aramchol) Galmed	New Molecular Entity	Gastrointestinal Agents	Discovery	Oral	Fast Track	Non-Alcoholic Steato-Hepatitis (NASH)
(MV-NB-02, its bivalent ganglioside vaccine consisting of GD2-lactone and GD3-lactone each covalently conjugated to keyhole hemocyanin); MV-NB-02 MabVax Therapeutics	Biologic	Antineoplastics & Adjunctive Therapies	Phase 1	Subcutaneous	Orphan Drug	Treatment of Neuroblastoma

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Current Development Status	Route of Administration	FDA Designation or Status Awarded	Use(s) Receiving Designation / Status
(heat killed whole cell mycobacterium obuense); IMM-101 Immodulon Therapeutics	Biologic	Antineoplastics & Adjunctive Therapies	Discovery	Intradermal	Orphan Drug	Treatment of Pancreatic Cancer
(fluoro-cyclopentenylcytosine); RX-3117 Rexahn	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Phase 1	Oral	Orphan Drug	Treatment of Pancreatic Cancer
NOXCURECF (nitric oxide) Advanced Inhalation Therapies	New Indication	Medical Devices	Discovery	Inhalation	Orphan Drug	Treatment of Cystic Fibrosis
(cannabidiol) Insys Therapeutics	New Indication; New Formulation	Antineoplastics & Adjunctive Therapies	Discovery	Unknown	Orphan Drug	Treatment of Glioma
(glucagon infusion) Xeris	New Formulation	Endocrine & Metabolic Drugs	Phase 2	Subcutaneous	Orphan Drug	Prevention of Chronic, Severe Hypoglycemia Related to Congenital Hyperinsulinism
(aldoxorubicin) CytRx	New Formulation	Antineoplastics & Adjunctive Therapies	Phase 2	Intravenous	Orphan Drug	Treatment of Glioblastoma Multiforme; Treatment of Small Cell Lung Cancer; Treatment of Ovarian Cancer
OPDIVO (nivolumab) Bristol Myers Squibb	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Pending Approval	Intravenous	Breakthrough Therapy	Advanced Melanoma

patent litigations/generic filings

Trade Name (generic name) Company(ies)	Generic Company(ies) Filer(s)	Therapeutic Class	Route of Administration	Use(s)	Patents Involved	Comments
ONGLYZA (saxagliptin hydrochloride) AstraZeneca	Watson	Antidiabetics	Oral	Adjunct to Diet and Exercise to Improve Glycemic Control in Adults with Type 2 Diabetes Mellitus	RE44,186	Patent infringement lawsuit following a Paragraph IV certification as part of Watson's filing of an ANDA to manufacture a generic version of AstraZeneca's ONGLYZA.
ZORTRESS (everolimus) Novartis	Breckenridge; Roxane	Immunosuppressive Agents	Oral	Prophylaxis of Organ Rejection (Kidney or Liver Transplant) in Adult Patients	5,665,772; 6,004,973; 6,239,124; 6,455,518	Patent infringement lawsuit following a Paragraph IV certification as part of the defendants' filing of ANDAs to manufacture a generic version of Novartis' ZORTRESS.
TREANDA (bendamustine hydrochloride) Cephalon/Teva	Ben Venue; Hikma; West-Ward; Eagle; Nang Kuang; Sagent	Antineoplastics & Adjunctive Therapies	Intravenous	Chronic Lymphocytic Leukemia or Indolent B-cell Non-Hodgkin Lymphoma	Eagle: 8,791,270; Others: 8,791,270; 8,445,524; 8,436,190; 8,609,863	Patent infringement lawsuit following a Paragraph IV certification as part of the defendants' filing of ANDAs to manufacture a generic version of Cephalon's TREANDA.
ACANYA (clindamycin phosphate / benzoyl peroxide) Dow; Valeant	Taro	Acne Products	Topical	Topical Treatment of Acne Vulgaris	8,288,434; 8,663,699	Patent infringement lawsuit following a Paragraph IV certification as part of Taro's filing of an ANDA to manufacture a generic version of Dow's ACANYA.

Trade Name (generic name) Company(ies)	Generic Company(ies) Filer(s)	Therapeutic Class	Route of Administration	Use(s)	Patents Involved	Comments
PREZISTA (darunavir) Janssen	Cipla	Antiretrovirals	Oral	Treatment of Human Immunodeficiency Virus (HIV-1) Infection in Combination with Ritonavir and with Other Antiretroviral Agents	7,700,645; 7,126,015; 7,595,408; 8,518,987; 7,470,506; 8,597,876	Patent infringement lawsuit following a Paragraph IV certification as part of Cipla's filing of an ANDA to manufacture a generic version of Janssen's PREZISTA.
NEUPRO (rotigotine transdermal system) UCB	Watson	Antiparkinson Agents	Transdermal	Parkinson's Disease; Moderate to Severe Primary Restless Legs Syndrome	6,699,498; 6,884,434; 7,413,747; 8,246,979; 8,246,980; 8,617,591	Patent infringement lawsuit following a Paragraph IV certification as part of Watson's filing of an ANDA to manufacture a generic version of UCB's NEUPRO.
PENNSAID (diclofenac sodium) Mallinckrodt	Hi-Tech	Antiinflammatory Agents - Topical	Topical	Osteoarthritis of the Knees	8,217,078; 8,546,450; 8,618,164; 8,741,956	Patent infringement lawsuit following a Paragraph IV certification as part of Hi- Tech's filing of an ANDA to manufacture a generic version of Mallinckrodt's PENNSAID.
GIAZO (balsalazide disodium) Salix	Mylan	Inflammatory Bowel Agents	Oral	Ulcerative Colitis	6,197,341; 8,497,256	Patent infringement lawsuit following a Paragraph IV certification as part of Mylan's filing of an ANDA to manufacture a generic version of Salix's GIAZO.
XYREM (sodium oxybate) Jazz	Par	Psychotherapeutic and Neurological Agents - Misc.	Oral	Cataplexy in Narcolepsy; Excessive Daytime Sleepiness (EDS) in Narcolepsy	8,731,963; 8,772,306	Patent infringement lawsuit following a Paragraph IV certification as part of Par's filing of an ANDA to manufacture a generic version of Jazz's XYREM.
NAMENDA XR (memantine hydrochloride) Forest/Actavis	Lupin; Par; Anchen; Amerigen	Antidementia Agents	Oral	Moderate to Severe Dementia of the Alzheimer's Type	8,039,009; 8,168,209; 8,173,708; 8,283,379; 8,329,752; 8,362,085; 8,598,233	Patent infringement lawsuit following a Paragraph IV certification as part of defendants' filing of an ANDA to manufacture a generic version of Forest's NAMENDA XR.
PROLENSA (bromfenac) Bausch & Lomb	Lupin	Ophthalmics - Misc.	Intraocular	Postoperative Inflammation and Reduction of Ocular Pain in Patients who have Undergone Cataract Surgery	8,754,131	Patent infringement lawsuit following a Paragraph IV certification as part of Lupin's filing of an ANDA to manufacture a generic version of B&L's PROLENSA.
PHOSLO Gelcaps (calcium acetate) Fresenius	Zydus; Amnel	Phosphate Binder Agents	Oral	Control of Hyperphosphatemia in End Stage Renal Failure	8,563,032	Patent infringement lawsuit based on defendants' anticipated manufacture and sale of a generic calcium acetate capsule, having filed an ANDA to manufacture a generic version of Fresenius' PHOSLO.

Trade Name (generic name) Company(ies)	Generic Company(ies) Filer(s)	Therapeutic Class	Route of Administration	Use(s)	Patents Involved	Comments
GLEEVEC (imatinib mesylate) Novartis	Dr. Reddy's	Antineoplastics & Adjunctive Therapies	Oral	Philadelphia Chromosome Positive Chronic Myeloid Leukemia; Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia; Myelodysplastic/ Myeloproliferative Diseases; Aggressive Systemic Mastocytosis; Hypereosinophilic Syndrome and/or Chronic Eosinophilic Leukemia; Dermatofibrosarcoma Protuberans; Kit (CD117) Positive GIST	6,894,051; RE43,932	Patent infringement lawsuit following a Paragraph IV certification as part of Dr. Reddy's filing of an ANDA to manufacture a generic version of Novartis' GLEEVEC.
EXELON Patch (rivastigmine tartrate) Novartis	Zydus; Cadila	Antidementia Agents	Transdermal	Mild, Moderate, and Severe Dementia of the Alzheimer's Type; Mild to Moderate Dementia Associated with Parkinson's Disease	6,316,023; 6,335,031	Patent infringement lawsuit following a Paragraph IV certification as part of Zydus' filing of an ANDA to manufacture a generic version of Novartis' EXELON Patch.
ZYMAXID (gatifloxacin) Allergan	Micro Labs	Ophthalmic Antiinfectives	Intraocular	Treatment of Bacterial Conjunctivitis	6,333,045	Patent infringement lawsuit following a Paragraph IV certification as part of Micro Labs' filing of an ANDA to manufacture a generic version of Allergan's ZYMAXID.
BARACLUDE (entecavir) Bristol Myers Squibb	Amneal	Hepatitis B Agents	Oral	Chronic Hepatitis B Virus Infection	5,206,244	Patent infringement lawsuit following a Paragraph IV certification as part of Amneal's filing of an ANDA to manufacture a generic version of Bristol Myer Squibb's BARACLUDE.
AMPYRA (dalfampridine) Acorda	Mylan	Multiple Sclerosis Agents	Oral	Improve Walking in Patients with Multiple Sclerosis (MS)	5,540,938; 8,007,826; 8,354,437; 8,440,703; 8,663,685	Patent infringement lawsuit following a Paragraph IV certification as part of Mylan's filing of an ANDA to manufacture a generic version of Acorda's AMPYRA.
SAPHRIS (asenapine maleate) Forest/Actavis	Sigmapharm	Antipsychotics / Antimanic Agents	Oral	Schizophrenia	5,763,476; 7,741,358	Patent infringement lawsuit following a Paragraph IV certification as part of Sigmapharm's filing of an ANDA to manufacture a generic version of Forest's SAPHRIS.
REMODULIN (treprostinil sodium) United Therapeutics	Teva	Cardiovascular Agents - Misc.	Subcutaneous; Intravenous	Pulmonary Arterial Hypertension (PAH) (WHO Group 1)	Teva: 6,765,117; 8,497,393; 7,999,007; 8,653,137; 8,658,694 Sandoz: 8,497,393	Patent infringement lawsuit following a Paragraph IV certification as part of Teva's filing of an ANDA to manufacture a generic version of United Therapeutic's REMODULIN.

Trade Name (generic name) Company(ies)	Generic Company(ies) Filer(s)	Therapeutic Class	Route of Administration	Use(s)	Patents Involved	Comments
REMICADE (infliximab) Janssen	Hospira	Inflammatory Bowel Agents	Intravenous	Crohn's Disease; Ulcerative Colitis; Rheumatoid Arthritis; Ankylosing Spondylitis; Psoriatic Arthritis; Plaque Psoriasis	6,284,471; 7,223,396; 7,846,442; 8,298,537; 8,383,120	Declaratory judgment of non-infringement and invalidity based on Hospira's anticipated manufacture and sale of its INFLECTRA product, a biosimilar to Janssen's REMICADE.
AGGRENOX (dipyridamole / acetylsalicylic acid) Boehringer Ingelheim	Mylan	Platelet Aggregation Inhibitors	Oral	Reduce the Risk of Stroke in Patients who have had Transient Ischemia of the Brain or Completed Ischemic Stroke due to Thrombosis	6,015,577	Patent infringement lawsuit following a Paragraph IV certification as part of Mylan's filing of an ANDA to manufacture a generic version of Boehringer Ingelheim's AGGRENOX.
VELCADE (bortezomib) Millenium	Glenmark	Antineoplastics & Adjunctive Therapies	Subcutaneous; Intravenous	Multiple Myeloma; Mantle Cell Lymphoma	6,713,446; 6,958,319	Patent infringement lawsuit following a Paragraph IV certification as part of Glenmark's filing of an ANDA to manufacture a generic version of Millenium's VELCADE.
DIPRIVAN (propofol) Fresenius	Emcure	General Anesthetics	Intravenous	Initiation and Maintenance of Monitored Anesthesia Care (MAC) Sedation; Combined Sedation and Regional Anesthesia; Induction and Maintenance of General Anesthesia; Intensive Care Unit (ICU) Sedation of Intubated, Mechanically Ventilated Patients	8,476,010	Patent infringement lawsuit following a Paragraph IV certification as part of Emcure's filing of an ANDA to manufacture a generic version of Fresenius' DIPRIVAN.
NORVIR (ritonavir) AbbVie	Hetero	Antiretrovirals	Oral	In Combination with Other Antiretroviral Agents for the Treatment of HIV-1 Infection	8,691,878	Patent infringement lawsuit following a Paragraph IV certification as part of Hetero's filing of an ANDA to manufacture a generic version of AbbVie's NORVIR.
ABILIFY (aripiprazole) Otsuka	Zhejiang Huahai; Huahai US; Princeton; Solco; Ajanta; Teva	Antipsychotics / Antimanic Agents	Oral	Schizophrenia; Bipolar I Disorder; Adjunctive Treatment of Major Depressive Disorder (MDD); Irritability Associated with Autistic Disorder; Agitation Associated with Schizophrenia or Bipolar I Disorder	8,017,615; 8,580,796; 8,642,760	Patent infringement lawsuit following a Paragraph IV certification as part of the defendants' filing of ANDAs to manufacture a generic version of Otsuka's ABILIFY.
FASLODEX (fulvestrant) AstraZeneca	Sagent	Antineoplastics & Adjunctive Therapies	Intramuscular	Treatment of Hormone Receptor Positive Metastatic Breast Cancer in Postmenopausal Women with Disease Progression Following Antiestrogen Therapy	6,774,122; 7,456,160; 8,329,680; 8,466,139	Patent infringement lawsuit following a Paragraph IV certification as part of Sagent's filing of an ANDA to manufacture a generic version of AstraZeneca's FASLODEX.

Trade Name (generic name) Company(ies)	Generic Company(ies) Filer(s)	Therapeutic Class	Route of Administration	Use(s)	Patents Involved	Comments
ISTODAX (romidepsin) Celgene	InnoPharma	Antineoplastics & Adjunctive Therapies	Intravenous	Cutaneous T-Cell Lymphoma; Peripheral T-Cell Lymphoma	7,608,280; 7,611,724	Patent infringement lawsuit following a Paragraph IV certification as part of InnoPharma's filing of an ANDA to manufacture a generic version of Celgene's ISTODAX.
ADDERALL XR (mixed salts of a single-entity amphetamine product) Shire	Corepharma	ADHD/Anti- Narcolepsy /Anti- Obesity/Anorexiant Agents	Oral	Attention Deficit Hyperactivity Disorder (ADHD)	RE42,096; RE41,148	Patent infringement lawsuit following a Paragraph IV certification as part of Corepharma's filing of an ANDA to manufacture a generic version of Shire's ADDERALL XR.
BUTRANS (buprenorphine transdermal system) Purdue	Actavis	Analgesics & Anesthetics	Transdermal	Management of Pain Severe Enough to Require Daily, Around-the-Clock, Long-Term Opioid Treatment for which Alternative Treatment Options are Inadequate	RE41408; RE41489; RE41571	Patent infringement lawsuit following a Paragraph IV certification as part of Actavis' filing of an ANDA to manufacture a generic version of Purdue's BUTRANS.
OFIRMEV (acetaminophen) Cadence	InnoPharma	Analgesics & Anesthetics	Intravenous	Management of Mild to Moderate Pain; Management of Moderate to Severe Pain with Adjunctive Opioid Analgesics; Reduction of Fever	6,028,222; 6,992,218	Patent infringement lawsuit following a Paragraph IV certification as part of InnoPharma's filing of an NDA (under § 505(b)(2) of the Food, Drug and Cosmetic Act) to manufacture a generic version of Cadence's OFIRMEV.
CLOLAR (clofarabine) Genzyme	Emcure	Antineoplastics & Adjunctive Therapies	Intravenous	Acute Lymphoblastic Leukemia	5,661,136	Patent infringement lawsuit following a Paragraph IV certification as part of Emcure's filing of an ANDA to manufacture a generic version of Genzyme's CLOLAR.

other/miscellaneous news

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Route of Administration	Current or Potential Use(s)	Comments
(sacubitril / valsartan trisodium); LCZ-696; Novartis	New Molecular Entity; New Combination	Cardiovascular Agents	Oral	Heart Failure (reduced ejection fraction (REF))	Novartis plans to file the NDA for LCZ-696 for review with the US FDA by the end of 2014.
buprenorphine (buccal, BEMA) BioDelivery ; Endo	New Formulation	Analgesics & Anesthetics	Oral	BioErodible MucoAdhesive (BEMA) Transmucosal Formulation for Moderate to Severe Chronic Pain in Patients Requiring Around-the- Clock Opioid Therapy for an Extended Period of Time	BioDelivery BioSciences announced that BEMA Buprenorphine is on track for late 2014 or early 2015 NDA filing by partner Endo Pharmaceuticals.

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Route of Administration	Current or Potential Use(s)	Comments
ZTLIDO (lidocaine patch 1.8%) Scilex	New Formulation	Analgesics & Anesthetics	Transdermal	Treatment of Postherpetic Neuralgia	Scilex anticipates filing a new drug application in the first quarter of 2015.
GBV-006 Globavir Biosciences	New Combination	Antiinfective Agents	Unknown	Treatment of Ebola Virus	Globavir Biosciences announced intentions to develop its lead drug candidate, GBV006, for the treatment of the current Ebola Virus outbreak in West Africa. Globavir will seek approval for the use of GBV006, a combination of FDA approved drugs, through an established compassionate use regulatory pathway.
(alirocumab) Sanofi; Regeneron	New Molecular Entity	Cardiovascular Agents	Subcutaneous	Hypercholesterolemia	Sanofi and Regeneron anticipate alirocumab regulatory submissions in the U.S. and EU by the end of 2014. In the U.S., the companies intend to use a Priority Review Voucher to obtain priority review status for the alirocumab regulatory submission.
CINQUIL (reslizumab) Teva	New Molecular Entity	Respiratory Agents	Intravenous; Subcutaneous	Eosinophilic Asthma	Regulatory submissions in the U.S. planned for the first half of 2015.
AMPION Ampio	New Molecular Entity	Analgesics & Anesthetics	Intraarticular	Treatment of Acute Osteoarthritis of the Knee (OAK)	Ampio plans to submit the BLA before the end of Q1 2015.
(insulin peglispro) Eli Lilly	New Formulation	Endocrine & Metabolic Drugs	Subcutaneous	Type 1 & Type 2 Diabetes Mellitus (DM)	Lilly plans to submit for regulatory review to the FDA by the end of Q1 2015.
LETAIRIS (ambrisentan) Gilead Sciences	New Indication	Cardiovascular Agents	Oral	First-Line Combination Therapy with Tadalafil in Patients with Pulmonary Arterial Hypertension	Gilead plans to submit the AMBITION data in a supplemental new drug application (sNDA) to FDA by the end of 2014.
(odanacatib) Merck	New Molecular Entity	Endocrine & Metabolic Drugs	Oral	Treatment of Postmenopausal Osteoporosis	Merck now expects to submit the New Drug Application for odanacatib with the FDA in 2015 as opposed to H2 2014.
CYRAMZA (ramucirumab) Eli Lilly	New Indication	Antineoplastics & Adjunctive Therapies	Intravenous	Metastatic Colorectal Cancer (mCRC)	Lilly plans to present data from the RAISE trial (a Phase III study of CYRAMZA (ramucirumab) in combination with chemotherapy in patients with metastatic colorectal cancer (mCRC) at a scientific meeting in 2015 and expects to initiate regulatory submissions in the first half of 2015.
EYLEA (afibercept) Regeneron	New Indication	Ophthalmic Agents	Intravitreal	Treatment of Diabetic Retinopathy in Patients with Diabetic Macular Edema (DME)	Regeneron plans to submit a supplemental Biologics License Application (sBLA) in the U.S. for diabetic retinopathy in patients with DME later this year.
ZINBRYTA (daclizumab) Biogen Idec; AbbVie	New Formulation; New Indication	Misc. Psychotherapeutic & Neurological Agents	Subcutaneous	Relapsing Remitting Multiple Sclerosis (RRMS)	A FDA filing is expected in H1 2015.
RAYALDEE (calcifediol) OPKO Health	New Formulation	Endocrine & Metabolic Drugs	Oral	Secondary Hyperparathyroidism (SHPT) in Patients with Stage 3 or 4 Chronic Kidney Disease (CKD) and Vitamin D Insufficiency	A New Drug Application (NDA) submission to the FDA is planned for the end of 2014.
VESNEO (latanoprostene bunod) Bausch & Lomb	New Molecular Entity	Ophthalmic Agents	Intraocular	Glaucoma; Ocular Hypertension	Bausch + Lomb expects to submit a New Drug Application (NDA) to the FDA for the approval of VESNEO in mid-2015.

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Route of Administration	Current or Potential Use(s)	Comments
(levodopa); CVT-301 Acorda ; Civitas Therapeutics	New Formulation	Misc. Psychotherapeutic & Neurological Agents	Inhalation	Parkinson's Disease (PD)	A pivotal Phase III study of CVT-301 for treatment of Off episodes in people with PD is expected to begin enrolling in early 2015 and if successful, a filing for regulatory approval in the United States is expected by the end of 2016.
ANTHIM (oblitoximab) Elusys Therapeutics	New Molecular Entity	Antiinfective Agents	Intravenous; Intramuscular	Treatment of Inhalational Anthrax	A Biologics License Application (BLA) is expected to be filed in Q4 2014.
(testosterone undecanoate); LPCN- 1021 Lipocine	New Formulation	Endocrine & Metabolic Drugs	Oral	Male Hypogonadism	Lipocine expects to file a New Drug Application (NDA) in the second half of 2015.
(elvitegravir / cobisistat / emtricitabine / TAF) Gilead Sciences	New Combination	Antiinfective Agents	Oral	Fixed-Dose, Single Tablet Formulation for Treatment of HIV-1 Infection	Gilead plans to submit a NDA in Q4 2014.
(pegfilgrastim biosimilar); CHS-1701 Coherus BioSciences	Biosimilar	Hematological Agents	Subcutaneous	Neutropenia	Coherus expects to file a biosimilar license application in 2016.
(adalimumab biosimilar); CHS-1420 Coherus BioSciences	Biosimilar	Analgesics & Anesthetics	Subcutaneous	Rheumatoid Arthritis (RA)	Coherus expects to file for regulatory approval of CHS-1420 in 2016.
CARBAVANCE The Medicines Company	New Formulation; New Combination	Antiinfective Agents	Intravenous	Complicated Urinary Tract Infections	The Medicines Company expects to file a NDA in 2016.
(secukinumab) Novartis	New Molecular Entity	Analgesics & Anesthetics	Intravenous; Subcutaneous	Psoriatic Arthritis (PsA)	Novartis announced that global regulatory applications for secukinumab in psoriatic arthritis are planned for 2015.
(sub-micron loteprednol etabonate) Bausch & Lomb	New Formulation	Ophthalmic Agents	Intraocular	Treatment of Pain & Inflammation Following Cataract Surgery	Bausch & Lomb expects to file NDA in H2 2015 and expects to launch the product in the U.S. in H2 2016.
ZALVISO (sufentanil sublingual tablet system) AcelRx	New Formulation	Analgesics & Anesthetics	Sublingual	Pre-Programmed, Non- Invasive, Handheld System for the Management of Moderate to Severe Acute Pain in Adult Patients in the Hospital Setting	AcelRx is targeting resubmission of the ZALVISO NDA in Q1 2015.
ANDROXAL (enclomiphene citrate) Repros	New Formulation	Endocrine & Metabolic Drugs	Oral	Secondary Hypogonadism	Repros continues to believe that a NDA will be filed around the end of 2014.

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