Nevada Medicaid Pharmacy and Therapeutics Committee Meeting

March 28, 2019

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NOTICE OF PUBLIC MEETING – PHARMACY AND THERAPEUTICS COMMITTEE

AGENDA

Date of Publication:

Date and Time of Meeting: **Thursday, March 28, 2019 at 1:00 PM**

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

Place of Meeting:

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

Please check with staff to verify room location

North Location:
Optum Office
9850 Double R Blvd
Ste 200
Reno, NV 89521

Webinar Registration:
https://optum.webex.com/optum/onstage/g.php?MTID=ee98bab98e724ebd24d73f77fbb74255b

OR

www.webex.com, select "Join", enter Meeting Number 644 842 292, your name and email and then select, "Join".

A Password should not be necessary, but if asked, enter, "jEAtDb3@"

OR

Audio Only: **1-763-957-6300**
Event Number: 644 842 292

Follow the instructions that appear on your screen to join the teleconference. Audio will also be broadcast over the internet (VoIP).

Reasonable efforts will be made to assist and accommodate physically challenged persons desiring to attend the meeting. Please call Tanya Benitez at: 775-684-3722 or email Tanya.Benitez@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

1. Call to Order and Roll Call

2. Public Comment

3. Administrative

a. **For Possible Action**: Review and Approve Meeting Minutes from November 15, 2018

b. Status Update by DHCFP
   i. Public Comment

4. Proposed New Drug Classes

a. Anti-migraine Agents – Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists

   i. Public Comment
   ii. Drug Class Review Presentation – OptumRx

iii. **For Possible Action**: Committee Discussion and Action
    1. Approve Clinical/Therapeutic Equivalency of Agents in Class
    2. Identify Exclusions/Exceptions for Certain Patient Groups
iv. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
v. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

b. Toxicology Agents - Substance Abuse Agents - Withdrawal Agents

i. Public Comment
ii. Drug Class Review Presentation – OptumRx
iii. **For Possible Action**: Committee Discussion and Action
    1. Approve Clinical/Therapeutic Equivalency of Agents in Class
    2. Identify Exclusions/Exceptions for Certain Patient Groups
iv. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
v. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

c. Toxicology Agents - Substance Abuse Agents - Opiate Antagonist Extended Release Injections

i. Public Comment
ii. Drug Class Review Presentation – OptumRx
iii. **For Possible Action**: Committee Discussion and Action
    1. Approve Clinical/Therapeutic Equivalency of Agents in Class
    2. Identify Exclusions/Exceptions for Certain Patient Groups
iv. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
v. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

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

a. Anti-infective Agents - Antivirals - Influenza Agents

i. Public Comment
ii. Drug Class Review Presentation – OptumRx

iii. **For Possible Action**: Committee Discussion and Action
    1. Approve Clinical/Therapeutic Equivalency of Agents in Class
    2. Identify Exclusions/Exceptions for Certain Patient Groups
iv. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
v. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

b. Autonomic Agents - Sympathomimetics - Self-injectable Epinephrine

i. Public Comment
ii. Drug Class Review Presentation – OptumRx
iii. **For Possible Action**: Committee Discussion and Action
    1. Approve Clinical/Therapeutic Equivalency of Agents in Class
    2. Identify Exclusions/Exceptions for Certain Patient Groups
iv. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
v. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

c. Hormones and Hormone Modifiers - Androgens

i. Public Comment
ii. Drug Class Review Presentation – OptumRx
iii. **For Possible Action**: Committee Discussion and Action
    1. Approve Clinical/Therapeutic Equivalency of Agents in Class
    2. Identify Exclusions/Exceptions for Certain Patient Groups
iv. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
v. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

d. Ophthalmic Agents – Antiglaucoma Agents

i. Public Comment
ii. Drug Class Review Presentation – OptumRx
iii. **For Possible Action**: Committee Discussion and Action
    1. Approve Clinical/Therapeutic Equivalency of Agents in Class

2. Identify Exclusions/Exceptions for Certain Patient Groups

iv. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy

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

e. Ophthalmic Agents - Ophthalmics for Dry Eye Disease

i. Public Comment

ii. Drug Class Review Presentation – OptumRx

iii. **For Possible Action**: Committee Discussion and Action

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

iv. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy

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

6. Established Drug Classes

a. Toxicology Agents - Substance Abuse Agents - Mixed Opiate Agonists/Antagonists (Oral)

i. Public Comment

ii. Drug Class Review Presentation – OptumRx

iii. **For Possible Action**: Committee Discussion and Action

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

iv. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy

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

b. Analgesics - Analgesic/Miscellaneous - Neuropathic Pain/Fibromyalgia Agents

i. Public Comment

ii. Drug Class Review Presentation – OptumRx

iii. **For Possible Action**: Committee Discussion and Action

1. Approve Clinical/Therapeutic Equivalency of Agents in Class

2. Identify Exclusions/Exceptions for Certain Patient Groups

iv. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy

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

c. Anti-infective Agents - Antivirals - Anti-hepatitis Agents - Polymerase Inhibitors/Combination Products

i. Public Comment

ii. Drug Class Review Presentation – OptumRx

iii. **For Possible Action**: Committee Discussion and Action

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

iv. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy

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

d. Dermatological Agents - Topical Anti-Infectives - Topical Antifungals (Onychomycosis)

i. Public Comment

ii. Drug Class Review Presentation – OptumRx

iii. **For Possible Action**: Committee Discussion and Action

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

iv. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy

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

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

8. Closing Discussion

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

PLEASE NOTE: **Items may be taken out of order at the discretion of the chairperson. Items may be combined for consideration by the public body. Items may be pulled or removed from the agenda at any time. If an action item is not completed within the time frame that has been allotted, that action item will be continued at a future time designated and announced at this meeting by the chairperson. All public comment may be limited to 5 minutes.**

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

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

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

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

We are pleased to make accommodations for members of the public who have disabilities and wish to attend the meeting. If special arrangements are necessary, notify the Division of Health Care Financing and Policy as soon as possible and at least ten days in advance of the meeting, by e-mail at: ellen.felsing@dhcfp.nv.gov, in writing, at 1100 East William Street, Suite 101, Carson City, Nevada 89701 or call Ellen Felsing at (775) 684-3684.

Summary of P&T Committee

Pharmacy and Therapeutics Committee (P&T)

By statute (NRS 422.402-422.405), the State of Nevada requires the DHCFP to establish and maintain a Preferred Drug List (PDL). The Pharmacy and Therapeutics Committee (P&T) was established to identify prescription drugs to be included on the PDL. The PDL is not restricted formulary. Drugs not on the PDL are still available to recipients if they meet the Standard Preferred Drug List Exception criteria.

The P&T committee consists of at least 9 but not more than 11 members who are Governor-appointed physicians and pharmacists. Members must be licensed to practice in the State of Nevada and either an actively practicing physician or an actively practicing pharmacist. The DHCFP Chief of Pharmacy Services serves as Coordinator to the P&T Committee. Meetings are held quarterly and are open to the public. Anyone wishing to address the P&T Committee may do so. Public comment is limited to 5 minutes per speaker/organization (due to time constraints). Anyone presenting documents for consideration must provide sufficient copies for each committee member and a copy (electronic preferred) for the official record.

For pharmacists and physicians wishing to serve on the Pharmacy & Therapeutics Committee, please visit the Governor's Boards and Commissions webpage using the link below.

http://gov.nv.gov/Board/Boards/

Current Board Members:

Shamim Nagy, MD, Chair

Joseph Adashek, MD

Evelyn Chu, Pharm.D.

Mark Crumby, Pharm.D.

Mark Decerbo, Pharm.D.

Michael Hautekeet, R.Ph

Sapandeep Khurana, MD

Brian Passalacqua, MD

Kate Ward, Pharm.D.

Steven Zuchowski, MD

Pharmacy and Therapeutics (P&T) Meeting scheduled for 2019

Date	South Nevada Location	North Nevada Location
June 27, 2019	Springs Preserve – Las Vegas	Optum Office – Reno
September 27, 2019	Springs Preserve – Las Vegas	Optum Office – Reno
December 5, 2019	Springs Preserve – Las Vegas	Optum Office – Reno

Web References

Preferred Drug List:

https://www.medicaid.nv.gov/providers/rx/PDL.aspx

Medicaid Services Manual (MSM) Chapter 1200:

http://dhcfp.nv.gov/Resources/AdminSupport/Manuals/MSM/C1200/Chapter1200/

Pharmacy and Therapeutics Committee Bylaws:

http://dhcfp.nv.gov/uploadedFiles/dhcfpnvgov/content/Boards/CPT/PandT_Bylaws.pdf

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."

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 non-preferred 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

Current Preferred Drug List

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

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

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

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

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

Preferred Products	PA Criteria	Non-Preferred Products
BISOPROLOL BISOPROLOL/HCTZ BYSTOLIC®* CARVEDILOL LABETALOL METOPROLOL (Reg Release) NADOLOL PINDOLOL PROPRANOLOL PROPRANOLOL/HCTZ SOTALOL TIMOLOL	*Restricted to ICD-10 codes J40-J48	
Calcium-Channel Blockers		
AFEDITAB CR® AMLODIPINE CARTIA XT® DILTIA XT® DILTIAZEM ER DILTIAZEM HCL DYNACIRC CR® EXFORGE® EXFORGE HCT® FELODIPINE ER ISRADIPINE LOTREL® NICARDIPINE NIFEDIAC CC NIFEDICAL XL NIFEDIPINE ER NISOLDIPINE ER TAZTIA XT® VERAPAMIL VERAPAMIL ER		
Vasodilators		
Inhaled		
VENTAVIS® TYVASO®		
Oral		
ADCIRCA® ORENITRAM® SILDENAFIL TRACLEER®		ADEMPAS® LETAIRIS® OPSUMIT® REVATIO ® TADALAFIL UPTRAVI®

Preferred Products	PA Criteria	Non-Preferred Products
Antilipemics		
Bile Acid Sequestrants		
COLESTIPOL CHOLESTYRAMINE WELCHOL®		QUESTRAN®
Cholesterol Absorption Inhibitors		
ZETIA®		EZETIMIBE
Fibric Acid Derivatives		
FENOFIBRATE FENOFIBRIC GEMFIBROZIL		ANTARA® FENOGLIDE® FIBRICOR® LIPOFEN® LOFIBRA® TRICOR® TRIGLIDE® TRILIPIX®
HMG-CoA Reductase Inhibitors (Statins)		
ATORVASTATIN CRESTOR® QL FLUVASTATIN LOVASTATIN PRAVASTATIN SIMVASTATIN		ADVICOR® ALTOPREV® AMLODIPINE/ATORVASTATIN CADUET® EZETIMIBE-SIMVASTATIN LESCOL® LESCOL XL® LIPITOR® LIPTRUZET® LIVALO® MEVACOR® PRAVACHOL® ROSUVASTATIN SIMCOR® VYTORIN® ZOCOR® ZYPITAMAG®
Niacin Agents		
NIASPAN® (Brand only) NIACIN ER (ALL GENERICS)		NIACOR®
Omega-3 Fatty Acids		
LOVAZA® VASCEPA®		OMEGA-3-ACID OMTRYG®

Preferred Products	PA Criteria	Non-Preferred Products
Dermatological Agents		
Antipsoriatic Agents		
Topical Vitamin D Analogs		
DOVONEX® CREAM SORILUX® (FOAM) TACLONEX® SUSP VECTICAL® (OINT)		CALCITENE® CALCIPOTRIENE CALCIPOTRIENE OINT/BETAMETHAZONE ENSTILAR ® (AER) TACLONEX OINT
Topical Analgesics		
CAPSAICIN FLECTOR® LIDOCAINE LIDOCAINE HC LIDOCAINE VISCOUS LIDOCAINE/PRILOCAINE PENNSAID® VOLTAREN® GEL		DICLOFENAC (gel/sol) EMLA® LIDODERM® QL LIDAMANTLE®
Topical Anti-infectives		
Acne Agents: Topical, Benzoyl Peroxide, Antibiotics and Combination Products		
ACANYA® AZELEX® 20% cream BENZACLIN® BENZOYL PEROXIDE (2.5, 5 and 10% only) CLINDAMYCIN ONEXTON GEL®	PA required if over 21 years old	 ACZONE GEL® BENZOYL PER AEROSOL CLINDAMYCIN AEROSOL CLINDAMYCIN/BENZOYL PEROXIDE GEL DUAC CS® ERYTHROMYCIN ERYTHROMYCIN/BENZOYL PEROXIDE SODIUM SODIUM SULFACETAMIDE/SULFUR SULFACETAMIDE
Impetigo Agents: Topical		
MUPIROCIN OINT		ALTABAX® CENTANY® MUPIROCIN CREAM
Topical Antifungals (onychomycosis)		
CICLOPIROX SOLN TERBINAFINE TABS	PA required	JUBLIA® KERYDIN® PENLAC® ITRACONAZOLE

Preferred Products	PA Criteria	Non-Preferred Products
Topical Antivirals		
ABREVA® XERESE® CREAM ZOVIRAX®, OINTMENT		ACYCLOVIR OINT DENAVIR®
Topical Scabicides		
NIX® PERMETHRIN RID® SKLICE® ULESFIA®	* PA required	EURAX® LINDANE MALATHION NATROBA® * OVIDE® SPINOSAD
Topical Anti-inflammatory Agents		
Immunomodulators: Topical		
ELIDEL® QL EUCRISA® PROTOPIC® QL	Prior authorization is required for all drugs in this class	TACROLIMUS
Topical Antineoplastics		
Topical Retinoids		
RETIN-A MICRO®(Pump and Tube) TAZORAC® ZIANA®	Payable only for recipients up to age 21.	ADAPALENE GEL AND CREAM ATRALIN® AVITA® DIFFERIN® EPIDUO® TRETINOIN TRETIN-X® VELTIN®
Electrolytic and Renal Agents		
Phosphate Binding Agents		
CALCIUM ACETATE CAP ELIPHOS® RENAGEL® RENVELA®		AURYXIA ® CALCIUM ACETATE TAB FOSRENOL® PHOSLO® PHOSLYRA® SEVELAMER CARBONATE VELPHORO®
Gastrointestinal Agents		
Antiemetics		
Miscellaneous		
Diclegis® OTC Doxylamine 25mg/Pyridoxine 10mg		BONJESTA®
Serotonin-receptor antagonists/Combo		
GRANISETRON QL		AKYNZEO®

Preferred Products	PA Criteria	Non-Preferred Products
ONDANSETRON QL	PA required for all medication in this class	ANZEMET® QL KYTRIL® QL SANCUSO® ZOFRAN® QL ZUPLENZ® QL
Antiulcer Agents		
H2 blockers		
FAMOTIDINE RANITIDINE RANITIDINE SYRUP*	*PA not required for < 12 years	
Proton Pump Inhibitors (PPIs)		
NEXIUM® CAPSULES NEXIUM® POWDER FOR SUSP* PANTOPRAZOLE	PA required if exceeding 1 per day *for children ≤ 12 yrs.	ACIPHEX® DEXILANT® ESOMEPRAZOLE LANSOPRAZOLE OMEPRAZOLE OTC TABS PREVACID® PRILOSEC® PRILOSEC® OTC TABS PROTONIX®
Functional Gastrointestinal Disorder Drugs		
AMITIZA® * LINZESS®	* PA required for Opioid Induced Constipation	MOVANTIK® * RELISTOR® * SYMPROIC® TRULANCE®
Gastrointestinal Anti-inflammatory Agents		
APRISO® ASACOL HD® ASACOL®SUPP BALSALAZIDE® CANASA® DELZICOL® LIALDA ® MESALAMINE ENEMA SUSP PENTASA® SULFASALAZINE DR SULFASALAZINE IR		COLAZAL® GIAZO® MESALAMINE (GEN LIALDA) MESALAMINE (GEN ASACOL HD)
Gastrointestinal Enzymes		
CREON® ZENPEP®		PANCREAZE® PANCRELIPASE PERTZYE®

Preferred Products	PA Criteria	Non-Preferred Products
		ULTRESA® VIOKACE®
Genitourinary Agents		
Benign Prostatic Hyperplasia (BPH) Agents		
5-Alpha Reductase Inhibitors		
DUTASTERIDE FINASTERIDE		AVODART® DUTASTERIDE/TAMSULOSIN JALYN® PROSCAR®
Alpha-Blockers		
DOXAZOSIN TAMSULOSIN TERAZOSIN		ALFUZOSIN CARDURA® FLOMAX® MINIPRESS® PRAZOSIN RAPAFLO® UROXATRAL®
Bladder Antispasmodics		
BETHANECHOL OXYBUTYNIN TABS/SYRUP/ER TOVIAZ® VESICARE®		DETROL® DETROL LA® DITROPAN XL® ENABLEX® FLAVOXATE GELNIQUE® MYRBETRIQ® OXYTROL® SANCTURA® TOLTERODINE TROSPIUM
Hematological Agents		
Anticoagulants		
Oral		
COUMADIN® ELIQUIS® * JANTOVEN® PRADAXA® * QL WARFARIN XARELTO ® *	* No PA required if approved diagnosis code transmitted on claim	SAVAYSA®*
Injectable		
FONDAPARINUX ENOXAPARIN FRAGMIN®		ARIXTRA® INNOHEP® LOVENOX®

Preferred Products	PA Criteria	Non-Preferred Products
Erythropoiesis-Stimulating Agents		
ARANESP® QL PROCRIT® QL	PA required Quantity Limit	EPOGEN® QL MIRCERA® QL RETACRIT®
Platelet Inhibitors		
AGGRENOX® ANAGRELIDE ASPIRIN BRILINTA® * QL CILOSTAZOL® CLOPIDOGREL DIPYRIDAMOLE	* PA required	ASPIRIN/DIPYRIDAMOLE DURLAZA® EFFIENT® * QL PLAVIX® PRASUGREL ZONTIVITY® YOSPRALA®
Hormones and Hormone Modifiers		
Androgens		
ANDROGEL® ANDRODERM®	**PA required** **PA Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-72.pdf	AXIRON® FORTESTA® NATESTO® STRIANT® TESTIM® TESTOSTERONE GEL VOGELXO®
Antidiabetic Agents		
Alpha-Glucosidase Inhibitors/Amylin analogs/Misc.		
ACARBOSE GLYSET® SYMLIN® (PA required)		CYCLOSET® PRECOSE®
Biguanides		
FORTAMET® GLUCOPHAGE® GLUCOPHAGE XR® METFORMIN EXT-REL (Glucophage XR®) GLUMETZA® METFORMIN (Glucophage®) RIOMET®		METFORMIN (GEN GLUMETZA)
Dipeptidyl Peptidase-4 Inhibitors		
JANUMET® JANUMET XR® JANUVIA® JENTADUETO® KOMBIGLYZE XR®		ALOGLIPTIN ALOGLIPTIN-METFORMIN ALOGLIPTIN-PIOGLITAZONE KAZANO® NESINA®

Preferred Products	PA Criteria	Non-Preferred Products
ONGLYZA® TRADJENTA®		OSENI®
Incretin Mimetics		
BYDUREON® * BYDUREON® PEN * BYETTA® * TRULICITY® VICTOZA® *	* PA required	ADLYXIN® BYDUREON® BCISE * OZEMPIC® SOLIQUA® TANZEUM® XULTOPHY®
Insulins (Vials, Pens and Inhaled)		
APIDRA® HUMALOG® HUMULIN® LANTUS® LEVEMIR ® NOVOLIN® NOVOLOG® TRESIBA FLEX INJ		ADMELOG® AFREZZA® BASAGLAR® FIASP® HUMALOG® U-200 TOUJEO SOLO® 300 IU/ML
Meglitinides		
NATEGLINIDE (Starlix®) PRANDIMET® PRANDIN® STARLIX®		
Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors		
FARXIGA® INVOKANA® JARDIANCE®		GLYXAMBI® INVOKAMET® INVOKAMET® XR QTERN® SEGLUROMET® STEGLATRO® STEGLUJAN™ SYNJARDY® SYNJARDY® XR XIGDUO XR®
Sulfonylureas		
AMARYL® CHLORPROPAMIDE DIABETA® GLIMEPIRIDE (Amaryl®) GLIPIZIDE (Glucotrol®) GLUCOTROL® GLUCOVANCE®		

Preferred Products	PA Criteria	Non-Preferred Products
GLIPIZIDE EXT-REL (Glucotrol XL®) GLIPIZIDE/METFORMIN (Metaglip®) GLYBURIDE MICRONIZED (Glynase®) GLYBURIDE/METFORMIN (Glucovance®) GLUCOTROL XL® GLYBURIDE (Diabeta®) GLYNASE® METAGLIP® TOLAZAMIDE TOLBUTAMIDE		
Thiazolidinediones		
ACTOPLUS MET XR® ACTOS® ACTOPLUS MET® AVANDAMET® AVANDARYL® AVANDIA® DUETACT®		
Pituitary Hormones		
Growth hormone modifiers		
GENOTROPIN® NORDITROPIN®	**PA required for entire class** https://www.medicaid.nv.gov/Downloads/provider/FA-67.pdf	HUMATROPE® NUTROPIN AQ® OMNITROPE® NUTROPIN® SAIZEN® SEROSTIM® SOMAVERT® TEV-TROPIN® ZORBTIVE®
Progestins for Cachexia		
MEGESTROL ACETATE, SUSP		MEGACE ES®
Monoclonal Antibodies for the treatment of Respiratory Conditions		
NUCALA® XOLAIR®		CINQAIR® FASENRA®
Musculoskeletal Agents		
Antigout Agents		
ALLOPURINOL COLCHICINE TAB/CAP PROBENECID		COLCRYS® TAB MITIGARE® CAP ZURAMPIC®

Preferred Products	PA Criteria	Non-Preferred Products
PROBENECID/COLCHICINE ULORIC®		ZYLOPRIM®
Bone Resorption Inhibitors		
Bisphosphonates		
ALENDRONATE TABS		ACTONEL® ALENDRONATE SOLUTION ATELVIA® BINOSTO® BONIVA® DIDRONEL® ETIDRONATE FOSAMAX PLUS D® IBANDRONATE SKELID®
Nasal Calcitonins		
CALCITONIN-SALMON		MIACALCIN®
Restless Leg Syndrome Agents		
PRAMIPEXOLE REQUIP XL ROPINIROLE		HORIZANT® MIRAPEX® MIRAPEX® ER REQUIP
Skeletal Muscle Relaxants		
BACLOFEN CHLORZOXAZONE CYCLOBENZAPRINE DANTROLENE METHOCARBAMOL METHOCARBAMOL/ASPIRIN ORPHENADRINE CITRATE ORPHENADRINE COMPOUND TIZANIDINE		
Neurological Agents		
Alzheimers Agents		
DONEPEZIL DONEPEZIL ODT EXELON® PATCH EXELON® SOLN MEMANTINE TABS		ARICEPT® 23mg ARICEPT® GALANTAMINE GALANTAMINE ER MEMANTINE SOL MEMANTINE XR NAMENDA® TABS NAMENDA® XR TABS NAMZARIC®

Preferred Products	PA Criteria	Non-Preferred Products
		RAZADYNE® RAZADYNE® ER RIVASTIGMINE CAPS RIVASTIGMINE TRANSDERMAL
Anticonvulsants		
APTIOM® (NEW) BANZEL® BRIVIACT® CARBAMAZEPINE CARBAMAZEPINE XR CARBATROL ER® CELONTIN® DEPAKENE® DEPAKOTE ER® DEPAKOTE® DIVALPROEX SODIUM DIVALPROEX SODIUM ER EPIDIOLEX® (NEW) EPITOL® ETHOSUXIMIDE FELBATOL® FYCOMPA® GABAPENTIN GABITRIL® KEPPRA® KEPPRA XR® LAMACTAL ODT® LAMACTAL XR® LAMICTAL® LAMOTRIGINE LEVETIRACETAM LYRICA® NEURONTIN® OXCARBAZEPINE SABRIL® STAVZOR® DR TEGRETOL® TEGRETOL XR® TOPAMAX® TOPIRAGEN® TOPIRAMATE (IR AND ER) TRILEPTAL® VALPROATE ACID VIMPAT®	PA required for members under 18 years old	OXTELLAR XR® POTIGA® QUDEXY XR® TROKENDI XR® SPRITAM®

	Preferred Products	PA Criteria	Non-Preferred Products
	ZARONTIN® ZONEGRAN® ZONISAMIDE		
Barbiturates			
	LUMINAL® MEBARAL® MEPHOBARBITAL SOLFOTON® PHENOBARBITAL MYSOLINE® PRIMIDONE	PA required for members under 18 years old	
Benzodiazepines			
	CLOBAZAM (NEW) CLONAZEPAM CLORAZEPATE DIASTAT® DIAZEPAM DIAZEPAM rectal soln KLONOPIN® TRANXENE T-TAB® VALIUM®	PA required for members under 18 years old	ONFI®
Hydantoins			
	CEREBYX® DILANTIN® ETHOTOIN FOSPHENYTOIN PEGANONE® PHENYTEK® PHENYTOIN PRODUCTS	PA required for members under 18 years old	
Anti-Migraine Agents			
Serotonin-Receptor Agonists			
	RELPAX® RIZATRIPTAN ODT SUMATRIPTAN TABLET ZOLMITRIPTAN ODT	PA required for exceeding Quantity Limit	ALMOTRIPTAN AMERGE® AXERT® FROVA® ELETRIPTAN FROVATRIPTAN SUCCINATE IMITREX® MAXALT® TABS MAXALT® MLT NARATRIPTAN ONZETRA XSAIL® RIZATRIPTAN BENZOATE

Preferred Products	PA Criteria	Non-Preferred Products
		SUMATRIPTAN INJECTION SUMATRIPTAN/NAPROXEN SUMATRIPTAN NASAL SPRAY SUMAVEL® TREXIMET® ZEMBRACE SYMTOUCH ZOLMITRIPTAN ZOMIG® ZOMIG® ZMT
Antiparkinsonian Agents		
Non-ergot Dopamine Agonists		
PRAMIPEXOLE ROPINIROLE ROPINIROLE ER		MIRAPEX® MIRAPEX® ER NEUPRO® REQUIP® REQUIP XL®
Ophthalmic Agents		
Antiglaucoma Agents		
ALPHAGAN P® AZOPT® BETAXOLOL BETOPTIC S® BRIMONIDINE CARTEOLOL COMBIGAN® DORZOLAM DORZOLAM / TIMOLOL LATANOPROST LEVOBUNOLOL LUMIGAN® METIPRANOLOL RHOPRESSA® SIMBRINZA® TIMOLOL DROPS/ GEL SOLN TRAVATAN Z® TRAVATAN®		ALPHAGAN® BETAGAN® BETOPTIC ® BIMATOPROST COSOPT PF® COSOPT® OCUPRESS® OPTIPRANOLOL® TIMOPTIC XE® TIMOPTIC® TRAVOPROST TRUSOPT® VYZULTA® XALATAN® ZIOPTAN®
Ophthalmic Antihistamines		
BEPREVE® KETOTIFEN PAZEO® ZADITOR OTC®		ALAWAY® AZELASTINE ALOMIDE ALOCRIL ELESTAT® EMADINE®

Preferred Products	PA Criteria	Non-Preferred Products
		EPINASTINE LASTACRAFT® OLOPATADINE (drop/sol) OPTIVAR® PATADAY® PATANOL®
Ophthalmic Anti-infectives		
Ophthalmic Macrolides		
ERYTHROMYCIN OINTMENT		
Ophthalmic Quinolones		
BESIVANCE® CIPROFLOXACIN LEVOFLOXACIN MOXEZA® VIGAMOX®		CILOXAN® MOXIFLOXACIN OFLOXACIN® ZYMAXID®
Ophthalmic Anti-infective/Anti-inflammatory Combinations		
NEO/POLY/DEX PRED-G SULF/PRED NA SOL OP TOBRADEX OIN TOBRADEX SUS ZYLET SUS		BLEPHAMIDE MAXITROL NEO/POLY/BAC OIN /HC NEO/POLY/HC SUS OP TOBRA/DEXAME SUS TOBRADEX SUS TOBRADEX ST SUS
Ophthalmic Anti-inflammatory Agents		
Ophthalmic Corticosteroids		
ALREX® DEXAMETHASONE DUREZOL® FLUOROMETHOLONE LOTEMAX® PREDNISOLONE		FLAREX® FML® FML FORTE® MAXIDEX® OMNIPRED® PRED FORTE® PRED MILD® VEXOL®
Ophthalmic Nonsteroidal Anti-inflammatory Drugs (NSAIDs)		
DICLOFENAC FLURBIPROFEN ILEVRO® KETOROLAC NEVANAC®		ACULAR® ACULAR LS® ACUVAIL® BROMDAY® BROMFENAC® PROLENSA®
Ophthalmics for Dry Eye Disease		
ARTIFICIAL TEARS RESTASIS®		RESTASIS® MULTIDOSE XIIDRA®

Preferred Products	PA Criteria	Non-Preferred Products
Otic Agents		
Otic Anti-infectives		
Otic Quinolones		
CIPRODEX® CIPRO HC® OTIC SUSP OFLOXACIN		CIPROFLOXACIN SOL 0.2% CETRAXAL® OTIPRIO® OTOVEL® SOLN
Psychotropic Agents		
ADHD Agents		
ADDERALL XR® AMPHETAMINE SALT COMBO IR ATOMOXETINE (NEW) DEXMETHYLPHENIDATE DEXTROAMPHETAMINE SA TAB DEXTROAMPHETAMINE TAB DEXTROSTAT® DYANAVEL® FOCALIN XR® GUANFACINE ER METADATE CD® METHYLIN® METHYLIN ER® METHYLPHENIDATE METHYLPHENIDATE ER (All forms generic extended release) METHYLPHENIDATE SOL PROCENTRA® QUILLICHEW® QUILLIVANT® XR SUSP RITALIN LA® VYVANSE®	**PA required for entire class** **Children's Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-69.pdf **Adult Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-68.pdf	ADDERALL® ADZENYS® (NEW) AMPHETAMINE SALT COMBO XR APTENSIO XR® CLONIDINE HCL ER (NEW) CONCERTA® COTEMPLA XR®-ODT DAYTRANA® DESOXYN® DEXEDRINE® DEXTROAMPHETAMINE SOLUTION EVEKEO® FOCALIN® INTUNIV® KAPVAY® METADATE ER® MYDAYIS® RITALIN® STRATTERA® (NEW) ZENZEDI®
Antidepressants		
Other		
BUPROPION BUPROPION SR BUPROPION XL DULOXETINE *	PA required for members under 18 years old * PA required	APLENZIN® BRINTELLIX® CYMBALTA® * DESVENLAFAXINE FUMARATE

Preferred Products	PA Criteria	Non-Preferred Products
MIRTAZAPINE	*No PA required if ICD-10 - M79.1; M60.0-M60.9, M61.1.*	EFFEXOR® (ALL FORMS)
MIRTAZAPINE RAPID TABS		FETZIMA®
PRISTIQ®		FORFIVO XL®
TRAZODONE		KHEDEZLA®
VENLAFAXINE (ALL FORMS)		VIIBRYD®
		WELLBUTRIN®
Selective Serotonin Reuptake Inhibitors (SSRIs)		
CITALOPRAM	PA required for members under 18 years old	CELEXA®
ESCITALOPRAM		FLUVOXAMINE QL
FLUOXETINE		LEXAPRO®
PAROXETINE		LUVOX®
PEXEVA®		PAXIL®
SERTRALINE		PROZAC®
		SARAFEM®
		ZOLOFT®
Antipsychotics		
Atypical Antipsychotics - Oral		
ARIPIPRAZOLE		ABILIFY®
CLOZAPINE	**PA required for Ages under 18 years old**	CLOZARIL®
FANAPT®		FAZACLO®
LATUDA®		GEODON®
NUPLAZID®*		
OLANZAPINE		INVEGA®
QUETIAPINE		PALIPERIDONE
QUETIAPINE XR		
REXULTI®	**PA Forms:**	
RISPERIDONE	https://www.medicaid.nv.gov/Downloads/provider/FA-70A.pdf (ages 0-5)	RISPERDAL®
SAPHRIS®	https://www.medicaid.nv.gov/Downloads/provider/FA-70B.pdf (ages 6-18)	SEROQUEL®
VRAYLAR®		SEROQUEL XR®
ZIPRASIDONE	*(No PA required Parkinson's related psychosis ICD code on claim)	ZYPREXA®
Anxiolytics, Sedatives, and Hypnotics		
ESTAZOLAM	No PA required if approved diagnosis code transmitted on claim (All agents in this class)	AMBIEN®
FLURAZEPAM		AMBIEN CR®
ROZEREM®		BELSOMRA®

Preferred Products	PA Criteria	Non-Preferred Products
TEMAZEPAM TRIAZOLAM ZALEPLON ZOLPIDEM		DORAL® ESZOPICLONE EDLUAR® HETLIOZ® INTERMEZZO® LUNESTA® SILENOR® SOMNOTE® SONATA® ZOLPIDEM CR ZOLPIMIST®
	PA required for members under 18 years old	
Psychostimulants		
Narcolepsy Agents		
Provigil® *	* (No PA required for ICD-10 code G47.4)	MODAFINIL NUVIGIL® XYREM®
Respiratory Agents		
Nasal Antihistamines		
DYMISTA® PATANASE®		ASTEPRO® AZELASTINE OLOPATADINE
Respiratory Anti-inflammatory Agents		
Leukotriene Receptor Antagonists		
MONTELUKAST ZAFIRLUKAST ZYFLO® ZYFLO CR®		ACCOLATE® SINGULAIR® ZILEUTON ER
Nasal Corticosteroids		
FLUTICASONE TRIAMCINOLONE ACETONIDE		BECONASE AQ® FLONASE® FLUNISOLIDE NASACORT AQ® NASONEX® OMNARIS® QNASL® RHINOCORT AQUA® VERAMYST® XHANCE™ ZETONNA®
Phosphodiesterase Type 4 Inhibitors		
DALIRESP® QL	PA required	
Long-acting/Maintenance Therapy		
ADVAIR DISKUS® ADVAIR HFA®		AEROSPAN HFA® AIRDUO®

Preferred Products	PA Criteria	Non-Preferred Products
ANORO ELLIPTA® ARNUITY ELLIPTA® ASMANEX® BEVESPI® DULERA® FLOVENT DISKUS® QL FLOVENT HFA® QL FORADIL® PULMICORT FLEXHALER® PULMICORT RESPULES®* QVAR® SEREVENT DISKUS® QL		ALVESCO® ARCAPTA NEOHALER® ARMONAIR® BREO ELLIPTA® BROVANA® BUDESONIDE NEBS* FLUTICASONE PROPIONATE/SALMETEROL INCRUSE ELLIPTA ® LONHALA MAGNAIR® PERFOROMIST NEBULIZER® QVAR® REDIHALER™ SEEBRI NEOHALER® SPIRIVA RESPIMAT® TRELEGY ELLIPTA®
SPIRIVA® HANDIHALER STIOLTO RESPIMAT® STRIVERDI RESPIMAT® TUDORZA® SYMBICORT®		UTIBRON NEOHALER ®
Short-Acting/Rescue Therapy		
ALBUTEROL NEB/SOLN ATROVENT® COMBIVENT RESPIMAT® IPRATROPIUM NEBS IPRATROPIUM/ALBUTEROL NEBS QL LEVALBUTEROL* NEBS PROVENTIL® HFA XOPENEX® HFA* QL		LEVALBUTEROL* HFA PROAIR RESPICLICK® PROAIR® HFA VENTOLIN HFA® XOPENEX® Solution* QL
Toxicology Agents		
Antidotes		
Opiate Antagonists		
EVZIO ® NALOXONE NARCAN® NASAL SPRAY		
Substance Abuse Agents		
Mixed Opiate Agonists/Antagonists		
BUNAVAIL® SUBOXONE® ZUBSOLV®	PA required for class	BUPRENORPHINE / NALOXONE

Meeting Minutes

BRIAN SANDOVAL
Governor

RICHARD WHITLEY, MS
Director

CODY PHINNEY
Acting Administrator

DEPARTMENT OF HEALTH AND HUMAN SERVICES
DIVISION OF HEALTH CARE FINANCING AND POLICY
1100 East William Street, Suite 101
Carson City, Nevada 89701
Telephone (775) 684-3676 • Fax (775) 687-3893
http://dhcfp.nv.gov

P&T MEETING - MEETING MINUTES

Date and Time of Meeting: **Thursday, November 15, 2018 at 1:00 PM**

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

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

Attendees

Board Members (Present)
Shamim Nagy, MD, Chair
Michael Hautekeet, RPh
Evelyn Chu, Pharm.D.
Mark Decerbo, Pharm.D.
Steven Zuchowski, MD
Adam Zold, Pharm.D.
Brian Passalacqua, MD
Kate Ward, Pharm.D.
Mark Crumby, Pharm.D.

Board Members (Absent)
Joseph Adashek, MD
Sapandeep Khurana, MD

DHCFP:
Holly Long, Social Services Program Specialist III
Gabriel Lither, DAG

DHCFP (On-Line):
Beth Slamowitz, Pharm.D.
Victoria LeGarde, Social Services Program Specialist II

OptumRx:
Carl Jeffery, Pharm.D.
Kevin Whittington, RPh

Public (Las Vegas):
Dr. Kenneth Berry, Alkermes
Jody Legg, Alkermes
Kelly Holleman, Greenwich
Karen Einbinder, Greenwich
Mark Schwartz, GSK
Kim Lanbmeir, Sunovion
Phil Walsh, Sunovion
Amy Rodenburg, Allergan
David Freilich, Amneil
Sandy Sierawsky, Pfizer
Georgette Dzwilewski, Indivior
Leon Ravin, DPHB
Melissa Sommers, Novartis
Samir Banganore, Physician
Kelvin Yamashita, Sanofi

Public (On-line):
Rob Bigham, Shire
Lisa Wilson, Biogen

AGENDA

1. Call to Order and Roll Call

Meeting called to order at 1:00 PM.

Roll call:
Evelyn Chu, Pharm.D.
Michael Hautekeet, Pharm.D.
Shamim Nagy, MD, Chair
Gabriel Lither, DAG
Brian Passalacqua, MD
Steven Zuchowski, MD
Kate Ward, Pharm.D.
Mark Crumby, Pharm.D.
Mark Decerbo, Pharm.D.
Adam Zold, Pharm.D.
Holly Long
Camilla Hauck, RPh
Kevin Whittington, RPh

Carl Jeffery, Pharm.D.

2. Public Comment

Call for public comment.

3. Administrative

a. **For Possible Action**: Review and Approve Meeting Minutes from September 27, 2018

Motion to approve as submitted. Second. Voting: Ayes are unanimous, the motion carries.

b. Status Update by DHCFP

Holly Long – For the record, I'm Holly Long, DHCFP, Nevada Medicaid. I don't have any policy-specific updates related to the division, but I would like to give everyone an update as far as the antibiotic policy that we're working on. We briefly discussed it at the last meeting. The DUR Board did approve that three drug classes are going to be implemented possibly as early as February. That Drug Board Review will run in July and we identify that kickoff. We are looking at holding a webinar which will be over provider education for anybody that is interested and if anyone needs information for that, please provide us your information and I'll provide you the webinar information or any further answers to questions that you have. There have been some updates to what was provided last time. The three drug classes are the same. Third generation cephalosporins, the fluoroquinolones, and the oxazolidinones. Those three drug classes are specific drugs within each of those that will have prior authorization criteria for each of them. There is exception criteria which I would like to go ahead and read off because it seems to be where a lot of the confusion is around the policy. One of the exception criteria is if it's prescribed by an infectious disease specialist or by an emergency department provider. So remember, this is just outpatient. This doesn't affect hospital inpatient drugs related to antibiotics. Another is the cefixime. It's prescribed for the gonococcal infection where ceftriaxone is unavailable. And, lastly if the recipient resides in acute care, long-term acute care, or skilled nursing facility. And, again if anyone has any questions or would like to have more information, just provide me your contact information and I'll forward it to you. It's also posted on the Medicaid website under a newsletter of all the webinar information in there. It's going to be on December 4 at 1:30 where 2 hours will be provided for a presentation by the state and then also time set aside for questions and answers to be provided by the state and the antimicrobial stewardship specialists that we have.

Evelyn Chu, Pharm.D.: To clarify, all ED scripts will not require prior authorization?

Holly Long: Anything prescribed by infectious disease specialist or by an emergency department provider, it will not affect them.

i. Public Comment

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

a. Neurological Agents – Anticonvulsants

Kelly Holleman – My name is Kelly Holleman, I'm the associate director of Health Outcomes liaison for Greenwich BioSciences out of Carlsbad, California. I'm here to talk to you today about Epidiolex, cannabidiol, which has been rescheduled as a schedule V, just as a controlled substance. One of the things to kind of talk about when you talk about Epidiolex is the indications. It is indicated for seizures associated with LGS for Lennox-Gastaut Syndrome and for Dravet syndrome. These two syndromes are typically referred to as LGS and DS, are rare intractable and severe forms of epilepsy with childhood onset but they do go on into adulthood. These patients have multiple, sometimes hundreds of seizures a day that really, they lack any type of treatment that helps them to any great extent. Many times, they're on multiple medications. In our studies, the average number of medications that they were currently on were 3 and they had tried either 6 for LGS previously so they go through a lot of different medications to try to get resolution and often times they obviously do not. They also have developmental and physical disabilities, as well, from these seizures and one thing that I think is surprising to people is they have a high mortality rate. There is an issue called SUDEP, sudden unexpected death in epilepsy that these patients often have which really is concerning to the caregivers obviously. So our product, cannabidiol, is the active ingredient in Epidiolex. It's a highly purified and structurally distinct from other antiepileptic drugs that are currently on the market. It is plant based. It's a question that we get a lot. Although the exact mechanism is unknown at this time, there are several different theories. There's three that have been looked at. In the label, it talks about that it's multimodal and it does not exert its action on the cannabinoid receptors and when these cannabinoid receptors are stimulated, that's where you get the high and euphoria and that's what THC does, and there's really no discernible amount of THC in this product less than 0.015%. That's why in our studies we did not see any euphoria or high type of feeling. The FDA did require obviously because before cannabidiol could be used as a medicine, it's considered a schedule I so we worked in conjunction with the FDA on our abuse potential studies. We used patients that had used medications in the past that would cause them to have a high in the drug liking so they were recreational poly-drug users that were otherwise healthy. We used three different doses of Epidiolex and placebo and we also compared to Xanax and Marinol which are schedule 3 and 4. These patients did not have any discernable amount from placebo difference in their drug liking which we used a visual analog scale to ask them if they like the drug or if they want to take the drug again and there

was no discernible difference from placebo; however, there was a difference between the other controlled substance where they did feel that those were products that they would want to take again, and that they felt that they would like them. The efficacy and safety of Epidiolex has actually been studied in three trials that are the largest to date looking at seizure reduction in LGS and Dravet patients. These were randomized, double-blind, placebo-controlled multicenter 14-week trials. Patients were kept on their current AEDs and the site directors or the researchers were asked not to change their medications that they were currently only unless they absolutely had to, and then they were placed on Epidiolex either 10 mg/kg per day or 20 mg/kg per day, and Epidiolex did achieve its primary endpoint of median percent reduction in convulsive or drop seizures depending on study compared to placebo. We saw differences between 39 and 44% reduction which were statistically significant across all three trials; two of them were looking at LGS and one was looking at Dravet and both of the doses that were looked at compared to placebo, both the 10 mg and the 20 mg/kg per day. We also looked at a secondary endpoint of 50% reduction in seizures. This is very important to epileptologists and also caregivers. They want to say that there was a dramatic difference that they can notice. We did see in the LGS studies the statistically significant differences in that greater than 50% reduction. Dravet we saw numerical but it did not reach statistical significance. The safety profile is well characterize in Epidiolex. The adverse reactions that we saw in at least 10% or greater were somnolence, decreased appetite, diarrhea, transaminase elevation, fatigue, malaise, and some others, as well. Most of these adverse events and labels discussed, as well, were seen in the first 4 weeks. By 14 weeks, the majority of these adverse events such as somnolence, the ones that were at high incident, had either decreased or waned at the end of the study. There is more information obviously about warnings and contraindications. There are warnings and contraindications that are class effect so all AEDs have the same warnings and contraindications that you can find those in the full prescribing information. In summary, Epidiolex has demonstrated as effective for the treatment of LGS and Dravet, those seizures that are associated with those conditions, and has a well characterized safety profile. One thing to note, it's not indicated as adjunctive; however, we're not really promoting it as monotherapy. Our studies were monotherapy except for the patients that were not on monotherapy because obviously they were taking other medications at the time. We actually submitted to the FDA as adjunctive for the indication and the FDA came back and removed that. Thank you for your consideration in putting Epidiolex on the PDL for these patients that are suffering from these two horrific conditions. Thank you for your time.

Kim Lanbmeir: I'm the director of Healthy Economics and Optum Research with Sunovion Pharmaceuticals. Thank you for the opportunity to present on eslicarbazepine acetate which is commercially known as Aptiom, and obviously you've moved it to the preferred agents and I just wanted to highlight the indication

for Aptiom. Aptiom is indicated for the treatment of partial onset seizures, both as monotherapy and adjunctive therapy in patients 4 years of age and older. So again, I appreciated the opportunity to speak and again if you have any questions, I'm happy to address them.

Carl Jeffery: The new ones are Epidiolex. This is a new medication. We heard a good summary about the three studies that were done to get it approved. As you heard, the LGS and Dravet syndrome as the difficult ones to treat. This is the first in its medication. There is another medication that was approved for this as adjunctive therapy, called Diacomit. It is in your review but it's not available yet on the market, so we likely will see this again probably March by the time this one comes to the market. We have to have it available in the marketplace before we can really get a good idea of how to recommend it being used here. I think it's a promising medication for a difficult disease so it's one of the reasons we're recommending it as preferred. The other one is Aptiom. As we heard at the last meeting, it has a new indication for monotherapy. How we've addressed this class before is medications that have an indication for monotherapy as opposed to adjunctive therapy, we do make it preferred so that's really behind our recommendation. We do have some utilization numbers but because we include gabapentin in here, I think a lot of this gets washed out because most of the people taking gabapentin aren't using it for a seizure disorder and probably the same with the lamotrigine products, as well, and also the topiramate so I kind of doubt they're using these all for seizure disorders. I don't gather a lot of useful information from these utilization numbers because we're not really identifying what people are using maybe for some kind of seizure disorders. Here's a chart showing all of the currently available products within the class. So you can see on here the Diacomit, we'll probably bring this forward at future meetings, the other one, and I think this one was pretty recently added here and we didn't have information on this one, but the Afinitor, it's actually an oncology medication and it's being used for the indication for seizure disorders too so that will probably be in a future meeting, as well. Optum recommends the board consider these clinically and therapeutically equivalent.

Motion to accept as clinically and therapeutically equivalent. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: Continuing with our history of monotherapy versus adjunctive therapy, we recommend moving the Aptiom to preferred from non-preferred and the Epidiolex so technically, as she mentioned, it doesn't have the indication to make the distinction for monotherapy or adjunctive but I think 97% of the time in the studies it was given that subjects were on other medications but it's

got the potential to be used as monotherapy, but we're recommending it also be preferred and then the rest of the class remain the same.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

b. Toxicology Agents - Substance Abuse Agents - Mixed Opiate Agonists/Antagonists

Dr. Kenneth Berry: My name is Kenneth Berry. I'm a PharmD from Arizona and I'm a senior medical scientist liaison from Alkermes. I want to thank you for the opportunity to provide new information about Vivitrol, which is extended release naltrexone injectable suspension. I want to highlight a few clinical points today and economic points for you. First we note that Vivitrol is indicated for the treatment of alcohol dependence. It's also indicated for the treatment of opioid use disorder. Treatment should be part of a comprehensive management program that includes psychosocial support. Opioid dependent patients including those being treatment for alcohol should be opioid free for at least 7 to 10 days prior to initiating the Vivitrol. Vivitrol has some key points. It's a once-monthly extended release formulation of naltrexone and naltrexone is an opioid antagonist, blocker, and is the active ingredient in Vivitrol. Vivitrol is not an opioid replacement therapy and does not maintain physiologic opioid dependence. Vivitrol is not a controlled substance, is not associated with development of tolerance or dependence, and there's no potential for abuse and there's no diversion issues with Vivitrol. There's also no withdrawal syndrome associated with the discontinuation of Vivitrol. Now I'd like to highlight two clinical efficacy studies that were published in the last year. The first was one conducted by Cannon and Colleagues (phonetically) and published in JAMA Psychiatry October 2017. It was determined whether a treatment with Vivitrol will be as effective as daily Suboxone in maintaining abstinence from heroin and other illicit substances in newly detoxified individuals. The results show that Vivitrol was as effective as Suboxone treatment and maintaining abstinence from heroin and other illicit opiates and opiate patients in this 12-week study. Vivitrol did demonstrate significantly better improvement than Suboxone on several secondary measures, one being Vivitrol patients reported significantly less heroin cravings and thoughts than the Suboxone group and Vivitrol patients also reported greater satisfaction and willingness to recommend the treatment to other patients compared to Suboxone group. In the second study, it was published by Lee and Colleagues in Lancet in November 2017 and titled, "Comparative Effectiveness of Extended Release naltrexone Versus buprenorphine and naloxone for Opioid Relapse Prevention," better known at XBOT. So, it was found that Vivitrol was as effective as Suboxone in maintaining patients relapse free in this 24-week study once they began study medications. In those patients who initiated the treatment, several secondary measures were very similar for Vivitrol and Suboxone groups including the abstinent days, number of negative urine tests, and reduction in cravings. The average opiate craving was initially simply less for Vivitrol than the Suboxone group but they did converge at week 24. The pharmacoeconomic data I want to talk to you about this afternoon was regarding opiate dependence and a 6-month retrospective study of insurance

claims of over 10,000 claims, assess total healthcare costs involving inpatient, outpatient and pharmacy costs. In patients treated with Vivitrol, were all naltrexone, buprenorphine, and methadone. Results show that costs per patient was significantly lower than those using Vivitrol compared to methadone and no more expensive than buprenorphine or oral naltrexone due to the large fact that patients who treat with Vivitrol had fewer inpatient admissions compared to all other groups. These results supported Vivitrol's important part for option for patients being treated for opioid use disorder. I would like to entertain any questions from the board if I can.

Carl Jeffery: We don't have any recommended changes in this class to have the Board take any action. There was a new medication and a new combination of opioid agonist/antagonist mix called Cassipa. It again is in your binder but it was not available on the market yet so we don't have time to review it. Right now we're not making any recommendations in this class. As far as the injectable long acting, that's not something that's currently in the preferred drug list and something that we're considering, so there would be a couple classes that are in there. There's also some other new medications we're trying to figure out how to work those into the preferred drug list. More to come on those. I think they are valuable agents and I appreciate your input. We may see those but as far as this class goes, we're only talking about the mixed opioid agonist/antagonist.

Motion keep the class as it is. Second. Voting: Ayes are unanimous. The motion carries.

5. Established Drug Classes

a. Biologic Response Modifiers - Multiple Sclerosis Agents - Specific Symptomatic Treatment

Carl Jeffery: The first one is generic for Ampyra, dalfampridine. It's generic for Ampyra. It's AB-rated. Just to remind the Board, we do have these separated out from the other MS drugs because it has the specific indication to improve walking but the other ones were not so specific symptom treatment because that's why we have it broken down separately but right now it's the only one that's in its class. Optum recommends the Board consider these. We've only had 28 claims in the last quarter so not a whole lot of utilization on these. Right now it's all the brand name, of course, as the generic just recently came out. Optum recommends the Board consider these clinically and therapeutically equivalent.

Motion to accept as clinically and therapeutically equivalent. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: So, with that introduction to the generic, Optum recommends the Board considers making the generic preferred and the brand name non-preferred.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

b. Neurological Agents - Anticonvulsants – Benzodiazepines

Carl Jeffery: Another generic, for the Onfi this time, it's now available. Again, AB-rated, same indications as the brand name, injection treatment for the seizures with LGS patients at age 2. This one we break from tradition a little bit. When we looked at the utilization numbers, this is kind of why we're breaking from it a little bit. We have almost 400 claims for it in the last quarter for the brand Onfi. It seems like it's a well-used medication. It is adjunctive therapy but to get the Onfi at this point, you'd still need to jump through some hoops to get the prior authorization and so looking at the utilization that clonazepam I am skeptical they are being used for any kind of seizure disorder. With the Onfi, I'm pretty confident it was probably just limited to some kind of seizure disorder. The first order is Optum recommends the Board consider these clinically and therapeutically equivalent.

Motion to accept as clinically and therapeutically equivalent. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: Optum recommends that clobazam be considered preferred just because it has utilization numbers to show, even though it's not a primary treatment and it should be considered preferred.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

c. Psychotropic Agents - ADHD Agents

Carl Jeffery: We have a couple new generics on here but really no new products within the class. The clonidine ER is really what prompted us to bring the class to the Board. It's available now. It's the generic for the Kapvay. Relatively I think it's been out for a little while but it is available now as monotherapy or adjunctive therapy for the treatment of ADHD. It's like the generic of Intuniv, guanfacine-ER, available is preferred but right now you can see the utilization numbers. No surprise I think with the methylphenidate and the guanfacine being our higher utilizers and then the generic Adderall and the Vyvanse actually is used quite a bit as well. Optum recommends the Board consider these clinically and therapeutically equivalent.

Motion to accept as clinically and therapeutically equivalent. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: With the introduction of the generic, we had the opportunity to evaluate the class and the Adzenys is really one that hasn't moved the market share as we thought it might so our recommendation is to move that one back to non-preferred. It's an amphetamine extended release. There is another one that is already similar to it; the Evekeo is the similar agent in that same class and we have a preferred one, amphetamines in there, too. The Dyanavel is the extended release amphetamine. So we already have one on there, and then the generic Strattera; it's time to switch that one over so the brand would be non-preferred and the generic, atomoxetine, would

make it preferred. Our recommendation is to make the generic Strattera, atomoxetine, as preferred but the brand, Adzenys, clonidine-ER, and Strattera as nonpreferred.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

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

Carl Jeffery: We have a couple products. We have a new medication that's Xofluza which I think is like Tamiflu. It's just a little bit different, it's one dose, but it has to be caught within 48 hours. We're going to bring that back to the next meeting. It didn't make it out in time for us to review it at this time, but we'll make the next one. This new I think it is a biologic for the Humira and then there's a new Meloxicam which I'm not sure why anybody's still pursuing new NSAIDs but interesting. A couple of new indications that I think are noteworthy is the canagliflozin has got the indication for the reduced risk of cardiovascular events and then the rivaroxaban so J&J has been hard at it to get those approved but the combination with aspirin to reduce major cardiovascular events.

Mark Decerbo, Pharm.D.: Carl, coming back to the opioid dependence, do you need anything from us in terms of single agent class, or that will come to that in the future.

Carl Jeffery: Yeah, certainly from a provider's standpoint. I think you have better insight into what maybe would work best is creating a preferred or non-preferred and so certainly if you have any ideas about how these should fit together, maybe they should be lumped all together into a single class or have separate injectable long-acting agents separated. We would welcome any insight from the Board.

Mark Decerbo, Pharm.D.: At this point, I wouldn't be opposed to co-mingling them together so the single agents and the mixed agents. I think as we see more development and then eventually it will probably get messy but for now, I wouldn't have a problem kind of mixing them together.

Carl Jeffery: If you would like to see the injectable long acting, in with the Suboxone and Zubsolv.

Mark Decerbo, Pharm.D.: I think that would work for now.

Carl Jeffery: There's also a new medication, the Lucemyra, for treating the symptoms of opioid withdrawal. I don't know if you have an opinion on where you'd like to maybe see that fit in.

Mark Decerbo, Pharm.D.: I am not familiar with that agent, so I'm not sure.

Holly Long: Before we wrap up, I just want to apologize to the first of the meeting. I should have introduced our new member and so my apologies. We do have two new

members that are part of the committee. Dr. Brian Passalacqua and Dr. Steven Zuchowski. Welcome. We're very happy that you're both here.

7. Closing Discussion

a. Public comments on any subject

b. Date and location of the next meeting

Carl Jeffery: We booked this facility for 2019 and we will be back here March 28, 2019. We will also have a location in the North in Reno we are testing out. So we will have separate meetings again.

c. Adjournment

Meeting adjourned at 1:41 PM.

Proposed New Drug Classes

INTRODUCTION

- Migraine is a common, recurrent, incapacitating disorder characterized by moderate to severe headaches and disabling features, including nausea, vomiting, neurologic symptoms, photophobia, and phonophobia (*International Headache Society [IHS] 2013, Starling et al 2015).*
- There are 4 phases of a migraine attack, although not all migraine attacks unfold into all 4 phases. These phases include prodrome, development of aura, the headache phase, and postdrome. Combined, all 4 phases can last anywhere between 3 and 5 days (*Burgos−Vega et al 2015).*
- The pathophysiology of migraines is assumed to involve the activation of trigeminal sensory nerves, which triggers the release of vasoactive neuropeptides including CGRP, neurokinin A, and substance P. CGRP is involved in migraine pathophysiology through nociceptive mechanisms in the trigeminovascular system. CGRP is a vasodilator and is found at higher concentrations during a migraine attack. Vasodilation of dural blood vessels may occur with extravasation of dural plasma, resulting in inflammation *(Goadsby et al 2017, Starling et al 2015, Silberstein et al 2012)*.
- The International Classification of Headache Disorders (ICHD) defines chronic migraine as ≥ 15 headache days per month for > 3 months with the features of migraine headache for at least 8 migraine days per month (MMD). The most common cause of symptoms suggestive of chronic migraine is medication overuse. According to the ICHD, around 50% of patients apparently with chronic migraine revert to an episodic migraine type after drug withdrawal; such patients are in a sense wrongly diagnosed with chronic migraine. In most clinical trials, migraine that is not chronic (ie, with < 15 headache days per month) is considered to be episodic migraine, although the condition is not clearly defined in the ICHD (*IHS 2013, Silberstein et al 2008, Starling et al 2015*).
- Migraines have a global prevalence of 15 to 18% and are a leading cause of disability worldwide. Chronic migraine is estimated to occur in 2 to 8% of patients with migraine, whereas episodic migraine occurs in more than 90% of patients (*Global Burden of Disease Study [GBD] 2016, IHS 2013, Lipton et al 2016, Manack et al 2011*).
- Treatments for migraines are divided into acute and preventive therapies. Evidence and reputable guidelines clearly delineate appropriate therapies for episodic migraine treatment and prophylaxis; options stretch across a wide variety of therapeutic classes and are usually oral therapies. For the prevention of migraines, treatment options include oral prophylactic therapies, injectable prophylactic therapies, and neuromodulator devices. Guidelines discourage the overuse of acute headache therapies, including analgesics, triptans, and ergots, which can precipitate medication overuse headache. Additionally, opioids and barbiturates should not be prescribed as they may contribute to the development of chronic daily headache (*American Migraine Foundation [AMF] 2017, Edvinsson et al 2017, IHS 2013, Silberstein et al 2008, Silberstein et al 2012, Simpson et al 2016, Starling et al 2015)*.
  - Oral prophylactic therapies have modest efficacy; however, certain oral therapies may not be appropriate for individual patients due to intolerability or eventual lack of efficacy.
  - Onabotulinumtoxin A (Botox), the first injectable drug approved for the prophylaxis of chronic migraine, has been found to be ineffective for the prophylactic treatment of episodic migraines.
  - Other options include devices which leverage electrical, temperature−altering, or magnetic approaches to treatment (ie, Cefaly, SpringTMS, and gammaCore); these devices are considered to have no significant adverse events known or expected.
- The CGRP pathway is important in pain modulation. Erenumab-aooe is a fully human monoclonal antibody, which potently binds to the CGRP receptor in a competitive and reversible manner with greater selectivity than to other human calcitonin family receptors (eg, calcitonin, amylin, and adrenomedullin). Fremanezumab-vfrm and galcanezumab-gnlm are 2 humanized monoclonal antibodies that target and potently bind the CGRP ligand, in most cases both the α and β isoforms (*Dodick et al 2018[b], Edvinsson 2017, Goadsby et al 2017, Silberstein et al 2017, Sun et al 2016, Tepper et al 2017*).
- Medispan class: Migraine products – monoclonal antibodies; Calcitonin gene−related peptide (CGRP) receptor antagonists

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Aimovig (erenumab−aooe)	–
Ajovy (fremanezumab-vfrm)	–
Emgality (galcanezumab-gnlm)	–

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Aimovig (erenumab−aooe)	Ajovy (fremanezumab-vfrm)	Emgality (galcanezumab-gnlm)
Preventive treatment of migraine in adults	✔	✔	✔

(*Prescribing information: Aimovig 2018, Ajovy 2018, Emgality 2018)*

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

CLINICAL EFFICACY SUMMARY

- Erenumab-aooe has been studied in approximately 2500 patients across 4 trials in patients with episodic or chronic migraine subtypes and 1 open-label extension (OLE) trial with data from interim analyses in published and unpublished formats.
- Fremanezumab-vfrm has been studied in approximately 2005 patients across 3 trials in patients with episodic or chronic migraine subtypes, with data in published formats. In fremanezumab-vfrm trials, the definition of a headache or migraine day for the primary endpoint required a consecutive 2 hour (episodic) or 4 hour (chronic) duration of pain, compared to other CGRP inhibitor trials which required a duration of ≥ 30 minutes.
- Galcanezumab-gnlm has been studied in approximately 2886 patients across 3 trials in patients with episodic or chronic migraine subtypes and 1 long-term safety trial with unpublished data to 1 year.
- The definition of the primary and secondary endpoints differed in the prevention of episodic and chronic migraine trials. Additional differences included but were not limited to, co-morbid conditions, concomitant medications, a requirement of stable doses of migraine prevention medication (if co-administered) for certain durations, the definition of headache, migraine headache, and migraine day. Some CGRP inhibitor trials allowed patients to receive concomitant preventive migraine medication during treatment. Also, some chronic migraine trials allowed for the inclusion of patients with medication overuse headache.

Episodic migraine

Erenumab-aooe

- The STRIVE trial was a 6-month, double-blind (DB), placebo-controlled (PC), multi-center (MC), Phase 3 trial in which 955 patients with episodic migraine were randomized to placebo (n = 319), erenumab-aooe 70 mg (n = 317), or erenumab-aooe 140 mg (n = 319) once monthly. The primary endpoint was the change in mean MMD from baseline to months 4 to 6, which favored treatment with erenumab−aooe 70 mg (mean change vs placebo, −1.4; 95% confidence interval [CI], −1.9 to −0.9; p < 0.001) and erenumab−aooe 140 mg (mean change vs placebo, −1.9; 95% CI, −2.3 to −1.4; p < 0.001). Erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 70 mg vs placebo, 16.7%; odds ratio [OR], 2.13; difference for 140 mg vs placebo, 23.4%; OR, 2.81). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 70 mg vs placebo, −0.9; difference for 140 mg vs placebo, −1.4) (*Goadsby et al 2017*).
- The ARISE trial was a 12-week, DB, PC, MC, Phase 3 trial in which 577 patients with episodic migraine were randomized to placebo (n = 291) or erenumab-aooe 70 mg (n = 286) once monthly. The primary endpoint was the change in MMD from baseline to weeks 9 to 12, which favored treatment with erenumab−aooe 70 mg (mean change vs placebo, −1.0; 95% CI, −1.6 to −0.5; p < 0.001). Compared to placebo, erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference, 10.2%; OR, 1.59). Erenumab−aooe was also

associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference, −0.6) (*Dodick et al 2018[a]*).

- The LIBERTY trial was a 12-week, DB, PC, MC, Phase 3b trial in which 246 patients with episodic migraine who failed 2 to 4 prior preventive migraine treatments were randomized to placebo (n = 125) or erenumab-aooe 140 mg (n = 121) once monthly. The primary endpoint was the proportion of patients with ≥ 50% reduction in MMD from baseline to the last 4 weeks of DB treatment (weeks 9 to 12), which erenumab−aooe significantly increased over placebo (difference, 16.6%; OR, 2.73; 95% CI, 1.43 to 5.19; p = 0.002). Compared to placebo, a total of 5.9% more patients treated with erenumab−aooe 140 mg reported a 100% reduction in MMD, or migraine cessation. Erenumab 140 mg/month compared with placebo significantly reduced the MMD (difference, −1.61; 95% CI, −2.70 to −0.52; p = 0.004). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference, −1.73) (*Reuter et al 2018[a,b]*).

Fremanezumab-vfrm

- The HALO-EM trial was a 12-week, DB, PC, MC, Phase 3 trial in which 875 patients with episodic migraine were randomized to placebo (n = 294), fremanezumab-vfrm 225 mg once monthly (n = 290), or fremanezumab-vfrm 675 mg once quarterly (n = 291). The primary endpoint was the change in mean MMD, which favored treatment with fremanezumab-vfrm 225 mg (mean change vs placebo, −1.5; 95% CI, −2.0 to −0.9; p < 0.001) and fremanezumab-vfrm 675 mg (mean change vs placebo, −1.3; 95% CI, −1.8 to −0.7; p < 0.001). Of note, HALO-EM was powered to detect a 1.6-day difference in the MMD between the fremanezumab-vfrm and placebo groups, but effect sizes resulted in a 1.5-day reduction for the fremanezumab-vfrm monthly dosing group and a 1.3-day reduction for the fremanezumab-vfrm quarterly dosing group. Although the threshold was not reached, a minimal clinically important difference has not been established for this particular outcome. Compared to placebo, greater MMD reductions were also observed in patients who were prescribed fremanezumab-vfrm 225 mg (mean change vs placebo, −1.3) and 675 mg (mean change vs placebo, −1.1) as monotherapy. Fremanezumab-vfrm significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 225 mg vs placebo, 19.8%; OR, 2.36; difference for 675 mg vs placebo, 16.5%; OR, 2.06). Additionally, fremanezumab-vfrm was associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 225 mg vs placebo, −1.4; difference for 675 mg vs placebo, −1.3) (*Dodick et al 2018[b]*).

Galcanezumab-gnlm

- The EVOLVE-1 and EVOLVE-2 trials were 6-month, DB, PC, MC, Phase 3 trials in 858 and 915 patients with episodic migraine, respectively. Patients were randomized to placebo (EVOLVE-1, n = 433; EVOLVE-2, n = 461), galcanezumab-gnlm 120 mg once monthly (EVOLVE-1, n = 213; EVOLVE-2, n = 231), or galcanezumab-gnlm 240 mg once monthly (EVOLVE-1, n = 212; EVOLVE-2, n = 223). Patients in the galcanezumab-gnlm 120 mg group received a loading dose of 240 mg at the first injection only. The EVOLVE-1 trial included a North American population and the EVOLVE-2 trial included a global population. The primary endpoint was the change in mean monthly migraine headache days (MMHD) (*Stauffer et al 2018, Skljarevski et al 2018*).
  - In EVOLVE-1, the primary endpoint outcome favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −1.9; 95% CI, −2.5 to −1.4; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.8; 95% CI, −2.3 to −1.2; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 23.7%; OR, 2.64; difference for 240 mg vs placebo, 22.3%; OR, 2.50). Compared to placebo, a total of 9.4% more patients treated with galcanezumab-gnlm 120 mg and 9.4% more treated with galcanezumab-gnlm 240 mg reported a 100% reduction in MMHD, or migraine cessation. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −1.8; difference for 240 mg vs placebo, −1.6) (*Stauffer et al 2018*).
  - In EVOLVE-2, the primary endpoint outcome favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −2.0; 95% CI, −2.6 to −1.5; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.9; 95% CI, −2.4 to −1.4; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 23.0%; OR, 2.54; difference for 240 mg vs placebo, 21.0%; OR, 2.34). Compared to placebo, a total of 5.8% more patients treated with galcanezumab-gnlm 120 mg and 8.1% more treated with galcanezumab-gnlm 240 mg reported migraine cessation. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −1.8; difference for 240 mg vs placebo, −1.7) (*Skljarevski et al 2018*).

Chronic migraine

Erenumab-aooe

- Erenumab-aooe was studied in a 12−week, DB, PC, MC, Phase 2 trial in which 667 patients with chronic migraine were randomized to placebo (n = 286), erenumab−aooe 70 mg (n = 191), or erenumab−aooe 140 mg (n = 190) once monthly. The primary endpoint was the change in MMD from baseline to weeks 9 to 12, which favored treatment with erenumab−aooe 70 mg and erenumab−aooe 140 mg (mean change for both doses vs placebo, −2.5; 95% CI, −3.5 to −1.4; p < 0.0001). Erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 70 mg vs placebo, 17%; OR, 2.2; difference for 140 mg vs placebo, 18%; OR, 2.3). Both erenumab−aooe 70 mg (difference, −1.9) and erenumab−aooe 140 mg (difference, −2.6) significantly reduced the mean acute migraine−specific medication days; however, the higher 140 mg dose had a greater reduction numerically over placebo and reductions may be dose−dependent (*Tepper et al 2017*).

Fremanezumab-vfrm

- Fremanezumab-vfrm was studied in a 12-week, DB, PC, MC, Phase 3 trial, HALO-CM, in which 1130 patients with chronic migraine were randomized to placebo (n = 375), fremanezumab-vfrm 225 mg once monthly (n = 379), or fremanezumab-vfrm 675 mg once quarterly (n = 376). Patients in the fremanezumab-vfrm 225 mg group received a loading dose of 675 mg at the first injection only. The primary endpoint was the change in mean headache days (MHD), which favored treatment with fremanezumab-vfrm 225 mg (mean change vs placebo, −2.1; standard error [SE], ± 0.3; p < 0.001) and fremanezumab-vfrm 675 mg (mean change vs placebo, −1.8; SE, ± 0.3; p < 0.001). Fremanezumab-vfrm significantly increased the proportion of patients achieving ≥ 50% reduction in MHD (difference for 225 mg vs placebo, 22.7%; OR, 2.73; difference for 675 mg vs placebo, 19.5%; OR, 3.13). Additionally, fremanezumab-vfrm was associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 225 mg vs placebo, −2.3; difference for 675 mg vs placebo, −1.8) (*Silberstein et al 2017*).

Galcanezumab-gnlm

- Galcanezumab-gnlm was evaluated in a 12-week, DB, PC, MC, Phase 3 trial, REGAIN, in which 1113 patients with chronic migraine were randomized to placebo (n = 558), galcanezumab-gnlm 120 mg once monthly (n = 278), or galcanezumab-gnlm 240 mg once monthly (n = 277). Patients in the galcanezumab-gnlm 120 mg group received a loading dose of 240 mg at the first injection only. The primary endpoint was the change in MMHD, which favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −2.1; 95% CI, −2.9 to −1.3; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.9; 95% CI, −2.7 to −1.1; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 12.2%; OR, 2.10; difference for 240 mg vs placebo, 12.1%; OR, 2.10). Compared to placebo, a total of 0.2% more patients treated with galcanezumab-gnlm 120 mg and 0.8% more treated with galcanezumab-gnlm 240 mg reported migraine cessation, this was not statistically different for either dose group. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −2.5; difference for 240 mg vs placebo, −2.1) (*Detke et al 2018*).

Open-label extensions (OLE) and long-term safety studies

- One published OLE with data to 1 year and 1 unpublished abstract with data to ≥ 3 years evaluated erenumab-aooe 70 mg (protocol amended to include 140 mg doses) in patients with episodic migraine. Of 472 patients in the parent study, a total of 308 patients completed 1 year of open-label (OL) treatment. For the ≥ 3 year assessment, of the 383 patients enrolled in the OLE, 250 continued into the 140 mg once monthly dosing. At the time of interim analysis, 236 patients remained in the OLE (*Amgen [data on file] 2018, Ashina et al 2017, Ashina et al 2018*).
  - There may be greater improvements with sustained therapy based on a 1-year OLE interim analysis of episodic migraine patients treated with erenumab-aooe 70 mg once monthly. Patients had a mean value of 8.8 MMDs at parent study baseline. After 3 months of treatment in the parent study, the number of MMDs was reduced to 6.3 days (mean change of 2.5 days). After a total of 16 months of treatment, the number of MMDs was reduced to 3.7 days (mean change of 5.1 days). After 64 weeks, a total of 65% (n = 184) of episodic migraine patients achieved a ≥ 50% reduction in MMDs and 26% (n = 73) had achieved a migraine-free status. The most frequently reported adverse events (≥ 4.0 per 100 patient-years) were viral upper respiratory tract infection, upper respiratory tract infection, sinusitis, influenza, and back pain.
- One unpublished OLE evaluated erenumab-aooe 70 mg (protocol amended to include 140 mg doses) with data to 1 year in patients with chronic migraine. A total of 609 patients with chronic migraine enrolled in the OLE. A total of 199 increased their dose from 70 mg to 140 mg by week 28 (*Amgen [data on file] 2018, Tepper et al 2018*).

- Patients with chronic migraine had a mean value of 18.8 MMDs at parent study baseline. After a total of 1 year of treatment, the number of MMDs was reduced to 8.5 in the erenumab-aooe 70 mg group and 10.5 in the erenumab-aooe 140 mg group. After 1 year of erenumab-aooe 70 mg and 140 mg monthly dosing, a total of 53% and 67% of chronic migraine patients achieved a ≥ 50% reduction in MMDs and 6% and 13% had achieved a migraine-free status, respectively. The most frequently reported adverse events (≥ 2.0 per 100 patient-years) were viral upper respiratory tract infection, upper respiratory tract infection, sinusitis, and arthralgia.

- Another unpublished safety study, the CGAJ study, evaluated galcanezumab-gnlm 120 mg (plus 240 mg loading dose) and 240 mg monthly dosing to 1 year in patients with episodic or chronic migraine. At baseline, 80.7% of patients in the galcanezumab-gnlm 120 mg arm and 77.0% in the galcanezumab-gnlm 240 mg arm had episodic migraine. A total of 270 patients who had a history of ≥ 4 MMHDs and ≥ 1 headache-free day/month for the past 3 months continued galcanezumab-gnlm treatment (*Eli Lilly and Company [data on file] 2018, Emgality [dossier] 2018, Stauffer et al 2017*).
  - At baseline, patients had a mean value of 9.7 to 11.4 (standard deviation [SD], 6.0 to 6.6) MMHDs. After a total of 1 year of treatment, the number of MMHDs was reduced to 5.6 days in the galcanezumab-gnlm 120 mg group and 6.5 days in the galcanezumab-gnlm 240 mg group. After ≥ 12 consecutive months of treatment, 24.2% of patients treated with galcanezumab-gnlm 120 mg and 34.8% of patients treated with galcanezumab-gnlm 240 mg maintained response. The most frequently reported adverse events (incidence ≥ 15.0%) were injection site pain, nasopharyngitis, and upper respiratory tract infections. One patient discontinued due to suicidal ideation in the galcanezumab-gnlm 120 mg group. There were no overall concerns regarding safety or tolerability.
- Caution should be exercised in applying results from extension trials. The OL design may contribute to biased reports. Extension trials may have biased outcomes because those experiencing benefit are included in extension trials; results are useful for reporting trends in treatment. Additionally, there is no comparator to account for placebo effects.

CLINICAL GUIDELINES

- According to the American Academy of Neurology and American Headache Society (AAN/AHS) − Evidence−based guideline update on the pharmacologic treatment for episodic migraine prevention in adults (*Silberstein et al 2012*), the following medications are effective preventive treatment options (see Appendix A for a definition of classifications):
  - Level A (established efficacy and > 2 Class I trials):
    - Antiepileptic drugs: divalproex sodium, sodium valproate, and topiramate
    - Beta blockers: metoprolol, propranolol, and timolol
    - Triptans (for menstrual related migraine [MRM]): for short−term prophylaxis, frovatriptan
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Antidepressants: amitriptyline and venlafaxine
    - Beta blockers: atenolol and nadolol
    - Triptans (for MRM): for short−term prophylaxis, naratriptan and zolmitriptan
  - Level C (possibly effective and 1 Class II trial):
    - Angiotensin−converting enzyme (ACE) inhibitors: lisinopril
    - Angiotensin II receptor blockers (ARBs): candesartan
    - Alpha agonists: clonidine and guanfacine
    - Antiepileptic drugs: carbamazepine
    - Beta blockers: nebivolol and pindolol
    - Antihistamines: cyproheptadine
- The AAN recommends onabotulinumtoxin A as an effective treatment option that should be offered for chronic migraine. However, onabotulinumtoxin A is considered ineffective for the treatment of episodic migraines and should not be offered. There is insufficient evidence to compare the effectiveness of botulinum neurotoxin A with that of oral prophylactic topiramate (*Simpson et al 2016*).

SAFETY SUMMARY

- Fremanezumab-vfrm and galcanezumab-gnlm are contraindicated in patients with serious hypersensitivity to the active ingredient or any of the excipients. Mild to moderate hypersensitivity reactions (eg, rash, pruritus, urticaria) were reported in trials with fremanezumab-vfrm and galcanezumab-gnlm.
  - There are no contraindications or warnings and precautions associated with erenumab−aooe.

- The CGRP inhibitors generally have a similar incidence of adverse events as placebo. Very few severe adverse events and treatment discontinuations due to adverse events were reported. The most common adverse reactions observed in CGRP inhibitor studies included injection site reactions (all agents) and constipation (erenumab-aooe only).
- Caution should be exercised as long-term safety is unknown. CGRP is a vasodilator and is found at higher concentrations during a migraine attack. In the 1-year interim analysis of an OLE study with erenumab-aooe, 2 patients had severe adverse events (an arteriosclerosis event and a myocardial ischemia event), of which 1 was fatal and 1 was confounded by sumatriptan administration. No additional concerns were raised within the OLE at ≥ 3 years, including any cardiovascular events. In a long-term safety study of patients treated with galcanezumab-gnlm for 1 year, 1 patient discontinued due to suicidal ideation in the galcanezumab-gnlm 120 mg group. The long-term implications of prolonged CGRP inhibition are not fully established and safety has not been fully characterized *(Amgen [data on file] 2018, Ashina et al 2017, Ashina et al 2018, Eli Lilly and Company [data on file] 2018, Stauffer et al 2017, Tepper et al 2018)*.
- There are no adequate data on the risks associated in patients who are pregnant or nursing, or in adolescent or pediatric populations.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Aimovig (erenumab−aooe)	Auto-injector	SC	Once monthly	May be self−administered by patients in the abdomen, thigh, or back of upper arm. Latex−sensitive patients may have an allergic reaction to the needle shield within the white cap and the gray needle cap of the syringe. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, erenumab-aooe has a limited stability of 7 days.
Ajovy (fremanezumab-vfrm)	Prefilled syringe	SC	Once monthly or once every 3 months	May be self−administered by patients in the abdomen, thigh, or back of upper arm. The prefilled syringe cap is not made with natural rubber latex. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, fremanezumab-vfrm has a limited stability of 24 hours.
Emgality (galcanezumab-gnlm)	Auto-injector	SC	Once monthly	May be self−administered by patients in the abdomen, thigh, back of upper arm or buttocks. The cap is not made with natural rubber latex.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, galcanezumab-gnlm has a limited stability of 7 days.

See the current prescribing information for full details

Note: With all of the CGRP inhibitors, there are no data in pregnant women or breastfed infants. A benefit/risk assessment should be taken into consideration prior to administering.

CONCLUSION

- Migraine is a common, recurrent, incapacitating disorder characterized by moderate to severe headaches and disabling features, including nausea, vomiting, neurologic symptoms, photophobia, and phonophobia. Migraines have a spectrum of frequency and severity that can significantly affect the quality of life of patients.
- Guidelines have not been updated to include the CGRP inhibitors. Current evidence−based prophylactic treatment options and guidance are limited for chronic migraine, and oral prophylactic medications prescribed for episodic migraine are often used also for the preventive treatment of chronic migraine. Prophylactic migraine treatment options include oral agents (mainly anti−seizure agents, antidepressants, and beta blockers), injectable agents (onabotulinumtoxin A for chronic subtypes only), or neuromodulation devices for migraine or headache attacks (ie, Cefaly, Spring TMS, gammaCore). Certain oral therapies may not be appropriate for individual patients due to intolerability or eventual lack of efficacy. There is no optimal prophylactic migraine therapy and head-to-head trials are lacking.
- The CGRP inhibitors (erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm) are novel agents developed as alternatives for patients who do not tolerate, or do not have an adequate response to, currently marketed preventive migraine therapies. Like other preventive medications for migraine, the CGRP inhibitors are not likely to render patients migraine-free. Based on 3 to 6 month data, primary endpoint reductions are similar to many oral prophylactic therapies; however, comparisons are limited as endpoints have been inconsistently defined. There are limited analyses and trials examining efficacy in patients who failed ≥ 2 prior preventive therapies; however, available data suggest that these patients may achieve greater reductions in migraine/headache frequency. Further research is warranted.
- There are no head-to-head studies with the CGRP inhibitors and no prophylactic migraine agent is clearly superior to others.
  - Compared to placebo, the CGRP inhibitors consistently demonstrated modest but statistically significant reductions in primary endpoint measures (eg, MMD, MMH, or MMHD) ranging from 1.0 to 2.5 days after 3 to 6 months of treatment. Overall, the odds for a 50% reduction in MM(H)D were approximately 1.6 to 3.1 times higher with the CGRP inhibitors than placebo with numbers-needed to treat (NNTs) ranging from 3 to 10.
- Lack of information during pregnancy and breastfeeding is a consideration as many migraine patients are women of childbearing potential. The unknown risks of monoclonal antibodies and the effects on certain conditions are not fully characterized. Important co-morbid populations that suffer migraines were excluded from trials (eg, anxiety, depression, hypertension, and fibromyalgia), which also limits the generalizability to broader groups. There are no data in adolescents and children. Based on current data, the safety profiles of the CGRP inhibitors are generally mild with the most common adverse effects observed being injection site reactions.
- Overall, the CGRP inhibitors represent another therapy option in the prevention of episodic or chronic migraine. Fremanezumab-vfrm is the only agent in the class that may be administered quarterly, which may fulfill a niche in patients who are non-adherent with treatment. Based on currently available evidence, the mild safety profile of these agents may support a role in a subset of patients unable to tolerate established oral prophylactic therapies. Further long-term study is warranted.

APPENDIX

- **Appendix A. AAN levels of evidence classification** *(Gronseth et al 2011)*

Rating of recommendation	
A	Established as effective, ineffective, or harmful for the given condition in the specified population

B	Probably effective, ineffective, or harmful for the given condition in the specified population
C	Possibly effective, ineffective, or harmful for the given condition in the specified population
U	Data inadequate or conflicting; given current knowledge, treatment is unproven.
Rating of therapeutic article	
Class I	RCT in representative population with masked outcome assessment. The following are required: a) concealed allocation; b) primary outcome(s) is/are clearly defined; c) exclusion/inclusion criteria are clearly defined; d) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias; e) certain requirements are needed for noninferiority or equivalence trials claiming to prove efficacy for 1 or both drugs.
Class II	Cohort study that meets a–e (Class I) or RCT that lacks 1 criterion from above (b−e).
Class III	Controlled trials (including well−defined natural history controls or patients serving as own controls), a description of major confounding differences between groups, and where outcome assessment is independent of patient treatment.
Class IV	Does not include patients with the disease, different interventions, undefined/unaccepted interventions or outcomes measures, and/or no measures of effectiveness or statistical precision presented or calculable.

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INTRODUCTION

Products for Treatment of Opioid Dependence

- The American Psychiatric Association (APA) defines opioid use disorder as a syndrome characterized by a problematic pattern of opioid use, leading to clinically significant impairment or distress (*APA 2013*).
  - In 2015, approximately 2 million Americans had a substance use disorder involving prescription pain relievers and 591,000 had a substance use disorder involving heroin (*American Society of Addiction Medicine [ASAM] 2016*).
- Methadone, buprenorphine (with or without naloxone), and naltrexone are Food and Drug Administration (FDA)-approved for the detoxification and maintenance treatment of opioid dependence (*Micromedex 2.0 2018*).
  - Methadone products, when used for the treatment of opioid addiction in detoxification or maintenance programs, may be dispensed only by opioid treatment programs (and agencies, practitioners or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority. Certified treatment programs may dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (Code of Federal Regulations, Title 42, Sec 8).
  - The Drug Addiction Treatment Act of 2000 expanded the clinical context of medication-assisted opioid addiction treatment by allowing qualified physicians to dispense or prescribe specifically approved medications, like buprenorphine, for the treatment of opioid addiction in treatment settings other than the traditional Opioid Treatment Program. In addition, DATA reduced the regulatory burden on physicians who choose to practice opioid addiction therapy by permitting qualified physicians to apply for and receive waivers of the special registration requirements defined in the Controlled Substances Act (*Center for Substance Abuse Treatment 2004*).
  - Naltrexone, an opioid antagonist, is only indicated for the prevention of relapse after opioid detoxification; patients must be opioid-free for at least 7 to 10 days prior to initiation of naltrexone therapy in order to avoid precipitation of withdrawal.
- All buprenorphine products are Schedule III controlled substances (*Drugs@FDA 2018*).
- In 2012, Reckitt Benckiser Pharmaceuticals notified the FDA that they were voluntarily discontinuing production of Suboxone (buprenorphine/naloxone) sublingual tablets as a result of increasing concerns over accidental pediatric exposure with the tablets. The unique child-resistant, unit-dose packaging of the film formulation is believed to be a contributing factor to reduce exposure rates in children. Generic formulations of the sublingual tablets remain available.
- In November 2017, the FDA approved Sublocade (buprenorphine ER) subcutaneous injection for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days.
  - Sublocade is injected as a liquid and the subsequent precipitation of the polymer creates a solid depot which contains buprenorphine. Buprenorphine is released via diffusion from, and the biodegradation of, the depot.
- Lofexidine, an oral central alpha-2 agonist, was approved in May 2018 for the mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults. This product is indicated for short-term use, up to 14 days, during the period of peak opioid withdrawal symptoms.
- Included in this review are the products that are FDA-approved to be used in the treatment of opioid dependence; however, methadone products are not included since they must be dispensed in an opioid treatment program when used for the treatment of opioid addiction in detoxification.
- Medispan Class: Opioid Use Disorder Agents

Table 1. Medications for Treatment of Opioid Dependence Included Within Class Review

Drug	Generic Availability
Single Entity Agents	
Lucemyra (lofexidine) tablet	-
naltrexone hydrochloride* tablet	✔

Drug	Generic Availability
Sublocade (buprenorphine) subcutaneous injection	-
Subutex (buprenorphine)* sublingual tablet	✔
Vivitrol (naltrexone) intramuscular injection	-
Combination Products	
Bunavail (buprenorphine/naloxone) buccal film	-
Suboxone‡ (buprenorphine/naloxone) sublingual tablets	✔
Suboxone (buprenorphine/naloxone) sublingual film	✔ †
Zubsolv (buprenorphine/naloxone) sublingual tablets	-

*Brand name product was discontinued; however, generic formulations are available.
‡Suboxone tablets were discontinued; however, generic formulations are available and brand name Suboxone is available as a film.
†Dr. Reddy and Mylan received FDA approval for AB-rated generic versions of the Suboxone sublingual film. Mylan has not yet launched their generic version. The manufacturer (Indivior) of brand Suboxone also announced it will pursue an immediate injunction against Dr. Reddy's "at-risk" launch.

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

Products for Emergency Treatment of Opioid Overdose

- Opiate overdose continues to be a major public health problem in the United States (U.S.). It has contributed significantly to accidental deaths among those who use or abuse illicit and prescription opioids. The number of opioid overdoses has risen in recent years, partly due to a nearly 4-fold increase in the use of prescribed opioids for the treatment of pain. Overdose deaths involving prescription opioid analgesics increased to about 19,000 deaths in 2014, more than 3 times the number in 2001 (*Substance Abuse and Mental Health Services Administration [SAMHSA] 2016)*.
- Death following opioid overdose can be averted by emergency basic life support and/or the timely administration of an opioid antagonist such as naloxone. As a narcotic antagonist, naloxone displaces opiates from receptor sites in the brain and reverses respiratory depression, which usually is the cause of overdose deaths *(SAMHSA 2016, World Health Organization [WHO] 2014)*.
- Naloxone is provided to patients through the regular course of medical care, by pharmacist-initiated collaborative practice agreements, or through community-based opioid overdose prevention programs (*Doe-Simkins 2014*).
- Recognizing the potential value of providing naloxone to laypersons, some states have passed laws and changed regulations authorizing prescribers to provide naloxone through standing orders and/or to potential overdose witnesses as well as protecting those who administer naloxone from penalties for practicing medicine without a license (*MMWR 2012, Coffin 2018*).
- In patients with opioid overdose, naloxone begins to reverse sedation, respiratory depression, and hypotension within 1 to 2 minutes after intravenous (IV) administration, 2 to 5 minutes after intramuscular (IM) or subcutaneous (SC) administration, and 8 to 13 minutes after intranasal (IN) administration. Since the half-life of naloxone is much shorter than that of most opioids, repeated administration may be necessary (*Lexicomp 2018)*.
- Naloxone was first approved by the FDA in 1971. In April 2014, an auto-injector formulation of naloxone was approved (Evzio) which incorporates both audio and visual instructions to guide the person administering the drug during a medical emergency. In November 2015, the FDA approved the first IN formulation of naloxone (Narcan nasal spray). Prior to the approval of these products, naloxone was only available in glass vials and ampules, which were distributed with syringes and needles for manual injection or with syringes and atomizers for off-label IN administration (*Evzio FDA Summary Review 2014*).
- Included in this review are the naloxone products that are FDA-approved for opioid overdose.
- Medispan Class: Opioid Antagonists

Table 2. Medications for Emergency Treatment of Opioid Overdose Included Within Class Review

Drug	Generic Availability
Evzio (naloxone hydrochloride [HCl]) auto-injector	-
Narcan (naloxone HCl)* injection	✔
Narcan (naloxone HCl) nasal spray	-

*Narcan injection was discontinued; however, generic formulations are available

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

INDICATIONS

Table 3. Food and Drug Administration Approved Indications for Buprenorphine and Buprenorphine/Naloxone Products

Indication	Single Entity Agent		Combination Products			
	Sublocade (buprenorphine) subcutaneous injection	Subutex (buprenorphine) sublingual tablets	Bunavail (buprenorphine/ naloxone) film	Suboxone (buprenorphine /naloxone) sublingual tablets	Suboxone (buprenorphine/ naloxone) film	Zubsolv (buprenorphine /naloxone) sublingual tablets
Treatment of opioid dependence			✔		✔	✔
Treatment of opioid dependence and is preferred for induction		✔				
Maintenance treatment of opioid dependence				✔		
Treatment of moderate to severe opioid use disorder†	✔					

†For use in patients who initiated treatment with transmucosal buprenorphine-containing product, followed by dose adjustment for at least 7 days.

(*Prescribing information: buprenorphine sublingual tablets 2018, buprenorphine/naloxone sublingual tablets 2018, Bunavail 2018, Sublocade 2018, Suboxone film 2018, Zubsolv 2018*)

Table 4. Food and Drug Administration Approved Indications for Other Medications Used in Opioid Dependence

Indication	Lucemyra (lofexidine) tablets	naltrexone hydrochloride tablets	Vivitrol (naltrexone HCl) injection
Mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation	✔		
Blockade of the effects of exogenously administered opioids		✔	
Treatment of alcohol dependence		✔	✔
Prevention of relapse to opioid dependence following opioid detoxification			✔

(*Prescribing information: Lucemyra 2018, naltrexone tablets 2017, Vivitrol 2015*)

Table 5. Food and Drug Administration Approved Indications for Naloxone Products

Indication	Evzio (naloxone HCl) auto-injector	Narcan (naloxone HCl) injection	Narcan (naloxone HCl) nasal spray
Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system (CNS) depression	✔		✔
Complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids, including propoxyphene, methadone, and certain mixed agonist-antagonist analgesics: nalbuphine, pentazocine, butorphanol, and cyclazocine		✔	
Diagnosis of suspected or acute opioid overdosage		✔	
Adjunctive agent to increase blood pressure in the management of septic shock		✔	

(*Prescribing information: Evzio 2016, naloxone injection 2015, Narcan nasal spray 2017*)

Limitations of use

- Prescription of Narcan nasal spray 2 mg should be restricted to opioid-dependent patients expected to be at risk for severe opioid withdrawal in situations where there is a low risk for accidental or intentional opioid exposure by household contacts.

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

CLINICAL EFFICACY SUMMARY

Products for Treatment of Opioid Dependence

- Clinical trials have demonstrated that buprenorphine/naloxone is practical and safe for use in diverse community treatment settings including primary care offices (*Amass et al 2004, Fiellin et al 2008*).
- Studies have shown that in adult patients with opioid dependence, the percentage of opioid negative urine tests was significantly higher for both buprenorphine and buprenorphine/naloxone compared to placebo, while no significant difference was seen between the 2 active treatment groups (*Daulouede et al 2010, Fudala et al 2003*). In addition, a small randomized controlled trial (N=32) also showed no significant difference in withdrawal symptoms between buprenorphine and buprenorphine/naloxone (*Strain et al 2011*).
- Several studies have compared the effectiveness of short-term detoxification to medium- or long-term maintenance treatment with buprenorphine monotherapy or buprenorphine/naloxone. Three studies have shown higher treatment retention rate or self-reported drug use with longer treatment duration compared to detoxification; however, 1 of the studies showed no significant difference in the percentage of positive urine tests between the 2 treatment groups at 12 weeks (*Kakko et al 2003, Woody et al 2008, Weiss 2011*).
- In a meta-analysis of 21 randomized controlled trials, patients receiving buprenorphine at doses ≥16 mg/day were more likely to continue treatment compared to patients receiving doses <16 mg/day; however, no significant difference was seen in the percentage of opioid positive urine tests between the high- and low-dose groups (*Fareed et al 2012*).

- Studies that compared different dosing regimens of buprenorphine showed no difference in rate of treatment retention, percentage of urine tests positive for opioids, or withdrawal symptoms (*Bickel et al 1999, Gibson et al 2008, Petry et al 1999, Schottenfeld et al 2000*).
- One study found that buprenorphine/naloxone sublingual film was comparable to the sublingual tablet form in dose equivalence and clinical outcomes (*Lintzeris et al 2013*).
- A randomized, parallel-group, noninferiority trial (N=758) found that for the treatment of patients with opioid dependence, Zubsolv (buprenorphine/naloxone) sublingual tablets was noninferior to generic buprenorphine sublingual tablets during induction and was noninferior to buprenorphine/naloxone sublingual film during early stabilization (*Gunderson et al 2015*).
- Buprenorphine has been compared to methadone in several clinical studies and reviewed in multiple meta-analyses. Overall, studies have demonstrated that buprenorphine-based therapy was as effective as methadone in the management of opioid dependence (*Farre et al 2002, Gibson et al 2008, Gowing et al 2017, Johnson et al 1992, Kamien et al 2008, Law et al 2017, Meader et al 2010, Perry et al 2013, Petitjean et al 2001, Soyka et al 2008, Strain et al 2011).* However, when low doses of buprenorphine were studied (≤8 mg/day), high doses of methadone (≥50 mg/day) proved to be more efficacious *(Farre et al 2002, Ling et al 1996, Mattick et al 2014, Schottenfeld et al 1997*).
- In a 24-week, Phase 3, double blind, placebo-controlled, randomized controlled trial (N=504), the efficacy and safety of multiple subcutaneous injections of buprenorphine (100 mg and 300 mg) over 24 weeks were assessed in treatment-seeking patients with opioid use disorder. Buprenorphine injection was shown to be superior vs placebo in achieving more illicit opioid-free weeks ($p < 0.0001$). The proportion of patients achieving treatment success (defined as any patient with at least 80% of urine samples negative for opioids combined with self-reports negative for illicit opioid use from week 5 through week 24) was statistically significantly higher in both groups receiving buprenorphine compared to the placebo group (28.4% [300 mg/100 mg], 29.1% [300 mg/300mg], and 2% [placebo]) ($p < 0.0001$) *(FDA Advisory Committee Briefing Document, Sublocade Prescribing Information)*.
- Extended-release intramuscular naltrexone was compared to buprenorphine/naloxone sublingual film in a 24-week, open-label, randomized controlled trial (N=570). More induction failures were seen with extended-release intramuscular naltrexone; as a result, in the intention-to-treat analysis, relapse-free survival was lower with extended-release intramuscular naltrexone compared to sublingual buprenorphine/naloxone. However, among patients who were able to successfully initiate treatment, extended-release intramuscular naltrexone had similar efficacy to buprenorphine/naloxone in terms of relapse prevention (*Lee et al 2018*). A 12-week, randomized, open-label, noninferiority trial (N=159) similarly found that extended-release intramuscular naltrexone was noninferior to oral buprenorphine/naloxone in terms of negative urine drug tests and days of opioid use (*Tanum et al 2017).*
- In a meta-analysis examining the efficacy of oral naltrexone for maintenance treatment of opioid dependence, oral naltrexone was no better than placebo or no pharmacologic treatment in terms of treatment retention or use of the primary substance of abuse. Based on the results of 1 study, it was also not significantly different from buprenorphine for retention, abstinence, and side effects (*Minozzi et al 2011*).
- The safety and efficacy of lofexidine for inpatient treatment of opioid withdrawal symptoms was examined in an 8-day, randomized, double-blind, placebo-controlled trial (N=264). In this study, patients treated with lofexidine had lower scores on the Short Opioid Withdrawal Scale (SOWS) Gossop scale on day 3 compared to placebo. More patients in the placebo group terminated study participation early (*Gorodetzky et al 2017).* Similar resulted were found in another, unpublished trial *(Lucemyra prescribing information 2018)*. Meta-analyses have found that although lofexidine reduces withdrawal symptoms compared to placebo, it is less effective than buprenorphine for managing opioid withdrawal in terms of withdrawal severity, withdrawal duration, and likelihood of treatment completion *(Gowing et al 2016, Gowing et al 2017)*. It is likely to be less effective than buprenorphine or methadone for opioid detoxification (*Meader 2010*).

Products for Emergency Treatment of Opioid Overdose

- The approval of Evzio auto-injector and Narcan nasal spray were based on pharmacokinetic bioequivalence studies comparing these products to a generic naloxone product, delivered SC or IM. No clinical studies were required by the FDA (*Prescribing information: Evzio 2016, Narcan 2017*).
  - The manufacturers also conducted a human factors validation study in which participants were asked to deliver a simulated dose of the drug to a mannequin without training and most demonstrated appropriate use of the device (*FDA Summary Review: Evzio 2014, Narcan nasal spray 2015*).
- Studies have suggested that IN naloxone is an effective option in the treatment of opioid overdose (*Kelly et al 2005, Kerr et al 2009, Merlin et al 2010, Robertson et al 2009, Sabzghabaee et al 2014*).

- A meta-analysis of naloxone studies found that lay administration of naloxone was associated with significantly increased odds of recovery compared with no naloxone administration (odds ratio: 8.58, 95% confidence interval [CI], 3.90 to 13.25) (*Giglio et al 2015*).
- A 2-year, non-randomized intervention study found that prescription of naloxone to patients who were prescribed long-term opioids for chronic pain was associated with a 47% decrease in opioid-related emergency visits per month after 6 months and a 63% decrease after 1 year compared to those who did not receive naloxone (*Coffin et al 2016*).

CLINICAL GUIDELINES

- The American Academy of Pediatrics (AAP), APA, American Society of Addiction Medicine (ASAM), Center for Substance Abuse Treatment (CSAT)/United States Substance Abuse and Mental Health Services Administration (SAMHSA), and the Veterans Health Administration (VHA) have published guidelines for the treatment of opioid dependence. In general, these guidelines support access to pharmacological therapy for the management of opioid dependence. Buprenorphine/naloxone combination products may be used for induction and maintenance. In pregnant women for whom buprenorphine therapy is selected, buprenorphine alone (ie, without naloxone) is recommended. Naltrexone may be considered for the prevention of relapse, although outcomes with this medication are often adversely affected by poor adherence. Extended-release injectable naltrexone may reduce, but not eliminate, some of the problems with oral naltrexone adherence. The VHA guideline recommends extended-release injectable naltrexone if opioid agonist treatment is not feasible; it does not recommend for or against oral naltrexone (*CSAT 2004, CSUP 2016, Kampman 2015, Kleber et al 2006, Kraus et al 2011, VHA 2015*).
- Clinical practice guidelines from ASAM and VHA recommend against withdrawal management alone due to the high risk of relapse compared with treatment with maintenance therapy. However, opioid withdrawal can be managed with either gradually tapering doses of opioid agonists or use of alpha-2 adrenergic agonists (eg, clonidine) along with other non-narcotic medications *(Kampman 2015, VHA 2015).*
  - Using tapering doses of opioid agonists has been shown to be superior to alpha-2 adrenergic agonists in terms of retention and opioid abstinence. However, the use of non-opioid medications may be the only option available to clinicians in some healthcare settings and may also facilitate the transition of patients to opioid antagonist medications (eg, naltrexone) and help prevent subsequent relapse.
- Various organizations including the World Health Organization (WHO) and the ASAM have endorsed the availability of naloxone for patients, bystanders, and first responders for the emergency management of suspected opioid overdose. It is recommended that people who are likely to witness an overdose should have access to and be trained in the use of naloxone (*WHO 2014, Kampman 2015*).
  - According to the WHO guidelines for community management of opioid overdose, naloxone is effective when delivered by IV, IM, SC, and IN routes of administration. Persons using naloxone should select a route of administration based on the formulation available, their skills in administration, the setting, and local context.

SAFETY SUMMARY

Products for Treatment of Opioid Dependence

- Buprenorphine and buprenorphine/naloxone products are contraindicated in patients with known hypersensitivity to the active ingredients.
- Buprenorphine products have several warnings and precautions, including: Abuse potential; respiratory depression; CNS depression; unintentional pediatric exposure; neonatal opioid withdrawal; adrenal insufficiency; risk of opioid withdrawal with abrupt discontinuation of treatment; hepatitis and hepatic events; hypersensitivity reactions; precipitation of opioid withdrawal signs and symptoms; use in patients with impaired hepatic function; impairment of ability to drive or operate machinery; orthostatic hypotension; elevation of cerebrospinal fluid pressure; elevation of intracholedochal pressure; and effects in acute abdominal conditions
- Concomitant use of buprenorphine and benzodiazepines or other CNS depressants increases the risk for adverse events, including overdose, respiratory depression, and death. Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use. This additional warning was added to opioid products in February 2018 after data demonstrated an increased risk of mortality in patients receiving benzodiazepines while on opioid maintenance treatment (*Abrahamsson et al 2017, FDA Drug Safety Communication 2017*).

- The buprenorphine subcutaneous injection also has several unique warnings and precautions, including: serious harm or death could result if administered IV (boxed warning); risks associated with treatment of emergent acute pain; use in patients at risk for arrhythmia.
- In the treatment of addiction involving opioid use in pregnant women, the buprenorphine/naloxone combination product is not recommended for use (insufficient evidence); however, the buprenorphine monoproduct is a reasonable and recommended option for use.
- Similar to other opiate products, these products may increase intracholedochal pressure, increase cerebrospinal fluid pressure, and obscure diagnosis or exacerbate acute abdominal symptoms.
- These products should not be used as analgesics.
- The most common adverse reactions observed with buprenorphine and buprenorphine/naloxone products include headache, insomnia, nausea, pain, sweating, and withdrawal syndrome.
- All of the buprenorphine-containing products have an associated risk evaluation and mitigation strategy (REMS) program (*REMS@FDA 2018*).
- Lofexidine has several warnings and precautions, including: risk of hypotension, bradycardia, and syncope; risk of QT prolongation; increased risk of CNS depression with concomitant use of CNS depressant drugs; and increased risk of opioid overdose in patients who complete opioid discontinuation and resume opioid use.
- Sudden discontinuation of lofexidine can cause a marked rise in blood pressure and symptoms that include diarrhea, insomnia, anxiety, chills, hyperhidrosis, and extremity pain. Lofexidine should be discontinued by gradually reducing the dose.
- The most common adverse reactions observed with lofexidine include orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth.
- The safety of lofexidine in pregnancy has not been established.
- Naltrexone products are contraindicated in: patients receiving opioid analgesics; patients currently dependent on opioids (including those currently maintained on opioid agonists); patients in acute opioid withdrawal; individuals who have failed a naloxone challenge test or have a positive urine screen for opioids; individuals with a history of sensitivity to naltrexone or other components of the product; and individuals with acute hepatitis or liver failure (oral naltrexone only). Extended-release injectable naltrexone is contraindicated in patients with hypersensitivity to polylactide-co-glycolide (PLG), carboxymethylcellulose, or any other component of the diluent.
- Naltrexone can precipitate withdrawal if given to an opioid-dependent patient. Prior to initiating naltrexone, an opioid-free interval of 7 to 10 days is recommended for patients previously dependent on short-acting opioids; patients transitioning from buprenorphine or methadone may be vulnerable to precipitation of withdrawal symptoms for up to 2 weeks. A naloxone challenge test may be helpful to determine whether or not the patient has had a sufficient opioid-free period prior to initiating naltrexone.
- Patients may be more vulnerable to opioid overdose after discontinuation of naltrexone due to decreased opioid tolerance.
- Monitor patients on naltrexone for the development of depression or suicidality.
- Warnings unique to extended-release intramuscular naltrexone include: injection site reactions, which may be severe; eosinophilic pneumonia; hypersensitivity reactions, including anaphylaxis; use in patients with thrombocytopenia or any coagulation disorder; and interference with certain immunoassay methods of urine opioid detection.
- The most common adverse reactions observed with oral naltrexone include difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea/vomiting, low energy, joint and muscle pain, and headache. The most common adverse reactions observed with extended-release intramuscular naltrexone include hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache.
- There are no adequate and well-controlled studies of naltrexone in pregnant women; it should be used only if the potential benefit justifies the potential risk to the fetus.
- Extended-release intramuscular naltrexone has a REMS program due to the risk of severe injection site reactions (*REMS@FDA 2018*).

Products for Emergency Treatment of Opioid Overdose

- These products are contraindicated in patients with hypersensitivity to naloxone or to any of the other ingredients.
- These products carry warnings and precautions for risks of recurrent respiratory and CNS depression, limited efficacy with partial agonists or mixed agonists/antagonists (eg, buprenorphine, pentazocine), and precipitation of severe opioid withdrawal.

- Naloxone may precipitate acute withdrawal symptoms in opioid-dependent patients including anxiety, tachycardia, sweating, piloerection, yawning, sneezing, rhinorrhea, nausea, vomiting, diarrhea, increased blood pressure, and abdominal or muscle cramps. Opioid withdrawal signs and symptoms in neonates also include convulsions, excessive crying, and hyperactive reflexes.

DOSING AND ADMINISTRATION

Table 6a. Dosing and Administration for Products for Treatment of Opioid Dependence

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single Entity Agents				
Lucemyra (lofexidine)	Tablet	Oral	4 times daily at 5- to 6-hour intervals	• May be continued for up to 14 days with dosing guided by symptoms • Adjust dose for patients with hepatic or renal impairment
Naltrexone hydrochloride	Tablet	Oral	Single daily dose May also be dosed every other day or every 3 days	• Contraindicated in patients with acute hepatitis or liver failure • Use caution in patients with hepatic or renal impairment
Sublocade (buprenorphine)	Subcutaneous injection	SC	Monthly (minimum 26 days between doses)	• Can only be administered by a healthcare provider • Patients with moderate or severe hepatic impairment are not candidates for this product
Subutex (buprenorphine)	Sublingual tablets	Oral	Single daily dose	• Severe hepatic impairment: Consider reducing the starting and titration incremental dose by half and monitor for signs and symptoms of toxicity or overdose.
Vivitrol (naltrexone extended-release)	Intramuscular injection	IM	Monthly or every 4 weeks	• Can only be administered by a healthcare provider • Use caution in patients with moderate to severe renal impairment
Combination Products				
Bunavail, Suboxone, Zubsolv (buprenorphine/ naloxone)	Buccal film (Bunavail) Sublingual film (Suboxone) Sublingual tablet (Zubsolv; generics equivalent to Suboxone tablet)	Oral	Bunavail: Single daily dose (except day 1 of induction for patients dependent on heroin or other short-acting opioid products: start with an initial dose of 2.1 mg/0.3 mg and repeat at approximately 2 hours, under supervision, to a total dose of 4.2 mg/0.7 mg based on the control of acute withdrawal symptoms) Suboxone: Single daily dose (except day 1 of induction:	• These products should generally be avoided in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			titrate in buprenorphine 2 mg to 4 mg increments at approximately 2 hour intervals based on the control of acute symptoms) Sublingual tablet generics (Suboxone): Single daily dose Zubsolv: Single daily dose (except day 1 of induction: divided into 1 to 2 tablets of 1.4 mg/0.36 mg at 1.5 to 2 hour intervals)	

See the current prescribing information for full details

Table 6b. Equivalent Doses of Buprenorphine/Naloxone Combination Products[a]

Bunavail buccal film	buprenorphine/naloxone sublingual tablets and/or Suboxone sublingual film	Zubsolv sublingual tablets
-	2 mg/0.5 mg	1.4 mg/0.36 mg
2.1 mg/ 0.3 mg	4 mg/1 mg	2.9 mg/0.71 mg
4.2 mg/ 0.7 mg	8 mg/2 mg	5.7 mg/1.4 mg
6.3 mg/1 mg	12 mg/3 mg	8.6 mg/2.1 mg
	16 mg/4 mg	11.4 mg/2.9 mg

[a] Systemic exposures of buprenorphine and naloxone may differ when patients are switched from tablets to films or vice versa.

Table 7. Dosing and Administration for Products for Emergency Treatment of Opioid Overdose

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Evzio (naloxone HCl)	Auto-injector	IM/SC	• After initial dose, additional doses should be administered, using a new device, if the patient does not respond or responds and then relapses into respiratory depression. • Additional doses may be given every 2 to 3 minutes until emergency medical assistance arrives.	• The requirement for repeat doses depends upon the amount, type, and route of administration of the opioid being antagonized.
Naloxone HCl	Vials, prefilled syringe, solution cartridge	IV	*Adults:* • An initial dose may be administered IV. It may be repeated at 2 to 3 minute intervals if the desired degree of counteraction and improvement in respiratory functions are not obtained.	• IM or SC administration may be necessary if the IV route is not available. • The American Academy of Pediatrics, however, does not endorse SC or IM administration in opiate intoxication since absorption may be erratic or delayed.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Children: • The usual initial dose in children is given IV; a subsequent dose may be administered if the desired degree of clinical improvement is not obtained.	
Narcan (naloxone HCl)	Nasal spray	Intranasal	• A single spray should be administered into 1 nostril. • Additional doses should be administered, using a new nasal spray device in alternating nostrils, if the patient does not respond or responds and then relapses into respiratory depression. Additional doses may be given every 2 to 3 minutes until emergency medical assistance arrives.	

CONCLUSION

Products for Treatment of Opioid Dependence

- Buprenorphine sublingual tablets, buprenorphine/naloxone sublingual tablets, Bunavail (buprenorphine/naloxone) buccal film, Sublocade (buprenorphine) subcutaneous injection, Suboxone (buprenorphine/naloxone) sublingual film, and Zubsolv (buprenorphine/naloxone) sublingual tablets are used for the treatment of opioid dependence. Some products are indicated for maintenance treatment only, while others are indicated for both induction and maintenance.
- Buprenorphine is suggested as a first-line maintenance treatment for opioid use disorder; it may be preferred over methadone because it is safer and does not require clinic-based treatment. Buprenorphine is typically administered in a combination product with naloxone, an opioid antagonist, to discourage abuse. These agents are Schedule III controlled substances (*Strain 2018*).
- Clinical trials have demonstrated that buprenorphine/naloxone is practical and safe for use in diverse community treatment settings including primary care offices (*Amass et al 2004, Fiellin et al 2008*).
- Physicians prescribing buprenorphine for opioid dependency must undergo specialized training due to the potential for abuse and diversion. Because of these risks, buprenorphine monotherapy should be reserved for patients who are pregnant or have a documented allergy to naloxone (*DATA 2000, CSAT 2004*).
- Overall, studies have demonstrated that buprenorphine-based therapy was as effective as methadone in the management of opioid dependence (*Farre et al 2002, Gibson et al 2008, Gowing et al 2017, Johnson et al 1992, Kamien et al 2008, Meader et al 2010, Petitjean et al 2001, Soyka et al 2008, Mattick et al 2014, Strain et al 2011*).
- The most common adverse reactions observed with buprenorphine and buprenorphine/naloxone products include headache, insomnia, nausea, pain, sweating, and withdrawal syndrome. These products also have REMS criteria.
- Lofexidine is an oral central alpha-2 agonist indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation.
- Meta-analyses have found that although lofexidine reduces withdrawal symptoms compared to placebo, it is less effective than buprenorphine for managing opioid withdrawal in terms of withdrawal severity, withdrawal duration, and likelihood of treatment completion *(Gowing et al 2016, Gowing et al 2017)*. It is likely to be less effective than buprenorphine or methadone for opioid detoxification (*Meader 2010*).

- The most common adverse reactions observed with lofexidine include orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth.
- Naltrexone is an opioid antagonist. Oral naltrexone is indicated for the treatment of alcohol dependence and blockade of the effects of exogenously administered opioids. Extended-release intramuscular naltrexone is indicated for the treatment of alcohol dependence and the prevention of relapse to opioid dependence following opioid detoxification. In order to initiate naltrexone treatment, patients must be opioid-free for at least 7 to 10 days to avoid precipitation of withdrawal.
- In a meta-analysis examining the efficacy of oral naltrexone for maintenance treatment of opioid dependence, oral naltrexone was no better than placebo or no pharmacologic treatment in terms of treatment retention or use of the primary substance of abuse. Based on the results of 1 study, it was also not significantly different from buprenorphine for retention, abstinence, and side effects (*Minozzi et al 2011*). Extended-release intramuscular naltrexone has been shown to have similar efficacy to oral buprenorphine/naloxone among patients who are able to successfully initiate treatment (*Lee et al 2018, Tanum et al 2017*).
- The most common adverse reactions observed with oral naltrexone include difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea/vomiting, low energy, joint and muscle pain, and headache. The most common adverse reactions observed with extended-release intramuscular naltrexone include hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache. Extended-release intramuscular naltrexone also has a REMS program.
- The AAP, APA, ASAM, CSAT/SAMHSA, and VHA publish guidelines for the treatment of opioid dependence. These guidelines support access to pharmacological therapy for the management of opioid dependence. Buprenorphine/naloxone combination products may be used for induction and maintenance. In pregnant women for whom buprenorphine therapy is selected, buprenorphine alone (ie, without naloxone) is recommended. Naltrexone may be considered for the prevention of relapse, although outcomes with this medication are often adversely affected by poor adherence. Extended-release injectable naltrexone may reduce, but not eliminate, some of the problems with oral naltrexone adherence. The VHA guideline recommends extended-release injectable naltrexone if opioid agonist treatment is not feasible; it does not recommend for or against oral naltrexone (*CSAT 2004, CSUP 2016, Kampman et al 2015, Kleber et al 2006, Kraus et al 2011, VHA 2015).*
- Clinical practice guidelines from ASAM and VHA recommend against withdrawal management alone due to the high risk of relapse compared with treatment with maintenance therapy. However, opioid withdrawal can be managed with either gradually tapering doses of opioid agonists or use of alpha-2 adrenergic agonists (eg, clonidine) along with other non-narcotic medications. Lofexidine has not been added to practice guidelines but it likely has a similar place in therapy as clonidine *(Kampman 2015, VHA 2015).*

Products for Emergency Treatment of Opioid Overdose

- Naloxone is the standard of care to treat opioid overdose. It has been used by medical personnel for over 40 years and its use outside of the medical setting has gained traction through improvements in legislation and community-based opioid overdose prevention programs.
- Evzio (naloxone HCl) auto-injector, naloxone HCl injection, and Narcan (naloxone HCl) nasal spray are approved for treatment of known or suspected opioid overdose. Prior to the approval of Evzio and Narcan nasal spray, naloxone was only available in glass vials and ampules, which were distributed with syringes and needles for manual injection or with syringes and atomizers for off-label IN administration (*Evzio FDA Summary Review 2014*).
- Naloxone can be administered IV, IM, or SC using naloxone vials/syringes as well as IM or SC using an auto-injector device (Evzio). Although Narcan nasal spray is the first IN formulation to be FDA-approved, naloxone has historically been given IN off-label via kits containing a syringe and an atomization device. Potential advantages of IN administration of naloxone include easier disposal, no needle stick risk, and avoidance of needle anxiety. Both Evzio and Narcan nasal spray are designed for use by laypersons.
- The approval of Evzio and Narcan nasal spray were based on pharmacokinetic bioequivalence studies. No new clinical studies were required by the FDA.
- Various organizations including WHO and ASAM have endorsed the availability of naloxone for patients, bystanders, and first responders for the emergency management of suspected opioid overdose. It is recommended that people who are likely to witness an overdose should have access to and be trained in the use of naloxone (*WHO 2014, Kampman 2015*).

- According to the WHO guidelines for community management of opioid overdose, naloxone is effective when delivered by IV, IM, SC, and IN routes of administration. Persons using naloxone should select a route of administration based on the formulation available, their skills in administration, the setting, and local context.

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

INTRODUCTION

- Influenza is an infectious respiratory illness caused by the influenza A and influenza B viruses. Influenza epidemics occur annually in the United States, typically from late fall to early spring. Although the majority of infected individuals recover without complications, some cases of influenza result in severe illness or death *(Grohskopf et al 2018)*.
- The virus is primarily transmitted through direct contact with large-particle respiratory droplets from an infected individual's coughs and sneezes. It is also spread through contact with surfaces contaminated by infected respiratory droplets. Adults begin to shed virus 1 day prior to symptom onset, and they remain contagious for 5 to 7 days after falling ill *(Centers for Disease Control and Prevention [CDC] 2016)*.
- Signs and symptoms of uncomplicated influenza illness include fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis. Complications of influenza infection include sinusitis, otitis media, pneumonia, sepsis, and exacerbation of chronic medical conditions. Elderly adults, young children, pregnant women, and patients with chronic medical conditions have a higher risk of developing complications from influenza *(CDC 2018[a])*.
- Annual influenza vaccination is the most effective method for preventing seasonal influenza virus infection and its complications. Antiviral prescription medications are also available for influenza prophylaxis and treatment; however, antiviral chemoprophylaxis is not a substitute for annual influenza vaccination *(Grohskopf et al 2018)*.
- Initiation of antiviral therapy to treat influenza is recommended as early as possible for patients with confirmed or suspected influenza who are hospitalized; have severe, complicated, or progressive illness; or are at higher risk for influenza complications *(Fiore et al 2011)*.
- Three classes of antiviral medications are available and included in this review. The adamantanes include amantadine and Flumadine (rimantadine). The neuraminidase inhibitors include Rapivab (peramivir), Relenza (zanamivir), and Tamiflu (oseltamivir). Currently, the only endonuclease inhibitor on the market is Xofluza (baloxavir marboxil), which was approved by the Food and Drug Administration (FDA) in late October 2018.
- Resistance to adamantanes is high (> 99%) among currently circulating influenza A virus strains, and these agents lack activity against influenza B virus. Therefore, amantadine and rimantadine are not recommended for treatment or chemoprophylaxis during the current influenza season *(CDC 2018[b])*.
- The neuraminidase inhibitors and baloxavir marboxil are active against both influenza A and influenza B viruses. Peramivir, zanamivir, oseltamivir, and baloxavir marboxil are the only antivirals recommended for the current influenza season in the United States *(CDC 2018[b])*.
- Circulating influenza viruses may evolve, and drug-resistant influenza virus strains have been reported. Prescribers should refer to influenza drug susceptibility patterns when selecting an antiviral agent *(CDC 2018[b])*.
- Medispan class: Antiparkinson, Dopaminergic and Influenza Agents. The only agent from the Antiparkinson, Dopaminergic category that will be included in this review is amantadine for the influenza indication.

Table 1. Medications Included Within Class Review

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

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

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

Indication[1]	amantadine[2]	Flumadine (rimantadine)	Rapivab[3] (peramivir)	Relenza[4] (zanamivir)	Tamiflu[5] (oseltamivir)	Xofluza (baloxavir marboxil)
Treatment of acute uncomplicated influenza in patients 12 years and older who have been symptomatic for no more than 48 hours						✔

[1] The changing of viruses over time is a limitation of use for antivirals. The emergence of resistance mutations could decrease drug effectiveness. Other factors, such as changes in viral virulence, may also diminish the clinical benefit of antivirals. Prescribers should consider available information on influenza drug susceptibility patterns and treatment effects when selecting an antiviral.
[2] Amantadine is also indicated in the treatment of parkinsonism and drug-induced extrapyramidal reactions.
[3] Limitations of use for peramivir:
- Efficacy is based on clinical trials of naturally occurring influenza in which the predominant influenza infections were influenza A virus; a limited number of subjects infected with influenza B virus were enrolled.
- Efficacy could not be established in patients with serious influenza requiring hospitalization.

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

[5] Limitations of use for oseltamivir:
- Not recommended for patients with end-stage renal disease not undergoing dialysis.

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

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

CLINICAL EFFICACY SUMMARY

Adamantanes

- Clinical trials have demonstrated that the adamantanes are effective in both the prophylaxis and treatment of influenza A virus *(Bryson et al 1980, Crawford et al 1988, Dolin et al 1982, Hall et al 1987, Hayden et al 1989, Jackson et al 2011, Jefferson et al 2006[a], Jefferson et al 2006[b], Monto et al 1995, Reuman et al 1989)*.
- One systematic review assessed the efficacy and safety of adamantanes in healthy adults by analyzing 20 prophylaxis and 13 treatment randomized trials comparing amantadine or rimantadine with placebo. For prophylaxis, amantadine was 61% better than placebo at reducing influenza risk ($p < 0.001$). Although rimantadine was 72% better than placebo at preventing influenza, statistical significance was not achieved. There was significant heterogeneity between the prophylaxis trials, and only a small sample size was available for rimantadine compared to amantadine. For treatment, amantadine and rimantadine both reduced the duration of fever by 1 day. Both agents caused gastrointestinal side effects, but amantadine caused significantly more adverse effects in the central nervous system than rimantadine *(Jefferson et al 2006[a])*.
- The adamantanes are not currently recommended for treatment of influenza due to high levels of resistance in influenza A viruses and lack of efficacy against influenza B viruses (*CDC 2018[b], Uyeki et al 2018*).

Neuraminidase inhibitors

- The neuraminidase inhibitors have demonstrated efficacy for their respective indications. Zanamivir inhalation and oral oseltamivir are effective in both the prophylaxis and treatment of influenza A and B. Clinical trials have demonstrated a reduction in laboratory-confirmed influenza, illness, fever duration, secondary complications, and household contacts with influenza infection *(Aoki et al 2003, Chik et al 2004, Cooper et al 2003, Fry et al 2014, Halloran et al 2007, Hayden et al 1997, Hayden et al 1999, Hayden et al 2000, Hayden et al 2004, Hedrick et al 2000, Hiba et al 2011, Kaiser et al 2003, Kawai et al 2005, Kawai et al 2006, Lin et al 2006, MIST Study Group 1998, Monto et al 1999[a], Monto et al*

1999[b], Monto et al 2002, Nicholson et al 2000, Peters et al 2001, Reuman et al 1989, Singh et al 2003, Treanor et al 2000, Turner et al 2003, Wang et al 2012, Welliver et al 2001, Whitley et al 2001).

- One systematic review analyzed 20 oseltamivir and 26 zanamivir randomized, placebo-controlled trials in order to better define their efficacy and safety. In prophylaxis trials, the risk of symptomatic influenza was reduced by 3.05% in patients treated with oseltamivir compared to placebo and 1.98% in patients treated with zanamivir compared to placebo. In adults, the time to first alleviation of symptoms was reduced by 0.7 days ($p < 0.0001$) in patients receiving oseltamivir compared to placebo and 0.6 days ($p < 0.00001$) in patients receiving zanamivir compared to placebo. Oseltamivir significantly reduced the time to alleviation of symptoms in non-asthmatic children and decreased the incidence of self-reported pneumonia. Zanamivir significantly reduced the risk of bronchitis in adults with influenza. Neither treatment was a significant improvement over placebo in time to symptom alleviation in asthmatic children or risk of hospitalizations, otitis media, or sinusitis. Many studies included were at a high risk of selection bias due to inadequate reporting and a high risk of attrition bias due to selective reporting. All trials were sponsored by the manufacturers *(Jefferson et al 2014)*.
- In a systematic review of other published systematic reviews and meta-analyses, treatment of influenza with neuraminidase inhibitors (oseltamivir or zanamivir) was found to be likely effective in reducing mortality among hospitalized patients; the odds of mortality appeared especially lower when therapy was started early (≤ 48 hours of symptom onset). When used for treatment in the general population, these agents appear to reduce the duration of symptoms by approximately 0.5 to 1 day. Both oseltamivir and zanamivir were found likely to be effective at reducing secondary symptomatic influenza transmission when used prophylactically (*Doll et al 2017*).
- Peramivir intravenous (IV) infusion is approved for the treatment of influenza A and B in adults. The primary endpoint for the main clinical trial supporting FDA approval of peramivir was time to alleviation of symptoms. The trial evaluated 296 previously healthy adults presenting with the onset of influenza-like illness within the previous 48 hours and a positive influenza rapid antigen test. In this multicenter, double-blind, placebo-controlled clinical trial, patients were randomized to peramivir 300 mg, 600 mg, or placebo as a single IV dose. Acetaminophen use was permitted. Patients self-reported body temperature, symptoms, and resumption of activities over 14 days. The primary endpoint, the median time to alleviation of symptoms, was significantly earlier with peramivir 300 mg (59.1 hours) and 600 mg (59.9 hours) compared to placebo (81.8 hours; both $p = 0.0092$). There was no significant difference in the incidence of all adverse events in patients receiving peramivir compared to placebo. Diarrhea was the most common adverse event, occurring in 14.1%, 15.2% and 17% of the peramivir 300 mg, 600 mg, and placebo groups, respectively *(Kohno et al 2010)*.
- Although studies have evaluated peramivir in hospitalized patients and in children, both of these populations are not included in the FDA-approved labeling *(De Jong et al 2014, Ison et al 2014, Ison et al 2013, Sugaya et al 2012)*. The Phase 3 clinical trial of peramivir in hospitalized influenza patients failed to meet its primary endpoint of reducing the time to clinical resolution compared to placebo. There are no clinical endpoints that have been validated for clinical trials of neuraminidase inhibitors treating hospitalized patients with influenza *(FDA 2014)*. In 2009, the United States issued an Emergency Use Authorization (EUA) program allowing peramivir for the treatment of suspected or confirmed 2009 H1N1 influenza A virus infection in hospitalized patients *(Birnkrant 2009)*. Patients eligible for treatment were hospitalized, unable to tolerate or unresponsive to other available antivirals, or lacked a dependable oral or inhalation drug delivery route. The Public Health Emergency determination for the 2009 H1N1 influenza pandemic expired on June 23, 2010 *(CDC 2010)*.
- Numerous placebo-controlled trials have demonstrated the efficacy of neuraminidase inhibitors individually, but head-to-head trials directly comparing the agents are limited. One randomized, double-blind, placebo-controlled safety trial compared the use of oseltamivir, zanamivir and placebo in 390 healthy adults for influenza chemoprophylaxis over 16 weeks. The study showed that both treatments were well tolerated compared to placebo, and there were no discontinuations due to adverse events *(Anekthananon et al 2013)*.
- A Phase 3, multinational, multicenter, double-blind, randomized, noninferiority trial compared a single dose of 300 or 600 mg IV peramivir to 5 days of oral oseltamivir in 1,091 patients with seasonal influenza. The primary endpoint, time to alleviation of influenza symptoms, had a median of 78.0 hours in patients receiving 300 mg of peramivir, 81.0 hours in patients receiving 600 mg of peramivir, and 81.8 hours in patients receiving oseltamivir. Both strengths of peramivir were noninferior to oseltamivir with a noninferiority margin of 0.170. There was no significant difference between treatments in the incidence of complications of influenza infection *(Kohno et al 2011)*.
- A meta-analysis including 2 controlled clinical trials and 5 observational trials (N = 1676) examined the comparative efficacy of IV peramivir and oral oseltamivir in the treatment of seasonal influenza. No significant differences between treatments were noted for the following outcomes: mortality, hospital length of stay, virus titer 48 hours after admission, and incidence of adverse events. However, the time to resolution of influenza symptoms or fever was shorter with peramivir than with oseltamivir treatment (mean difference, -7.17 hours; $p < 0.01$) (*Lee et al 2017*).

- Observational studies comparing the clinical efficacy of peramivir, zanamivir, and oseltamivir in treating influenza have demonstrated within-class variation in the time to alleviation of influenza symptoms. The lack of robust data from randomized, head-to-head trials prevents the recommendation of one neuraminidase inhibitor over another. Local and seasonal susceptibility trends, route of administration, and patient-specific factors such as age and compliance should be taken into account when selecting an agent for antiviral drug therapy *(Kawai et al 2008, Takemoto et al 2013)*.
- While influenza virus strains resistant to specific neuraminidase inhibitors have emerged, overall resistance remains low. According to surveillance data on seasonal influenza virus strains, the rate of resistance to oseltamivir is 1 to 3% and resistance to zanamivir is < 1% *(Li et al 2015)*.

Endonuclease inhibitor

- In a Phase 3, double-blind, randomized, placebo- and oseltamivir-controlled trial (CAPSTONE-1), 1436 patients 12 to 64 years of age with influenza-like illness were randomized in a 2:2:1 ratio to receive a single, weight-based oral dose of baloxavir marboxil, treatment-dose oseltamivir for 5 days, or matching placebo. The primary endpoint, time to alleviation of influenza symptoms, was 53.7 hours (95% confidence interval [CI], 49.5 to 58.5) with baloxavir marboxil compared with 80.2 hours (95% CI, 72.6 to 87.1) with placebo ($p < 0.001$). The median time to alleviation of symptoms was similar between baloxavir marboxil and oseltamivir (53.5 hours and 53.8 hours, respectively). Treatment-related adverse events were more common with oseltamivir (8.4%) than baloxavir marboxil (4.4%; $p = 0.009$), or placebo (3.9%) (*Hayden et al 2018*).

CLINICAL GUIDELINES

- Annual influenza vaccination is the most effective method for preventing seasonal influenza virus infection and its complications. All individuals 6 months of age and older should receive an influenza vaccination each year, unless contraindicated. Prophylactic antiviral administration is not a substitute for early influenza vaccination *(Grohskopf et al 2018)*.
- Amantadine and rimantadine are not recommended for antiviral treatment or prophylaxis of influenza in the United States due to high rates of resistance in influenza A viruses and lack of efficacy against influenza B viruses *(American Academy of Pediatrics [AAP] 2018, Fiore et al 2011, CDC 2018[b], Uyeki et al 2018)*.
- Key recommendations from the CDC include the following (*CDC 2018[b]*):
  - Widespread or routine use of antiviral medications for prophylaxis is not recommended except as one of multiple interventions to control institutional influenza outbreaks. Routine use of post-exposure chemoprophylaxis is not recommended, but may be considered in certain patients who are either not candidates for vaccination or received their annual vaccination less than 2 weeks prior to exposure. Oseltamivir and zanamivir are agents recommended for chemoprophylaxis.
  - The antivirals recommended for influenza treatment in the current influenza season include oseltamivir, zanamivir, peramivir, and baloxavir marboxil. Treatment of influenza with antiviral therapy is recommended as early as possible for patients with confirmed or suspected influenza who are hospitalized; have severe, complicated, or progressive illness; or are at a high risk for complications.
  - Populations at a high risk for influenza complications and recommended to receive antiviral treatment include children younger than 2 years old, adults age 65 and above, pregnant or postpartum women, American Indians, Alaska Natives, obese patients with a body mass index (BMI) of 40 kg/m^2 and above, patients younger than 19 years old receiving long-term treatment with aspirin, residents of nursing homes, and patients with immunosuppression, chronic disorders (eg, pulmonary, cardiovascular, renal, hepatic, hematological and metabolic), or neurologic conditions.
  - Early antiviral treatment can shorten the duration of fever and illness symptoms, and may reduce the risk of influenza-related complications such as otitis media, pneumonia, and respiratory failure. In observational studies, early treatment with oseltamivir has been reported to reduce deaths in hospitalized adults and shorten the duration of hospitalization in children. Clinical benefit is greatest when antiviral treatment is administered early, especially within 48 hours of influenza illness onset.
- Key recommendations from the Infectious Diseases Society of America include the following (*Uyeki et al 2018*):
  - Clinicians should start antiviral treatment as soon as possible for adults and children with documented or suspected influenza who are hospitalized, have severe or progressive illness, or are at high risk of complications; children < 2 years and adults ≥ 65 years of age; and women who are pregnant or within 2 weeks postpartum.

- Clinicians can consider antiviral treatment for patients with documented or suspected influenza who are not at high risk of complications if they are outpatients with illness onset ≤ 2 days before presentation, or symptomatic outpatients who are household contacts or healthcare providers of persons at high risk of developing complications.
- A single neuraminidase inhibitor (oseltamivir, zanamivir, or peramivir) is recommended for treatment; combination neuramidase inhibitors are not recommended.
- Antiviral drugs should not be used for routine or widespread chemoprophylaxis outside of institutional outbreaks. Antiviral chemoprophylaxis with oral oseltamivir or inhaled zanamivir can be considered for individuals in certain situations, eg, those at high risk for complications who are not eligible for vaccination or for whom the vaccine is expected to have low effectiveness, and those in close contact with individuals at high risk of complications who are not eligible for vaccination or chemoprophylaxis.

SAFETY SUMMARY

- Common adverse events with adamantanes include nausea, dizziness, insomnia, headache, anorexia, dry mouth, and agitation.
- Amantadine and rimantadine should be used with caution in patients with epilepsy due to an increased risk for seizures.
- Amantadine has anticholinergic effects and is contraindicated in patients with untreated angle closure glaucoma. There have also been reports of death from overdose and suicide attempts with amantadine.
- Common adverse events with neuraminidase inhibitors include nausea, vomiting, and headache. The most common adverse effect with peramivir is diarrhea.
- All 3 neuraminidase inhibitors have labeled warnings for neuropsychiatric events such as hallucinations and delirium. Patients should be monitored for signs of abnormal behavior.
- Oseltamivir and peramivir have warnings for serious skin and hypersensitivity reactions, including Stevens-Johnson Syndrome.
- Zanamivir has a warning for bronchospasm and should not be used in patients with asthma or chronic obstructive pulmonary disease. It is also contraindicated in patients with milk protein allergies.
- Common adverse events with baloxavir marboxil include diarrhea, headache, bronchitis, nausea, and nasopharyngitis.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration*

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
amantadine	Capsules, oral solution, tablets	Oral	Once daily or twice daily Adults: 200 mg once daily or 100 mg twice daily Pediatric patients: 1 to 9 years: 4.4 to 8.8 mg/kg/day not to exceed 150 mg per day 9 to 12 years: 100 mg twice daily The safety and efficacy of amantadine in newborn infants and infants below the age of 1 year have not been established.	Should be taken for 10 days following a known exposure. If using in conjunction with vaccine until antibody response, take for 2 to 4 weeks. Treatment of illness should be started within 24 to 48 hours of symptom onset and continued for 24 to 48 hours after symptoms disappear. For adult patients intolerant to 200 mg daily dose because of central nervous system or other toxicities: 100 mg daily dose Because amantadine is primarily excreted in the urine, it accumulates when renal function declines. Thus, the dose of amantadine should be reduced in patients with renal impairment and in individuals

				who are 65 years of age or older according to the following: For CrCl = 30 to 50 mL/min: 200 mg 1st day, then 100 mg daily For CrCl = 15 to 29 mL/min: 200 mg 1st day, then 100 mg on alternate days For CrCl < 15 mL/min and HD: 200 mg every 7 days For patients ≥ 65 years: 100 mg once daily The dose of amantadine may need reduction in patients with congestive heart failure, peripheral edema, or orthostatic hypotension.
Flumadine (rimantadine)	Tablets	Oral	Twice daily **Adults (17 years and older)** Treatment: 100 mg twice daily for 7 days Prophylaxis: 100 mg twice daily **Pediatric patients** Prophylaxis in patients 1 to 9 years: 5 mg/kg/day, not to exceed 150 mg per day 10 to 16 years: Refer to the adult dose The safety and efficacy of rimantadine in pediatric patients below the age of 1 year have not been established.	Treatment of illness should be started within 48 hours of symptoms. A suspension can be made from the tablets and is stable for 14 days. Dose adjustment in patients ≥ 65 years: 100 mg once daily Dose adjustment in patients with CrCl < 29 mL/min: 100 mg daily Dose adjustment in patients with severe hepatic dysfunction: 100 mg daily
Rapivab (peramivir)	Injection	IV	Patients ≥ 13 years: 600 mg as a single dose Patients < 13 years: 2 to 12 years: 12 mg/kg (maximum dose 600 mg) as a single dose Safety and effectiveness in	One time dose should be provided within 2 days of onset of influenza symptoms A single dose administered by IV infusion for a minimum of 15 minutes. Peramivir must be diluted prior to administration.

			pediatric patients < 2 years of age have not been established.	Dose adjustment in adults and adolescents 13 years of age or older with CrCl = 30 to 49 mL/min: 200 mg Dose adjustment in pediatric patients 2 to 12 years of age with CrCl = 30 to 49 mL/min: 4 mg/kg Dose adjustment in adults and adolescents 13 years of age or older with CrCl = 10 to 29 mL/min: 100 mg Dose adjustment in pediatric patients 2 to 12 years of age with CrCl = 10 to 29 mL/min: 2 mg/kg HD: Administer after dialysis
Relenza (zanamivir)	Inhalation powder (in blisters)	Oral inhalation via Diskhaler device	Once daily or twice daily, depending on the indication Treatment (≥ 7 years): 10 mg twice daily for 5 days Prophylaxis in household setting (≥ 5 years): 10 mg once daily for 10 days Prophylaxis in community outbreak (adults and adolescents): 10 mg once daily for 28 days	The 10 mg dose is provided by 2 inhalations (one 5 mg blister per inhalation). Patients scheduled to use an inhaled bronchodilator at the same time as zanamivir should use their bronchodilator before taking zanamivir. If zanamivir is prescribed for children, it should be used only under adult supervision and instruction, and the supervising adult should first be instructed by a healthcare professional. Due to the low systemic bioavailability of zanamivir following oral inhalation, no dosage adjustments are necessary for patients with renal impairment; however, the potential for drug accumulation should be considered.
Tamiflu (oseltamivir)	Capsules, powder for oral suspension	Oral	Once daily or twice daily, depending on the indication **Patients ≥ 13 years** Treatment: 75 mg twice daily for 5 days Prophylaxis: 75 mg once daily for at least 10 days following close contact with an infected individual and up to 6 weeks during a community outbreak. In immunocompromised	Start treatment within 48 hours of symptom onset or close contact with the infected individual. Taking with food may enhance tolerability. In an emergency, a suspension can be made from capsules. Dosage adjustment is recommended for patients with a CrCl between 10 and 60 mL/minute and for patients with ESRD undergoing routine HD or CAPD. Not recommended for patients with ESRD not undergoing dialysis.

			patients, may be continued for up to 12 weeks. **Patients < 13 years** Treatment: • 2 weeks to < 1 year: 3 mg/kg twice daily for 5 days • 1 to 12 years: 30 to 75 mg twice daily for 5 days; specific weight-based dosing recommendations as follows: ○ ≤ 15 kg: 30 mg twice daily ○ 15.1 kg to 23 kg: 45 mg twice daily ○ 23.1 kg to 40 kg: 60 mg twice daily ○ ≥ 40.1 kg: 75 mg twice daily Prophylaxis: • 1 to 12 years: 30 to 75 mg once daily for 10 days; specific weight-based dosing recommendations as follows: ○ ≤ 15 kg: 30 mg once daily ○ 15.1 kg to 23 kg: 45 mg once daily ○ 23.1 kg to 40 kg: 60 mg once daily ○ ≥ 40.1 kg: 75 mg once daily • During a community outbreak, can continue for up to 6 weeks (or up to 12 weeks in immuno-compromised patients).	No dosage adjustment for mild to moderate hepatic impairment. Safety not evaluated in patients with severe hepatic impairment.
Xofluza (baloxavir marboxil)	Tablets	Oral	Single, weight-based dose Patients 40 kg to < 80 kg: • Single dose of 40 mg Patients ≥ 80 kg: • Single dose of 80 mg Safety and effectiveness in pediatric patients < 12 years of age have not been established.	Initiate treatment within 48 hours of symptom onset. Take orally as a single dose with or without food; however, coadministration with dairy products, calcium-fortified beverages, polyvalent cation-containing laxatives, antacids, or oral supplements should be avoided. No dosage adjustment is recommended for CrCl ≥ 50 mL/min or mild to moderate

				hepatic impairment; safety has not been evaluated in severe renal or hepatic impairment.

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

CONCLUSION

- The first line of protection against influenza is vaccination. All individuals 6 months of age and older without contraindications should receive yearly influenza vaccination *(AAP 2018, Fiore et al 2011, Grohskopf et al 2018)*.
- Antivirals are available for the prevention and treatment of influenza. Overall, the adamantanes, the neuraminidase inhibitors, and baloxavir marboxil (an endonuclease inhibitor) have demonstrated safety and efficacy for their respective indications. However, amantadine and rimantadine are not currently recommended due to high rates of resistance in circulating influenza virus strains *(CDC 2018[b])*.
- Zanamivir and oseltamivir are both effective in preventing influenza and are recommended in certain situations for chemoprophylaxis, but are not substitutes for annual vaccination *(CDC 2018[b], Uyeki et al 2018)*. Peramivir and baloxavir marboxil are not approved or recommended for influenza prophylaxis *(CDC 2018[b])*.
- Peramivir, zanamivir, oseltamivir, and baloxavir marboxil effectively treat influenza by reducing the duration of fever and illness. Initiation of treatment is recommended as soon as possible for patients with suspected influenza who are hospitalized, severely ill, or at high risk for influenza complications (*CDC 2018[b]*).
- Limited within-class comparisons prevent the recommendation of one neuraminidase inhibitor over another. Factors to consider when selecting an antiviral agent include the route of administration, seasonal and geographical susceptibility trends, and patient-specific factors such as age and compliance *(Takemoto et al 2013)*.
- The most common adverse events with amantadine and rimantadine are nausea, insomnia, dizziness, headache, anorexia, dry mouth, and agitation. The adamantanes are associated with an increased risk for seizures.
- The most common adverse events with zanamivir and oseltamivir are headache, nausea, and vomiting. Diarrhea is the most common adverse event with peramivir. The neuraminidase inhibitors have a labeled warning for neuropsychiatric events such as delirium and abnormal behavior leading to injury.
- The most common adverse events with baloxavir marboxil are diarrhea, headache, bronchitis, nausea, and nasopharyngitis.

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INTRODUCTION

- Anaphylaxis, a potentially fatal disorder, is a severe, acute, multisystem syndrome with rapid onset resulting from a sudden release of mast cell- and basophil-derived mediators into circulation. Most commonly, it results from immunologic reactions to foods, medications, and insect stings. In humans, the heart, vasculature system, and lungs are predominantly affected during an anaphylactic reaction, and fatalities can result from circulatory collapse and respiratory arrest. Symptoms consist of progressive swelling, breathing difficulty, and itchy rash, leading to shock and potentially death (*Singletary et al 2015, Sicherer et al 2017*).
- Epinephrine can be life-saving when administered as rapidly as possible once anaphylaxis is recognized, and is the treatment of choice because the benefits associated with epinephrine are greater than any other available pharmacologic intervention (e.g., antihistamines, bronchodilators, glucocorticoids). Epinephrine is the only agent that prevents and reverses airflow obstruction in the upper and lower respiratory tracts, as well as cardiovascular collapse. The therapeutic actions of epinephrine result from alpha-1 (α1), beta-1 (β1), and beta-2 (β2) adrenergic receptor agonist effects and include increased vasoconstriction (α1), increased peripheral vascular resistance (α1), decreased mucosal edema (α1), increased inotropy (β1), increased chronotropy (β1), increased bronchodilation (β2), and decreased release of mediators of inflammation from mast cells and basophils (β2) (*Campbell et al 2014, Sicherer et al 2017*).
- In general, pharmacologic treatment of anaphylaxis is based upon extrapolation from therapies utilized in cardiac arrest and asthma, uncontrolled clinical trials with humans who develop anaphylaxis during insect sting challenges, randomized controlled trials of interventions such as epinephrine in people not experiencing anaphylaxis at the time of administration, and animal anaphylaxis models. Randomized, placebo-controlled trials that meet current standards have not been performed for any pharmacologic intervention in humans experiencing anaphylaxis. Of note, placebo-controlled trials with epinephrine will never be performed, due to ethical considerations in a disorder that can kill within minutes and mandates prompt epinephrine administration.
- The epinephrine products for anaphylaxis include Adrenaclick, Auvi-Q, EpiPen, EpiPen Jr, and Symjepi, with authorized generics available for Adrenaclick, EpiPen, and EpiPen Jr. An AB-rated (therapeutically equivalent) generic for EpiPen and EpiPen Jr was recently approved by the Food and Drug Administration (FDA), but has not yet launched in the marketplace (*Orange Book: Approved drug products with therapeutic equivalence evaluations 2018*). These epinephrine products are all FDA-approved for the emergency treatment of severe allergic reactions. All agents are available to be administered as an intramuscular or subcutaneous injection into the anterolateral aspect of the thigh. Based on clinical trial data, intramuscular administration is preferred as it consistently provides a more rapid increase in the plasma and tissue concentrations of epinephrine (*Sicherer et al 2017, Simons et al 1998, Simons et al 2001*).
- Differences among the various agents include specific packaging and administration requirements. Each agent is available as a 0.15 and/or 0.3 mg injection, except Symjepi, which is only available as a 0.3 mg injection, and Auvi-Q, which is also available as a 0.1 mg injection. Symjepi is only available as a prefilled syringe that requires manual insertion of the needle into the thigh, while all other agents are available as auto-injectors. In addition, Symjepi, Adrenaclick, and Adrenaclick's authorized generics' needles are exposed after the injection. Auvi-Q has the unique characteristic of being the first epinephrine auto-injector with audio instructions that instructs patients and caregivers through the injection process.
- These agents are intended for immediate administration in patients with a history of anaphylactic reaction, and prompt prehospital epinephrine injection is associated with a lower risk of hospitalization and fatality. Furthermore, these agents are designed for emergency supportive therapy and are not intended to substitute immediate medical care. In conjunction with the administration of one of these agents, patients should seek appropriate medical care (*Sicherer et al 2017*).
- Medispan class: Anaphylaxis therapy agents.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Adrenaclick (epinephrine injection)*	-†
Auvi-Q (epinephrine injection)	-
EpiPen (epinephrine injection)	-†‡
EpiPen Jr (epinephrine injection)	
Symjepi (epinephrine injection)	-

*Adrenaclick brand is currently not marketed.
† Authorized generics are available for all strengths. These generics are rated as "BX" and are not considered to be therapeutically equivalent by the FDA due to insufficient data.
‡ An AB-rated generic has been approved by the FDA on 8/16/18, but launch is currently pending. Generics given an "AB" rating by the FDA are considered to be therapeutically equivalent to the reference drug.

(*Drugs@FDA 2018, FDA listing of authorized generics 2018, Orange Book: Approved drug products with therapeutic equivalence evaluations 2018*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Epinephrine
Emergency treatment of severe allergic reactions (Type 1) including anaphylaxis to stinging insects (e.g., order Hymenoptera, which include bees, wasps, hornets, yellow jackets and fire ants), biting insects (e.g., triatoma, mosquitoes), allergen immunotherapy, foods, drugs, diagnostic testing substances (e.g., radiocontrast media) and other allergens, as well as anaphylaxis to unknown substances (idiopathic anaphylaxis) or exercise-induced anaphylaxis.	✔

(*Prescribing information: Adrenaclick 2016, Auvi-Q 2017, EpiPen 2018, EpiPen Jr 2018, Symjepi 2017*)

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

CLINICAL EFFICACY SUMMARY

- A thorough literature search failed to retrieve any clinical trials evaluating the epinephrine products for anaphylaxis in their FDA-approved indications. It has been noted that controlled clinical trials evaluating epinephrine for this indication will never be performed, due to ethical considerations in a disease that can kill within minutes and mandates prompt epinephrine administration.
- Epinephrine is essential for the treatment of anaphylaxis as it is the only pharmacologic intervention that prevents and reverses obstruction to airflow in the upper and lower respiratory tracts. Immediate pre-hospital administration of epinephrine is associated with a lower risk of hospitalization and death in patients with anaphylaxis (*Bock et al 2001, Bock et al 2007, Boyce et al 2010, Campbell et al 2014, Fineman et al 2015, Fleming et al 2015, Golden et al 2017, Kemp et al 2008, Lieberman et al 2015, Sampson et al 1992, Sampson et al 2014, Sicherer et al 2017, Simons et al 1998, Simons et al 2001*).
- A randomized crossover study in healthy adults revealed that Auvi-Q and EpiPen were bioequivalent and had similar peak, total epinephrine exposure, and safety profiles after a single injection of 0.3 mg (*Edwards et al 2013*).

CLINICAL GUIDELINES

- Current clinical guidelines including those from the American Academy of Pediatrics, the World Allergy Organization, and the Joint Task Force on Practice Parameters representing the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology consistently recommend epinephrine as the first-line medication of choice for the treatment of anaphylaxis due to its life-saving effects. It is suggested that patients who have a history of anaphylaxis or systemic reaction to allergens, including insect stings or foods, be prescribed an injectable epinephrine agent and be advised to carry it with them at all times. Consideration may also be given to patients who do not have a history of anaphylaxis but are at high risk of an anaphylactic reaction (*Boyce et al 2010, Campbell et al 2014, Golden et al 2017, Kemp et al 2008, Lieberman et al 2015, Sampson et al 2014, Sicherer et al 2017, Simons et al 2015*).
- The guidelines state that auto-injectors are preferred over prefilled syringes in the community setting due to ease of use and accuracy of dosing, but do not differentiate between the individual auto-injector products. Choice of an epinephrine agent should be evaluated on an individual patient basis; some factors to consider are size, ease of use, ease of carrying, needle protection, and cost.
- Antihistamines, glucocorticoids, and bronchodilators may be used as adjunct therapy to epinephrine, but should not be used as initial or sole therapy as these agents do not have any life-saving properties (*Lieberman et al 2015, Sicherer et al 2017, Simons et al 2015*).

SAFETY SUMMARY

- There are no absolute contraindications to the use of the epinephrine products for anaphylaxis in a life-threatening allergic reaction.
- Epinephrine is essential for the treatment of anaphylaxis. Patients with a history of severe allergic reactions should be instructed about the circumstances under which epinephrine should be administered.
- Epinephrine should be administered with caution to patients with cardiac arrhythmias, coronary artery or organic heart disease or hypertension, or in patients who are on medications that may sensitize the heart to arrhythmias. In patients with coronary insufficiency or ischemic heart disease, epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias. The presence of these conditions is not a contraindication to epinephrine administration in an acute, life-threatening situation.
- Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by *Clostridia* (gas gangrene) have been reported at the injection site following epinephrine injection for anaphylaxis. To decrease the risk of *Clostridium* infection, do not inject the drug into the buttock. Should signs and symptoms of infection occur, patients should seek medical care.
- Epinephrine is not intended as a substitute for immediate medical care; in conjunction with its administration, patients should seek appropriate medical care. More than 2 sequential doses of epinephrine should only be administered under direct medical supervision.
- Epinephrine should only be injected into the anterolateral aspect of the thigh. In children, the leg should be held firmly in place prior to and during injection to reduce injury, as lacerations, bent needles, embedded needles, and other injuries have been observed after epinephrine auto-injector administration on children. Avoid accidental injection into the hands or feet as this may result in loss of blood flow to the area. If an accidental injection occurs, patients should inform a health care provider when he/she goes to the nearest emergency room for further treatment of anaphylaxis.
  - An analysis evaluated 22 cases of epinephrine auto-injector-related injuries including lacerations and embedded needles in children. In response, product warnings were updated to require immobilization of a child's leg prior to and during injection, and injection time for the EpiPen and EpiPen Jr was reduced from 10 to 3 seconds (*Brown et al 2016*).
- Possible inadvertent intravascular administration should also be avoided.
- Epinephrine is the preferred treatment for serious allergic reactions or other emergency situations. Epinephrine auto-injectors, Adrenaclick, and Auvi-Q contain sodium bisulfite; whereas, EpiPen, EpiPen Jr, and Symjepi contain sodium metabisulfite. Thus, all forms of epinephrine used for anaphylaxis contain sulfites that may cause allergic-type reactions

including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons. Because the alternatives to epinephrine in a life-threatening situation may not be satisfactory, the presence of a sulfite should not deter administration of the agent for the treatment of serious allergic or other emergency situations, even in a sulfite-sensitive patient.

- Adverse reactions to epinephrine include transient, moderate anxiety; apprehensiveness; restlessness; tremor; weakness; dizziness; sweating; palpitations; pallor; nausea and vomiting; headache, and/or respiratory difficulties. These symptoms occur in some persons receiving therapeutic doses of epinephrine, but are more likely to occur in patients with hypertension or hyperthyroidism. Large doses of epinephrine can cause acute hypertension. Arrhythmias, including fatal ventricular fibrillation, have been reported, particularly in patients with underlying cardiac disease or those receiving certain drugs. Rapid rises in blood pressure have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease. Angina may occur in patients with coronary artery disease. The potential for epinephrine to produce these types of adverse reactions does not contraindicate its use in an acute, life-threatening allergic reaction.
- Several drug-drug interactions exist with epinephrine. Patients who receive epinephrine while concomitantly taking cardiac glycosides or diuretics should be observed carefully for the development of cardiac arrhythmias. The effects of epinephrine may be potentiated by tricyclic antidepressants, monoamine oxidase inhibitors, levothyroxine sodium, and certain antihistamines. The cardiostimulating and bronchodilating effects of epinephrine are antagonized by beta-adrenergic blocking drugs. The vasoconstricting and hypertensive effects of epinephrine are antagonized by alpha-adrenergic blocking drugs. Ergot alkaloids may also reverse the pressor effects of epinephrine.
- There are no adequate or well-controlled studies of the acute effect of epinephrine in pregnant women. Although animal reproductive studies have shown an adverse effect on the fetus, epinephrine is still considered the first-line medication of choice for anaphylaxis during pregnancy due to its life-saving effects.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Epinephrine	Auto-injectors (Adrenaclick, Auvi-Q, EpiPen, EpiPen Jr) Prefilled syringe (Symjepi)	Intramuscular or subcutaneous injection	Inject 1 dose; an additional dose may be needed with severe persistent anaphylaxis. More than 2 sequential doses of epinephrine should only be administered under direct medical supervision.	Dosing is based on weight: • Patients 7.5 to 15 kg: 0.1 mg • Patients 15 to 30 kg: 0.15 mg • Patients ≥ 30 kg: 0.3 mg Since the doses of epinephrine delivered from the various agents within this class are fixed, physicians should consider other forms of injectable epinephrine if doses lower than those available from these agents are felt to be necessary. Injection should be administered into the anterolateral aspect of the thigh, through clothing if necessary; do not administer repeated injections at the same site. As a prefilled syringe, Symjepi requires the patient or caregiver to

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				manually inject the needle into the skin.

See the current prescribing information for full details

CONCLUSION

- Anaphylaxis, a potentially fatal disorder, is an acute, multisystem syndrome resulting from a sudden release of mast cell- and basophil-derived mediators into the circulation.
- Foods, medications, and insect stings that cause a subsequent immunologic reaction are the most common reason for an anaphylactic reaction to occur. In humans, the heart, vasculature system, and lungs are predominantly affected during anaphylaxis, and fatalities can result from circulatory collapse and respiratory arrest. Current clinical guidelines recommend prompt epinephrine injection for sudden onset of any anaphylaxis symptoms after exposure to an allergen that previously caused anaphylaxis in a patient.
- Epinephrine can be life-saving when administered as rapidly as possible once anaphylaxis is recognized, and is the only pharmacologic intervention that prevents and reverses obstruction to airflow in the upper and lower respiratory tracts (*Boyce et al 2010, Campbell et al 2014, Fineman et al 2015, Golden et al 2017, Kemp et al 2008, Lieberman et al 2015, Sampson et al 2014, Sicherer et al 2017, Simons et al 1998, Simons et al 2001, Simons et al 2015*).
- Acting as an agonist at α1, β1 and β2 adrenergic receptors, epinephrine works in the emergency treatment of anaphylaxis by causing increased vasoconstriction (α1), increased peripheral vascular resistance (α1), decreased mucosal edema (α1), increased inotropy (β1), increased chronotropy (β1), increased bronchodilation (β2) and decreased release of mediators of inflammation from mast cells and basophils (β2). Of note, clinical trials evaluating epinephrine for emergency anaphylaxis treatment will never be performed, due to ethical considerations in a disorder that can kill within minutes and mandates prompt epinephrine administration (*Song et al 2014*).
- Adrenaclick, Auvi-Q, EpiPen, EpiPen Jr, and Symjepi are all FDA-approved for the emergency treatment of severe allergic reactions. As noted in their FDA-approved package labeling, epinephrine is essential for the treatment of anaphylaxis, and these agents are designed for emergency supportive therapy. They are not intended to substitute immediate medical care; in conjunction with the administration of one of these agents, patients should seek appropriate medical care.
- All of these epinephrine products for anaphylaxis are available as single use injections to be administered, by the patient or caregiver, as an intramuscular or subcutaneous injection into the anterolateral aspect of the thigh. Intramuscular administration is preferred as it consistently provides a more rapid increase in the plasma and tissue concentrations of epinephrine.
- Differences among the various epinephrine agents include specific packaging and administration requirements. Adrenaclick, Auvi-Q, EpiPen, and EpiPen Jr are available as auto-injectors, while Symjepi is only available as a prefilled syringe that requires manual insertion of the needle into the thigh. Each agent is available as a 0.15 and 0.3 mg injection, except Symjepi, which is only available as a 0.3 mg injection, and Auvi-Q, which is also available as a 0.1 mg injection. Auvi-Q is the only epinephrine agent that contains audio instructions to guide patients and caregivers through the injection process.

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INTRODUCTION

- Male hypogonadism is characterized by a lack of function of the gonads (testes). It can be categorized by the level of the reproductive system in which the defect occurs (*Dandona and Rosenberg, 2010*).
  - Primary hypogonadism is hypogonadism resulting from a defect of the gonads.
  - Secondary hypogonadism, also known as hypogonadotropic hypogonadism, results from defects in the hypothalamus or pituitary.
- Male hypogonadism may manifest with testosterone deficiency and/or infertility. Clinical signs and symptoms depend primarily on the age at the onset of the condition (*Petak et al, 2002*).
- 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 ability to concentrate, and an increased risk of osteoporosis and fractures (*Petak et al, 2002*).
- Intramuscular (IM) and topical testosterone preparations are generally recommended for the management of hypogonadism in adult male patients. The oral alkylated androgens are generally not recommended because of poor androgen effects, adverse lipid changes, and hepatic side effects (*Bhasin et al, 2018; Mulhall et al, 2018; Petak et al, 2002; Wang et al, 2008*).
- Androgens included in this review are Androderm (testosterone) transdermal system; Androgel, Fortesta, Testim, and Vogelxo (testosterone) topical gels; Methitest (methyltestosterone) oral tablets, methyltestosterone oral capsules; Aveed (testosterone undecanoate) injection; testosterone topical solution; danazol oral capsules; Depo-Testosterone (testosterone cypionate) injection; Natesto (testosterone) nasal gel; Striant (testosterone) buccal system; Testopel (testosterone) pellets for subcutaneous implantation; and testosterone enanthate injection.
- With the exception of danazol, all agents in this review are Food and Drug Administration (FDA)-approved for the management of male hypogonadism. Danazol is FDA-approved for the treatment of endometriosis and hereditary angioedema.
- Methyltestosterone capsules and tablets; Testopel (testosterone) pellets for subcutaneous implantation; and testosterone enanthate are also FDA-approved for the treatment of delayed puberty in males.
- Methyltestosterone capsules and tablets and testosterone enanthate are also FDA-approved for metastatic mammary cancer in females.
- All testosterone products are controlled substances (C-III). Danazol, an androgen, is not a controlled substance.
- Testosterone gels and solutions have risk evaluation and mitigation strategy (REMS) programs consisting of a medication guide with information on proper application, potential adverse effects, and preventing inadvertent exposure to others, specifically women and children. Aveed has a REMS program related to post-injection reactions (*Drugs@FDA, 2018*).
- This review primarily focuses on the use of androgens for the management of male hypogonadism.
- Non-labeled indications, such as anemia, hormone therapy for transgender patients, and acquired immunodeficiency syndrome (AIDS)-associated wasting syndrome are not addressed in this review.
  - Due to the number of branded products in different formulations, generic names and formulations will be used throughout the review.
  - The agents included in this review are listed in Table 1.
  - Other androgen products are not included in this review.
    - Oxandrolone is a synthetic testosterone derivative FDA-indicated for cachexia.
    - Oxymetholone is an anabolic steroid with androgenic properties FDA-indicated for anemias and myelofibrosis (*Micromedex, 2018*).
- Compounded products and combination products containing testosterone are not included in this review.
- Medispan therapeutic class: Androgens

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Androderm (testosterone transdermal system) patch	-
Androgel, Fortesta, Testim, Vogelxo (testosterone) topical gel	✔ *
Methitest (methyltestosterone) tablets, methyltestosterone capsules	-/ ✔ §
Aveed (testosterone undecanoate)	-
testosterone topical solution	✔ ¥
danazol	✔ †
Depo-Testosterone (testosterone cypionate)	✔
Natesto (testosterone) nasal gel	-
Striant (testosterone) buccal system	-
Testopel (testosterone) pellets for subcutaneous implantation	-
testosterone enanthate	✔ ‡

* A-rated generics are available for Androgel 1% gel. Although an A-rated generic has been FDA-approved for the 1.62% gel, generic availability of this strength has been delayed based on settlement agreements. Authorized generics are available for Testim, Vogelxo, and Fortesta. In addition, the FDA has determined that Testim and Vogelxo are therapeutically equivalent.
¥ Branded product, Axiron, is no longer manufactured, but it is still available as a generic.
† Branded product, Danocrine, is no longer manufactured, but it is still available as a generic.
‡ Branded product, Delatestryl, is no longer manufactured, but it is still available as a generic.
§ Branded products, Android and Testred (methyltestosterone capsules), are no longer manufactured, but are still available as generics. Methitest is only available as a branded product.

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	danazol	methyltestosterone	testosterone buccal	testosterone gel	testosterone nasal gel	testosterone implant	testosterone patch	testosterone topical solution	testosterone cypionate	testosterone enanthate	testosterone undecanoate*
Replacement therapy in males for deficiency or absence of endogenous testosterone due to primary hypogonadism (congenital or acquired)		✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Replacement therapy in males for deficiency or absence of endogenous testosterone due to hypogonadotropic hypogonadism (congenital or acquired)		✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Stimulation of puberty in carefully selected males with clearly delayed puberty that is not secondary to a pathological disorder		✔				✔				✔	
Treatment of metastatic mammary cancer in women with inoperable metastatic (skeletal) mammary cancer who are 1 to 5 years menopausal		✔								✔	
Treatment of endometriosis amenable to hormonal management	✔										
Prevention of attacks of angioedema of all types	✔										
Limitations of Use:											
Safety and efficacy in men with “age-related hypogonadism” have not been established		✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Safety in males under the age of 18 years has not been established			✔	✔	✔		✔	✔			✔
Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure				✔ †							

*Aveed should only be used in patients who require testosterone replacement therapy and in whom the benefits of the product outweigh the serious risks of pulmonary oil microembolism (POME) and anaphylaxis.
† Androgel, Testim, and Vogelxo only

(*Prescribing information: Androderm, 2018; Androgel 1%, 2016; Androgel 1.62%, 2016; Android, 2015; Aveed, 2018; danazol, 2018; Depo-Testosterone, 2017; Fortesta, 2017; Methitest, 2016; Natesto, 2016; Striant, 2016; Testim, 2018; Testopel, 2016; testosterone enanthate, 2017; testosterone topical solution, 2018; Testred, 2015; Vogelxo, 2017*)

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

CLINICAL EFFICACY SUMMARY

- Male Hypogonadism
  - In clinical studies, testosterone transdermal system (Androderm), topical gel (Androgel, Fortesta, Testim) and topical solution have been shown to increase serum testosterone and lean body mass, decrease body fat, and improve sexual function in men with hypogonadism. Increases in hemoglobin, hematocrit and prostate specific antigen (PSA) were observed (*Brock et al, 2016, Dobs et al, 2012; Grober et al, 2008; McNicholas et al, 2003; Roy et al, 2017; Steidle et al, 2003; Swerdloff et al, 2000; Wang et al, 2000; Wang et al, 2004; Wang et al, 2011*).
  - A network meta-analysis of 87 randomized and 51 non-randomized studies concluded that testosterone replacement therapies, as a class, improved quality of life, libido, depression, and sexual function as compared to placebo (*Elliott et al, 2017*). Additionally, individual product comparisons were also made. Most endpoints did not reveal significant differences between products, but the 1% testosterone gel was significantly better than the patch for improvement in libido.
  - A 36-month extension study demonstrated that long-term treatment with testosterone topical gel (Androgel) maintained increased levels of serum testosterone as well as improvements in sexual function, positive mood, and body composition. A gradual but significant improvement in hip and spine bone mineral density was also observed. Increases in hemoglobin and hematocrit plateaued at 12 months, and clinically insignificant increases in high-density lipoprotein cholesterol, serum creatinine, and total bilirubin were seen. Serum levels of PSA showed no further significant increases past 6 months of treatment. Treatment-emergent adverse events included application site reactions, acne, and gynecomastia (*Wang et al, 2004*).
  - Head-to-head studies comparing testosterone topical gel (Androgel, Testim) to testosterone patch (Androderm) have shown greater improvement in serum testosterone levels, lean body mass, and sexual function as well as fewer adverse events with testosterone gel compared to testosterone patches in men with hypogonadism (*McNicholas et al, 2003; Steidle et al, 2003; Swerdloff et al, 2000; Wang et al, 2000*).
  - In an open-label study, hypogonadal men on testosterone replacement therapy with suboptimal response underwent brand substitution and switched between Androgel and Testim. More patients who switched from Androgel to Testim experienced improvements in libido, erectile function, and energy levels compared to those who switched from Testim to Androgel. Changing from Testim to Androgel eliminated or minimized unwanted adverse effects (*Grober et al, 2008).*
  - Testosterone buccal system (Striant) was compared to testosterone transdermal system or testosterone topical gel in 2 randomized controlled studies with hypogonadal men. Testosterone buccal system was shown to lead to serum testosterone levels within normal ranges that were similar to testosterone topical gel and transdermal system (*Dobs et al, 2004; Korbonits et al, 2004*).
  - A double-blind, randomized controlled trial showed that testosterone cypionate improved grip strength and increased hemoglobin compared to placebo in hypogonadal men (*Sih et al, 1997*).
  - An open-label trial comparing 4 different dosing regimens of testosterone enanthate in men with primary hypogonadism showed that testosterone enanthate 200 mg every 2 weeks and 300 mg every 3 weeks were most effective in suppressing serum luteinizing hormone to normal, while 100 mg every week and 200 mg every 2 weeks were effective in suppressing follicle-stimulating hormone to normal (*Snyder et al, 1980*).
  - In a small, open-label study, methyltestosterone was associated with improvement in sexual function in men with profound testosterone deficiency but no noticeable changes in levels of energy, mood, or feeling of well-being (*Morales et al, 1994*).
  - Aveed was approved via the 505(b)(2) pathway. The primary clinical trial submitted for its approval was a Phase 3, multi-center, open-label, 84-week, pharmacokinetic and safety study of testosterone undecanoate in hypogonadal men. Adult males with primary or secondary hypogonadism and testosterone levels < 300 ng/dL were given 750 mg of testosterone undecanoate IM at baseline, 4 weeks, and every 10 weeks thereafter for a total of 9 injections (N = 130). At week 14 (after the third dose), the percentage of the 117 patients still enrolled with an average serum total testosterone concentration within the normal range (300 to 1000 ng/dL) was 94% (95% confidence interval [CI], 89.7 to 98.3%). The percentage of patients with a maximum total testosterone concentration < 1500 ng/dL was 92%. The authors concluded that testosterone undecanoate 750 mg achieved sustained, consistent serum testosterone in the normal range during a 10-week dosing interval (*Morgentaler et*

al, 2008). Additional trials of testosterone undecanoate have been completed, but published results are limited. In 1 trial, the dose was not specified, but testosterone undecanoate was demonstrated to be effective in a large number of patients (*Zitzmann et al, 2013*). One study demonstrated improvement in scores on the Aging Male Symptoms (AMS) scale, which is 1 measurement of health-related quality of life, when testosterone undecanoate 1000 mg was used (*Ho et al, 2012*).

- One study with a 6-year follow up measured mortality in patients with type 2 diabetes (N = 581) with low vs. normal testosterone levels (some of whom were treated with testosterone gel or testosterone undecanoate to maintain normal levels). The authors found that patients with low testosterone had higher mortality rates than those with normal levels (17.2 vs. 9%; p = 0.003) (*Muraleedharan et al, 2013*).
- The Testosterone Trials were a coordinated set of clinical trials designed to determine whether testosterone would benefit men with age-related low testosterone levels. Initial results from 3 of the 7 trials have been published (*Snyder et al, 2016*). Each participant was enrolled in 1 or more of the 3 trials (the Sexual Function Trial, the Physical Function Trial, and the Vitality Trial). In addition to the results for the individual trials, the primary efficacy outcome of each trial was assessed among participants across all 3 trials. Patients (N = 790) aged ≥ 65 years with serum testosterone levels < 275 ng/dL were assigned to receive either testosterone gel (Androgel 1%) or placebo for 1 year.
  - Sexual function: Participants taking testosterone experienced an increase in sexual activity as assessed by question 4 on the Psychosexual Daily Questionnaire (PDQ-Q4) in both the Sexual Function Trial (mean difference, 0.58; p < 0.001) and among all trial participants (mean difference, 0.62; p < 0.001). Testosterone treatment was also associated with increased sexual desire and improved erectile function.
  - Physical function: Among patients enrolled in the Physical Function Trial, testosterone was not associated with a significant difference vs. placebo in the percentage of patients achieving a ≥ 50 meter increase in the 6-minute walking distance (6MWD) (odds ratio [OR], 1.42; p = 0.2); there was also no difference in the mean change from baseline in 6MWD. There was no significant difference in the percentage of patients with an increase of ≥ 8 points in the physical function domain (PF-10) of the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36); however, there was a significant difference in the mean change from baseline in PF-10 score (mean difference, 2.75 points; p = 0.03). When results from the 3 trials combined were considered, there was a significant difference in the percentage of patients with a ≥ 50 meter increase in 6MWD (OR, 1.76; p = 0.003) as well as each of the secondary physical function endpoints.
  - Vitality: Among patients in the Vitality Trial, testosterone was not associated with a significant difference vs. placebo in vitality as determined by an increase of ≥ 4 points on the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale (OR, 1.23; p = 0.3). However, improvements were observed on several secondary endpoints, including the SF-36 vitality score (mean difference, 2.41 points; p = 0.03), the positive and negative affect schedule (PANAS) positive affect score (mean difference, 0.47 points; p = 0.04), the PANAS negative affect score (mean difference, -0.49 points; p < 0.001), and the patient health questionnaire (PHQ-9) depression score (mean difference, -0.72 points; p = 0.004). There was no significant difference in the percentage of patients with an increase of ≥ 4 points on the FACIT-Fatigue score when results of the 3 trials combined were considered (OR, 1.23; p = 0.22); however, the effect of testosterone on the mean change from baseline in the FACIT-Fatigue score was significant (mean difference, 1.27; p = 0.006).
  - Safety: No significant differences between groups were demonstrated in cardiac adverse events. Seven men in each group had major adverse cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes) during the treatment period, and 2 patients in the testosterone group and 9 in the placebo group had major adverse cardiovascular events in the subsequent year. More patients assigned to testosterone had an increase in PSA of ≥ 1 ng/dL (23 vs 8); 1 man (in the testosterone group) was diagnosed with prostate cancer during the treatment period, and 2 patients in the testosterone group and 1 in the placebo group were diagnosed in the subsequent year. A hemoglobin level ≥ 17.5 g/dL was observed in 7 men in the testosterone group and none in the placebo group. No difference was seen in the international prostate symptom score (IPSS).

- Conclusions: Testosterone supplementation had small-to-moderate effects on all measures of sexual function and some measures of physical function, mood, and depressive symptoms. Although cardiovascular events were not increased with testosterone supplementation, the trial was not large enough to exclude smaller increases in risk. In addition, safety with respect to prostate cancer and urinary symptoms cannot be generalized because men with a high risk of prostate cancer and men with moderately severe urinary symptoms were excluded from the trial.

- Separate publications reported additional results from the Testosterone Trials. The Cognitive Function Trial included a subgroup of men (n = 493) with age-associated memory impairment (*Resnick et al, 2017*). Testosterone replacement did not improve delayed paragraph recall in these patients at 6 and 12 months (adjusted estimated difference, -0.07; p = 0.88). In the Cardiovascular Trial (n = 170) coronary computed tomographic angiography (CCTA) was used to determine whether testosterone slowed the progression of noncalcified coronary artery plaque. It was found that testosterone treatment was associated with a significantly greater increase in noncalcified plaque volume after 12 months of treatment compared with placebo: estimated difference, 41 mm^3; p = 0.003 (*Budoff et al, 2017*). The Bone Trial (n = 211) found testosterone treatment to significantly improve mean spine and hip volumetric bone mass density compared with placebo (*Snyder et al, 2017*).
- A randomized, double-blind, placebo-controlled trial found that once daily application of testosterone 2% solution for 12 weeks restored normal testosterone levels, and led to significant improvements in sex drive in men with hypogonadism; improvements in energy levels were variable (*Brock et al, 2016*).
- Meta-analyses have evaluated the potential adverse effects associated with testosterone use. One found that patients treated with testosterone had higher rates of cardiovascular-related events than patients treated with placebo (*Xu et al, 2013*). However, another meta-analysis that included both randomized controlled and epidemiological studies found no difference in the risk of major cardiovascular events between testosterone and placebo (*Corona et al, 2018*). Calof and colleagues found that patients treated with testosterone had a greater rate of prostate events and elevated hematocrit compared to patients treated with placebo (*Calof et al, 2005*).

- Delayed puberty and delayed growth
  - Testosterone products, including testosterone enanthate and methyltestosterone have been studied in the treatment of delayed growth and puberty in adolescent males. These products have demonstrated increased growth (weight and height) in the time periods studied, but it is difficult to determine the long-term effects on bone health as the trials had relatively limited durations and study populations (*Kaplan et al, 1973; Rosenfeld et al, 1982; Soliman et al, 1995*).
- Endometriosis
  - Danazol is used for the palliative treatment of endometriosis in patients in whom alternative hormonal therapy (eg, estrogen and progestin or testosterone) is ineffective, intolerable or contraindicated (*Micromedex, 2018*). A meta-analysis of 5 placebo-controlled trials concluded that danazol was effective in relieving pain and improving laparoscopic scores in women with endometriosis; however, its use was limited by the occurrence of androgenic adverse effects (*Selak et al, 2007*).
- Hereditary angioedema
  - Studies have reported that danazol was beneficial in reducing the frequency and severity of acute attacks and increasing the serum levels of C1 esterase inhibitor and the fourth component of complement (*Bork et al, 2008; Gelfand et al, 1976*).
- Treatment of metastatic mammary cancer
  - Studies on the use of methyltestosterone have not been included in the detailed review. Endocrine therapy (including androgens) may be used for metastatic breast cancer in post-menopausal women. Androgens are rarely used (often considered last-line therapy) in the treatment of metastatic breast cancer. While response rates may be reasonable, adverse effects, including virilization, edema, and jaundice, limit their clinical applicability compared to other treatment options (*Ma, 2018*).

CLINICAL GUIDELINES

- Male hypogonadism
  - The American Urological Association recommends the use of testosterone replacement therapy in men with testosterone deficiency but provides no specific guidance other than to avoid methyltestosterone (*Mulhall et al, 2018*). The European Association of Urology (EAU) recommends

that choice of therapy should be based on risk vs benefit decisions between the provider and patient and states that short-acting therapies may be preferred when initiating therapy (*Dohle et al, 2018*). The Endocrine Society recommends all testosterone products in appropriate doses, with the exceptions of danazol and methyltestosterone (*Bhasin et al, 2018*). A joint statement by the International Society of Andrology (ISA), International Society for the Study of the Aging Male (ISSAM), EAU, European Academy of Andrology (EAA), and American Society of Andrology (ASA) agrees that decisions should be made based on patient and prescriber preference and tolerability, but states that methyltestosterone should be avoided due to potential liver toxicity (*Wang et al, 2008*). The American Association of Clinical Endocrinologists (AACE) also agrees with the recommendation to avoid methyltestosterone (*Petak et al, 2002*).

- Endometriosis
  - Both the American Society for Reproductive Medicine (ASRM) and American Congress of Obstetricians and Gynecologists (ACOG) have guidelines for the treatment of endometriosis, but only the ASRM specifically addresses danazol (*ACOG, 2010; ASRM, 2014*). This guideline states that danazol has been used for the treatment of endometriosis, but hyperandrogenic side effects (hirsutism, acne, weight gain, and deepening of the voice) are common (*ASRM, 2014*).
- Hereditary angioedema
  - Guidelines for hereditary angioedema include the use of danazol for prevention of attacks, but state that it should be used cautiously and in the lowest dose possible, and should be avoided in certain populations (patients < 16 years of age, and pregnant or breastfeeding women) (*Cicardi et al, 2012; Cicardi et al, 2014; Craig et al, 2012; Zuraw et al, 2013*).

SAFETY SUMMARY

- Boxed Warnings:
  - Danazol: use in pregnancy is contraindicated; thromboembolism, thrombotic and thrombophlebitic events, and life-threatening or fatal strokes have been reported; experience with long-term therapy is limited; and therapy has been associated with several cases of benign intracranial hypertension.
  - Testosterone, topical gel and solution: virilization has been reported in children who were secondarily exposed to testosterone gel.
  - Testosterone undecanoate has a boxed warning for post-injection pulmonary oil microembolism (POME) and anaphylactic reactions.
- REMS programs
  - Testosterone topical gel and solution have REMS programs consisting of a medication guide to promote proper use, limit unwanted exposure, and provide safety information.
  - Testosterone undecanoate products have a single shared REMS program that restricts its use to specific healthcare facilities and providers who have been adequately trained to assess and treat post-injection reactions, including POME and anaphylaxis.
- Major contraindications include active thrombosis or thromboembolic disease (danazol only); androgen-dependent tumors or breast or prostate cancer; known hypersensitivity; serious cardiac, hepatic, or renal disease; use in pregnant or breastfeeding women or women who may become pregnant; porphyria (danazol only); and undiagnosed abnormal genital bleeding (danazol only).
- Although Depo-Testosterone, methyltestosterone, Testopel, and testosterone enanthate do not specifically list breastfeeding as a contraindication within their prescribing information, breastfeeding should be halted if these agents are required (*Briggs et al, 2017*).
- Key warnings include bone growth changes, adverse effects on spermatogenesis, cardiovascular risk (eg, myocardial infarction, stroke, etc.), serum lipid changes, blood glucose changes, edema with or without heart failure, gynecomastia, hepatic adverse effects, polycythemia, prostate cancer, priapism, virilizing effects in women and/or children, worsening of benign prostatic hyperplasia (BPH), and the potential for abuse of testosterone products. Additionally, use of testosterone has been subject to abuse leading to serious cardiovascular and psychiatric adverse reactions. If suspected, serum testosterone concentrations should be monitored.
- Transdermal testosterone patches contain aluminum that may burn the skin if worn during a magnetic resonance imaging scan. Testosterone gel and topical solution formulations are flammable until dry.

- Common side effects include application-related reactions for topical and buccal products, injection site reactions for injected products, edema, hepatic adverse effects, prostate effects, increased hematocrit, weight gain, and virilizing effects.
- In January 2014, the FDA announced that it was investigating the risk of cardiovascular events (ie, stroke, heart attack, and death) in men taking FDA-approved testosterone products, based on the results of 2 trials that suggested an increased cardiovascular risk. At that time, the FDA had not made any conclusions and recommended that patients not discontinue prescribed testosterone products without first discussing any questions or concerns with their health care provider (*FDA drug safety communication, 2014*). On March 3, 2015, the FDA issued an updated safety announcement clarifying the approved uses of prescription testosterone products for men who have low testosterone caused by certain medical conditions and not for treating low testosterone due to aging. Additionally, the manufacturers of all approved testosterone products were required to add information to the labeling about a possible increased risk of heart attacks and strokes in patients taking testosterone. Manufacturers are also required to conduct a well-designed clinical trial to more clearly address the question of whether an increased risk of heart attack or stroke exists among users of these products. In April 2015, the FDA approved labeling revisions to several sections of the prescribing information for all of the testosterone products to clarify the approved uses, confirm the medical condition causing low testosterone using lab testing, and add a new warning related to potential increased cardiovascular risk (*FDA drug safety communication, 2015*). In October 2016, the FDA finalized labelling regarding abuse and dependence of testosterone along with the adverse health outcomes associated with abuse (*FDA drug safety communication, 2016*). The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) issued a joint position statement in September 2015 on the association of testosterone and cardiovascular risk. Although they agreed with the FDA that the risk/benefit of testosterone replacement therapy is not well established in aging-associated hypogonadism and large-scale, prospective, randomized controlled trials are needed, the joint committee determined that the FDA directive lacked clarity. They recommended that decisions on testosterone replacement should be guided by the signs, symptoms, and testosterone concentrations rather than the underlying cause (*Goodman et al, 2015*). Newer data suggest that increases in cardiovascular events may be due to widespread use of testosterone therapies without appropriate monitoring, and patients with cardiovascular disease may safely receive androgen therapy for the treatment of hypogonadism (*Tanna et al, 2016*).
- A trial (N = 308) was designed to determine the effect of testosterone administration on subclinical atherosclerosis progression in men ≥ 60 years of age with low or low-normal baseline testosterone levels. Treatment continued for a 3-year period. In this study, testosterone replacement did not result in a significant difference in the rate of change in common carotid artery intima-media thickness or coronary artery calcium. However, the trial was not designed to determine the effects of testosterone replacement on cardiovascular events (*Basaria et al, 2015*).
- A European observational study of hypogonadal, elderly men (mean age 59 years) (N = 115) evaluated the effects of testosterone undecanoate on various parameters for up to 10 years of use. Injections of testosterone were given every 12 weeks. Body weight and body mass index were significantly reduced from the previous year for 8 years and waist circumference was significantly lower from the previous year for 7 years. The hemoglobin A1C and ratio of triglycerides to high-density lipoprotein were significantly reduced from the second year onward. Fasting blood glucose showed improvement after the first year of testosterone replacement. No major cardiovascular events were observed (*Yassin et al, 2016*).
- A European observational study of hypogonadal men with a history of cardiovascular disease (N = 77, mean age 61 years) evaluated the effects of testosterone therapy for up to 8 years. A marked and significant weight loss was observed after 8 years of continuous use. Beneficial effects were also observed on body mass index, lipid parameters, blood pressure, and glycemic control. No patient suffered a major adverse cardiovascular event during the full observation time (*Haider et al 2016*).
- In a European multinational longitudinal disease registry of 99 men with hypogonadism, 750 (75%) initiated testosterone replacement therapy. CV event rates for men receiving testosterone were not statistically different from untreated men (p = 0.70). Regardless of treatment assignment, CV event rates were higher in older men and in those with increased CV risk factors or a prior history of CV events (*Maggi et al, 2016*).

- In a European prospective registry of men with hypogonadism, 360 men who received testosterone undecanoate were compared to 296 men who did not receive testosterone treatment (*Traish et al, 2017*). Deaths and CV parameters were tracked for 8 years. In contrast to previous studies, patients receiving testosterone had a lower mortality rate than the control group (estimated incidence difference, 0.0804; 95% CI, 0.0189 to 0.3431). In this cohort, there were no CV-related deaths in the testosterone group and 19 CV-related deaths in the control group.
- Although testosterone therapy was previously thought to be contraindicated in men with a history of prostate cancer, recent data suggest that use does not increase risk of de novo prostate cancer, progression of the disease, or biochemical recurrence in men with hypogonadism and a history of non-high-risk prostate cancer; safety data for testosterone use in high-risk cancer patients are limited and use in this patient population remains controversial (*Davidson et al, 2016; Nguyen et al, 2016*).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Androderm (testosterone transdermal system) (C-III)	Transdermal system	top	Hypogonadotropic hypogonadism (congenital or acquired in males) and primary hypogonadism (congenital or acquired in males): Apply once nightly	Apply patches to back, abdomen, upper arms or thighs. Rotate the site of application with an interval of 7 days between applications to the same site. Avoid swimming, showering or washing the application site for a minimum of 3 hours after application. When discarding a used patch, it should be folded in half so the sticky sides stick together and thrown away in household trash.
Androgel, Fortesta, Testim, Vogelxo (testosterone) (C-III)	Topical gel	top	Hypogonadotropic hypogonadism (congenital or acquired in males) and primary hypogonadism (congenital or acquired in males): Apply once daily (preferably in the morning)	Apply the topical gel in the following area: Androgel 1%: shoulders, upper arms and/or abdomen Androgel 1.62%: upper arms and shoulders Fortesta: front and inner thighs Testim, Vogelxo: shoulders and/or upper arms Allow application sites to dry before dressing. Cover the application sites with clothing to prevent transfer to another person.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Wash hands with soap and water after application. Avoid swimming, showering or washing the application site for a minimum of: ○ 2 hrs after Androgel 1.62%, Fortesta, Vogelxo, and Testim ○ 5 hrs after Androgel 1%
Methitest, (methyltestosterone) tablets, methyltestosterone capsules (CIII)	Capsules Tablets	oral	Delayed puberty (males): 10-50 mg/d for a limited duration (eg, 4-6 mos) Hypogonadotropic hypogonadism (congenital or acquired in males) and primary hypogonadism (congenital or acquired in males): 10-50 mg/d Metastatic mammary cancer (females): 50-200 mg/d	Dosage will depend on age, sex, diagnosis, patient's response to treatment, and appearance of adverse effects.
Aveed (testosterone undecanoate) (C-III)	Injectable solution	IM	Hypogonadotropic hypogonadism (congenital or acquired in males) and primary hypogonadism (congenital or acquired in males): Inject at initiation, 4 wks, and every 10 wks thereafter	Observe patients in the healthcare setting for 30 minutes following injection for symptoms of serious POME reactions or anaphylaxis. Inject deeply into the gluteal muscle at a 90° angle over 60 to 90 seconds. Between consecutive injections, alternate the injection site between the left and right buttock.
Testosterone (C-III)	Topical solution	top	Hypogonadotropic hypogonadism (congenital or acquired in males) and primary	Apply to the axilla with an applicator.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			hypogonadism (congenital or acquired in males): Apply once daily in the morning	Use at least 2 minutes after antiperspirant or deodorant use. Allow application sites to dry before dressing. Cover the application sites with clothing to prevent transfer to another person. Rinse the metered dose pump applicator with water after application. Avoid swimming, showering or washing the application site for a minimum of 2 hours after application.
Danazol	Capsules	oral	Treatment of endometriosis (females): Twice daily; continue uninterrupted for 3-6 mos (up to 9 mos) Treatment of hereditary angioedema: Twice to 3 times daily; after a favorable response, decrease dose by 50% or less at intervals of 1 to 3 months or longer depending on the frequency of attacks; individualize dose based on patient response	Treatment of endometriosis should begin during menstruation; otherwise, ensure that patient is not pregnant while on treatment.
Depo-Testosterone (testosterone cypionate) (C-III)	Injectable solution	IM	Hypogonadotropic hypogonadism (congenital or acquired in males) and primary hypogonadism (congenital or acquired in males): Inject every 2-4 wks	Dosage will depend on age, sex, diagnosis, patient's response to treatment, and appearance of adverse effects. Inject the preparation slowly and deeply into the gluteal muscle.
Natesto (testosterone nasal gel)	Nasal gel	intranasal	Hypogonadotropic hypogonadism (congenital or	Administer once in the morning, afternoon, and evening (6 to 8 hrs apart).

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
(C-III)			acquired in males) and primary hypogonadism (congenital or acquired in males): Apply intranasally 3 times daily	Clear nasal passage prior to intranasal administration. Do not blow the nose or sniff for 1 hour after administration.
Striant (testosterone buccal system) (C-III)	Buccal system	oral	Hypogonadotropic hypogonadism (congenital or acquired in males) and primary hypogonadism (congenital or acquired in males): Apply to gum region twice daily	The buccal system should be placed against the gum and held firmly in place with a finger over the lip and against the product for 30 seconds to ensure adhesion. Place Striant in a comfortable position just above the incisor tooth (on either side of the mouth). Rotate sides of mouth with each application. Remove by gently sliding it downwards from the gum. The system should be removed before brushing or flossing the teeth. Do not chew or swallow.
Testopel (testosterone) pellets for subcutaneous implantation (C-III)	Pellets	SC	Delayed puberty (males): Doses vary based on needs and are typically less than for hypogonadotropic hypogonadism; inject SC for a limited duration (eg, 4 to 6 months of treatment) Hypogonadotropic hypogonadism (congenital or acquired in males) and primary hypogonadism (congenital or acquired in males): Inject SC every 3-6 mos	In the face of complications, the pellets should be removed. In addition, pellets may slough out. Pellet implantation is less flexible for dosage adjustment. Great care should be used when estimating the amount of testosterone needed. Lower doses may be used on initiation and then increased gradually. Approximately one-third of the material is absorbed in the first month, one-fourth in the second month, and one-sixth in the third month. Frequency may vary based on patient needs.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
testosterone enanthate (C-III)	Injectable solution	IM	Delayed puberty: Inject IM every 2-4 wks for a limited duration (eg, 4-6 mos) Hypogonadotropic hypogonadism (congenital or acquired in males) and primary hypogonadism (congenital or acquired in males): Inject IM every 2-4 wks Metastatic mammary cancer (females): Inject IM every 2-4 wks	Inject the preparation slowly and deeply into the gluteal muscle. Dosage and duration of therapy will depend on age, sex, diagnosis, patient's response to treatment and appearance of adverse effects.

See the current prescribing information for full details

CONCLUSION

- Androgens included in this review are Androderm (testosterone) transdermal system; Androgel, Fortesta, Testim, and Vogelxo (testosterone) topical gels; methyltestosterone oral capsules; Aveed (testosterone undecanoate) injection; testosterone topical solution; danazol oral capsules; Depo-Testosterone (testosterone cypionate) injection; Methitest (methyltestosterone) oral tablets; Natesto (testosterone) nasal gel; Striant (testosterone) buccal system; Testopel (testosterone) pellets for subcutaneous implantation; and testosterone enanthate injection.
- With the exception of danazol, all agents in this review are FDA-approved for the management of male hypogonadism. Danazol is FDA-approved for the treatment of endometriosis and hereditary angioedema.
- All androgen products, with the exception of danazol, are controlled substances (C-III). Testosterone gels and solutions have REMS programs consisting of a medication guide with information on proper application, potential adverse effects, and preventing inadvertent exposure to others, specifically women and children. Aveed has a REMS program related to post-injection reactions (*Drugs@FDA, 2018*).
- In clinical studies, testosterone buccal and topical products have been shown to increase serum testosterone levels and/or improve lean body mass, decrease body fat, and improve sexual function in men with hypogonadism (*Dobs et al, 2004; Dobs et al, 2012; Grober et al, 2008; Korbonits et al, 2004; McNicholas et al, 2003; Steidle et al, 2003; Swerdloff et al, 2000; Wang et al, 2000; Wang et al, 2004; Wang et al, 2011*).
- Initial results from a coordinated set of clinical trials in men with age-related low testosterone levels demonstrated small-to-moderate improvements in sexual function and some measures of physical function, mood, and depressive symptoms (*Snyder et al, 2016*).
- Head-to-head studies comparing testosterone topical gel to testosterone transdermal system have shown greater improvement in serum testosterone levels, lean body mass, and sexual function as well as fewer adverse events with testosterone gel compared to testosterone patches in men with hypogonadism (*McNicholas et al, 2003; Steidle et al, 2003; Swerdloff et al, 2000; Wang et al, 2000*).

- Increases in hemoglobin, hematocrit, and PSA have been observed in clinical studies (*Wang et al, 2000*). Severe hepatotoxicity has been associated more commonly with oral androgen than topical androgen therapy, and liver function tests should be monitored periodically.
- Meta-analyses have demonstrated an increased risk of cardiovascular events and prostate events, whereas a long-term observational study found reduced mortality in patients with type 2 diabetes who had low testosterone vs. normal testosterone levels. A European 10-year observational study of elderly men demonstrated improvement in weight, body mass index, and glycemic parameters with no reports of major adverse cardiovascular events. Similarly, a European 8-year observational study of hypogonadal men with a history of cardiovascular disease demonstrated improvement in weight, body mass index, lipid parameters, blood pressure, and glycemic control with no major adverse cardiovascular events during the full observation time. Another European 8-year observational study observed lower rates of mortality, including CV-related deaths, in hypogonadal men receiving testosterone compared to those not receiving treatment (*Calof et al, 2005; Muraleedharan et al, 2013; Xu et al, 2013, Yassin et al, 2016, Haider et al, 2016; Traish et al, 2017*).
- Although testosterone therapy was previously thought to be contraindicated in men with a history of prostate cancer, recent data suggest that use does not increase risk of de novo prostate cancer, progression of the disease, or biochemical recurrence in men with hypogonadism and a history of non-high-risk prostate cancer; safety data for testosterone use in high-risk cancer patients are limited and use in this patient population remains controversial (*Davidson et al, 2016; Nguyen et al, 2016*).
- In March 2015, the FDA issued a safety announcement clarifying the approved uses of prescription testosterone products for men who have low testosterone caused by certain medical conditions, discouraging the treatment of low testosterone due to aging, and requiring manufacturers of all approved testosterone products to add information to the labeling regarding a possible increased risk of heart attacks and strokes in patients taking testosterone and to conduct a well-designed clinical trial to more clearly address the question of whether an increased risk of heart attack or stroke exists among users of these products. In April 2015, the FDA approved labeling revisions to several sections of the prescribing information for all of the testosterone products to clarify the approved uses, confirm the medical condition causing low testosterone using lab testing, and add a new warning related to a potential increased cardiovascular risk (*FDA drug safety communication, 2015*). The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) issued a joint position statement in September 2015 recommending testosterone replacement be guided by the signs, symptoms, and testosterone concentrations rather than the underlying cause (*Goodman et al, 2015*). Newer data suggest that increases in cardiovascular events may be due to widespread use of testosterone therapies without appropriate monitoring, and patients with cardiovascular disease may safely receive androgen therapy for the treatment of hypogonadism (*Tanna et al, 2016*).
- According to current consensus guidelines, IM and topical testosterone preparations are generally recommended for the management of hypogonadism in adult male patients while the oral (capsule or tablet) androgen therapies are generally not recommended for this condition due to poor androgen effects, adverse lipid changes, and hepatic side effects. The selection of a specific testosterone replacement therapy should be a joint decision between an informed patient and physician after considering patient preferences, the pharmacokinetic profiles of the respective agents, treatment burden, and cost. Furthermore, currently available guidelines do not give preference to one topical preparation vs. another (*Bhasin et al, 2018; Dohle et al, 2018; Mulhall et al, 2018; Petak et al, 2002; Wang et al, 2008*).

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INTRODUCTION

- Glaucoma is an optic neuropathy that causes gradual degeneration of the cells making up the optic nerve. Glaucoma is among the leading causes of blindness worldwide, and in 2020, an estimated 3.2 million people worldwide are anticipated to be blind due to glaucoma (*Flaxman et al 2017*). Open-angle glaucoma is the most common form; other forms include angle-closure, congenital, and secondary glaucoma *(Jacobs 2018[a])*. Patients with open-angle glaucoma initially experience peripheral visual field loss, followed by central field loss, which may progress to irreversible blindness if untreated *(Jacobs 2018[a])*. The exact etiology of open-angle glaucoma is unknown *(Jacobs 2018[a])*. Major risk factors for developing open-angle glaucoma include advanced age, African or Hispanic/Latino descent, elevated intraocular pressure (IOP), family history of glaucoma, low ocular perfusion pressure, type 2 diabetes mellitus, and myopia *(Ellis et al 2000, Girkin et al 2004, Lesk et al 2007, Prum et al 2016)*.
- Elevated IOP is the only major risk factor for glaucoma that is treatable. Available evidence suggests that lowering IOP inhibits or reduces the progression of optic nerve damage *(Jacobs 2018[a])*. Treatment may be initiated in patients with a raised IOP despite having no visual field loss or optic nerve damage *(Jacobs 2018[a])*. An IOP > 22 mmHg is generally considered to be elevated and would be treated by most clinicians; however, this number varies according to screening methods, risk factors, and disease progression *(Jacobs 2018[a])*. The target IOP should be individualized based on response to therapy and disease progression in order to maintain IOP within a range that is unlikely to adversely affect patients' health-related quality of life *(Jacobs 2018[b])*. The American Academy of Ophthalmology (AAO) recommends an initial target IOP reduction of 25% from pretreated baseline IOP. However, depending on the severity of disease, this target may vary since there is no consensus target IOP below which further visual loss and optic nerve damage will be prevented *(Prum et al 2016)*.
- The current treatment of glaucoma focuses on decreasing IOP by 1 of 3 methods: laser therapy, surgery, or medical intervention *(Prum et al 2016)*. Medical intervention is generally used as initial therapy prior to laser or surgical treatment *(Jacobs 2018[b])*. Medical intervention includes 5 classes of ophthalmic drugs used for the long-term management of glaucoma: alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, miotics or parasympathomimetics, and prostaglandin analogues *(Jacobs 2018[b], Micromedex 2018)*. These treatments reduce IOP by either decreasing the amount of aqueous humor produced by the ciliary body or by increasing uveoscleral outflow *(Micromedex 2018, Prum et al 2016)*. Miotics and prostaglandin analogues increase aqueous outflow, while beta-blockers and carbonic anhydrase inhibitors decrease aqueous humor production *(Micromedex 2018)*. Alpha-agonists decrease the amount of aqueous humor formed and increase its outflow *(Micromedex 2018, Prum et al 2016)*.
- Guidelines published in 2010 by the American Optometric Association (AOA) do not recommend preferential use of any drug class, although current guidelines by the AAO generally recommend ophthalmic prostaglandin analogues as first-line pharmacologic therapy in patients with elevated IOP *(AOA 2010, Prum et al 2016)*. Combination or monotherapy with agents from an alternative pharmacologic class is recommended for patients who experience intolerable adverse events or who do not achieve the optimal IOP reduction with first-line agents *(Jacobs 2018[b])*.
- Medispan Classes: Beta-Blockers – Ophthalmic; Miotics – Cholinesterase Inhibitors; Miotics – Direct Acting; Ophthalmic Carbonic Anhydrase Inhibitors; Ophthalmic Rho Kinase Inhibitors; Ophthalmic Selective Alpha Adrenergic Agonists; Prostaglandins – Ophthalmic; Alpha Adrenergic Agonist and Carbonic Anhydrase Inhibitor Combination; Beta-blockers – Ophthalmic Combinations
  - Note that bimatoprost is also available as Latisse (bimatoprost ophthalmic solution) 0.03% and indicated to treat hypotrichosis of the eyelashes by increasing their growth including length, thickness and darkness. Latisse is applied nightly directly to the skin of the upper eyelid margin at the base of the eyelashes using an applicator. Latisse is included here for informational purposes since it contains the same ingredient used for the reduction of elevated IOP.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Alpha-Agonists	
Alphagan P (brimonidine tartrate ophthalmic solution) 0.1% and 0.15% *	✔ †

Drug	Generic Availability
brimonidine tartrate ophthalmic solution 0.2% ‡	✔
Iopidine (apraclonidine ophthalmic solution) 0.5% and 1% §	✔
Beta-Blockers	
Betagan (levobunolol hydrochloride ophthalmic solution) 0.25% and 0.5%	✔
betaxolol hydrochloride ophthalmic solution 0.5% ‖	✔
Betimol (timolol ophthalmic solution) 0.25% and 0.5% ¶	-
Betoptic S (betaxolol hydrochloride ophthalmic suspension) 0.25%	-
carteolol hydrochloride ophthalmic solution 1% #	✔
Istalol (timolol maleate ophthalmic solution) 0.5%	✔
metipranolol ophthalmic solution 0.3% **	✔
Timoptic (timolol maleate ophthalmic solution) 0.25% and 0.5%	✔
Timoptic in Ocudose (timolol maleate ophthalmic solution) 0.25% and 0.5%	-
Timoptic-XE (timolol maleate ophthalmic gel forming solution [GFS]) 0.25% and 0.5%	✔
Carbonic Anhydrase Inhibitors	
Azopt (brinzolamide ophthalmic suspension) 1%	-
Trusopt (dorzolamide hydrochloride ophthalmic solution) 2%	✔
Miotics	
Phospholine Iodide (echothiophate iodide for ophthalmic solution) 0.125%	-
Isopto Carpine (pilocarpine ophthalmic solution) 1%, 2%, and 4%	✔
Prostaglandin Analogues	
bimatoprost ophthalmic solution 0.03%	✔
Latisse (bimatoprost ophthalmic solution) 0.03%	✔
Lumigan (bimatoprost ophthalmic solution) 0.01% ††	-
Travatan Z (travoprost ophthalmic solution) 0.004% ‡‡	-
Vyzulta (latanoprostene bunod ophthalmic solution) 0.024%	-
Xalatan (latanoprost ophthalmic solution) 0.005%	✔
Xelpros (latanoprost ophthalmic emulsion) 0.005%	-
Zioptan (tafluprost ophthalmic solution) 0.0015%	-
ROCK Inhibitor	
Rhopressa (netarsudil ophthalmic solution) 0.02%	-
Combinations	
Combigan (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5%	-
Cosopt (dorzolamide hydrochloride/timolol maleate ophthalmic solution) 2%/0.5%	✔
Cosopt PF (dorzolamide hydrochloride/timolol maleate ophthalmic solution) 2%/0.5%	✔
Simbrinza (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2%	-

* Does not contain benzalkonium chloride; contains Purite 0.005% as a preservative.
† The Alphagan P 0.15% strength is available generically; however, the 0.1% strength is only available as a branded product.
‡ Branded Alphagan 0.2% is no longer marketed.
§ Apraclonidine 0.5% is available generically, and Iopidine 0.5% brand product has been discontinued due to business reasons. Iopidine 1% strength is only available as a branded product.
‖. Brand Betoptic is no longer available.
¶ Formulated as timolol hemihydrate.
# Brand Ocupress is no longer available.
** Brand OptiPranolol is no longer available.
†† Allergan discontinued brand Lumigan (bimatoprost) 0.03% in 2012; the discontinuation was not due to safety concerns. Generic bimatoprost 0.03% is available, but generic 0.01% is not.
‡‡ The original benzalkonium chloride-containing travoprost formulation (brand name: Travatan) was approved by the FDA on March 16, 2001; however, Travatan was discontinued by Alcon in June 2010. In March 2013, travoprost with benzalkonium chloride by Par Pharmaceuticals was approved by an abbreviated new drug application (ANDA); however, this generic product was discontinued on September 7, 2016 *(Clinical Pharmacology 2018)*. Only the brand product, Travatan Z, remains available.

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

INDICATIONS

Table 2A. Food and Drug Administration Approved Indications (Part 1 of 2)

Drug	Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension	Short-term adjunctive therapy in patients on maximally tolerated medical therapy who require additional IOP reduction	Control or prevent postsurgical elevations in IOP that occur in patients after argon laser trabeculoplasty, argon laser iridotomy, or Nd:YAG posterior capsulotomy	Reduction of elevated IOP in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP
Alpha-Agonists				
Alphagan P (brimonidine tartrate) *	✔			
Iopidine (apraclonidine)		✔ (0.5% only)	✔ (1% only)	
Beta-Blockers				
Betagan (levobunolol)	✔ ‡			
Betimol (timolol)	✔			
Betoptic S (betaxolol) †	✔ ‡			
carteolol	✔ ‡			
Istalol (timolol maleate)	✔			
metipranolol	✔			
Timoptic / Timoptic in Ocudose (timolol maleate)	✔			
Timoptic-XE (timolol maleate GFS)	✔			
Carbonic Anhydrase Inhibitors				
brinzolamide	✔			
dorzolamide	✔			
Prostaglandin Analogues				
latanoprost	✔			
Lumigan (bimatoprost) §	✔			
Travatan Z (travoprost)	✔			
Vyzulta (latanoprostene bunod)	✔			
Xelpros (latanoprost)	✔			
Zioptan (tafluprost)	✔			
ROCK Inhibitor				
Rhopressa (netarsudil)	✔			

Drug	Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension	Short-term adjunctive therapy in patients on maximally tolerated medical therapy who require additional IOP reduction	Control or prevent postsurgical elevations in IOP that occur in patients after argon laser trabeculoplasty, argon laser iridotomy, or Nd:YAG posterior capsulotomy	Reduction of elevated IOP in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP
Combinations				
Combigan (brimonidine/timolol) ‖				✔
Cosopt / Cosopt PF (dorzolamide/timolol) ¶	✔			
Simbrinza (brinzolamide/brimonidine)	✔			

* Generic brimonidine 0.2% shares the same indication as brand Alphagan P.
† Generic betaxolol ophthalmic solution shares the same indication as brand Betoptic S ophthalmic suspension.
‡ Products are indicated for reduction of elevated IOP in patients with chronic open-angle glaucoma or ocular hypertension.
§ Generic bimatoprost 0.03% shares the same indication as brand Lumigan.
‖ The IOP-lowering of Combigan dosed twice a day was slightly less than that seen with the concomitant administration of timolol maleate ophthalmic solution, 0.5% dosed twice a day, and brimonidine tartrate ophthalmic solution, 0.2% dosed 3 times per day.
¶ Cosopt / Cosopt PF are indicated for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers (failed to achieve target IOP after multiple measurements over time). The IOP-lowering of Cosopt twice daily was slightly less than that seen with the concomitant administration of timolol 0.5% twice daily and dorzolamide 2% 3 times daily.

(Prescribing information: Alphagan P 2013, Azopt 2015, Betagan 2017, betaxolol hydrochloride ophthalmic solution 2017, Betimol 2017, Betoptic S 2017, bimatoprost ophthalmic solution 0.03% 2017, brimonidine tartrate ophthalmic solution 2018, carteolol hydrochloride ophthalmic solution 2016, Combigan 2015, Cosopt 2015, Cosopt PF 2017, Iopidine 0.5% 2018, Iopidine 1% 2018, Istalol 2016, Latisse 2017, Lumigan 2017, metipranolol ophthalmic solution 2011, Rhopressa 2017, Simbrinza 2015, Timoptic 2016, Timoptic in Ocudose 2017, Timoptic-XE 2018, Travatan Z 2017, Trusopt 2014, Vyzulta 2018, Xalatan 2017, Xelpros 2018, Zioptan 2017)

Table 2B. Food and Drug Administration Approved Indications (Part 2 of 2)

Drug	Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension	Accommodative esotropia	Induction of miosis	Management of acute angle-closure glaucoma	Prevention of postoperative elevated IOP associated with laser surgery	Chronic open-angle glaucoma. Subacute or chronic angle-closure glaucoma after iridectomy or where surgery is refused or contraindicated; certain non-uveitic secondary types of glaucoma, especially glaucoma following cataract surgery.
Miotics						
Isopto Carpine (pilocarpine)	✔		✔	✔	✔	

Drug	Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension	Accommodative esotropia	Induction of miosis	Management of acute angle-closure glaucoma	Prevention of postoperative elevated IOP associated with laser surgery	Chronic open-angle glaucoma. Subacute or chronic angle-closure glaucoma after iridectomy or where surgery is refused or contraindicated; certain non-uveitic secondary types of glaucoma, especially glaucoma following cataract surgery.
Phospholine Iodide (echothiophate iodide)		✔				✔

(Prescribing information: Isopto Carpine 2010, Phospholine Iodide 2017)

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

CLINICAL EFFICACY SUMMARY

Drug Class Comparisons

- In a large systematic review of medical therapy compared to various surgical treatments, evidence was insufficient to show that medical, laser, or surgical treatments of open-angle glaucoma prevented progressive visual field loss, optic nerve damage, any kind of patient reported outcomes, or visual impairment. Very little direct comparative evidence is available *(Boland et al 2012, Boland et al 2013)*.
- A network meta-analysis included 114 randomized controlled trials (n = 20,725) evaluating single active ophthalmic agents for the treatment of primary open-angle glaucoma *(Li et al 2016)*. All trials compared active first-line drugs to no treatment or placebo or another single topical agent for glaucoma. The mean reductions in IOP at 3 months (reported as mmHg) were as follows: bimatoprost 5.61 (95% confidence interval [CI], 4.94 to 6.29), latanoprost 4.85 (95% CI, 4.24 to 5.46), travoprost 4.83 (95% CI, 4.12 to 5.54), levobunolol 4.51 (95% CI, 3.85 to 5.24), tafluprost 4.37 (95% CI, 2.94 to 5.83), timolol 3.70 (95% CI, 3.16 to 4.24), brimonidine 3.59 (95% CI, 2.89 to 4.29), carteolol 3.44 (95 % CI, 2.42 to 4.46), levobetaxolol 2.56 (95% CI, 1.52 to 3.62) (currently not available in U.S.), apraclonidine 2.52 (95% CI, 0.94 to 4.11), dorzolamide 2.49 (95% CI, 1.85 to 3.13), brinzolamide 2.42 (95% CI, 1.62 to 3.23), betaxolol 2.24 (95% CI, 1.59 to 2.88), and unoprostone 1.91 (95% CI, 1.15 to 2.67) (currently not available in the U.S.). The authors concluded that the ophthalmic prostaglandin analogues have the greatest effect on IOP.
- A network meta-analysis evaluated 72 randomized controlled trials (n = 19,916) that reported efficacy and safety of medications for the treatment of primary open-angle glaucoma or ocular hypertension over at least 3 months (*Li et al 2018*). A total of 15 treatments were directly compared for change in IOP. Compared to prostaglandin analogues, beta-blockers showed relatively weaker ability to lower IOP, followed by alpha-agonists and carbonic anhydrase inhibitors. The most powerful combinations for dual therapy included prostaglandin analogues with another agent for lowering IOP; combinations with 2 non-prostaglandin analogues had lower efficacy in controlling IOP than monotherapy with a prostaglandin analogue. More severe hyperemia was associated with prostaglandin analogues compared to any other monotherapy, with beta-blockers having the lowest effect on the incidence of hyperemia. Most 2-drug combinations with prostaglandin analogues also led to serious hyperemia with the exception of the combination of prostaglandin analogues and alpha-agonists.
- A network meta-analysis evaluated data from 28 randomized controlled trials in patients with primary open-angle glaucoma or ocular hypertension for peak (n = 6841) and trough (n = 6953) effect of 8 drugs (*van der Valk et al 2009*). The studies assessed bimatoprost, travoprost, latanoprost, brimonidine, timolol, dorzolamide, betaxolol, and brinzolamide. All drugs differed from placebo in reducing IOP. At the peak, the largest reduction in mean IOP was observed with the prostaglandin analogues – bimatoprost, travoprost, and latanoprost. At the trough, the largest reduction in mean IOP was also with the prostaglandin analogues with bimatoprost followed by latanoprost and travoprost.

- The ophthalmic prostaglandin analogues have consistently demonstrated comparable or greater efficacy when compared to dorzolamide/timolol *(Coleman et al 2003, Fechtner et al 2004, Konstas et al 2008, Lesk et al 2008, Ozturk et al 2007, Sharpe et al 2008)*. Bimatoprost 0.03% significantly reduced the mean IOP compared to dorzolamide/timolol in a 6 week crossover trial (p = 0.03) (*Sharpe et al 2008*). In patients uncontrolled on beta-blocker monotherapy, bimatoprost also significantly reduced the mean IOP at 8 AM compared to dorzolamide/timolol in a 3 month study *(Coleman et al 2003)*. However, in a small study of 65 patients with primary open-angle glaucoma or ocular hypertension, the efficacy of lowering IOP was similar between bimatoprost and dorzolamide/timolol over a 6 month study period (p = 0.48) (*Ozturk et al 2007*). A meta-analysis of 14 randomized controlled trials found that latanoprost was associated with greater efficacy in lowering the diurnal mean IOP compared to the combination of dorzolamide/timolol in patients who were inadequately controlled with timolol monotherapy. Latanoprost was as effective as dorzolamide/timolol in patients without prior timolol treatment (*Cheng et al 2009*).
- A meta-analysis of 11 randomized controlled trials with 1256 patients with open angle glaucoma or ocular hypertension showed significant reductions in IOP with latanoprost compared to timolol. Latanoprost resulted in an average 1.6 mmHg further lowering in IOP compared to timolol (p < 0.001) (*Zhang et al 2001*).

Alpha-Agonists

- The comparative clinical trial data regarding the safety and efficacy of the ophthalmic alpha-agonists are limited. When the ophthalmic alpha-agonists are used for the management of postoperative elevations in IOP, both ophthalmic brimonidine and apraclonidine are effective treatment options with similar efficacy *(Barnes et al 1999, Chen et al 2001, Chen et al 2005, Sterk et al 1998)*.
- In a meta-analysis of 2 double-blind, multicenter, parallel group, randomized controlled trials, brimonidine purite 0.1%, brimonidine purite 0.15%, and brimonidine 0.2% were compared for safety and tolerability over 12 months. In 1 study, brimonidine purite 0.15% had lower ocular treatment-related adverse events including allergic conjunctivitis, conjunctival hyperemia, and eye discharge compared to brimonidine 0.2% (p ≤ 0.025). The second study found a statistically significantly lower overall incidence of treatment-related adverse events with brimonidine purite 0.1% compared to brimonidine 0.2% (p = 0.014). The pooled data demonstrated a reduced overall incidence of treatment-related adverse events proportional to the reductions in the concentration of the active ingredient (p < 0.001) (*Cantor et al 2009*).
- A Cochrane review of 22 randomized controlled trials (n = 2112) assessed the effectiveness of medications administered perioperatively to prevent temporarily increased IOP after laser trabeculoplasty in patients with open-angle glaucoma *(Zhang et al 2017)*. Compared to placebo, fewer patients who received any IOP-lowering medication (apraclonidine, acetazolamide, brimonidine, pilocarpine) experienced IOP increase ≥ 10 mmHg within 2 hours (risk ratio, 0.05; 95% CI, 0.01 to 0.20; moderate-certainty evidence). This effect was maintained up to 24 hours after the operation. In 3 studies, perioperative brimonidine was associated with higher rates of conjunctival blanching compared to placebo. In a comparison of perioperative brimonidine vs. apraclonidine (3 randomized controlled trial), the review was unable to determine whether brimonidine or apraclonidine was better in preventing IOP increases within 2 hours after surgery due to inconsistency, imprecision of the estimated effect, and study bias (risk ratio, 2.28; 95% CI, 0.32 to 16.03; very low-certainty evidence). The authors concluded that it is unclear whether one medication in the alpha-agonist class is better than another. There was no notable difference between apraclonidine and pilocarpine in the mean change in IOP measurement from pre-procedure to 2 hours after surgery.

Beta-Blockers

- Timolol has been a frequent comparator in numerous clinical trials with agents for the treatment of glaucoma and ocular hypertension. Head-to-head studies in the ophthalmic beta-blocker class involving patients with open-angle glaucoma or ocular hypertension have shown that all treatments are efficacious in decreasing IOP from baseline; however, conflicting results were seen when groups were compared to each other. Studies that reported adverse events categorized all events as mild to moderate; the most frequent adverse events reported included burning or stinging upon instillation and tearing (*Berry et al 1984, Berson et al 1985, Boozman et al 1988, Evans et al 1999, Geyer et al 1998, Halper et al 2002, Krieglstein et al 1987, Miki et al 2004, Mills et al 1986, Mundorf et al 2004, Schenker et al 2000, Shedden et al 2001, Sonty et al 2009, Stewart et al 1986, Stewart et al 2002, Vogel et al 1989, Walters et al 1998, Watson et al 2001*).
- Studies involving patients with open-angle glaucoma or ocular hypertension comparing betaxolol 0.5% to timolol maleate 0.5% have found conflicting results with regard to decrease in IOP from baseline *(Berry et al 1984, Evans et al 1999, Miki et al 2004, Stewart et al 1986, Vogel et al 1989)*.

- Specifically, one study found that betaxolol 0.5% maintained the decrease in IOP that occurred from earlier treatment with timolol maleate 0.5% (*Miki et al 2004*).
- In another study, betaxolol 0.5% was not found to significantly lower IOP after a washout period following treatment with timolol maleate 0.5% (p = 0.09) (*Evans et al 1999*).
- In a separate study, betaxolol 0.5% was shown to produce a significant decrease in IOP from baseline at weeks 1 through 12 when both the mean IOP value averaged for both eyes and the worse eye were analyzed (p ≤ 0.001). In this same study, timolol maleate 0.5% was not found to produce a significant decrease in IOP during weeks 1 through 8 when the mean IOP was averaged for both eyes (p ≤ 0.05), as well as at week 12 when the worse eye was analyzed (p values not reported) *(Vogel et al 1989)*.
- Additional studies have found that the difference from baseline in IOP was significant for both betaxolol and timolol groups, and there was no difference between groups in the reduction of IOP *(Berry et al 1984, Stewart et al 1986)*.
- All studies reported mild adverse events including burning or stinging upon instillation and tearing. Although several studies have reported that betaxolol 0.5% was associated with more burning and/or stinging upon instillation than timolol 0.5%, only 1 study found this difference to be statistically significant *(Berry et al 1984, Vogel et al 1989)*.

- One study compared ophthalmic formulations of betaxolol 0.5% to carteolol hydrochloride 1% and timolol 0.25% and found that all 3 treatments significantly decreased IOP from baseline. However, carteolol 1% and timolol 0.25% achieved greater reductions in IOP than betaxolol 0.5% initially and maintained this difference through the follow up period (p values not reported). Eventually, betaxolol 0.5% achieved the same level of IOP after 12 months. In this study, the lowest number of adverse events was reported in the carteolol 1% group, followed by timolol 0.25%, and betaxolol 0.5% groups (p values not reported) *(Watson et al 2001)*.
- Studies involving levobunolol 0.25%, 0.5%, and 1% found this agent to significantly decrease IOP from baseline; however, significant treatment differences in IOP reduction were not found when compared to ophthalmic formulations of metipranolol 0.6%, timolol maleate 0.25%, or timolol GFS 0.5% *(Berson et al 1985, Boozman et al 1988, Geyer et al 1998, Halper et al 2002, Krieglstein et al 1987, Walters et al 1998)*.
  - Specifically, when levobunolol 0.5% was compared to metipranolol 0.6%, both groups saw significant differences from baseline IOP after 12 weeks of treatment with decreases of -7.2 mmHg in the levobunolol 0.5% group and -7.4 mmHg in the metipranolol 0.6% group (p value not reported) *(Krieglstein et al 1987)*.
  - When levobunolol 0.25% was compared to timolol maleate 0.25%, the mean changes in IOP from baseline to 48 weeks were reported as -5.1 mmHg in the levobunolol 0.25% group and -4.6 mmHg in the timolol maleate 0.25% group (p value not reported) *(Boozman et al 1988)*.
  - The majority of studies did not report significant differences in adverse events between treatment groups. However, in a study between levobunolol 0.5% and timolol GFS 0.5%, significantly more patients in the levobunolol 0.5% group experienced at least 1 adverse event (p = 0.024). Additionally, the incidence of burning and/or stinging was found to be significantly higher in the levobunolol 0.5% group (p < 0.001) *(Halper et al 2002)*.
- One study compared metipranolol 0.3% to timolol 0.25% and found that both treatments significantly decreased IOP from baseline. There was a larger reduction in IOP in the metipranolol 0.3% group; however, the difference was not found to be statistically significant (p value not reported) *(Mills et al 1986)*.
- Studies comparing different formulations of ophthalmic timolol consisted of timolol-LA (Istalol), timolol maleate 0.5%, timolol in sorbate 0.5%, and timolol maleate GFS 0.5% (Timoptic-XE) *(Mundorf et al 2004, Schenker et al 2000, Shedden et al 2001, Sonty et al 2009, Stewart et al 2002)*. The studies showed that all forms of ophthalmic timolol significantly decreased IOP from baseline, and no significant differences were found with regard to reductions in IOP between formulations.
  - One study found that timolol-LA (Istalol) significantly decreased heart rate when compared to timolol maleate 0.5% (p < 0.05) and also caused more stinging and burning (p = 0.001) *(Mundorf et al 2004)*.
  - A separate study that compared timolol maleate GFS 0.5% to timolol 0.5% found that the patients in the GFS group had significantly more blurred vision as well as tearing (p = 0.04 for both). However, the same study also found that timolol 0.5% caused significantly more burning and stinging when compared to the GFS (p = 0.04). It was also found that timolol maleate GFS 0.5% caused less decline in heart rate after 12 weeks of treatment (p = 0.024); however, this was not found to be significant at 24 weeks of treatment *(Shedden et al 2001)*.

Beta-Blockers compared to other drug classes

- When beta-blockers were compared to single entity formulations of carbonic anhydrase inhibitors and prostaglandin analogues, conflicting results were found with regard to the difference in IOP-lowering effect *(Cantor et al 2001,*

Haneda et al 2006, Ikeda et al 2008, March et al 2000, Rusk et al 1998, Silver et al 1998, Strahlman et al 1995, Varma et al 2009, Walters et al 2004).
- In studies between betaxolol 0.25% and brimonidine 0.2% as well as dorzolamide 2%, no significant differences were seen between groups (*Cantor et al 2001, Rusk et al 1998, Strahlman et al 1995*).
- Similar results were found in studies comparing timolol 0.5% to brinzolamide 1% and latanoprost 0.005% as well as in a study comparing carteolol 1% and latanoprost 0.005% (*March et al 2000, Varma et al 2009, Haneda et al 2006*).
- In a separate study comparing timolol GFS 0.5% to bimatoprost 0.03% and latanoprost 0.005%, it was found that bimatoprost 0.03% significantly reduced IOP from baseline when compared to timolol GFS 0.5% ($p < 0.001$). This same study also showed that latanoprost 0.005% provided significantly more IOP reduction from baseline when compared to timolol GFS 0.5% ($p < 0.002$) *(Walters et al 2004)*.
- In an additional study, latanoprost 0.005% was found to provide significantly more IOP reduction from baseline when compared to betaxolol 0.25%, carteolol 1%, and nipradilol 0.25% ($p < 0.05$) *(Ikeda et al 2008)*.

Carbonic Anhydrase Inhibitors
- Trials support the FDA-approved indications for ophthalmic formulations of brinzolamide and dorzolamide. The trials evaluated the effectiveness of these agents over 1 week to 18 months and demonstrated that carbonic anhydrase inhibitors are a viable treatment option for the management of elevated IOP (*Jacobs 2018[b])*. However, the efficacy of ophthalmic carbonic anhydrase inhibitors in reducing vision loss due to glaucoma has not been established in clinical trials (*Jacobs 2018[b])*.
- Single agent ophthalmic carbonic anhydrase inhibitors, brinzolamide and dorzolamide, were evaluated in a multicenter, parallel group study. Reduction in IOP from baseline was statistically significant in each group ($p < 0.001$); however, the changes in IOP from baseline were comparable between the treatment groups (p value not reported) *(Silver 1998).* In a safety trial, significantly fewer patients reported ocular discomfort, specifically burning and stinging, with brinzolamide compared to dorzolamide ($p < 0.001$). Taste disturbance was reported in up to 12% of patients in the brinzolamide group, while only 8.5% of patients in the dorzolamide group experienced this adverse event *(Silver 2000).*
- Similar reductions in IOP were also observed when the agents were used in combination with timolol *(Michaud et al 2001).*

Carbonic Anhydrase Inhibitors compared to other classes
- The single agent carbonic anhydrase inhibitors were compared to beta-blockers *(March et al 2000, Rusk et al 1998, Strahlman et al 1995)*. Brinzolamide was compared to timolol, while dorzolamide was compared to timolol and betaxolol. In these trials, timolol demonstrated a greater reduction in IOP than both brinzolamide and dorzolamide.
  - In a double-blind, multicenter, parallel group, randomized controlled trial, timolol was associated with a statistically significant reduction in IOP compared to brinzolamide, administered either twice or 3 times daily ($p = 0.0002$) *(March et al 2000).*
  - When dorzolamide was compared to betaxolol or timolol in a 1 year, double-blind, parallel group, randomized controlled trial, all 3 treatment groups exhibited comparable IOP lowering from baseline (23, 21, and 25%, respectively; p value not reported) *(Strahlman et al 1995)*.
  - Another multicenter randomized controlled trial found dorzolamide and betaxolol to be comparable in terms of IOP reduction from baseline (p value not reported) *(Rusk et al 1998).*
  - The safety and efficacy of brinzolamide and dorzolamide were compared to brimonidine. All 3 groups in this study received the study treatment as add-on therapy to a prostaglandin analogue of the clinicians' choice. Brimonidine was associated with a significantly greater reduction in IOP than either brinzolamide or dorzolamide after 1 and 4 months of therapy ($p < 0.001$ for both groups) *(Bournias et al 2009)*.

Miotics
- The clinical trial data regarding the safety and efficacy of the ophthalmic miotics are very limited. These agents have been available for many years and are recognized as an established treatment option (*Prum et al 2016*). No clinical trials have been published in the last 30 years on echothiophate iodide.

Miotics compared to other drug classes
- For the treatment of glaucoma, ophthalmic pilocarpine has demonstrated comparable efficacy to reduce IOP to ophthalmic carbonic anhydrase inhibitors, beta-blockers, and prostaglandin analogues *(Bayer et al 2004, Diestelhorst et*

al 2000, Hartenbaum et al 1999). A trial has evaluated pilocarpine plus a beta-blocker and found that pilocarpine is an effective agent at reducing IOP with comparable efficacy to prostaglandin analogues *(Diestelhorst et al 2000).*

- In a head-to-head trial comparing apraclonidine to pilocarpine administered 15 minutes before ophthalmic surgery, no significant differences were observed between the agents in their ability to reduce IOP after surgery *(Ren et al 1999).*

Prostaglandin Analogues

- Several meta-analyses with the prostaglandin analogues have been published. Ophthalmic bimatoprost appears to have the greatest efficacy in reducing IOP; however, trials have not consistently demonstrated a difference in IOP reduction between travoprost and latanoprost *(Aptel et al 2008, Cheng et al 2008, Honrubia et al 2009, Li et al 2006, Lin et al 2014, Sawada et al 2012)*.
  - A systematic review of 32 randomized controlled trials compared prostaglandin analogues for primary open-angle glaucoma, using timolol as a reference comparator. The analysis found that bimatoprost was most likely to achieve treatment success, defined as a 30% reduction in IOP (relative risk, 1.59; 95% CI, 1.28 to 1.98). The relative risk for treatment success with latanoprost was 1.32 (95% CI, 1.00 to 1.74), for travoprost was 1.33 (95% CI, 1.03 to 1.72), and for tafluprost was 1.1 (95% CI, 0.85 to 1.42). In terms of tolerability, bimatoprost was associated with the highest risk of developing hyperemia, while latanoprost had the lowest risk *(Lin et al 2014)*.
  - The results of a meta-analysis with 8 trials (n = 1610) demonstrated that reductions in IOP were significantly greater with bimatoprost 0.03% compared to travoprost at 8 AM (p = 0.004) and 12 noon (p = 0.02), but not at 4 PM (p = 0.19) or 9 PM (p = 0.07). Bimatoprost 0.03% also demonstrated greater reductions in IOP compared to latanoprost at all time points. There were no statistically significant differences between latanoprost and travoprost at any time point *(Aptel et al 2008)*.
  - Results from a meta-analysis by Li et al did not demonstrate a significant difference in IOP reductions between bimatoprost 0.03% and travoprost (p = 0.8) or latanoprost and travoprost (p = 0.07) in 12 studies with 3048 patents with open-angle glaucoma or ocular hypertension *(Li et al 2006)*.
  - A meta-analysis of 13 trials evaluating adverse events associated with the ophthalmic prostaglandin analogues showed that latanoprost had a lower incidence of conjunctival hyperemia compared to both bimatoprost 0.03% and travoprost (p < 0.0001 for both) *(Honrubia et al 2009)*.
- Tafluprost was FDA approved in 2012, several years after other prostaglandin analogues; therefore, tafluprost data has not been included in many meta-analyses. Available trials suggest that tafluprost may have a similar IOP-lowering effect as latanoprost, but less than that of travoprost *(Konstas et al 2013, Schnober et al 2010, Traverso et al 2010, Uusitalo et al 2010[b])*.
  - One trial found no significant difference in IOP reduction from baseline between tafluprost and travoprost following 6 weeks of treatment (difference, 0.17 mmHg; 95% CI, -1.268 to 1.608; p = 0.811) *(Traverso et al 2010)*.
  - In a 6 week crossover trial, travoprost significantly reduced IOP from baseline compared to tafluprost (7.2 vs. 6.6 mmHg; p = 0.01). Adverse events were similar between the treatment groups *(Schnober et al 2010)*.
  - In a randomized, double-blind trial (n = 533), tafluprost demonstrated non-inferiority to latanoprost after 24 months (p < 0.05). No difference in the incidence of adverse events was reported between treatments *(Uusitalo et al 2010[b])*.
  - Results from a similar trial demonstrated a significantly lower incidence of ocular irritation/burning, tearing, itching, dry eye sensation, and conjunctival hyperemia when switched from latanoprost to tafluprost due to ocular intolerance (p < 0.001 for all). Tafluprost also significantly reduced IOP compared to baseline treatment with latanoprost (16.4 vs. 16.8 mmHg; p = 0.049) *(Uusitalo et al 2010[a])*.
  - Tafluprost 0.0015% (preservative-free) once daily was compared to timolol 0.5% (preservative-free) twice daily for monotherapy treatment of 643 patients with glaucoma or ocular hypertension in a double-blind, active control, randomized controlled trial. Tafluprost was non-inferior to timolol in IOP reduction at all visits and time points based upon a prespecified non-inferiority margin of 1.5 mmHg. Conjunctival hyperemia was more frequently reported with tafluprost (4.4%) than timolol (1.2%; p = 0.016) *(Chabi et al 2012)*.
- A pooled analysis of 2 similarly designed, Phase 3, double-masked, active control, multicenter, non-inferiority trials (APOLLO and LUNAR; N = 840 total) found that latanoprostene bunod 0.024% administered once daily led to greater reductions in mean IOP when compared to timolol maleate 0.5% administered twice daily at all evaluation time points (IOP was measured at 8 AM, 12 PM, and 4 PM at week 2, week 6, and months 3, 6, 9, and 12) (p < 0.001 for all) (*Medeiros et al 2016, Weinreb et al 2016*, *Weinreb et al 2018*). A greater proportion of patients treated with latanoprostene bunod vs. timolol attained a mean IOP ≤ 18 mm Hg and an IOP reduction ≥ 25% from baseline (p <

0.001). Patients who switched over from timolol to latanoprostene bunod also experienced additional IOP lowering (p ≤ 0.009). Efficacy was maintained through 12 months of therapy.

- Latanoprostene bunod was also evaluated in a 28 day, Phase 2, randomized, investigator-masked, active control, multicenter, dose-ranging study (n = 413). The objective of the study was to assess the efficacy and safety of latanoprostene bunod vs. latanoprost 0.005%, and to determine the optimum drug concentrations of latanoprostene bunod in reducing IOP. Patients were randomized into 1 of 5 treatment groups, including 4 different concentrations of latanoprostene bunod (0.006%, 0.012%, 0.024%, and 0.040%) and latanoprost 0.005% *(Weinreb et al 2015)*.
  - Efficacy for latanoprostene bunod was dose-dependent and reached a plateau at 0.024% to 0.040%. Latanoprostene bunod 0.024% led to significantly greater reductions in mean diurnal IOP compared with latanoprost 0.005% at day 28 (-9 mmHg vs. -7.77 mmHg, respectively; p = 0.005).
  - A significantly greater proportion of patients had mean diurnal IOP ≤ 18 mmHg in the latanoprostene bunod 0.024% group at all measurement time points (p ≤ 0.046) compared to the latanoprost group.

ROCK Inhibitor

- The safety and efficacy of netarsudil were evaluated in 3 Phase 3, randomized, double-masked, active control, parallel group, multicenter trials. Patients were randomized to ophthalmic netarsudil or timolol maleate 0.5%. In these trials, the primary efficacy endpoint was the mean IOP, measured at multiple time points (8 AM, 12 PM, and 4 PM at week 2, week 6, and at 3 months). Netarsudil was considered to be non-inferior to timolol if the upper limit of the 2-sided 95% CIs around the difference (netarsudil – timolol) was within 1.5 mmHg at all time points and was within 1.0 mmHg at a majority of the time points *(Rhopressa FDA Medical Review, Rhopressa Prescribing Information, Serle et al 2018).*
  - Overall, netarsudil 0.02% dosed once a day demonstrated statistically significant reductions of up to 5 mmHg in IOP from baseline in the clinical trials.
  - In ROCKET-1, netarsudil failed in its primary endpoint; netarsudil was not non-inferior to timolol in patients with baseline IOP < 27 mmHg. However, netarsudil was non-inferior to timolol in patients with a baseline IOP < 25 mmHg in a post-hoc analysis. Netarsudil did have an IOP-lowering effect at baseline IOPs ≥ 25 mmHg, but was not statistically non-inferior to timolol when including these patients (*Rhopressa FDA Medical Review, Serle et al 2018)*.
  - In ROCKET-2, netarsudil achieved success in its primary endpoint, demonstrating non-inferiority to timolol in patients with a baseline IOP < 25 mmHg (*Rhopressa FDA Medical Review, Serle et al 2018)*.
  - In ROCKET-4, netarsudil achieved success in its primary endpoint, demonstrating non-inferiority to timolol in patients with a baseline IOP < 30 mmHg in the per-protocol (PP) population, but this result was not replicated in the intent-to-treat (ITT) population. In a secondary endpoint analysis, non-inferiority of netarsudil to timolol was demonstrated in patients with baseline IOP < 25 mmHg in both PP and ITT populations (*Rhopressa FDA Medical Review).*
- Netarsudil was also evaluated in a 28 day, Phase 2, dose-response, double-masked, active control, parallel group, multicenter trial evaluating netarsudil compared with latanoprost solution, in patients with open-angle glaucoma or ocular hypertension. The study found that netarsudil 0.02% was less effective than latanoprost by approximately 1 mmHg in patients with unmedicated IOPs of 22 to 35 mmHg (differences from latanoprost in the change from baseline mean diurnal IOP for netarsudil 0.02% were 0.9 mmHg at day 14 and 1.2 mmHg at day 28) (*Bacharach et al 2015*).

Fixed Dose Combinations

- Combigan (brimonidine/timolol)
  - The combination of brimonidine/timolol has been shown to be safe and effective in reducing mean IOP from baseline *(Craven et al 2005, Goñi et al 2005, Sherwood et al 2006)*. In clinical trials comparing the fixed combination to the individual components, the reduction of IOP with brimonidine/timolol dosed twice a day was slightly less than that seen with the concomitant administration of timolol maleate ophthalmic solution 0.5% dosed twice a day and brimonidine tartrate ophthalmic solution 0.2% dosed 3 times per day.
  - The combination of brimonidine/timolol was compared to latanoprost 0.005% in 148 patients with glaucoma or ocular hypertension in a randomized, investigator-masked study *(Katz et al 2012)*. The primary outcome, mean diurnal IOP at 12 weeks, did not demonstrate a significant difference between treatment groups at any time point or mean change from baseline at any time point at week 12. The reported mean diurnal IOP at week 12 was 17.8 mmHg for brimonidine/timolol and 17.9 mmHg for latanoprost (p = 0.794). The between-group mean difference in diurnal IOP at week 12 was -0.14 mmHg (95% CI, -1.27 to 0.98), demonstrating non-inferiority of fixed brimonidine/timolol to latanoprost based on predefined criteria. Nine patients in the combination group discontinued the study compared to

2 patients treated with latanoprost, mostly due to adverse effects. Treatment-related adverse events were reported in 16.4% of patients treated with brimonidine/timolol compared to 0% treated with latanoprost.

- Simbrinza (brinzolamide/brimonidine)
  - The efficacy and safety of the combination of brinzolamide/brimonidine were established in 2 double-blind, multicenter, randomized controlled trials. The brinzolamide/brimonidine 1%/0.2% combination was shown to significantly lower the mean IOP compared to either monotherapy (eg, brinzolamide and brimonidine) at all time points of the day in 2 identical, 3 month studies. Adverse events were mostly ocular in nature, and the combination group had a higher percentage of patients reporting adverse events compared to each monotherapy group *(Katz et al 2013, Nguyen et al 2013, Realini et al 2013)*.
    - An additional trial comparing the combination to each monotherapy evaluated secondary efficacy endpoints and safety over 6 months. The combination of brinzolamide/brimonidine had higher rates of adverse events and discontinuation rates. The mean IOP reductions after 6 months were similar to those observed after 3 months *(Whitson et al 2013)*. Another trial evaluating twice daily dosing was conducted after the US approval of the thrice daily dosing. Results were similar to those previously observed *(Aung et al 2014)*.
    - In another trial, compared with dorzolamide/timolol, brinzolamide/brimonidine provided significantly greater morning IOP reductions at 12 weeks *(Kozobolis et al 2017)*.

- Cosopt / Cosopt PF (dorzolamide/timolol)
  - In a study comparing dorzolamide/timolol to the individual components, the combination product was more effective at reducing IOP from baseline at all time periods over 3 months of treatment *(Clineschmidt et al 1998)*.
  - One open-label study evaluated the safety and efficacy of dorzolamide/timolol preservative-free formulation *(Renieri et al 2010).* Patients receiving the preservative-free product experienced a statistically significant reduction in IOP from baseline (p value not reported). Local tolerability improved in 79.3% of patients who switched to this formulation from other anti-glaucoma therapies. Of note, 84% of patients switching from Cosopt experienced an improvement in tolerability with the preservative-free dorzolamide/timolol formulation.
- Cosopt (dorzolamide/timolol) vs. Combigan (brimonidine/timolol)
  - Combined dorzolamide/timolol was compared to brimonidine/timolol, and both demonstrated significant reductions in IOP from baseline. The differences between groups were not found to be significant in any of the 3 studies (p value not reported) *(Gulkilik et al 2011, Martinez et al 2010, Siesky et al 2012)*. However, 2 other studies had conflicting findings. In a crossover study of 20 patients, brimonidine/timolol had significantly lower mean diurnal IOP than dorzolamide/timolol after 6 weeks (16.28 vs. 17.23 mmHg, respectively; $p = 0.03$) *(Garcia-Feijoo et al 2010)*. In a crossover study of 77 patients, dorzolamide/timolol was associated with a greater reduction in the mean 24-hour IOP level from baseline, compared to brimonidine/timolol (mean difference, 0.7 mmHg; $p < 0.001$). Likewise, the peak and minimum 24-hour IOP levels were significantly lower with dorzolamide/timolol compared to brimonidine/timolol ($p = 0.03$ and $p = 0.012$, respectively) *(Konstas et al 2012)*. It is not clear how population size and duration of the crossover studies affected these results.

CLINICAL GUIDELINES

American Optometric Association (AOA) – Care of the Patient with Open Angle Glaucoma (*AOA 2010*)

- The 2010 AOA guideline (currently under review) provides a summary of the efficacy and adverse effects for the various classes of pharmacologic therapy for open angle glaucoma, but does not specifically recommend one class over another. Combination therapy can be considered in patients who have not achieved optimal IOP reduction with a prostaglandin analogue.

American Academy of Ophthalmology (AAO) – Primary Open-Angle Glaucoma *(Prum et al 2016)*

- Medical therapy is presently the most common initial intervention to lower IOP. There are many drugs available for initial therapy, and medication choice may be influenced by potential cost, side effects, dosing schedules, and the degree of IOP lowering needed.
- Prostaglandin analogues are the most frequently used initial eye drops for lowering IOP. They are the most efficacious drugs for lowering IOP, and they are relatively safe. They are, therefore, often considered as initial medical therapy unless other considerations such as contraindications, cost, side effects, intolerance, or patient refusal preclude this.

- Other agents include beta-blockers, alpha-agonists, topical and oral carbonic anhydrase inhibitors, and parasympathomimetics.
- The AAO guidelines do not recommend one ophthalmic prostaglandin analogue over another.

- If a single medication is effective in lowering IOP but the target IOP is not reached, combination therapy or switching to an alternative therapy may be appropriate. Similarly, if a drug fails to reduce IOP sufficiently despite good adherence to therapy, it can be replaced with an alternative agent until effective medical treatment, whether alone or in combination, is established.

AAO – Esotropia and Exotropia Preferred Practice Pattern (*AAO 2017*)

- Guidelines for esotropia and exotropia from the AAO note that cholinesterase inhibitors such as echothiophate iodide reduce accommodative effort and convergence by stimulating ciliary muscle contraction (*AAO 2017*). Echothiophate iodide is among several treatment options that also include corrective lenses, bifocals, prism therapy, botulinum toxin injection, and extraocular muscle surgery.
  - Echothiophate iodide, in the long term, is less desirable than using corrective lenses because of systemic adverse effects such as diarrhea, asthma, and/or increased salivation and perspiration.

SAFETY SUMMARY

- Contraindications
  - Alpha-agonists are contraindicated in patients who have hypersensitivity to the ingredients or clonidine (apraclonidine).
    - Products containing apraclonidine are contraindicated in patients receiving monoamine oxidase inhibitors.
    - Products containing brimonidine are contraindicated in neonates and infants < 2 years of age.
  - Ophthalmic beta-blockers (as single entity agents or in combinations) are contraindicated in patients with a history of bronchial asthma or severe chronic obstructive pulmonary disease, cardiogenic shock, second or third degree atrio-ventricular block, sinus bradycardia, overt cardiac failure, and known hypersensitivity to any component of the product.
  - Echothiophate iodide is contraindicated in acute uveitis, angle-closure glaucoma, and in patients with known hypersensitivity to echothiophate iodide or any component of the formulation.
- Warnings
  - Alpha-agonists may potentiate syndromes associated with vascular insufficiency and should be used with caution in patients with severe cardiovascular disease, depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.
  - Beta-Blockers
    - Ophthalmic beta-blockers, as single entity or in combinations, may mask signs and symptoms of hypoglycemia; use with caution in patients with diabetes mellitus.
    - Ophthalmic beta-blockers may cause systemic adverse events including cardiovascular and respiratory adverse events.
    - Due to the potential for systemic effects with ophthalmic timolol use, exercise caution in patients with cardiac disease, diabetes, and anaphylactic reactions, as beta-blockers may alter response.
  - Warnings for the carbonic anhydrase inhibitors include the risk of corneal edema, bacterial keratitis, ocular adverse effects, and sulfonamide hypersensitivity.
    - Oral and ophthalmic carbonic anhydrase inhibitors should not be used concurrently due to the possibility of additive systemic effects.
    - Due to the brinzolamide component, Simbrinza labeling contains warnings for sulfonamide hypersensitivity reactions, and corneal edema in patients with low endothelial cell counts.
  - Miotics
    - The miosis caused by the ophthalmic miotics usually causes difficulty in dark adaptation; therefore, patients should be advised to exercise caution in night driving and other hazardous occupations in poor illumination.
    - Rare cases of retinal detachment have been reported when used in certain susceptible patients and those with pre-existing retinal disease; therefore, a thorough examination of the retina, including funduscopy, is advised in all patients prior to the initiation of ophthalmic miotics.
    - Caution is advised when administering ophthalmic pilocarpine solution for control of IOP in pediatric patients with primary congenital glaucoma.
    - Caution should be exercised when administering echothiophate iodide in patients with disorders that may respond adversely due to the potential for vagotonic effects.
    - Great caution should be used when administering other cholinesterase inhibitors (ie, succinylcholine), or with exposure to organophosphate or carbamate insecticides, at any time in patients receiving anticholinesterase medications including echothiophate iodide. Respiratory or cardiovascular collapse may occur. Use caution when treating glaucoma with echothiophate iodide in patients receiving systemic anticholinesterase medications for myasthenia gravis due to the risk of possible additive effects. Patients with active or a history of quiescent uveitis should consider avoiding echothiophate iodide. If used with caution, there is a potential for intense and persistent miosis and ciliary muscle contraction.
    - If cardiac irregularities occur with echothiophate iodide use, temporary or permanent discontinuation is recommended.
    - If salivation, urinary incontinence, diarrhea, profuse sweating, muscle weakness, or respiratory difficulties occur with echothiophate iodide use, temporary discontinuation of the medication is recommended.
  - Prostaglandin analogue class warnings include the risk of hyperpigmentation of ocular tissues and eyelash changes with darkening and thickening of eyelashes. Drugs in this class should be used with caution in patients with intraocular inflammation or macular edema.

- ROCK inhibitor
  - Bacterial keratitis: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.
- Adverse reactions
  - Alpha-Agonists
    - The most common adverse events (5 to 20% of patients) with brimonidine included allergic conjunctivitis, burning sensation, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, hypertension, ocular allergic reaction, oral dryness, and visual disturbance.
    - Common adverse events (5 to 15% of patients) with apraclonidine included ocular discomfort, ocular hyperemia, ocular pruritus, and dry mouth.
    - The alpha-agonists can potentially cause systemic adverse effects including somnolence and dizziness.
  - Beta-blockers
    - Local ocular adverse events reported with ophthalmic beta-blockers include blurred vision and instillation reactions (itching, burning, tearing).
  - Carbonic Anhydrase Inhibitors
    - Adverse events are primarily limited to local ocular effects including blurred vision, conjunctival hyperemia, foreign body sensation, ocular burning/stinging, ocular discharge, ocular pruritus, and pain.
    - Ophthalmic carbonic anhydrase inhibitors also are associated with alterations of taste which have been reported in up to 30% of patients.
  - Miotics
    - Most adverse events reported with the miotics are associated with the eye. Visual blurring, burning, eye irritation, and eye pain have been reported.
  - Prostaglandin Analogues
    - The most frequently reported adverse events associated with these agents are ocular in nature and include burning/stinging, hyperemia, pruritus, iris pigmentation changes, and growth and darkening of eyelashes.
  - ROCK inhibitor
    - The most common adverse event with Rhopressa was conjunctival hyperemia (53%). Other common (approximately 20%) ocular adverse reactions reported were corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5 to 10% of patients.
      - Corneal verticillata occurred in approximately 20% of the patients in controlled clinical studies. The corneal verticillata seen in Rhopressa-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes in patients. Most corneal verticillata resolved upon discontinuation of treatment.
- Drug interactions
  - Alpha-agonists may reduce pulse and blood pressure when administered with antihypertensives. When used with central nervous system depressants, alpha-agonists may have an additive or potentiating effect. Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine; it is not known whether the concurrent use of these agents with ophthalmic alpha-agonists can interfere with their IOP-lowering effect. Concomitant therapy of brimonidine and monoamine oxidase inhibitors may result in hypotension.
  - Drug interactions with ophthalmic beta-blockers include the potentiation of the effects of calcium channel blockers, beta-blockers, clonidine, and quinidine on the cardiovascular system.

DOSING AND ADMINISTRATION

- See the current prescribing information for full details.
- In general, patients should remove their contact lenses prior to the instillation of ophthalmic products.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Alpha-Agonists				
Alphagan P (brimonidine); brimonidine 0.2%	Ophthalmic solution Alphagan P does not contain benzalkonium chloride; instead, Purite 0.005% (0.05 mg/mL) is used for the preservative.	Ophthalmic	Three times daily	Safety and effectiveness have not been studied in pediatric patients < 2 years of age; contraindicated in pediatric patients < 2 years. Pregnancy Category B*
Iopidine (apraclonidine)	Ophthalmic solution	Ophthalmic	1% solution: once before and once after procedure 0.5% solution: Three times daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
Beta-Blockers				
Betagan (levobunolol)	Ophthalmic solution	Ophthalmic	Once or twice daily (varies by strength)	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
betaxolol hydrochloride	Ophthalmic solution	Ophthalmic	Twice daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy Category C‡
Betimol (timolol)	Ophthalmic solution	Ophthalmic	Twice daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy Category C‡
Betoptic S (betaxolol hydrochloride)	Ophthalmic suspension	Ophthalmic	Twice daily	Safety and efficacy in lowering IOP have been demonstrated in pediatric patients in a 3 month, multicenter, double-masked, active control trial. Pregnancy: Unclassified†
carteolol hydrochloride	Ophthalmic solution	Ophthalmic	Twice daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy Category C‡
Istalol (timolol maleate)	Ophthalmic solution	Ophthalmic	Once daily	Safety and effectiveness in pediatric patients have not been established.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Pregnancy Category C‡
metipranolol	Ophthalmic solution	Ophthalmic	Twice daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy Category C‡
Timoptic, Timoptic in Ocudose (timolol maleate)	Ophthalmic solution Benzalkonium chloride 0.01% is added as a preservative in Timoptic; the Ocudose solution is preservative-free.	Ophthalmic	Twice daily	Timoptic in Ocudose units should be discarded after a single administration to 1 or both eyes. Safety and effectiveness of timolol have been established when administered in pediatric patients aged 2 years and older. Pregnancy: Unclassified†
Timoptic-XE (timolol maleate GFS)	Ophthalmic gel forming solution	Ophthalmic	Once daily	Safety and effectiveness of timolol have been established when administered in pediatric patients aged 2 years and older. Pregnancy Category C‡
Carbonic Anhydrase Inhibitors				
brinzolamide	Ophthalmic suspension	Ophthalmic	Three times daily	A 3 month clinical trial with brinzolamide 1% dosed twice daily in pediatric patients 4 weeks to 5 years did not demonstrate a reduction in IOP from baseline. Pregnancy Category C‡
dorzolamide	Ophthalmic solution	Ophthalmic	Three times daily	Dorzolamide and its metabolite are excreted predominantly by the kidney; therefore, dorzolamide is not recommended in patients with severe renal impairment. Safety and IOP-lowering effectiveness of dorzolamide have been demonstrated in pediatric patients in a 3 month, multicenter, double-masked, active control trial. Pregnancy Category C‡
Miotics				

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Phospholine Iodide (echothiophate iodide)	Ophthalmic powder for reconstitution	Ophthalmic	Once or twice daily Chronic open-angle glaucoma: Twice daily; may be used once daily or once every other day Accommodative esotropia: Daily or every other day	Requires reconstitution. Store reconstituted solution at room temperature and discard any unused solution after 4 weeks. Pregnancy: Unclassified†
Isopto Carpine (pilocarpine)	Ophthalmic solution	Ophthalmic	Up to 4 times daily (varies by indication) Induction of miosis prior to procedure and prevention of postoperative elevated IOP: 15 to 60 minutes prior to surgery Management of acute angle-closure glaucoma: Initial: 1 drop up to 3 times over a 30 minute period; Maintenance: 4 times daily Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension: 4 times daily Dosing in children < 2 years of age: 3 times daily; children ≥ 2 years of age should follow adult dosing	Safety and effectiveness in pediatric patients have been established. Pregnancy Category C‡
Prostaglandin Analogues				
latanoprost	Ophthalmic solution Latanoprost 0.005% solution contains benzalkonium chloride 0.02%	Ophthalmic	Daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy Category C‡
Latisse (bimatoprost)	Ophthalmic solution	Ophthalmic	Daily	May be used in patients aged ≥ 5 years for hypotrichosis of the

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				eyelashes. Bimatoprost has been studied in patients aged 5 to 17 years who were post-chemotherapy or had alopecia and ages 15 to 17 years with hypotrichosis not associated with a medical condition. Pregnancy: Unclassified†
Lumigan (bimatoprost) 0.01%; generic bimatoprost 0.03%	Ophthalmic solution	Ophthalmic	Daily	Use in pediatric patients < 16 years of age is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy: Unclassified†
Travatan Z (travoprost)	Ophthalmic solution	Ophthalmic	Daily	Use in pediatric patients < 16 years of age is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy Category C‡
Vyzulta (latanoprostene bunod)	Ophthalmic solution	Ophthalmic	Daily	Use in pediatric patients < 16 years of age is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy: Unclassified†
Xelpros (latanoprost)	Ophthalmic emulsion Xelpros is preservative-free swollen micelle microemulsion.	Ophthalmic	Daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy Category C‡
Zioptan (tafluprost)	Ophthalmic solution	Ophthalmic	Daily	Use in pediatric patients is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy Category C‡
ROCK Inhibitor				
Rhopressa (netarsudil)	Ophthalmic solution	Ophthalmic	Daily	Safety and effectiveness in pediatric patients have not been established.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Pregnancy: Unclassified†
Combinations				
Combigan (brimonidine/timolol)	Ophthalmic solution	Ophthalmic	Twice daily	Safety and effectiveness of Combigan have been established in children ages 2 to 16 years of age; contraindicated in pediatric patients < 2 years. Pregnancy: Unclassified†
Cosopt / Cosopt PF (dorzolamide /timolol)	Ophthalmic solution Benzalkonium chloride 0.0075% is added as a preservative in Cosopt; Cosopt PF is preservative-free.	Ophthalmic	Twice daily	Safety and effectiveness of dorzolamide and timolol have been established when administered separately in children aged 2 years and older. Use of these drug products in children is supported by evidence from adequate and well-controlled studies in children and adults. Cosopt PF units should be discarded after a single administration to 1 or both eyes. Pregnancy Category C‡
Simbrinza (brinzolamide/ brimonidine)	Ophthalmic suspension	Ophthalmic	Three times daily	Brinzolamide has been studied in pediatric glaucoma patients 4 weeks to 5 years of age; brimonidine has been studied in pediatric patients 2 to 7 years of age. Simbrinza is contraindicated in neonates and infants < 2 years of age. Not studied in patients with severe renal impairment (creatinine clearance < 30 mL/min); since brinzolamide and its metabolite are excreted predominantly by the kidney, Simbrinza is not recommended in such patients. Pregnancy Category C‡

* Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
† In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.
‡ Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

CONCLUSION

- Treatment of glaucoma currently focuses on decreasing IOP by 1 of 3 methods: laser therapy, surgery, or medical intervention *(Prum et al 2016)*. There are no standard guidelines for a target IOP (*Jacobs 2018[b]*). Medical intervention includes 5 classes of ophthalmic agents used for the long-term management of glaucoma: alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, miotics, and prostaglandin analogues. Guidelines published in 2010 by the AOA (currently under review per the AOA website) do not recommend preferential use of any drug class, although current guidelines by the AAO generally recommend ophthalmic prostaglandin analogues as first-line pharmacologic therapy in patients with elevated IOP *(AOA 2010, Prum et al 2016)*.
  - Combination therapy with agents from other therapeutic classes should be used if the reduction in IOP on monotherapy is unsatisfactory *(AOA 2010, Prum et al 2016)*. Combination therapy can be given as separate drops or in fixed dose combinations which include brimonidine/timolol, brimonidine/brinzolamide, and dorzolamide/timolol.
  - Adherence is often poor with glaucoma treatment as the disease is asymptomatic for many years, and eye drops may be difficult to use or cause adverse effects (*Jacobs 2018[b]*).
  - The AAO and AOA guidelines have not been updated to include netarsudil, Xelpros (latanoprost ophthalmic emulsion), or Vyzulta (latanoprostene bunod).
- Among the ophthalmic prostaglandin analogues, studies have demonstrated statistically significant differences in IOP-lowering ability among agents in the class. However, the differences are generally small, and the clinical significance of these differences has not been established. Bimatoprost is generally considered to have the greatest IOP-reducing effect among the ophthalmic prostaglandin analogues *(Aptel et al 2008, Cheng et al 2008, Kammer et al 2010, Li et al 2016, Lin et al 2014, Weinreb et al 2018)*.
  - In addition to conjunctival hyperemia, ocular adverse events with the prostaglandin analogues include eye irritation, increase in the number and length of eyelashes, and changes in iris and lash pigmentation; the latter 2 are most notable if only 1 eye is treated. The ophthalmic prostaglandin analogues are considered to be better tolerated compared to other classes of medications used for the management of glaucoma *(Jacobs 2018[b])*.
- Several ophthalmic agents in these drug classes are used for other indications. Ophthalmic apraclonidine 1% is FDA-approved to control or prevent postsurgical elevations in IOP, while ophthalmic apraclonidine 0.5% is indicated as short-term adjunctive therapy in patients on maximally tolerated medical therapy who require additional IOP reduction. Ophthalmic pilocarpine is indicated for control of IOP, management of acute angle-closure glaucoma, prevention of postoperative elevated IOP associated with laser surgery, and reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension. Echothiophate iodide is indicated for chronic open-angle glaucoma and accommodative esotropia. The ophthalmic miotics are an established treatment option as they have been available since the 1960s.

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INTRODUCTION

- Dry eye syndrome refers to a group of disorders of the tear film that are due to reduced tear production or excessive tear evaporation (*American Academy of Ophthalmology [AAO] 2013*). The condition can be associated with discomfort and/or visual symptoms and may result in disease of the ocular surface. The ocular surface and tear-secreting glands are recognized to be responsible for the maintenance of tear production and to clear tears. Therefore, disease or dysfunction results in an unstable and poorly maintained tear film that causes ocular irritation symptoms and an epithelial disease known as keratoconjunctivitis sicca (KCS). Decreased tear secretion and clearance initiates an inflammatory response on the ocular surface, which plays a role in the pathogenesis of KCS. Symptoms of KCS include, but are not limited to, dryness, discomfort, irritation/pain, foreign body sensation, and blurred vision (*AAO 2013*).
- Rare complications of severe dry eyes include ocular surface keratinization; corneal scarring, thinning, or neovascularization; microbial or sterile corneal ulceration with possible perforation; and severe visual loss.
- Frequent instillation of ophthalmic medications (eg, natural tears) may cause dry eye symptoms by preventing the normal maintenance of the tear film. Other factors known to exacerbate symptoms of dry eye include environmental factors such as reduced humidity, air drafts, air conditioning, or heating. Associated systemic diseases include Sjögren's Syndrome, rosacea, and viral infection. Common drug-induced causes of dry eye symptoms include systemic medications such as anticholinergics, antidepressants, antihistamines, diuretics, and retinoids (*AAO 2013*).
- Medispan Therapeutic Class: Ophthalmic Immunomodulators

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Restasis, Restasis Multidose (cyclosporine ophthalmic emulsion)	-
Cequa (cyclosporine ophthalmic solution)	-
Xiidra (lifitegrast ophthalmic solution)	-

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Restasis, Restasis Multidose (cyclosporine ophthalmic emulsion)	Cequa (cyclosporine ophthalmic solution)	Xiidra (lifitegrast ophthalmic solution)
To increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca*	✔		
To increase tear production in patients with keratoconjunctivitis sicca		✔	
Treatment of the signs and symptoms of dry eye disease			✔

*Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

(*Restasis prescribing information 2017; Restasis Multidose prescribing information 2016, Xiidra prescribing information 2017, Cequa prescribing information 2018*)

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

CLINICAL EFFICACY SUMMARY

- The pivotal trials for cyclosporine ophthalmic emulsion were 2 randomized, placebo-controlled trials that included 877 patients and an open-label, extension trial that included 412 patients (*Barber et al 2005, Sall et al 2000*). All patients were diagnosed with moderate-to-severe KCS and decreased tear production based on the Schirmer tear test. The combined results of the 2 placebo-controlled trials demonstrated that cyclosporine ophthalmic emulsion 0.05% and 0.1% were associated with significant improvements from baseline in corneal staining, Schirmer tear test scores, Ocular Surface Disease Index (OSDI) scores, Subjective Facial Expression Rating Scale scores, and various dry eye related symptoms (*Sall et al, 2000*). Specifically compared to placebo, at 4 months, improvements in corneal staining were significant in both cyclosporine ophthalmic emulsion groups compared to placebo ($p \leq 0.044$), and at 6 months, only the cyclosporine ophthalmic emulsion 0.05% group demonstrated significance over placebo ($p = 0.008$). Additionally, at 6 months, improvements in Schirmer tear test scores were significantly greater for both cyclosporine ophthalmic emulsion groups compared to placebo ($p \leq 0.05$ for both) and from baseline scores (p values not reported). Improvements in OSDI and Subjective Facial Expression Rating Scale scores were significant compared to baseline for all treatment groups ($p < 0.001$), but there were no significant differences among these groups (p values not reported). Improvements in blurred vision were significantly greater in the cyclosporine ophthalmic emulsion 0.05% group than placebo at all follow-up visits ($p \leq 0.014$), and significant improvements were achieved at all time points within all treatment groups when compared to baseline for relief of dry eye symptoms including dryness ($p < 0.001$), sandy/gritty feeling ($p < 0.001$), and itching ($p \leq 0.038$). A Chinese, double-blind study used similar subjective ratings for dry eye symptoms and found that cyclosporine ophthalmic emulsion 0.05% improved measures over 8 weeks (*Chen et al 2010*).
- An open-label, extension trial was also conducted to determine the long-term safety of cyclosporine ophthalmic emulsion. After 3 consecutive 12-month periods, results demonstrated that cyclosporine ophthalmic emulsion was safe and well tolerated. Over 3 years, adverse events were found in 65.3% (269/412) of patients with ocular burning reported most commonly (12.1%). This trial also demonstrated sustained efficacy of cyclosporine ophthalmic emulsion over an extended period of time (*Barber et al 2005*).
- A trial comparing cyclosporine ophthalmic emulsion to punctal plugs or a combination of both demonstrated that both treatments improved the symptoms of dry eye, but punctal plugs achieved results more rapidly than cyclosporine ophthalmic emulsion (*Roberts et al 2007*).
- A systematic review of 18 RCTs examined the efficacy and safety of topical cyclosporine for treatment of dry eye disease. All cyclosporine formulations proved safe for the treatment of dry eye disease. Symptoms improved in 100% (9/9 RCTs), tear function improved in 72% (13/18 RCTs) and ocular surface damage was ameliorated in 53% (9/17 RCTs) (*Saccheti et al 2014*).
  - Statistical comparison of cyclosporine efficacy through a meta-analysis of data was not possible due to a lack of standardized criteria and comparable outcomes among studies.

- Two multicenter, randomized, controlled clinical studies evaluated the efficacy of cyclosporine ophthalmic solution 0.09% in 1048 patients with keratoconjunctivitis sicca. In both studies, there was a significantly ($p < 0.01$) higher percentage of eyes with increases of ≥ 10 mm from baseline in Schirmer wetting as compared to vehicle at day 84. This effect was seen in approximately 17% of Cequa-treated vs approximately 9% of vehicle-treated patients (*Cequa prescribing information 2018*).

- The safety and efficacy of lifitegrast ophthalmic solution for the treatment of dry eye disease were assessed in a total of 1181 patients (1067 of which received lifitegrast 5%) in four 12-week, randomized, multicenter, double-masked, vehicle-controlled studies (*Semba et al 2012, Sheppard et al 2014, Tauber et al 2015, Holland et al 2017*). The use of artificial tears was not allowed during the studies. The clinical trials evaluated various endpoints related to signs and symptoms of dry eye disease. However, the Food and Drug Administration (FDA) approval relied on an assessment of symptoms based on change from baseline in patient reported eye dryness score (EDS; 0 to 100 visual analogue [VAS] scale) and an assessment of signs based on the inferior corneal staining score (ICSS; 0 to 4 scale).
- A larger reduction in EDS favoring lifitegrast was observed in all studies at day 42 and day 84.

- EDS was used as a primary symptom endpoint in 2 of the 4 studies (OPUS-2 and OPUS-3); the other 2 evaluated EDS as a secondary endpoint.
- In OPUS-1, the primary symptom endpoint was the visual-related function subscale score of the Ocular Surface Disease Index (VR-OSDI) questionnaire. No difference between lifitegrast and placebo was seen in the mean change from baseline to day 84 (p = 0.7894) (*Sheppard et al 2014*).

- At day 84, a larger reduction in ICSS favoring lifitegrast was observed in 3 of the 4 studies (no statistically significant difference between lifitegrast and placebo was found in the OPUS-2 study).
- In a 1-year safety study (N = 331: 220 lifitegrast; 111 placebo), there were no serious ocular treatment-emergent adverse events (TEAEs). Overall, 53.6% of participants receiving lifitegrast experienced ≥ 1 ocular TEAE vs. 34.2% in the placebo group; most TEAEs were mild to moderate in severity, with burning, instillation site reaction, reduced visual acuity, dry eye, and dysgeusia reported most commonly (*Donnenfeld et al 2016*).
- Ocular comfort of lifitegrast was also assessed in OPUS-3 (n = 711). Drop comfort scores (0 = very comfortable, 10 = very uncomfortable) were assessed immediately after instillation and at 1, 2, and 3 minutes post-instillation. The results showed that drop comfort scores with lifitegrast improved within 3 minutes of instillation with scores approaching that of placebo (*Nichols et al 2018*).

CLINICAL GUIDELINES

- Clinical guidelines consider cyclosporine ophthalmic emulsion to be an appropriate therapy for patients with moderate dry eye syndrome, and also in the treatment of severe atopic KCS or for those patients with atopic KCS who have failed conventional therapy (*AAO 2013*). However, depending on patient preference and physician experience, any of the recognized treatment options for dry eye syndrome may be used to treat the disease regardless of the severity rating. The guidelines have not yet been updated to include lifitegrast.

SAFETY SUMMARY

- Cyclosporine ophthalmic emulsion
  - Cyclosporine ophthalmic emulsion is contraindicated in patients with known or suspected hypersensitivity to any ingredient in the formulation.
  - Warnings include the risk of eye injury and contamination when administering the medication if the vial tip touches the eye or other surfaces and use with contact lenses. Cyclosporine ophthalmic emulsion should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of cyclosporine ophthalmic emulsion.
  - Ocular burning is the most frequently reported adverse event. Other adverse events reported include ocular pain, conjunctival hyperemia, discharge, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).
- Cyclosporine ophthalmic solution
  - The ophthalmic solution has no contraindications for use.
  - Cyclosporine ophthalmic solution has similar warnings as the ophthalmic emulsion formulation.
  - Pain on drop instillation was the most frequently reported adverse event followed by conjunctival hyperemia. Other adverse events included blepharitis, eye irritation, headache, and urinary tract infection.
- Lifitegrast ophthalmic solution
  - Lifitegrast ophthalmic solution is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation.
  - The most commonly reported adverse events reported in 5 to 25% of patients were instillation site irritation, dysgeusia, and reduced visual acuity.
  - Other adverse events reported in 1 to 5% of patients included blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus, and sinusitis.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Restasis, Restasis Multidose (cyclosporine ophthalmic emulsion)	Ophthalmic emulsion	opth	To increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca: Ophthalmic emulsion: instill 1 drop in each eye twice daily approximately 12 hours apart	Cyclosporine ophthalmic emulsion can be used concomitantly with artificial tears; however, patients should allow for a 15-minute interval between the products. To avoid contamination, care should be taken not to touch the bottle tip to the eye or other surfaces. Restasis (single-dose vial): Discard vial immediately after use. Restasis Multidose is packaged in a multi-dose preservative-free 10 mL bottle containing 5.5 mL.
Cequa (cyclosporine ophthalmic solution)	Ophthalmic solution	opth	Instill 1 drop twice daily (approximately 12 hours apart)	Cyclosporine ophthalmic solution can be used concomitantly with artificial tears; however, patients should allow for a 15-minute interval between the products. To avoid contamination, care should be taken not to touch the bottle tip to the eye or other surfaces. Discard the vial immediately after use.
Xiidra (lifitegrast ophthalmic solution)	Ophthalmic solution	opth	Instill 1 drop twice daily (approximately 12 hours apart)	Contact lenses should be removed prior to the administration of lifitegrast and may be reinserted 15 minutes following administration. Discard the single-use container immediately after using in each eye.

See the current prescribing information for full details

CONCLUSION

- Restasis (cyclosporine ophthalmic emulsion) is the first ophthalmic emulsion FDA-approved to increase tear production in patients with KCS. Although the exact mechanism of action of this agent is unknown, it is assumed that it acts as a partial immunomodulator.
- Xiidra (lifitegrast ophthalmic solution) is the second prescription treatment to receive FDA-approval for treatment of dry eye disease. Lifitegrast is a novel small molecule integrin antagonist that inhibits T cell-mediated inflammation by blocking the binding of 2 important cell surface proteins (lymphocyte function-associated antigen 1 [LFA-1] and intercellular adhesion molecule 1 [ICAM-1]), thus lessening overall inflammatory responses. However, the exact mechanism of action of lifitegrast in dry eye disease is unknown.
- In August 2018, the FDA approved Cequa (cyclosporine ophthalmic solution) to increase tear production in patients with KCS (*Cequa prescribing information 2018)*. This is the first cyclosporine product to utilize nanomicellar technology. This formulation allows the drug molecule to overcome solubility difficulties, penetrate the eye's aqueous layer, and prevent the release of active lipophilic molecule prior to penetration.
- In clinical trials, cyclosporine ophthalmic emulsion demonstrated significant increases in tear production and decreases in dry eye symptoms compared to placebo and demonstrated safety for up to 3 years (*Sall et al 2000, Barber et al 2005,*

Roberts et al 2007). For the new cyclosporine ophthalmic solution, there was a significantly ($p < 0.01$) higher percentage of eyes with increases of ≥ 10 mm from baseline in Schirmer wetting as compared to vehicle at day 84 *(Cequa prescribing information 2018)*.

- Lifitegrast also demonstrated significant improvements in the signs and symptoms of dry eye disease compared with placebo in clinical trials. Lifitegrast was well tolerated with no unexpected adverse events in a 1-year safety exposure study (*Donnenfeld et al 2016, Holland et al 2017, Semba et al 2012, Sheppard et al 2014, Tauber et al 2015*).
- Clinical guidelines consider cyclosporine ophthalmic emulsion to be an appropriate therapy for patients with moderate to severe dry eye syndrome (*AAO 2013, AOA 2010*). Lifitegrast and the recently approved cyclosporine ophthalmic solution have not yet been incorporated into the guidelines.
- There are no comparative trials of cyclosporine ophthalmic emulsion or solution and lifitegrast ophthalmic solution.

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Established Drug Classes

INTRODUCTION

- Neuropathic pain is commonly described by patients as burning or electrical in nature and results from injury or damage to the nervous system (*Herndon et al 2017*). Management of neuropathic pain may prove challenging due to unpredictable patient response to drug therapy (*Attal et al 2010*).
- Fibromyalgia is characterized by chronic musculoskeletal pain with unknown etiology and pathophysiology. Patients typically complain of widespread musculoskeletal pain, fatigue, cognitive disturbance, psychiatric symptoms, and multiple somatic symptoms (*Goldenberg 2016[a]*). Fibromyalgia is often difficult to treat and requires a multidisciplinary, individualized treatment program (*Goldenberg 2016[b]*).
- This review focuses on medications that are approved by the Food and Drug Administration (FDA) for the treatment of fibromyalgia, neuropathic pain, and/or post-herpetic neuralgia (PHN). The products in this review include Cymbalta (duloxetine), Gralise (gabapentin ER), Horizant (gabapentin enacarbil ER), Lidoderm (lidocaine 5% patch), Lyrica (pregabalin), Lyrica CR (pregabalin ER), Neurontin (gabapentin), Nucynta ER (tapentadol ER), Qutenza (capsaicin), and Savella (milnacipran). These agents represent a variety of pharmacologic classes, including anticonvulsants, serotonin-norepinephrine reuptake inhibitors (SNRIs), extended-release (ER) opioids, and topical analgesics. As such, these agents hold additional FDA-approved indications that are outlined in Table 2; however, clinical information included within this review will not address the use of these agents for these additional indications (*Prescribing information: Cymbalta 2017, Gralise 2015, Horizant 2016, Lidoderm 2015, Lyrica 2017, Lyrica CR 2017, Neurontin 2017, Nucynta ER 2017, Qutenza 2013, Savella 2017*).
  - In February 2018, the FDA approved ZTlido (lidocaine 1.8% topical system) for the relief of pain associated with PHN. The product is not yet available commercially.
    - One ZTlido 1.8% topical system provides equivalent lidocaine exposure to one Lidoderm 5% patch.
- Medispan classes: Anticonvulsants - Misc.; Fibromyalgia Agents; Local Anesthetics – Topical; Opioid Agonists; Postherpetic Neuralgia (PHN) Agents; Restless Leg Syndrome (RLS) Agents; Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Diabetic Neuropathy

- Approximately 50% of patients with diabetes will eventually develop neuropathy. The high rate of diabetic neuropathy results in substantial patient morbidity, which includes recurrent lower extremity infections, ulcerations, and subsequent amputations (*Feldman et al 2015[a]*).
- The condition is categorized into distinct syndromes based on the neurologic distribution, although syndromes may overlap in some patients. The most frequently encountered diabetic neuropathies include distal symmetric polyneuropathy, autonomic neuropathy, polyradiculopathies, and mononeuropathies (*Feldman et al 2015[a]*).
- The 3 main components to the management of diabetic neuropathy are glycemic control, foot care, and pain management (*Feldman et al 2017[b]*).
  - Optimal glucose control is important for the prevention of diabetic neuropathy. Clinical trial evidence demonstrates that rigorous blood glucose control in patients with type 1 diabetes reduces the occurrence of diabetic neuropathy. In contrast, the role of glycemic control in established diabetic neuropathy is uncertain. Limited evidence suggests that neuropathic symptoms may improve with intensive antidiabetic therapy (*Feldman et al 2017[b]*).
  - Patients with diabetes should be counseled on the importance of daily foot care, including the inspection of feet for the presence of dry or cracking skin, fissures, and plantar callus formation. Regular foot examinations by a healthcare provider are also important (*Feldman et al 2017[b]*).
  - A small proportion of patients with diabetic neuropathy will experience painful symptoms, and in some instances the condition is self-limited. When treatment is necessary, options include antidepressants, anticonvulsants, capsaicin cream, lidocaine patches, alpha-lipoic acid, isosorbide dinitrate topical spray, and transcutaneous electrical nerve stimulation (*Feldman et al 2017[b]*).

Fibromyalgia

- Fibromyalgia is a chronic functional illness marked by widespread musculoskeletal pain for which no alternative cause can be identified. Fibromyalgia patients often experience neuropsychological symptoms of fatigue, unrefreshing sleep, cognitive dysfunction, anxiety, and depression (*Clauw et al 2009*).
  - Patients with fibromyalgia have pain that is typically above and below the waist on both sides of the body and involves the axial skeleton (neck, back, or chest). The pain attributable to fibromyalgia is poorly localized, difficult to ignore, severe in its intensity, and associated with a reduced functional capacity (*Crofford 2015*).
- The prevalence of fibromyalgia in the general US population is estimated to be 2% (*Williams et al 2009*). It is more common in women than in men, with a ratio of approximately 9:1 (*Crofford 2015*).
- There is an increased prevalence of other syndromes associated with pain and fatigue, including chronic fatigue syndrome, temporomandibular disorder, chronic headaches, irritable bowel syndrome, interstitial cystitis/painful bladder syndrome, and other pelvic pain syndromes in fibromyalgia patients (*Clauw et al 2009, Crofford 2015*).

PHN

- PHN is generally defined as the persistence of the pain of herpes zoster for more than three months after resolution of the rash. It affects 10 to 15% of patients with herpes zoster, with incidence increasing with age. The duration of PHN is highly variable among individuals (*Dubinsky et al 2004*).
- PHN, as well as acute herpetic neuralgia, can be a severe condition associated with profound psychological dysfunction, including impaired sleep, decreased appetite, and decreased libido (*Bajwa et al 2017*).
- Prevention of PHN involves either treatment of acute herpes zoster infection or use of a vaccine (*Bajwa et al 2017*). Administration of antiviral agents within 72 hours of the onset of herpes zoster can reduce the intensity and duration of acute illness, and can also prevent PHN. This may also be achieved with the administration of the tricyclic antidepressant, amitriptyline (*Dubinksy et al 2004*).
- A number of treatment modalities have been evaluated in the management of PHN and include tricyclic antidepressants, anticonvulsants, opioids, capsaicin, topical lidocaine, intrathecal glucocorticoids, N-methyl-D-aspartate receptor antagonists, botulinum toxin, cryotherapy, and surgery (*Bajwa et al 2017*).

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Cymbalta (duloxetine delayed-release)	✔
Gralise (gabapentin ER)*	-
Horizant (gabapentin enacarbil ER)*	-
Lidoderm (lidocaine transdermal patch)	✔
Lyrica (pregabalin)	-
Lyrica CR (pregabalin ER)	-
Neurontin (gabapentin)*	✔
Nucynta ER (tapentadol ER)	-
Qutenza (capsaicin transdermal patch)	-
Savella (milnacipran)	-
ZTlido (lidocaine topical system)	-

* Medication is not interchangeable with other gabapentin products because of differing pharmacokinetic profiles that affect the frequency of administration.
† ZTlido is not yet available commercially.

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

INDICATIONS

Table 2. FDA-Approved Indications

Indication	Cymbalta (duloxetine)	Gralise (gabapentin ER)	Horizant (gabapentin enacarbil ER)	Lidoderm, ZTlido (lidocaine)	Lyrica (pregabalin)	Lyrica CR (pregabalin ER)	Neurontin (gabapentin)	Nucynta ER (tapentadol)	Qutenza (capsaicin)	Savella (milnacipran)
Adjunctive therapy for adult patients with partial onset seizures					✔					
Adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients > 3 years of age with epilepsy							✔			
Adjunctive therapy for patients 4 years of age and older with partial onset seizures					✔					
Management of chronic musculoskeletal pain	✔ †									
Management of fibromyalgia	✔				✔					✔
Management of neuropathic pain associated with diabetic peripheral neuropathy	✔				✔	✔		✔ §		
Management of neuropathic pain associated with spinal cord injury					✔					
Management of PHN		✔	✔		✔	✔	✔			
Relief of pain associated with PHN				✔					✔	
Moderate-to-severe primary restless legs syndrome			✔ ‡							
Treatment of generalized anxiety disorder	✔									
Treatment of major depressive disorder	✔									
Management of moderate to severe chronic pain in adults								✔ §		

† This has been established in studies of patients with chronic low back pain and chronic pain due to osteoarthritis.
‡ Gabapentin enacarbil is not indicated for patients who are required to sleep during the day and remain awake at night.
§ Indicated when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. Medication is not for use as: an as-needed analgesic; for pain that is mild or not expected to persist for an extended period of time; for acute pain; or for postoperative pain, unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time.

(*Prescribing information: Cymbalta 2017, Gralise 2015, Horizant 2016, Lidoderm 2015, Lyrica 2018, Lyrica CR 2017, Neurontin 2017, Nucynta ER 2017, Qutenza 2013, Savella 2017, ZTlido 2018*)

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

CLINICAL EFFICACY SUMMARY

Neuropathic Pain

- Pregabalin demonstrated significant improvements in pain relief, functional outcomes, and quality of life compared to placebo for the treatment of diabetic peripheral neuropathic pain. Commonly reported adverse events (AEs) in patients receiving pregabalin include dizziness, somnolence, infection, headache, dry mouth, weight gain, and peripheral edema (*Dworkin et al 2003, Freynhagen et al 2005, Guan et al 2011, Lesser et al 2004, Moon et al 2010, Rosenstock et al 2004, Roth et al 2010, Sabatowski et al 2004, Semel et al 2010, Sharma et al 2010, Skvarc et al 2010*).
- Tapentadol ER demonstrated superiority over placebo in alleviating pain and improving quality of life in patients with diabetic peripheral neuropathy. Tapentadol ER is associated with significant improvements in pain intensity scores, responder rates, and patient global impression of change (PGIC). Commonly reported AEs in patients receiving tapentadol ER include nausea, vomiting, and constipation (*Schwartz et al 2011*).
- Duloxetine demonstrated consistent superiority over 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 (SF-36), Pain-Related Sleep Interference, and Euro Quality of Life assessment (EQ-5D) scores. Commonly reported AEs in patients receiving duloxetine include nausea, somnolence, anorexia, and dysuria (*Armstrong et al 2007, Kajdasz et al 2007, Lunn et al 2014, Parsons et al 2016, Yan et al 2010*).
- Head-to-head trials among the neuropathic pain and fibromyalgia agents are rare. In a 52-week, open-label trial comparing duloxetine to routine care (gabapentin, amitriptyline, and venlafaxine) for the treatment of diabetic peripheral neuropathic pain, there were no significant differences observed between groups in EQ-5D questionnaire scores; however, results differed with regards to SF-36 subscale scores. In another trial, there were no significant between-group differences in SF-36 subscale scores; however, other subscale scores for physical functioning, bodily pain, mental health, and vitality favored duloxetine (*Raskin et al 2006, Wernicke et al 2007[b]*). A second head-to-head trial demonstrated duloxetine to be noninferior to pregabalin for the treatment of pain in patients with diabetic peripheral neuropathy who had an inadequate pain response to gabapentin (*Tanenberg et al 2011*). A post-hoc analysis of study patients who were taking concomitant antidepressants and those who were not taking antidepressants found duloxetine may provide better pain reduction in those patients who were not taking concomitant antidepressants (*Tanenberg et al 2014*). Another head-to-head trial found high-dose duloxetine or pregabalin monotherapy had no significant differences, as measured by Brief Pain Inventory Modified Short Form (BPI-MSF) average pain in comparison, with combination duloxetine and pregabalin therapy (*Tesfaye et al 2013*).
- Several large meta-analyses and systematic reviews have been conducted evaluating the neuropathic pain and fibromyalgia agents, which further support the safety and efficacy of these agents in FDA-approved indications (*Chou et al 2009, Edelsberg et al 2011, Lunn et al 2009, Lunn et al 2014, Meng et al 2014, Moore et al 2009, Moore et al 2014, Quilici et al 2009, Wernicke et al 2007[a]*). In a meta-analysis by Quilici et al, limited available clinical trial data suitable for indirect comparison demonstrated that duloxetine provides comparable efficacy and tolerability to that of gabapentin and pregabalin for the treatment of diabetic peripheral neuropathic pain (*Quilici et al 2009*).
- The efficacy of pregabalin in patients with neuropathic pain associated with spinal cord injury was established in 2 placebo-controlled trials, 1 of 12 weeks duration and the other of 16 weeks duration. Patients had neuropathic pain associated with spinal cord injury for at least 3 months or with relapses and remissions for at least 6 months. Patients were allowed to take opioids, non-opioid analgesics, antiepileptic drugs, muscle relaxants, and antidepressant drugs if doses were stable for 30 days prior to screening. Patients were also allowed to take acetaminophen and nonsteroidal anti-inflammatory drugs during the trial. In both trials, pregabalin (150 to 600 mg/day) significantly improved weekly pain scores, and increased the proportion of patients with at least a 30 or 50% reduction from baseline in pain score compared to placebo (*Lyrica prescribing information 2016*, *Siddall et al 2006, Vranken et al 2008*).

Fibromyalgia

- From the agents included in this review, the agents that have several randomized controlled trials (RCTs) and meta-analyses demonstrating their efficacy in the treatment of fibromyalgia include duloxetine, pregabalin, and milnacipran (*Arnold et al 2007, Arnold et al 2008, Arnold et al 2009, Clauw et al 2008, Crofford et al 2005, Hauser et al 2009[a], Hauser et al 2009[b], Hauser et al 2010, Hauser et al 2013, Lunn et al 2014, Mease et al 2009, Mease et al 2010, Russell et al 2008, Vitton et al 2004*).
  - A 2009 meta-analysis on the treatment of fibromyalgia syndrome with antidepressants found that antidepressants were associated with improved health-related quality of life. The largest effect size for pain reduction was seen with

the tricyclic antidepressant, amitriptyline, followed by monoamine oxidase inhibitors, moclobemide and pirlindole (medium effect size). Small effect sizes were observed with the selective serotonin reuptake inhibitors (SSRIs), fluoxetine and paroxetine, and the SNRIs, duloxetine and milnacipran. The authors concluded that short-term treatment with amitriptyline and duloxetine could be considered for fibromyalgia-associated pain and sleep disturbances (*Hauser et al 2009[a]*).

- In a meta-analysis of 5 RCTs, gabapentin and pregabalin reduced pain and improved sleep in patients with fibromyalgia. The pooled number-needed-to-treat to achieve ≥ 30% reduction in pain was 8.5. Anxiety, depressed mood, and fatigue were not improved with gabapentin or pregabalin treatment (*Hauser et al 2009[b]*).
- Results from another 2010 meta-analysis noted that duloxetine, milnacipran, and pregabalin have short-term (up to 6-month) efficacy data. The authors concluded that the choice of medication may be dependent on the differences with regard to the occurrence of the key symptoms of fibromyalgia syndrome and to AEs specific to individual drug (*Hauser et al 2010*).
- A systematic review and meta-analysis of 10 randomized trials involving 6038 patients concluded that duloxetine and milnacipran provided a small incremental benefit over placebo in pain reduction, and that the dropout rates for duloxetine and milnacipran due to AEs were higher than placebo (*Hauser et al 2013*).
- A systematic review of 6 randomized trials involving 2249 patients concluded that for the treatment of fibromyalgia, duloxetine 60 and 120 mg/day are effective with a similar magnitude of effect (low quality evidence). The effect in fibromyalgia may be achieved through a greater improvement in mental symptoms than somatic physical pain (*Lunn et al 2014*).
- A 2016 network meta-analysis of 9 RCTs (N = 5140) indirectly compared duloxetine, pregabalin, and milnacipran in the treatment of fibromyalgia. The probability of achieving > 30% improvement in pain scores was numerically highest with duloxetine 60 mg, followed by pregabalin 300 mg, milnacipran 100 mg, and milnacipran 200 mg. While the aforementioned treatment groups each demonstrated superiority over placebo, differences between active treatments did not achieve statistical significance (*Lee and Song 2016*).

PHN

- In patients with PHN, treatment with lidocaine 5% resulted in significant pain relief compared to placebo (*Galer et al 1999, Galer et al 2002, Meier et al 2003*). In addition, treatment with lidocaine 5% was associated with higher rates of patient preference, less use of rescue medication, and decreases in allodynia and neuropathic symptoms compared to placebo (*Galer et al 1999, Meier et al 2003*). An open-label trial evaluating lidocaine 5% for the management of PHN supports the findings of placebo-controlled trials (*Katz et al 2002*).
- Lidocaine 1.8% was approved via the 505(b)(2) pathway with no new efficacy trials. However, in a single-dose, crossover study conducted in 53 healthy volunteers, lidocaine 1.8% topical system demonstrated equivalent exposure (AUC) and peak concentration (C_{max}) of lidocaine to lidocaine 5% patch. In addition, based on a clinical study in 54 subjects, 47 subjects (87%) had adhesion scores of 0 (≥ 90% adhered) for all evaluations performed every 3 hours during the 12 hours of lidocaine 1.8% administration, 7 subjects (13%) had adhesion scores of 1 (≥ 75% to < 90% adhered) for at least 1 evaluation, and no subjects had scores of 2 or greater (< 75% adhered) *(ZTlido prescribing information 2018)*.
- In patients with PHN, treatment with capsaicin resulted in significant pain relief compared to low dose capsaicin 0.04% (*Backonja et al 2008, Derry et al 2017, Irving et al 2012*). Treatment with capsaicin was associated with improvement in PGIC, reduction in numeric pain rating scale (NPRS) scores, and reduction in neuropathic symptoms compared to low-dose capsaicin for up to 12 weeks of treatment (*Backonja et al 2008, Derry et al 2017, Irving et al 2012*). The long-term tolerability and safety of capsaicin was also demonstrated in a 52-week study, which found that repeat treatment with capsaicin (30 and 60 minutes) in addition to the standard of care therapies (antidepressants, antiepileptics, and/or opioids) was well tolerated with no negative functional or neurological effects when compared to standard of care therapies alone (*Vinik et al 2016*).
- Gabapentin also demonstrated superiority over placebo in alleviating pain, improving functional outcomes, and improving quality of life in patients with PHN. Treatment with gabapentin significantly improved average daily pain and sleep, Short form-McGill Pain Questionnaire (SF-MPQ), Patient and Clinician Global Impression of Change, SF-36, and Prolife of Mood States (POMS) scores in RCTs. Commonly reported AEs in patients receiving gabapentin included somnolence, drowsiness, dizziness, ataxia, peripheral edema, and infection (*Rice et al 2001, Rowbotham et al 1998*). In a trial comparing placebo, gabapentin monotherapy, morphine sustained-release monotherapy, and gabapentin and morphine sustained-release combination therapy, combination therapy achieved better analgesia at lower doses of each

agent compared to monotherapy with either agent in patients with PHN. Combination therapy was most commonly associated with constipation, sedation, and dry mouth (*Gilron et al 2005*). Within these clinical trials, doses of gabapentin of up to 3,600 mg/day were evaluated (*Gilron et al 2005, Rice et al 2001, Rowbotham et al 1998*).

- In 2 placebo-controlled trials, gabapentin ER achieved significant improvements in average daily pain and sleep interference scores (*Irving et al 2009, Wallace et al 2010*). In one of these trials, a larger proportion of patients receiving gabapentin ER reported ≥ 50% reduction from baseline in average daily pain scores compared to placebo (*Irving et al 2009*). In general, treatment with gabapentin ER was well tolerated; dizziness, headache, somnolence, and peripheral edema were the most commonly reported AEs (*Irving et al 2009, Wallace et al 2010*). Another placebo-controlled trial concluded that gabapentin ER may be particularly effective in patients with PHN presenting with sharp, dull, sensitive, or itchy pain (*Jensen et al 2009*). Within these clinical trials, doses of gabapentin ER of up to 1,800 mg/day were evaluated (*Irving et al 2009, Jensen et al 2009, Wallace et al 2010*).
- The efficacy of gabapentin enacarbil ER (1200, 2400, and 3600 mg/day) was established in a randomized, placebo-controlled, 12-week trial in adult patients with a documented medical diagnosis of PHN for ≥ 3 months (N = 371) and significant pain, as demonstrated by a minimum baseline 24-hour average Pain Intensity Numerical Rating Scale score ≥ 4 on the 11-point scale. Treatment with gabapentin enacarbil ER significantly improved the mean pain score and increased the proportion of patients with ≥ 50% reduction in pain score from baseline at all doses evaluated. A benefit over placebo was observed for all 3 doses of gabapentin enacarbil ER as early as Week 1 and was maintained at Week 12. Additional benefit of using doses of gabapentin enacarbil ER > 1200 mg/day was not demonstrated (*Zhang et al 2013*). Results of a second, published, placebo-controlled trial confirms these findings. Reported AEs were similar to those of gabapentin and gabapentin ER (ie, dizziness, headache, and nausea) (*Backonja et al 2011*).
- A meta-analysis of 7 trials evaluating gabapentin, gabapentin enacarbil ER, and gabapentin ER was conducted to determine the efficacy and safety of all gabapentin formulations for management of PHN. Although gabapentin was found to be superior to placebo in terms of pain reduction, global impression of change, and sleep quality, patients taking gabapentin were significantly more likely to experience AEs such as dizziness, somnolence, peripheral edema, ataxia, and diarrhea (*Meng et al 2014*).
- Pregabalin demonstrated consistent superiority over placebo in alleviating diabetic peripheral neuropathic pain and PHN-related pain. Two noncomparative, open-label trials evaluating pregabalin for the management of PHN supports the findings of placebo-controlled trials (*Ogawa et al 2010, Xochilcal-Morales et al 2010*). In one of these noncomparative trials, long-term treatment of PHN with pregabalin (52 weeks) was found to be safe and effective (*Ogawa et al 2010*). Patients with PHN who were transitioned to pregabalin from gabapentin demonstrated no significant difference in pain scores, based on a visual analog scale, with pregabalin compared to gabapentin. However, in a subset of patients who required an increase in the dosage of pregabalin to improve the analgesic effect after the transition, significant improvement in pain scores was observed (*Ifuku et al 2011*).
- Support for efficacy of pregabalin ER in PHN and diabetic peripheral neuropathy was based on the efficacy of Lyrica in these indications and 1 clinical trial in PHN (*Lyrica CR prescribing information 2017*). In this trial, pregabalin ER demonstrated a significantly longer time to loss of therapeutic response compared with placebo over a 13-week randomized withdrawal phase in a phase 3, double-blind, randomized trial *(Huffman et al 2017).*

CLINICAL GUIDELINES

Diabetic Neuropathy

- The 2011 American Academy of Neurology (AAN) guidelines, which were reaffirmed in 2016, recommend the following:
  - If clinically appropriate, pregabalin should be offered for treatment. Gabapentin and sodium valproate are other anticonvulsants that should be considered for treatment (*Bril et al 2011*).
  - Amitriptyline, venlafaxine, and duloxetine should be considered for treatment; there is insufficient evidence available to recommend one of these agents over another. Combination therapy with venlafaxine and gabapentin may be utilized for a better response.
  - The opioids, dextromethorphan, morphine sulfate, tramadol, and oxycodone should be considered for treatment; there is insufficient evidence available to recommend one of these agents over another.
  - With regards to other pharmacologic options, capsaicin and isosorbide dinitrate spray should be considered for treatment, while lidocaine patch may be considered.
- The 2018 American Diabetes Association (ADA) guideline acknowledges the lack of quality of life outcomes and recommends that treatment decisions follow a trial-and-error approach (*ADA 2018*).

- Pregabalin, duloxetine, and tapentadol ER have been approved for relief of diabetic peripheral neuropathy; however, none of these agents affords complete relief, even when used in combination.
- Either pregabalin or duloxetine is recommended as initial pharmacologic therapy for neuropathic pain in diabetes. The use of tapentadol ER is generally not recommended as a first or second-line therapy due to safety concerns such as high-risk for addiction, and the evidence for its use is considered weaker.
- Venlafaxine, amitriptyline, gabapentin, carbamazepine, tramadol, and topical capsaicin may also be effective and could be considered for treatment of painful diabetic peripheral neuropathy.

- In general, other published guidelines support recommendations from the AAN and ADA concerning the use of the neuropathic pain and fibromyalgia agents in the management of diabetic neuropathy (*Dworkin et al 2007, Handelsman et al 2015, Pop-Busui et al 2017*).

PHN

- According to the 2004 AAN guidelines, first-line therapies for the management of PHN include tricyclic antidepressants, gabapentin, pregabalin, opioids, and topical lidocaine. The use of these therapies for long-term management remains uncertain (*Dubinksy et al 2004*).
- In general, other published guidelines support recommendations from the AAN for the use of the neuropathic pain and fibromyalgia agents in the management of PHN (*Attal et al 2010, Dworkin et al 2007*).

Fibromyalgia

- According to the evidence-based recommendations for the management of fibromyalgia syndrome from the European League Against Rheumatism, non-pharmacologic interventions should be considered first-line therapy for the management of fibromyalgia symptoms. Pharmacologic therapy should only be initiated if there is a lack of effect with non-pharmacologic therapies, and should be tailored to meet the patient's needs. Recommended pharmacologic agents include low-dose amitriptyline, cyclobenzaprine, duloxetine, milnacipran, pregabalin, and tramadol (*Macfarlane 2017*).
- According to the 2012 Canadian Guidelines for the diagnosis and management of fibromyalgia syndrome, all classes of antidepressants are options for treatment of pain and other symptoms of fibromyalgia. Anticonvulsants are also options, though the guideline does not recommend specific agents (*Fitzcharles et al 2013*).

SAFETY SUMMARY

- Duloxetine and milnacipran carry a boxed warning for clinical worsening, suicidality, and unusual changes in behavior. There is an increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants. All SNRIs are not approved for use in pediatric populations. All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely, especially during the initial few months of a course of drug therapy and following changes in dosage.
- Tapentadol ER has a boxed warning for the potential for abuse, life-threatening respiratory depression, accidental exposure, risk of neonatal opioid withdrawal syndrome with prolonged use, and interactions with alcohol, benzodiazepines, or other central nervous system depressants that can cause profound sedation, respiratory depression, coma, and death.
- Gabapentin, pregabalin, and pregabalin ER carry warnings regarding the risk of anaphylaxis and/or angioedema after the first dose or during therapy.
- Topical lidocaine products have a warning for excessive dosing/overexposure, increased absorption on non-intact skin, risk of overexposure with external heat sources, and hypersensitivity reactions.
- The following key contraindications are included in the prescribing information:
  - Concomitant use or use within the last 14 days of monoamine oxidase inhibitors is contraindicated with duloxetine, milnacipran, and tapentadol ER.
  - Tapentadol ER is contraindicated in significant respiratory depression, acute or severe bronchial asthmas, or hypercarbia in an unmonitored setting or in the absence of resuscitative equipment, and in known or suspected paralytic ileus.
- The FDA requires a Risk Evaluation and Mitigation Strategy (REMS) program for ER and long-acting opioid analgesics, including tapentadol ER, to assure safe use of these medications.
- The following monitoring parameters are recommended with treatment:
  - Monitor for clinical worsening of depression, suicidality, or unusual changes in behavior with duloxetine, milnacipran, gabapentin ER, gabapentin enacarbil ER, pregabalin, pregabalin ER, and gabapentin treatment.

- Patients receiving tapentadol ER, duloxetine, or milnacipran should be monitored for signs of serotonin syndrome when used concurrently with other serotonergic agents (eg, SSRIs, SNRIs, tricyclic antidepressants, triptans, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's Wort). Tapentadol ER, duloxetine or milnacipran should not be used with drugs that impair metabolism of serotonin (eg, monoamine oxidase inhibitors [MAOIs], linezolid, and methylene blue).
- Monitor for signs of misuse, abuse, and addiction during tapentadol ER therapy. Patients should also be closely monitored for 72 hours after initiating tapentadol ER treatment and monitored throughout treatment due to an increased risk of respiratory depression.
- Patients receiving tapentadol ER, duloxetine, capsaicin, or milnacipran should have their blood pressure monitored prior to initiating treatment and periodically throughout treatment.
- Monitor for worsened seizure control in patients with a history of seizure disorder with the treatment of tapentadol ER, duloxetine, or milnacipran.
- Patients receiving tapentadol ER should be monitored for signs and symptoms of worsening biliary tract disease, including acute pancreatitis.

- In general, oral neuropathic pain and fibromyalgia agents are commonly associated with central nervous system-related AEs (eg, dizziness, drowsiness, somnolence). Peripheral edema and weight gain may also occur with use of these agents.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Cymbalta (duloxetine delayed-release)	Capsule	Oral	Once daily	Not recommended in ESRD, severe renal impairment (CrCl < 30 mL/min), or hepatic insufficiency
Gralise (gabapentin ER)	Tablet	Oral	Once daily	Administer with evening meal Reduce dose in CrCl of 30 to 60 mL/min; not recommended in CrCl < 30 mL/min or hemodialysis
Horizant (gabapentin enacarbil ER)	Tablet	Oral	Twice daily	Administer with food Reduce dose in CrCl < 60 mL/min or hemodialysis
Lidoderm, ZTlido (lidocaine)	Patch, topical system	Transdermal	Once daily	Apply for up to 12 hours within a 24-hour period Caution in patients with severe hepatic disease
Lyrica (pregabalin)	Capsule, oral solution	Oral	2 or 3 times daily	Schedule V controlled substance Reduce dose in CrCl < 60 mL/min
Lyrica CR (pregabalin ER)	Tablet	Oral	Once daily	Schedule V controlled substance Reduce dose in CrCl < 60 mL/min Administer after evening meal
Neurontin (gabapentin)	Capsule, oral solution, tablet	Oral	3 times daily	Reduce dose in CrCl < 60 mL/min
Nucynta ER (tapentadol ER)	Tablet	Oral	Twice daily	Schedule II controlled substance Do not use in severe renal impairment (CrCl < 30 mL/min) or severe hepatic impairment Reduce dose in moderate hepatic impairment
Qutenza (capsaicin)	Patch	Transdermal	60-minute application of up to 4 patches every 3 months	Only administered by physicians or health care professionals

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Savella (milnacipran)	Tablet	Oral	Twice daily	Reduce dose in CrCl < 30 mL/min Caution in patients with moderate renal impairment or severe hepatic impairment

Abbreviations: CrCl = creatinine clearance; ESRD = end-stage renal impairment
See the current prescribing information for full details

CONCLUSION

- Included in this review are the neuropathic pain and fibromyalgia agents, duloxetine, gabapentin ER, gabapentin enacarbil ER, lidocaine, pregabalin, pregabalin ER, gabapentin, tapentadol ER, capsaicin, and milnacipran. In general, these agents are FDA-approved for the treatment of diabetic peripheral neuropathic pain, PHN, and/or fibromyalgia.
- Clinical trials support the use of the neuropathic pain and fibromyalgia agents for their FDA-approved indications. Available data demonstrate that neuropathic pain and fibromyalgia agents provide relief from pain; some studies have demonstrated improvement in functional outcomes and quality of life. Direct comparisons among the various agents are rare, and consistent benefit of one agent over another has not been demonstrated.
- According to the available literature, tricyclic antidepressants and duloxetine demonstrate an ability to provide pain relief in patients with painful diabetic neuropathy. While pregabalin and valproate have both demonstrated usefulness in the management of diabetic neuropathy, available literature suggests that the utility of gabapentin is less certain. There is minimal evidence evaluating the use of topical lidocaine for the management of painful diabetic neuropathy. Strong opioids have demonstrated efficacy compared to placebo; however, prescribers may consider this as last line therapy due to concerns regarding long-term safety, including addiction potential and misuse (*Attal et al 2010, Feldman et al 2017[b], Schwartz et al 2011*).
  - Of the neuropathic pain and fibromyalgia agents included in the review, duloxetine, pregabalin, pregabalin ER, and tapentadol ER are approved for the management of diabetic neuropathy.
- For the management of PHN, available literature demonstrates that tricyclic antidepressants, gabapentin, pregabalin, opioids, topical capsaicin, botulinum toxin, and topical lidocaine are more effective compared to placebo (*Bajwa et al 2017*).
  - Of the neuropathic pain and fibromyalgia agents included in this review, gabapentin ER, gabapentin enacarbil ER, lidocaine, pregabalin, pregabalin ER, gabapentin, and capsaicin are approved for the management or relief of pain associated with PHN.
- For the management of fibromyalgia, available literature demonstrates that amitriptyline, cyclobenzaprine, duloxetine, gabapentin, milnacipran, and pregabalin are all appropriate treatment options. The choice of therapy is guided by specific symptoms, comorbidities, and patient preference (*Goldenberg 2016[b]*).
  - Of the neuropathic pain and fibromyalgia agents included in this review, duloxetine and pregabalin are approved for fibromyalgia.

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INTRODUCTION

- The hepatitis C virus (HCV) is an enveloped ribonucleic acid (RNA) virus that is transmitted through exposure to infected blood (*Centers for Disease Control and Prevention [CDC] 2018*).
  - Approximately 75 to 85% of people infected with HCV will develop chronic infection.
  - The CDC estimates that 3.5 million persons in the U.S. have chronic hepatitis C (CHC).
  - Chronic HCV infection can lead to the development of active liver disease, including cirrhosis and liver cancer. It is one of the most common indications for liver transplant (*CDC 2018*).
- There are 6 major genotypes of HCV, numbered 1 to 6. Genotypes are further divided into subtypes, designated by a letter (*Gower et al 2014*).
  - Genotype 1 is the most prevalent HCV genotype globally (~46% of cases), followed by genotype 3 (~22 to 30% of cases). Genotypes 2, 4, and 6 represent 22.8% of cases combined; genotype 5 represents less than 1% of cases worldwide (*Messina et al 2015, Gower et al 2014*).
  - In the U.S., the prevalence of genotype 1a, 1b, 2, 3, 4, and 6 is 46.2%, 26.3%, 10.7%, 8.9%, 6.3%, and 1.1%, respectively (*Gower et al 2014*).
- Due to the slow evolution of chronic infection, it is difficult to directly demonstrate whether treatment prevents complications of liver disease; therefore, response to treatment is defined by surrogate virologic parameters. The primary goal of therapy for hepatitis C is eradication of the virus. There are a number of different terms in use that are relevant to monitoring response to therapy:
  - Rapid virologic response (RVR): undetectable viral load at week 4
  - Early virologic response (EVR): at least a 2-log reduction in viral load by week 12 (partial EVR) or undetectable viral load by week 12 (complete EVR)
  - End-of-treatment response (ETR): undetectable viral load at the end of treatment
  - Sustained virologic response (SVR): undetectable viral load at the conclusion of therapy and 24 weeks after the conclusion of therapy (*Hepatitis C Support Project [HCSP] Fact Sheet 2015*).
- Obtaining an SVR is associated with a 97 to 100% chance of being HCV RNA negative during long-term follow-up. Furthermore, achieving an SVR is associated with decreased mortality, rates of hepatocellular carcinoma, liver-related complications, and the need for liver transplant. Thus, success at obtaining SVR is an important treatment goal and a common primary endpoint in the clinical trials of antiviral medications. Some trials report SVR at 12 weeks (SVR12) in addition to or instead of at 24 weeks (SVR24). There is a high degree of concordance between SVR12 and SVR24, and SVR12 is also considered an appropriate endpoint (*Chen et al 2013*).
- Over recent years, research has focused on oral HCV agents that act directly on viral targets. These direct-acting antivirals (DAAs) are stratified into 4 major categories: NS3/4A protease inhibitors, NS5B nucleoside polymerase inhibitors, NS5B nonnucleoside polymerase inhibitors, and NS5A inhibitors (*Liang et al 2013*).
  - The first DAA-containing regimens were single-ingredient DAAs that needed to be used in combination with peginterferon (PegIFN)/ribavirin (RBV). However, several IFN-free combination products and regimens have been approved since 2014. Some of these regimens also remove the need for RBV in select populations.
- This review provides information on the DAAs, including: Daklinza, Epclusa, Harvoni, Mavyret, Sovaldi, Viekira Pak, Vosevi, and Zepatier.
  - In May 2018, AbbVie announced the discontinuation of Viekira XR (ombitasvir/paritaprevir/ritonavir and dasabuvir) and Technivie (ombitasvir/paritaprevir/ritonavir). These discontinuations were voluntary, and not due to any safety, efficacy, or quality issues. These products will no longer be available, effective January 1, 2019 (*FDA Drug Shortages 2018*).
- Medispan Class: Hepatitis C Agents

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Daklinza (daclatasvir)	--
Epclusa (sofosbuvir/velpatasvir)	--*
Harvoni (ledipasvir/sofosbuvir)	--*
Mavyret (glecaprevir/pibrentasvir)	--
Sovaldi (sofosbuvir)	--
Viekira Pak (ombitasvir/paritaprevir/ritonavir and dasabuvir)	--
Vosevi (sofosbuvir/velpatasvir/voxilaprevir)	--
Zepatier (elbasvir/grazoprevir)	--

*Generic anticipated to launch in January 2019

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Daklinza (daclatasvir)	Epclusa (sofosbuvir-velpatasvir)	Harvoni* (ledipasvir/ sofosbuvir)	Mavyret (glecaprevir-pibrentasvir)	Sovaldi* (sofosbuvir)	Viekira Pak (ombitasvir/ paritaprevir/ ritonavir/ dasabuvir)	Vosevi† (sofosbuvir-velpatasvir-voxilaprevir)	Zepatier (elbasvir/ grazoprevir)
Genotype 1	✔	✔	✔	✔	✔	✔	✔	✔
Genotype 2		✔		✔	✔		✔	
Genotype 3	✔	✔		✔	✔		✔	
Genotype 4		✔	✔	✔	✔		✔	✔
Genotype 5		✔	✔	✔			✔	
Genotype 6		✔	✔	✔			✔	

* Harvoni and Sovaldi are the only agents approved in pediatric patients; Harvoni is indicated for the treatment of pediatric patients 12 years of age and older or weighing at least 35 kg with HCV genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis; Sovaldi is indicated for the treatment of chronic HCV genotype 2 or 3 infection in pediatric patients 12 years of age and older or weighing at least 35 kg without cirrhosis or with compensated cirrhosis for use in combination with ribavirin.

† Only approved in patients with genotypes 1, 2, 3, 4, 5, or 6 with prior failure to an NS5A inhibitor-containing regimen or patients with genotypes 1a or 3 previously treated with a sofosbuvir-containing regimen without an NS5A inhibitor.

(*Prescribing information: Daklinza 2017, Epclusa 2017, Harvoni 2017, Mavyret 2018, Sovaldi 2018, Viekira Pak 2018, Vosevi 2017, Zepatier 2018*)

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

CLINICAL EFFICACY SUMMARY

Daklinza

- The clinical safety and efficacy of daclatasvir in combination with sofosbuvir and with or without RBV was evaluated in 3 pivotal phase 3 trials.
  - ALLY-1 was a multicenter (MC), open-label (OL) study in patients (genotype 1 to 6 included) with advanced cirrhosis (n = 60) or patients with HCV recurrence post-liver transplant (N = 53). Patients received daclatasvir plus sofosbuvir plus RBV for 12 weeks. In the advanced cirrhosis cohort, 82% of genotype 1 patients achieved SVR12 (SVR12 in overall cohort: 83%). In the post-transplant cohort, 95% of genotype 1 patients achieved SVR12 (SVR12 in overall cohort: 94%) (*Poordad et al 2016*).

- ALLY-2 was a MC, OL, randomized study (n = 153) in patients (genotype 1 to 6 included) with HCV/human immunodeficiency virus (HIV) co-infection. Among patients who received 12 weeks of daclatasvir plus sofosbuvir therapy, 96% and 97% of treatment-naïve HCV genotype 1 and treatment-experienced HCV genotype 1a patients achieved SVR12, respectively. All treatment-naïve and treatment-experienced patients with genotype 1b (23/23), genotype 2 (13/13), genotype 3 (10/10), or genotype 4 (3/3) infection achieved SVR12 (*Wyles et al 2015*).
- ALLY-3 was a MC, OL study in genotype 3 patients (n = 152), including those with compensated cirrhosis. Patients received daclatasvir plus sofosbuvir for 12 weeks. The SVR12 rates were 90% in treatment-naïve patients and 86% in treatment-experienced patients, with an overall SVR12 rate of 89%. SVR12 rates were higher in patients without cirrhosis (96%) than in patients with cirrhosis. In cirrhotic treatment-naïve and treatment-experienced patients, the SVR12 rate was 58% and 69%, respectively (*Nelson et al 2015*).

- ALLY-3C was a phase 3, OL, MC, single-arm study that examined the efficacy of daclatasvir plus sofosbuvir plus RBV for 24 weeks in patients (n = 78) with HCV genotype 3 and compensated cirrhosis. SVR12 was achieved in 87% of patients; SVR12 rates were 93% and 79% for treatment-naïve and treatment-experienced patients, respectively (*Poordad et al 2018*).
- ALLY-3+ was a phase 3, OL, MC study that compared 12 weeks (n = 24) vs 16 weeks (n = 26) of daclatasvir plus sofosbuvir plus RBV in patients with advanced fibrosis or cirrhosis. SVR12 was 88% in the 12-week treatment group and 92% in the 16-week group, giving an overall rate in all treated patients of 90%. All patients with advanced fibrosis achieved SVR12 (*Leroy et al 2016*).
- Several recent real world and observational studies have also found daclatasvir plus sofosbuvir, with or without RBV, to be highly effective and well tolerated for the treatment of genotype 1 or 3 infection (*Alonso et al 2016, Pol et al 2017, Welzel et al 2016*).

Epclusa

- The clinical safety and efficacy of Epclusa was evaluated in 4 pivotal phase 3 trials.
  - ASTRAL-1 was a double-blind (DB), placebo-controlled, MC, randomized trial in previously treated or untreated patients who were chronically infected with HCV genotype 1, 2, 4, 5, or 6. Overall, the rate of SVR among patients who received 12 weeks of Epclusa was 99% (618/624) (95% confidence interval [CI], 98 to > 99), which was significantly superior to the prespecified performance goal of 85% ($p < 0.001$). None of the 116 patients in the placebo group had an SVR (*Feld et al 2015*).
  - ASTRAL-2 was an OL, active-control (AC), MC, randomized trial comparing Epclusa for 12 weeks (n = 134) vs sofosbuvir plus RBV for 12 weeks (n = 132) in patients with genotype 2 infection. The rate of SVR12 was 99% (133/134) (95% CI, 96 to 100) among those who had received Epclusa as compared with 94% (124/132) (95% CI, 88 to 97) among those who had received sofosbuvir plus RBV (*Foster et al 2015*).
  - ASTRAL-3 was an OL, AC, MC, randomized trial comparing Epclusa for 12 weeks (n = 277) vs sofosbuvir plus RBV for 24 weeks (n = 275) in patients with genotype 3 infection. The rate of SVR12 was 95% (95% CI, 92 to 98) among those who had received Epclusa, as compared with 80% (95% CI, 75 to 85) among those who had received sofosbuvir plus RBV. The overall SVR rate with Epclusa was significantly superior to that with sofosbuvir plus RBV. The strata-adjusted absolute difference was 14.8% (95% CI, 9.6 to 20.0, $p < 0.001$) (*Foster et al 2015*).
  - ASTRAL-4 was an OL, MC, randomized trial comparing Epclusa with or without RBV for 12 weeks or Epclusa for 24 weeks in patients infected with HCV genotypes 1 through 6 and with decompensated cirrhosis. Rates of SVR12 were 83% (95% CI, 74 to 90) in patients who received Epclusa for 12 weeks, 94% (95% CI, 87 to 98) among those who received Epclusa plus RBV for 12 weeks, and 86% (95% CI, 77 to 92) among those who received Epclusa for 24 weeks. Post-hoc analyses did not detect any significant differences in rates of SVR among the 3 treatment groups (*Curry et al 2015*).
- A randomized, OL trial conducted in Spain compared 12 weeks of Epclusa to 12 weeks of Epclusa plus RBV in patients (n = 204) with HCV genotype 3 and compensated cirrhosis. SVR12 rates were 91% and 96% in the Epclusa and Epclusa plus RBV groups, respectively (*Esteban et al 2018*).
- A meta-analysis of 6 randomized controlled trials (n = 1427) found that 12 weeks of Epclusa treatment resulted in SVR12 rates of 98.2%, 99.4%, 94.7%, 99.6%, 97.1%, and 98.8% in HCV genotypes 1, 2, 3, 4, 5, and 6, respectively (*Ahmed H et al 2018[a]*).

Harvoni

Adults

- The efficacy and safety of Harvoni were evaluated in 4 trials in genotype 1 HCV monoinfected patients, 1 trial in genotype 1 or 4 HCV/HIV-1 co-infected patients, 3 trials in genotype 4, 5, or 6 HCV monoinfected patients and 2 trials in genotype 1 or 4 HCV infected pre-transplant patients with decompensated cirrhosis (Child-Pugh B and C) or post-liver transplant.
  - ION-1 was a randomized, OL trial in treatment-naïve patients (n = 865) with genotype 1 HCV with or without cirrhosis. Patients were randomized to receive Harvoni for 12 or 24 weeks, with or without RBV. In the trial, SVR12 rates of 97 to 99% were achieved (*Afdhal et al 2014[a]*).
  - ION-2 was a randomized, OL trial in patients (n = 440) with genotype 1 HCV with or without cirrhosis who failed prior therapy with an IFN-based regimen, with or without a protease inhibitor. Patients were randomized to receive Harvoni for 12 or 24 weeks, with or without RBV. SVR12 rates of up to 99% were achieved (*Afdhal et al 2014[b]*).
  - ION-3 was a randomized, OL trial in treatment-naïve patients (n = 647) with non-cirrhotic HCV genotype 1 infection. Patients randomized to treatment with Harvoni for 8 or 12 weeks or Harvoni plus RBV for 8 weeks demonstrated SVR12 rates of 93 to 95% (*Kowdley et al 2014*).
  - ION-4 was an OL, MC trial in 335 patients evaluating 12 weeks of Harvoni in treatment-naïve and treatment-experienced cirrhotic or non-cirrhotic HIV/HCV co-infected patients. SVR12 rates were high overall (96%) with comparable rates to the HCV monoinfected population (*Naggie et al 2015*).
  - SIRIUS was a DB, MC, French study in which patients with cirrhosis who did not respond to PegIFN and RBV plus telaprevir or boceprevir, were randomized to placebo for 12 weeks followed by Harvoni plus RBV for 12 weeks (n = 77) or Harvoni plus placebo for 24 weeks (n = 78). The overall SVR12 rates were 96% and 97% for Harvoni plus RBV for 12 weeks and Harvoni plus placebo for 24 weeks, respectively (*Bourlière et al 2015*).
  - Study 1119 was an OL study evaluating Harvoni for 12 weeks in patients with genotype 4 (n = 44) or 5 infection (n = 41), with or without compensated cirrhosis. The study was conducted at 5 sites in France. There were high SVR12 rates (≥ 89%) with 12 weeks of Harvoni in all patient subgroups and similar rates for genotype 4 vs genotype 5 infection (*Abergel et al 2016*).
  - In an OL, randomized study, Harvoni for 12 weeks was compared to sofosbuvir plus RBV for 24 weeks in a cohort of Egyptian patients (n = 200) with treatment-naïve genotype 4 HCV. SVR12 was higher with Harvoni (99% vs 80% with sofosbuvir plus RBV) (*Ahmed OA et al 2018*). Another OL randomized study in Egyptian patients (n = 255) compared Harvoni and Harvoni plus RBV for 8 or 12 weeks. SVR12 rates were 95% and 90% among patients receiving 8 weeks of Harvoni and Harvoni plus RBV, respectively. The SVR12 rate for patients receiving 12 weeks of Harvoni (with or without RBV) was 98% (*Shiha et al 2018*).
  - ELECTRON-2 was an OL trial that enrolled patients from 2 centers in New Zealand. The trial evaluated Harvoni for 12 weeks in patients with genotype 6 infection (n = 25). The rate of SVR12 was 96%. The single patient who did not reach SVR12 was a patient who withdrew consent during week 8 of treatment and therefore did not receive the full course of treatment (*Gane et al 2015*).
  - SOLAR-1 and SOLAR-2 were OL, MC trials that evaluated 12 and 24 weeks of treatment with Harvoni in combination with RBV in patients with genotype 1 and 4 infection who had undergone liver transplantation and/or who had decompensated liver disease. The 2 trials were identical in study design. The SVR12 rates observed with 24 weeks of Harvoni plus RBV were similar to the SVR12 rates observed with 12 weeks of treatment. In pre-transplant patients with decompensated cirrhosis, the SVR12 rate for Harvoni plus RBV for 12 weeks was 87% (80/92). In post-transplant patients (with or without cirrhosis), the SVR12 was 93% (194/208) (*Charlton et al 2015; Manns et al 2016*).

Pediatric

- A phase 2, OL, MC study (N = 100) evaluated Harvoni for 12 weeks in patients aged 12 to 17 years with chronic HCV genotype 1 infection. Overall, 98% of patients reached SVR12. No patient had virologic failure; 2 patients who did not achieve SVR12 were lost to follow-up either during or after treatment (*Balistreri et al 2016*).

Mavyret

- The efficacy of Mavyret in patients who were treatment-naïve or treatment-experienced to combinations of PegIFN, RBV and/or sofosbuvir (PRS) with genotype 1, 2, 4, 5, or 6 infection without cirrhosis was studied in 5 trials using 8- or 12-week durations: ENDURANCE-1, ENDURANCE-2, ENDURANCE-4, SURVEYOR-1 (Part 2), and SURVEYOR-2 (Part 2 and Part 4).
  - ENDURANCE-1 was a randomized, MC, OL trial comparing the efficacy of 8 and 12 weeks of treatment with Mavyret in patients with genotype 1 infection with or without HIV-1 co-infection. The SVR rate was 99% (348/351) and 99.7%

(351/352) in the Mavyret 8- and 12-week arms, respectively (*Mavyret prescribing information 2018, Zeuzem et al 2018*).
  - ENDURANCE-4, SURVEYOR-1, and SURVEYOR-2 were OL, MC trials evaluating the safety and efficacy of Mavyret in treatment-naïve or PRS treatment-experienced patients. ENDURANCE-4 and SURVEYOR-1 evaluated 12 weeks of Mavyret in patients with genotypes 5 and 6. The overall SVR rate was 100% (57/57). SURVEYOR-2 evaluated 8 weeks of Mavyret in patients with genotypes 2, 4, 5, or 6; the SVR rate was 98% (193/197), 93% (43/46), 100% (2/2), and 100% (10/10), respectively (*Asselah et al 2017, Asselah et al 2018[a], Mavyret prescribing information 2018*).
  - ENDURANCE-2 was a randomized, DB, placebo-controlled, MC study assessing the efficacy of Mavyret for 12 weeks in non-cirrhotic patients with genotype 2 HCV (n = 196). The SVR12 rate in the treatment group was 99% (*Asselah et al 2018[a]*).
- The efficacy of Mavyret in patients who were treatment-naïve or PRS treatment-experienced with genotype 1, 2, 4, 5, or 6 with compensated cirrhosis was studied in the OL, single-arm EXPEDITION-1 trial. Patients were treated with 12 weeks of Mavyret. The overall SVR rate was 99% (145/146) (*Forns et al 2017*).
- The efficacy of Mavyret in patients without cirrhosis or with compensated cirrhosis who were treatment-naïve or PRS treatment-experienced with genotype 3 infection was studied in ENDURANCE-3 and in SURVEYOR-2 (Part 3).
  - ENDURANCE-3 was a randomized, OL, AC trial in treatment-naïve patients. Patients were randomized (2:1) to either Mavyret for 12 weeks or to the combination of Sovaldi and Daklinza for 12 weeks; subsequently the trial included a third non-randomized arm with Mavyret for 8 weeks. The SVR rate for 8 weeks of Mavyret, 12 weeks of Mavyret, and 12 weeks of Sovaldi plus Daklinza was 94.9% (149/157), 95.3% (222/233), and 96.5% (111/115), respectively. The treatment difference for 12 weeks of Mavyret vs 12 weeks of sofosbuvir plus daclatasvir was -1.2% (95% CI, -5.6% to 3.1%). The treatment difference for 8 weeks vs 12 weeks of Mavyret was -0.4% (95% CI, -5.4% to 4.6%) (*Mavyret prescribing information 2018, Zeuzem et al 2018*).
  - SURVEYOR-2 (Part 3) was an OL trial randomizing PRS treatment-experienced patients with genotype 3 infection without cirrhosis to 12 or 16 weeks of treatment. In addition, the trial evaluated the efficacy of Mavyret in genotype 3 infected patients with compensated cirrhosis in 2 dedicated treatment arms using 12-week (treatment-naïve only) and 16-week (PRS treatment-experienced only) durations. The SVR rate was 98% (39/40) in treatment-naïve patients with cirrhosis who were treated with 12 weeks of Mavyret. The SVR rate was 96% (66/69) in PRS treatment-experienced patients, with or without cirrhosis, who were treated with 16 weeks of Mavyret (*Mavyret prescribing information 2018, Wyles et al 2017*).
  - A pooled analysis of 5 trials in patients (n = 693) with HCV genotype 3 found that treatment with Mavyret for 8 or 12 weeks achieved SVR12 in 95% of treatment-naïve patients without cirrhosis; treatment-naïve patients with cirrhosis who were treated for 12 weeks had an SVR12 rate of 97%. Treatment-experienced patients without cirrhosis achieved SVR12 rates of 90% and 96% with 12 and 16 weeks of Mavyret treatment, respectively. Treatment-experienced patients with cirrhosis achieved SVR12 rates of 94% with 16 weeks of Mavyret treatment (*Flamm et al 2018*).
- ENDURANCE-5,6 was a single-arm, OL, MC trial examining the efficacy of Mavyret in patients (n = 84) with HCV genotypes 5 and 6. Patients without cirrhosis or with compensated cirrhosis were treated with 8 or 12 weeks of Mavyret, respectively. The overall SVR12 rate was 97.6%, with 95.7% and 98.4% of patients with HCV genotype 5 and 6 infections, respectively, achieving SVR12 (*Asselah et al 2018[b]*).
- EXPEDITION-2 was an OL study in HCV/HIV-1 co-infected patients (n = 153) evaluating Mavyret in HCV genotypes 1 through 6 with or without compensated cirrhosis for 8 or 12 weeks, respectively. Treatment-naïve and treatment-experienced patients were both included. The overall SVR12 rate was 98% (*Rockstroh et al 2018*).
- EXPEDITION-4 was an OL, single-arm, MC trial evaluating the safety and efficacy in patients with severe renal impairment (chronic kidney disease [CKD] Stages 4 and 5; 82% were on hemodialysis) with compensated liver disease (with and without cirrhosis). The study included patients with (19%) or without compensated cirrhosis (81%). The SVR rate was 98% (102/104). Of the 2 patients who failed, 1 discontinued the medication and the other was lost to follow-up *(Gane et al 2017, Mavyret prescribing information 2018).*
- MAGELLAN-1 was a randomized, OL trial in genotype 1- or 4-infected patients who failed a previous regimen containing an NS5A inhibitor and/or NS3/4A protease inhibitor. Due to higher rates of virologic failure and treatment-emergent drug resistance, the data did not support labeling for treatment of HCV genotype 1-infected patients who are both NS3/4A protease inhibitor and NS5A inhibitor-experienced (*Mavyret prescribing information 2018, Poordad et al 2017*).

- In protease inhibitor-experienced patients (but NS5A inhibitor-naïve), the SVR rate was 92% (23/25) for patients treated with Mavyret for 12 weeks. In NS5A-experienced patients (but protease inhibitor-naïve), the SVR rate was 94% (16/17).

- MAGELLAN-2 was an OL trial that included treatment-naïve or treatment-experienced patients (n = 100) with chronic HCV genotype 1 through 6 who had received a liver or kidney transplant. The overall SVR12 was 98% after 12 weeks of therapy (*Reau et al 2018*). In 2018, Mavyret received approval for use in liver and kidney transplant recipients (*Mavyret prescribing information 2018*).
- In a pooled analysis of 9 trials in patients (n = 2041) with HCV genotypes 1 through 6 without cirrhosis, treatment with Mavyret for 8 or 12 weeks resulted in SVR12 rates of 98% and 99%, respectively (*Puoti et al 2018*).

Sovaldi

Adults

- The clinical safety and efficacy of sofosbuvir were evaluated in 6 pivotal phase 3 trials.
  - NEUTRINO was a single-arm, OL study of sofosbuvir in combination with IFN and RBV in patients infected with HCV genotype 1, 4, 5, or 6. SVR was achieved in 90% of patients at 12 weeks (*Lawitz et al 2013*).
  - FISSION was a randomized, OL, AC, non-inferiority study in patients with HCV genotype 2 or 3. Patients received treatment with sofosbuvir plus RBV for 12 weeks or PegIFN plus RBV for 24 weeks. An SVR was reported in 67% of patients in both treatment groups at 12 weeks after the end of treatment (*Lawitz et al 2013*).
  - In POSITRON, HCV genotype 2 or 3 patients who had previously discontinued IFN therapy due to adverse events, who had a concurrent medical condition precluding therapy with an IFN, or who decided against treatment with an IFN-containing regimen were randomized to receive treatment with sofosbuvir and RBV or matching placebos. Rates of SVR at 12 weeks were significantly higher in the sofosbuvir treatment group compared to placebo (78 vs 0%, respectively; $p < 0.001$) (*Jacobson et al 2013*).
  - In FUSION, patients who did not achieve SVR with prior IFN therapy (relapsers or nonresponders) were randomized to receive treatment with sofosbuvir and RBV for 12 or 16 weeks. Rates of SVR were 50% with 12 weeks of treatment, as compared with 73% with 16 weeks of treatment (*Jacobson et al 2013*).
  - The VALENCE trial evaluated sofosbuvir in combination with RBV for the treatment of genotype 2 or 3 HCV infection in treatment-naïve patients or patients who did not achieve SVR with prior IFN-based treatment, including those with compensated cirrhosis. Rates of SVR were 93% in genotype 2 patients and 84% in genotype 3 patients (*Zeuzem et al 2014[a]*).
  - PHOTON-1 was an OL trial evaluating treatment with 12 or 24 weeks of sofosbuvir in combination with RBV in genotype 1, 2, or 3 CHC patients co-infected with HIV-1. Genotype 2 and 3 patients were either treatment-naïve or experienced, whereas genotype 1 patients were treatment-naïve. Rates of SVR were similar to those observed in patients with HCV mono-infection across all genotypes (*Sulkowski et al 2014*).

Pediatric

- Study 1112 was an OL trial evaluating treatment with Sovaldi in combination with RBV in pediatric patients 12 years of age and older with genotype 2 or 3 HCV infection. Patients with HCV genotype 2 or 3 infection in the trial were treated with Sovaldi and weight-based RBV for 12 or 24 weeks, respectively. The majority of patients were treatment-naïve (83%), and 73% were infected by vertical transmission; 40% were assessed as not having cirrhosis (the remainder did not have a cirrhosis determination). SVR12 rates were 100% (13/13) for patients with genotype 2 and 97% (38/39) for genotype 3. The single patient who did not achieve SVR was lost to follow-up after achieving SVR4 (*Wirth et al 2017*).

Vosevi

- The efficacy of Vosevi was evaluated in 2 pivotal trials in DAA-experienced patients.
  - POLARIS-1 was a randomized, DB, PC trial that evaluated 12 weeks of treatment with Vosevi compared with 12 weeks of placebo in DAA-experienced patients with genotype 1, 2, 3, 4, 5, or 6 HCV infection without cirrhosis or with compensated cirrhosis who previously failed a regimen containing an NS5A inhibitor. Overall, 51% of patients had been previously treated with ledipasvir (the NS5A component of Harvoni). The remaining patients were treated with other NS5A inhibitors. The overall SVR rate was 96% (253/263). The SVR rate was 99% (140/142) and 93% (113/121) in patients without cirrhosis and with cirrhosis, respectively (*Bourlière et al 2017*).
  - POLARIS-4 was a randomized, OL trial that evaluated 12 weeks of treatment with Vosevi and 12 weeks of treatment with Epclusa in patients with genotype 1, 2, 3, or 4 HCV infection without cirrhosis or with compensated cirrhosis who

had previously failed an HCV DAA-containing regimen that did not include an NS5A inhibitor. In the trial, prior DAA regimens contained sofosbuvir (85%) with the following: PegIFN and RBV or just RBV (69%), HCV NS3/4A protease inhibitor (boceprevir, simeprevir, or telaprevir; 15%) and investigational DAA (< 1%). The SVR12 rate was 98% (178/182) (95% CI, 95 to 99; significantly superior to the prespecified performance goal of 85% [p < 0.001]) for patients receiving Vosevi for 12 weeks. The SVR12 rate was 90% (136/151) (95% CI, 84 to 94, not significantly superior to the prespecified performance goal of 85% [p = 0.09]) for patients receiving Epclusa for 12 weeks. One patient had viral breakthrough and 14 patients relapsed (*Bourlière et al 2017*).

Viekira Pak

- Efficacy and safety of Viekira Pak were evaluated in 8 pivotal clinical trials with chronic HCV genotype 1 infection:
  - Treatment-naïve genotype 1a and 1b (SAPPHIRE-I)
  - Treatment-experienced genotype 1a and 1b (SAPPHIRE-II)
  - Treatment-experienced genotype 1b (PEARL-II)
  - Treatment-naïve genotype 1b (PEARL-III)
  - Treatment-naïve genotype 1a (PEARL-IV)
  - Treatment-naïve and -experienced genotype 1a and 1b with cirrhosis (TURQUOISE-II)
  - Treatment-naïve and -experienced genotype 1b with cirrhosis (TURQUOISE-III).
  - Treatment-naïve and -experienced genotype 1b with cirrhosis (TURQUOISE-IV)
- SAPPHIRE-I and SAPPHIRE-II were MC, randomized, DB, PC trials. Patients were randomized to Viekira Pak plus RBV for 12 weeks or placebo. Patients in the placebo treatment arm received placebo for 12 weeks, after which they received OL Viekira Pak plus RBV for 12 weeks (*Feld et al 2014, Zeuzem et al 2014[b]*).
  - In SAPPHIRE-I (n = 631), SVR12 was achieved in 96.2% (95% CI, 94.5 to 97.9) of patients receiving Viekira Pak with RBV. This rate was non-inferior and superior to the historical control rate with telaprevir plus PegIFN/RBV.
  - In SAPPHIRE-II (n = 394), SVR12 was achieved in 96.3% (95% CI, 94.2 to 98.4) of patients receiving Viekira Pak with RBV. This rate was non-inferior and superior to the historical control rate among patients who had previously been treated with PegIFN/RBV and who received retreatment with telaprevir plus PegIFN/RBV.
- In PEARL-II (n = 186), patients without cirrhosis were randomized to receive OL Viekira Pak with or without RBV for 12 weeks of treatment (*Andreone et al 2014*).
  - Rates of SVR12 were 96.6% (95% CI, 92.8 to 100) with Viekira Pak plus RBV and 100% (95% CI, 95.9 to 100) with Viekira Pak alone. Rates of SVR in both treatment groups were non-inferior and superior to the historical rate for telaprevir plus PegIFN/RBV in comparable treatment-experienced patients.
  - Non-inferiority of treatment with Viekira Pak alone compared to Viekira Pak plus RBV was met (treatment difference in SVR12 rates, 3.4% [95% CI, -0.4 to 7.2]).
- PEARL-III and PEARL-IV were MC, DB, placebo controlled trials. Patients without cirrhosis were randomized to receive Viekira Pak with or without RBV for 12 weeks of treatment (*Ferenci et al 2014*).
  - In PEARL-III (n = 419), treatment with Viekira Pak resulted in SVR12 rates of 99.5% (95% CI, 98.6 to 100) with RBV and 99% (95% CI, 97.7 to 100) without RBV in patients with genotype 1b infection.
  - In PEARL-IV (n = 305), treatment with Viekira Pak resulted in SVR12 rates of 97% (95% CI, 93.7 to 100) with RBV and 90.2% (95% CI, 86.2 to 94.3) without RBV in patients with genotype 1a infection.
- The OL TURQUOISE-II trial (n = 380) enrolled patients with compensated cirrhosis (Child-Pugh A) or liver scarring with few to no outward symptoms who were either treatment-naïve or PegIFN/RBV treatment-experienced. Patients were randomized to receive Viekira Pak in combination with RBV for 12 or 24 weeks of treatment. Patients who previously failed therapy with a treatment regimen that included a DAA were excluded (*Poordad et al 2014*).
  - Patients who received 12 weeks of treatment had an SVR12 response of 91.8% (97.5% CI, 87.6 to 96.1).
  - Those patients who received 24 weeks of treatment achieved an SVR12 rate of 95.9% (97.5% CI, 92.6 to 99.3).
  - Rates of SVR12 in the 12- and 24-week treatment groups were non-inferior and superior to the historical rate with telaprevir plus PegIFN/RBV among patients with HCV genotype 1 infection and cirrhosis. The difference in the rates of SVR between the 2 treatment groups was not significant.
- The OL TURQUOISE-III trial (n = 60) enrolled genotype 1b patients with compensated cirrhosis who were either treatment-naïve or PegIFN/RBV treatment-experienced. Patients were randomized to receive Viekira Pak for 12 weeks. SVR12 was achieved in all patients enrolled in the study (*Feld et al 2016*).
- The OL TURQUOISE-IV trial (n = 36) enrolled genotype 1b patients in Russia and Belarus with compensated cirrhosis who were either treatment-naïve or PegIFN/RBV treatment-experienced. Patients received Viekira Pak plus RBV for 12 weeks. SVR12 was achieved in all patients enrolled in the study (*Isakov et al 2018*).

- Safety and efficacy of Viekira Pak were also evaluated in liver transplant patients and in patients with HCV genotype 1 co-infected with HIV-1.
  - CORAL-I was a phase 2, OL trial in HCV genotype 1 liver transplant recipients who were at least 12 months post transplantation with mild fibrosis (Metavir score < F2). Patients received treatment with Viekira Pak with RBV for 24 weeks. Of the 34 patients enrolled, 33 achieved an SVR12, for a rate of 97% (95% CI, 85 to 100) (*Kwo et al 2014*).
  - TURQUOISE-I was a phase 3, randomized, OL trial in 63 patients with treatment-naïve or -experienced HCV genotype 1 infection who were co-infected with HIV-1. Patients on a stable antiretroviral therapy regimen were treated for 12 or 24 weeks with Viekira Pak in combination with RBV. SVR12 rates were 91% for patients with HCV genotype 1a infection and 100% for those with genotype 1b infection (*Wyles et al 2014*).

Zepatier

- The safety and efficacy of Zepatier were evaluated in 7 pivotal clinical trials including patients with genotype 1 or 4 infection. A small number of patients with other HCV genotypes were also included in the clinical trials; however, Zepatier is only indicated for genotypes 1 and 4.
  - C-EDGE TN was a DB, PC, MC, randomized study in treatment-naïve patients with genotype 1, 4, or 6 infection. Of the 316 patients receiving Zepatier for 12 weeks, 95% (95% CI, 92 to 97) achieved SVR12. SVR12 was achieved in 97% (95% CI, 90 to 100) of cirrhotic patients and 94% (95% CI, 90 to 97) of noncirrhotic patients (*Zeuzem et al 2015*).
  - C-EDGE CO-INFECTION was an OL, MC trial in treatment-naïve patients with genotype 1, genotype 4, and genotype 6 infection who were co-infected with HIV. All patients (n = 218) received Zepatier for 12 weeks. In the overall population, 96% achieved SVR12 (95% CI, 92.9 to 98.4), exceeding the historical reference rate of 70% (*Rockstroh et al 2015*).
  - C-SURFER was a DB, placebo-controlled, MC, randomized study, evaluating Zepatier for 12 weeks in patients with genotype 1 infection with CKD stage 4 to 5. Of the 122 patients receiving Zepatier, 6 were excluded from the modified full analysis set population for reasons other than virologic failure. Of the 116 remaining patients, 115 achieved SVR12, a rate better than the historical control rate of 45% ($p < 0.001$) (*Roth et al 2015*).
  - C-SCAPE was an OL, randomized study that evaluated the efficacy of Zepatier for 12 weeks, with or without RBV, in patients with genotype 4, 5, or 6 infection. In patients with genotype 4 infection, SVR12 was achieved in 100% (10/10) of patients receiving Zepatier with RBV vs 90% (9/10) in patients receiving Zepatier alone (*Brown et al 2015, Brown et al 2018*).
  - C-EDGE TE was an OL, MC, randomized study evaluating 12 or 16 weeks of Zepatier, with or without RBV in patients with genotype 1, 4, or 6 HCV infection and previous treatment with Peg IFN/RBV. SVR12 was achieved in 92.4% (97/105) receiving Zepatier alone for 12 weeks, 94.2% (98/104) receiving Zepatier plus RBV for 12 weeks, 92.4% (97/105) receiving Zepatier alone for 16 weeks, and 97.2% (103/106) receiving Zepatier plus RBV (*Kwo et al 2017*).
  - C-SALVAGE was an OL, MC study evaluating Zepatier plus RBV for 12 weeks in patients (n = 79) with genotype 1 infection who failed a regimen containing PegIFN/RBV and another DAA. SVR12 was achieved in 96% (95% CI, 89.3 to 99.2) of patients. The 3 patients not achieving SVR12 had a past history of virologic failure (*Forns et al 2015*).
  - C-CORAL was a randomized, DB, placebo-controlled study evaluating Zepatier for 12 weeks in treatment-naïve patients (n = 489) with genotype 1, 4, or 6 HCV infection. SVR12 was achieved in 94.4% of patients receiving Zepatier. SVR12 rates of 98.2%, 91.9%, and 66.7% were seen in patients with genotype 1b, 1a, and 6 infections, respectively (*Wei et al 2018*).
- A meta-analysis of 8 trials (n = 1297) found an overall SVR rate of 96.6% with Zepatier treatment in patients with genotype 1 HCV (*Ahmed H et al 2018[b]*).
- In a pooled analysis of clinical trial data, treatment-naïve and treatment-experienced patients with genotype 4 HCV infection (n = 155) had SVR12 rates of 96.4% (treatment-naïve) and 88.6% (treatment-experienced) after 12 or 16 weeks of Zepatier with or without RBV (*Asselah et al 2018[c]*).

CLINICAL GUIDELINES

- In order to provide healthcare professionals with timely guidance, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) have developed a web-based process for the rapid formulation and dissemination of evidence-based, expert-developed recommendations for hepatitis C management (*AASLD-IDSA 2018*).

  - Recommended regimens are those that are favored for most patients in a given group, based on optimal efficacy, favorable tolerability and toxicity profiles, and duration.
  - The guidance also lists alternative regimens, which are those that are effective but, relative to recommended regimens, have potential disadvantages, limitations for use in certain patient populations, or less supporting data than recommended regimens. For a listing of alternative regimens, refer to the web-based guidance for full details.
- For the general genotype 1 population, the guidance recommends 4 different regimens considered to have comparable efficacy: Epclusa, Harvoni, Mavyret, and Zepatier. The level of evidence and treatment duration depend on the genotype 1 subtype, prior treatment status (naïve or experienced), and the presence of cirrhosis.
- The guidance recommends Epclusa and Mavyret for patients with genotype 2 or 3 infection.
- The guidance recommends Epclusa, Harvoni, Mavyret, and Zepatier for the treatment of genotype 4 infection. The guidance recommends Epclusa, Harvoni, and Mavyret for treatment of genotype 5 and 6.
- The guidance provides recommendations for several unique patient populations, including patients who have failed prior therapy with DAAs, co-infection with HIV/HCV, decompensated cirrhosis, recurrent HCV infection in the post-transplant setting, or renal impairment. Some key recommendations include:
  - Epclusa, Harvoni (listed as an alternative for patients with compensated cirrhosis), and Mavyret are recommended for genotype 1 patients with prior failure to HCV NS3/4A protease inhibitors. Epclusa (genotype 1b), Mavyret (regardless of genotype 1 subtype), and Vosevi (genotype 1a) are recommended for patients with prior failure to sofosbuvir-containing regimens.
  - Vosevi is recommended in genotype 1, 3, 4, 5, or 6 patients with prior failure to an NS5A inhibitor-containing regimen.
  - Sovaldi-based regimens (ie, Epclusa, Harvoni, Sovaldi plus Daklinza) are recommended for patients with decompensated cirrhosis.
  - HIV/HCV-co-infected patients should be treated and re-treated the same as patients without HIV infection, after recognizing and managing interactions with antiretroviral medications.
  - For patients with stage 4 or 5 CKD (creatinine clearance below 30 mL/min), Mavyret (regardless of genotype) and Zepatier (genotypes 1 and 4 only) are recommended. For kidney transplant recipients, Harvoni (genotypes 1 and 4 only) and Mavyret are recommended.

SAFETY SUMMARY

- Due to the DAAs used in combination therapy with PegIFN and RBV, all contraindications to those 2 medications (PegIFN and RBV) also apply to the class. This includes a contraindication for use in pregnancy due to the RBV component.
- Mavyret is contraindicated in patients with severe hepatic impairment (Child-Pugh C) and coadministration with atazanavir and rifampin.
- Viekira Pak is contraindicated in patients with:
  - Moderate to severe hepatic impairment (Child-Pugh B and C) due to the risk of potential toxicity.
  - Known hypersensitivity to ritonavir (eg, toxic epidermal necrolysis or Stevens-Johnson syndrome).
  - Concomitant use of drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events.
  - Concomitant use of drugs that are moderate or strong inducers of CYP3A.
  - Concomitant use of drugs that are strong inducers or strong inhibitors of CYP2C8
- Vosevi is contraindicated in patients with rifampin coadministration.
- Zepatier is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C). It is also contraindicated with organic anion transporting polypeptides 1B1/3 (OATP1B1/3) inhibitors, strong inducers of CYP3A, and efavirenz.
- Daklinza is contraindicated in combination with drugs that strongly induce CYP3A.
- Key warnings and precautions for the DAAs include:
  - Serious symptomatic bradycardia may occur in patients taking amiodarone and sofosbuvir in combination with another DAA (eg, Sovaldi plus Daklinza, Epclusa, Harvoni, Vosevi).
  - Viekira Pak carries a risk of hepatic decompensation and hepatic failure in patients with cirrhosis.
- Overall, DAA combination therapies are well tolerated and discontinuations due to adverse events are not common.
  - The most common adverse reactions observed with each treatment regimen listed below include:
    - Daklinza in combination with Sovaldi: headache and fatigue
    - Daklinza in combination with Sovaldi and RBV: headache, anemia, fatigue, and nausea

- Epclusa: headache and fatigue
- Epclusa and RBV in patients with decompensated cirrhosis: fatigue, anemia, nausea, headache, insomnia, and diarrhea
- Harvoni: fatigue, headache, and asthenia
- Mavyret: headache and fatigue
- Sovaldi in combination with RBV: fatigue and headache
- Sovaldi in combination with PegIFN alfa and RBV: fatigue, headache, nausea, insomnia, and anemia
- Viekira Pak with RBV: fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia.
- Viekira Pak without RBV: nausea, pruritus, and insomnia
- Vosevi: headache, fatigue, diarrhea, and nausea
- Zepatier: fatigue, headache, and nausea.
- Zepatier with RBV: anemia and headache

- In October 2016, the FDA announced that a new *Boxed Warning* would be added to all DAAs for HCV infection, regarding the risk of hepatitis B virus (HBV) reactivation. This *Boxed Warning* was based on case reports submitted to the FDA and from the published literature of HCV/HBV co-infected patients treated with DAAs from November 2013 to July 2016 (*FDA 2016*).
  - HBV can become reactivated in any patient who has a current or previous infection with HBV and is treated with direct-acting antivirals. In a few cases, HBV reactivation in patients treated with direct-acting antivirals resulted in serious liver problems or death.
  - The *Boxed Warning* was added to the labeling for all of the DAAs in February 2017. The warning directs healthcare providers to test all patients for evidence of current or prior HBV infection before initiation of HCV treatment. HCV/HBV co-infected patients should be monitored for HBV reactivation and hepatitis flare during HCV treatment and post-treatment follow-up. Appropriate patient management for HBV infection should be initiated as clinically indicated.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Route	Usual Recommended Frequency	Comments
Daklinza (daclatasvir)	Oral	One tablet once daily (60 mg dose); must be used in combination with Sovaldi	*Recommended dosage modification with CYP3A inhibitors and inducers*: • Strong CYP3A inhibitors and certain HIV antiviral agents: 30 mg once daily • Moderate CYP3A inducers and nevirapine: 90 mg once daily *Duration of therapy:* • 12 to 24 weeks (when used in combination with Sovaldi)
Epclusa (sofosbuvir/velpatasvir)	Oral	One tablet once daily	• No dosage recommendation can be given for patients with severe renal impairment or end-stage renal disease (ESRD). *Duration of therapy:* • 12 weeks
Harvoni (ledipasvir/sofosbuvir)	Oral	One tablet once daily	• No dosage recommendation can be given for patients with severe renal impairment or ESRD.

Drug	Route	Usual Recommended Frequency	Comments
			Duration of therapy: • 12 to 24 weeks
Mavyret (glecaprevir/pibrentasvir)	Oral	Three tablets daily	• Contraindicated in patients with severe hepatic impairment (Child-Pugh C). Not recommended in patients with moderate hepatic impairment (Child-Pugh B). *Duration of therapy:* • 8 to 16 weeks
Sovaldi (sofosbuvir)	Oral	One tablet once daily; must be used in combination with RBV ± PegIFN or Daklinza	• Safety and efficacy have not been established in patients with severe renal impairment. *Duration of therapy:* • 12 to 24 weeks (when used in combination with Daklinza)
Viekira Pak (ombitasvir/paritaprevir/ritonavir and dasabuvir)	Oral	Two ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablets once daily (in the morning) and one dasabuvir 250 mg tablet twice daily (morning and evening)	• Contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C). *Duration of therapy:* • 12 to 24 weeks
Vosevi (sofosbuvir/velpatasvir/voxilaprevir)	Oral	One tablet once daily	• No dosage recommendation can be given for patients with severe renal impairment or ESRD. • Not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C). *Duration of therapy:* • 12 weeks
Zepatier (elbasvir/grazoprevir)	Oral	One tablet once daily	• Testing patients with HCV genotype 1a infection for the presence of virus with NS5A resistance-associated polymorphisms is recommended prior to initiation of treatment with Zepatier to determine dosage regimen and duration. • Contraindicated in patients with moderate hepatic impairment (Child-Pugh B) due to the lack of clinical safety and efficacy experience in HCV-infected Child-Pugh B patients, and in patients with severe hepatic impairment (Child-Pugh C) due

Drug	Route	Usual Recommended Frequency	Comments
			to a 12-fold increase in grazoprevir exposure. *Duration of therapy:* • 12 to 16 weeks

See the current prescribing information for full details

CONCLUSION

- Hepatitis C is a disease affecting primarily the liver that results from infection with the hepatitis C virus. Long-term complications include cirrhosis and hepatocellular carcinoma. Hepatitis C is the leading indication for liver transplant.
- Success at obtaining an SVR is an important treatment goal and a common primary endpoint in the clinical trials of antiviral medications.
- PegIFN-free, DAA combination regimens, such as Epclusa, Harvoni, Mavyret, and Zepatier have become the standard of care for the treatment of genotype 1 infection. There is a lack of head-to-head trial data available comparing these regimens, but they are considered to have comparable efficacy and safety for treating the general genotype 1 population (*AASLD-IDSA 2018*).
- The only DAA fixed-dose combination products approved and recommended for the treatment of genotypes 2 and 3 infection are Mavyret and Epclusa (*AASLD-IDSA 2018*).
- Similar to genotype 1, several DAA combination regimens have demonstrated high SVR rates for genotype 4 infection. Epclusa, Harvoni, Mavyret, and Zepatier are recommended by the AASLD-IDSA guidance (*AASLD-IDSA 2018*).
- Data are limited for treatment of genotype 5 and 6 infection; however, Epclusa, Harvoni, and Mavyret are approved by the FDA and supported by the AASLD-IDSA guidance (*AASLD-IDSA 2018*).
- Of the combination products, Epclusa and Harvoni are the preferred treatment options in patients with decompensated cirrhosis (Child-Pugh B and C). Mavyret and Zepatier are recommended for patients with advanced kidney disease.

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Therapeutic Class Overview
Antifungals, Oral

INTRODUCTION

- The oral class of antifungals includes multiple agents used to treat many different fungal infections, including aspergillosis, blastomycosis, histoplasmosis, candidiasis, onychomycosis, and ringworm infections (*Micromedex 2018).*
- The agents are often used in persons with human immunodeficiency virus (HIV) and neutropenia due to hematopoietic stem cell transplants, or after aggressive chemotherapy and radiation *(Centers for Disease Control and Prevention, National Institutes of Health, HIV Medicine Association of the Infectious Diseases Society of America [CDC/NIH/IDSA] 2018).*
- The most current treatment guidelines and therapy recommendations should be used when prescribing these agents, as resistant organisms have been reported.
- Clotrimazole, nystatin, and Oravig (miconazole) are not absorbed systemically. They are not used for systemic infections, but only for the treatment of oropharyngeal candidiasis *(Prescribing information: clotrimazole 2016, nystatin suspension 2017, Oravig 2016).*
- Cresemba (isavuconazonium sulfate), Diflucan (fluconazole), Vfend (voriconazole), and Noxafil (posaconazole) are available as oral and intravenous formulations. Ketoconazole and Lamisil (terbinafine) are available as oral and topical preparations. Sporanox (itraconazole) is only available as an oral formulation. Clotrimazole and nystatin are available as oral, topical, and vaginal formulations. Only the oral formulations will be discussed in this review.
- In May 2016, the Food and Drug Administration (FDA) recommended limiting the use of ketoconazole for the treatment of skin and nail fungal infections due to the risk of severe liver injuries and adrenal gland problems, and advised that it can lead to harmful drug interactions with other medications. Ketoconazole should be used for the treatment of certain fungal infections, known as endemic mycoses, only when alternative antifungal therapies are not available or tolerated *(FDA Drug Safety Communication 2016).*
- Medispan class: Antifungals, Imidazole-Related Antifungals

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Ancobon (flucytosine)	✔
clotrimazole	✔
Cresemba (isavuconazonium sulfate)	--
Diflucan (fluconazole)	✔
griseofulvin microsize	✔
Gris-PEG (griseofulvin ultramicrosize)	✔
ketoconazole	✔
Lamisil (terbinafine)	✔
Noxafil (posaconazole)	--
Nystatin	✔
Onmel (itraconazole) [a]	--
Oravig (miconazole)	--
Sporanox (itraconazole)	✔ [b]
Vfend (voriconazole)	✔

[a] As of November 2018 Onmel is temporarily unavailable due to manufacturing delays.
[b] Oral capsule only. A generic oral solution is listed in the Orange Book but is not currently marketed by the generic manufacturer.
(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	clotrimazole	fluconazole	flucytosine	griseofulvin	isavuconazonium sulfate	itraconazole	ketoconazole	nystatin	terbinafine	voriconazole	Noxafil (posaconazole)	Onmel (itraconazole)	Oravig (miconazole)
Oropharyngeal candidiasis	✔							✔			✔ a		✔
Oropharyngeal and esophageal candidiasis		✔				✔ b							
Esophageal candidiasis										✔ g			
Non-esophageal mucous membrane gastrointestinal candidiasis								✔ c					
Prophylactically to reduce the incidence of oropharyngeal candidiasis in patients immunocompromised by conditions that include chemotherapy, radiotherapy, or steroid therapy utilized in the treatment of leukemia, solid tumors, or renal transplantation	✔												
Serious infections caused by susceptible strains of *Candida* and/or *Cryptococcus*			✔ e										
Vaginal candidiasis		✔											
Cryptococcal meningitis		✔											
Prophylactically to decrease the incidence of candidiasis in patients undergoing bone marrow transplantation who receive cytotoxic chemotherapy and/or radiation therapy		✔											
Treatment of the following ringworm infections: tinea corporis (ringworm of the body), tinea pedis (athlete's foot), tinea cruris (ringworm of the groin and thigh), tinea barbae (barber's itch), tinea capitis (ringworm of the scalp), and tinea unguium (onychomycosis, ringworm of the nails), caused by one or more of the following genera of fungi: *Trichophyton rubrum, T. tonsurans, T. mentagrophytes, T. interdigitalis, T. verrucosum, T. megnini, T. gallinae, T. crateriform, T. sulphureum, T. schoenleini, Microsporum audouini, M. canis, M. gypseum* and *Epidermophyton floccosum*				✔									
Onychomycosis of the toenail or fingernail due to dermatophytes (tinea unguium)						✔ f			✔ c				
Onychomycosis of toenail caused by *Trichophyton rubrum* or *T. mentagrophytes* in non-immunocompromised patients												✔	
Treatment of the following systemic infections in patients who have failed or are intolerant to							✔						

Indication	clotrimazole	fluconazole	flucytosine	griseofulvin	isavuconazonium sulfate	itraconazole	ketoconazole	nystatin	terbinafine	voriconazole	Noxafil (posaconazole)	Onmel (itraconazole)	Oravig (miconazole)
other therapies: blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis													
Prophylaxis of invasive *Aspergillus* and *Candida* infections in patients, 13 years of age and older, who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy											✔		
Blastomycosis, pulmonary and extrapulmonary in immunocompromised and non-immunocompromised patients						✔ [d]							
Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, nonmeningeal histoplasmosis in immunocompromised and non-immunocompromised patients						✔ [d]							
Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy in immunocompromised and non-immunocompromised patients						✔ [d]							
Invasive aspergillosis					✔					✔ [g]			
Invasive mucormycosis					✔								
Candidemia in non-neutropenic patients and the following *Candida* infections: disseminated infections in skin and infections in abdomen, kidney, bladder wall, and wounds										✔ [g]			
Serious fungal infections caused by *Scedosporium apiospermum* (asexual form of *Pseudallescheria boydii*) and *Fusarium* species including *Fusarium solani*, in patients intolerant of, or refractory to, other therapy										✔ [g]			

[a] Including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole. Tablets should not be used for this indication.
[b] Oral solution only.
[c] Oral tablets only.
[d] Oral capsules only.
[e] Should be used in combination with amphotericin B for the treatment of systemic candidiasis and cryptococcosis because of the emergence of resistance to flucytosine.
[f] In non-immunocompromised patients.
[g] For use in patients 12 years of age or older.

(Prescribing information: Ancobon 2018, clotrimazole 2016, Cresemba 2018, Diflucan 2018, griseofulvin 2016, Gris-PEG 2017, ketoconazole 2018, Lamisil 2017, Noxafil 2017, nystatin suspension 2017, nystatin tablets 2016, Onmel 2012, Oravig 2016, Sporanox 2018, Vfend 2017)

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

CLINICAL EFFICACY SUMMARY

- The oral antifungal agents are FDA-approved for a variety of indications. Head-to-head clinical trials have been conducted to evaluate the efficacy of the oral antifungal agents for the treatment of various indications. However, head-to-head trials for all agents approved for each indication are not available.
- For the treatment of aspergillosis, open-label trials have demonstrated the effectiveness of itraconazole for the treatment of pulmonary aspergillosis in patients who are immunocompromised and/or refractory to amphotericin B *(Caillot 2003, Caillot et al 2001).* Another study demonstrated the superiority of itraconazole over standard supportive measures in chronic cavitary pulmonary aspergillosis (CCPA) *(Agarwal et al 2013).* Posaconazole has been shown to be effective in the treatment of invasive aspergillosis in patients who are refractory to at least 7 days of antifungal therapy or intolerant to conventional therapy *(Walsh et al 2007).* In the treatment of invasive mucormycosis, isavuconazonium sulfate was studied in a single-arm, open-label trial and was associated with an all-cause mortality rate of 38% through day 42 and an end-of-treatment success rate of 31%. Isavuconazonium sulfate was shown to be noninferior to voriconazole as treatment for invasive aspergillosis for all-cause mortality at day 42 *(McCormack 2015).* Another trial found isavuconazonium sulfate noninferior to voriconazole in all-cause mortality at day 42 in patients receiving primary treatment for invasive mold disease primarily caused by *Aspergillus* species *(Maertens 2016).*
- Open-label studies evaluating the use of itraconazole in the treatment of blastomycosis and histoplasmosis have demonstrated clinical response and/or success rates of 81 to 90% *(Dismukes et al 1992, Wheat et al 1995).* In a multicenter, prospective trial, a relapse-free rate of 95.3% was demonstrated at 1 year in patients treated with itraconazole for a first episode of mild to moderate disseminated histoplasmosis who had successfully completed 12 weeks of induction therapy with itraconazole *(Hecht et al 1997).*
- In a double-blind, randomized, controlled trial, fluconazole and itraconazole were compared in pediatric patients with signs of sepsis and positive blood cultures for *Candida* species. Statistically similar cure rates were observed between groups *(Mondal et al 2004*). In another randomized, controlled trial, voriconazole and amphotericin B were compared in patients with candidemia and demonstrated no significant difference between groups in rates of successful response. However, significantly more patients infected with *C. tropicalis* had a successful response to voriconazole compared to amphotericin B *(Kulberg et al 2005).*
- Fluconazole with or without flucytosine has also been compared to therapy with amphotericin B with or without flucytosine for the treatment of *Cryptococcus* species infection with somewhat conflicting results. In a multicenter, randomized, controlled trial, no significant difference in successful treatment in HIV-infected patients with cryptococcal meningitis was demonstrated with oral fluconazole vs amphotericin B, with or without flucytosine *(Saag et al 1992)*. Conversely, in a prospective, randomized controlled trial, significantly fewer treatment failures were demonstrated in patients with or without acquired immunodeficiency syndrome (AIDS) treated with amphotericin B plus flucytosine compared to oral fluconazole *(Larsen et al 1990).* A recent Cochrane review concluded that the most effective regimen for cryptococcal meningitis in patients with HIV is combination therapy with flucytosine and amphotericin B (*Tenforde et al 2018*).
- In the treatment of various dermatophyte infections, studies comparing ketoconazole and griseofulvin have shown conflicting results. Some studies demonstrate significantly better response to ketoconazole compared to griseofulvin *(Jolly et al 1983, Legendre and Steltz 1980)* while other studies failed to replicate this finding *(Gan et al 1987, Stratigos et al 1983, Tanz et al 1985, Tanz et al 1988).* Comparison of griseofulvin and terbinafine for the treatment of tinea corporis and tinea cruris showed significantly higher clinical and mycological cure rates for terbinafine at week 6 compared to griseofulvin and significantly higher rates of relapse with griseofulvin *(Voravutinon 1993).* A recent meta-analysis found that griseofulvin was more effective than terbinafine in treatment of children with tinea capitis caused by *Microsporum* species, and that terbinafine, itraconazole, and fluconazole are at least similar to griseofulvin in treatment of children with tinea capitis caused by *Trichophyton* species. The findings also suggested that terbinafine was more effective than griseofulvin in *T. tonsurans* infection *(Chen et al 2016).*

- A Cochrane review meta-analysis found limited results comparing antifungals for the treatment and prevention of oropharyngeal candidiasis in HIV positive children and adults, but did find fluconazole and ketoconazole were superior to nystatin in clinical cure. Itraconazole and fluconazole were superior to clotrimazole in clinical cure. They also found that fluconazole was effective for prevention *(Pienaar et al 2010).*
- Studies evaluating the oral antifungal agents as prophylaxis against fungal infections in immunocompromised patients have compared various agents head-to-head. A multicenter, prospective, randomized trial compared fluconazole, itraconazole solution, and posaconazole in patients after remission-induction chemotherapy. Significantly fewer invasive fungal infections occurred with posaconazole compared to fluconazole and itraconazole. Also of note, significantly fewer cases of invasive aspergillosis were observed and significantly fewer patients experienced treatment failure with posaconazole *(Cornely et al 2007).* Similarly, a study comparing fluconazole and posaconazole in patients with graft-versus-host-disease after hematopoietic stem cell transplantation demonstrated a significantly lower incidence of aspergillosis in the posaconazole group compared to the fluconazole group. Breakthrough fungal infections occurred in more patients in the fluconazole group *(Ullmann et al 2007).* A comparison between fluconazole and voriconazole in patients undergoing hematopoietic stem cell transplantation showed no significant difference between the groups' fungal-free survival rates and the incidence of invasive fungal infections *(Wingard et al 2010).* A network meta-analysis of 54 randomized trials concluded that posaconazole is the most effective antifungal for primary prophylaxis in patients with hematological malignancy, but mortality was similar among all of the agents included in the analysis (*Lee et al 2018*).
- Studies comparing the oral antifungal agents for the treatment of onychomycosis have shown varying results. Comparisons of itraconazole (continuous or pulse dose regimens) and terbinafine have demonstrated conflicting results. Some studies showed no difference between treatments *(Bahadir et al 2000, Degreef et al 1999, Honeyman et al 1997)* while others show significantly better results with terbinafine *(Brautigam 1998, Brautigam et al 1995, De Backer et al 1996, De Backer et al 1998, Evans et al 1999, Sigurgeirsson et al 1999, Sigurgeirsson et al 2002).* A study comparing griseofulvin microsize and terbinafine demonstrated significantly higher rates of negative cultures at 72 weeks with terbinafine compared to griseofulvin *(Hofmann et al 1995).* Similarly, 2 studies demonstrated significantly higher complete and mycological cure rates at 1 year for terbinafine compared to griseofulvin microsize *(Faergemann et al 1995, Haneke et al 1995).*
- A 2017 Cochrane review of oral antifungal agents for the treatment of onychomycosis concluded that terbinafine likely results in higher cure rates than azoles with similar tolerability. Terbinafine has better and tolerability than griseofulvin, and griseofulvin has similar cure rates compared to azoles but has worse tolerability (*Kreijkamp-Kaspers et al 2017*).
- In the treatment of vaginal candidiasis, oral fluconazole was found to be similar to topical antifungal agents in clinical response. These results were similar when comparing single-dose oral treatment with fluconazole and topical regimens of clotrimazole or miconazole for 1 dose *(van Heusden et al 1990, van Heusden et al 1994).*

CLINICAL GUIDELINES

- A variety of treatment guidelines address the role of the oral antifungals in the treatment of infectious diseases. Due to changing resistance patterns, guidelines should be frequently referenced.
  - Treatment guidelines are available for HIV and neutropenic patients to guide selection of an appropriate antifungal to use in specific situations *(Freifeld et al 2011, CDC/NIH/IDSA 2018, NIH/CDC/IDSA/Pediatric Infectious Diseases Society/American Academy of Pediatrics 2018).*
  - Guidelines for community acquired pneumonia (CAP), skin and soft-tissue infections (SSTI), and catheter-related infections also address the treatment of fungal causes of infection, although they are less common than bacterial infections in most patients *(Mandell et al 2007, Mermel et al 2009, Stevens et al 2014).*
  - Guidelines also address the role of oral fluconazole (as well as vaginal/local antimicrobials) in the treatment of fungal vaginosis *(American College of Gynecology [ACOG] 2006 (reaffirmed in 2017), CDC 2015, Pappas et al 2016).*
  - Finally, multiple guidelines address the role of these agents in the treatment of specific fungal infections as one agent may be preferred due to volume of literature support, coverage/susceptibility patterns, and safety. Species with specific guidelines include *Aspergillus* species *(Patterson et al 2016), Blastomyces* species *(Chapman et al 2008), Candida* species *(CDC/NIH/IDSA 2018, Pappas et al 2016),* Coccidioidomycosis *(CDC/NIH/IDSA 2018, Galgiani et al 2016), Cryptococcus* species *(CDC/NIH/IDSA 2018, Perfect et al 2010),* Histoplasmosis *(CDC/NIH/IDSA 2018, Wheat et al 2007),* and Sporotrichosis *(Kauffman et al 2007).*

SAFETY SUMMARY

- **Contraindications:**
  - Isavuconazonium sulfate: familial short QT syndrome
  - Griseofulvin: porphyria, hepatocellular failure, and women who are or may become pregnant
  - Ketoconazole: acute or chronic liver disease
  - Miconazole: hypersensitivity to milk protein concentrate
  - Itraconazole: treatment of onychomycosis in patients with evidence of ventricular dysfunction, or in women who intend to become pregnant
  - Terbinafine: chronic or active hepatic disease
- **Boxed Warnings:**
  - Flucytosine: use with extreme caution in patients with impaired renal function; close monitoring of hematologic, renal, and hepatic status of all patients is essential.
  - Ketoconazole should only be used to treat serious systemic fungal infections when other effective antifungal therapy is not available or tolerated, and the potential benefits are considered to outweigh the potential risks; serious hepatotoxicity including death or need for liver transplantation have occurred; coadministration of the following drugs is contraindicated: dofetilide, quinidine, pimozide, cisapride, methadone, disopyramide, dronedarone, and ranolazine due to potential QT prolongation and life-threatening ventricular dysrhythmias.
  - Itraconazole should not be administered for the treatment of onychomycosis in patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF; coadministration of methadone, disopyramide, dofetilide, dronedarone, quinidine, isavuconazole, ergot alkaloids (such as dihydroergotamine, ergometrine [ergonovine], ergotamine, methylergometrine [methylergonovine]), irinotecan, lurasidone, oral midazolam, pimozide, triazolam, felodipine, nisoldipine, ivabradine, ranolazine, eplerenone, cisapride, naloxegol, lomitapide, lovastatin, simvastatin, avanafil, ticagrelor and, in subjects with renal or hepatic impairment, colchicine, fesoterodine, and solifenacin is contraindicated. Coadministration with eliglustat is contraindicated in patients who are poor or intermediate metabolizers of CYP2D6 and in those taking strong or moderate CYP2D6 inhibitors. Coadministration of the former agents with itraconazole can cause elevated plasma concentrations of these drugs and may increase or prolong both the pharmacologic effects and/or adverse reactions to these drugs. Increased plasma concentrations of some of these drugs can lead to QT prolongation and ventricular tachyarrhythmias including occurrences of torsades de pointes, a potentially fatal arrhythmia.
- **Warnings/Precautions:**
  - Monitor for hepatotoxicity with all agents in the class.
  - Flucytosine: monitor hematologic status and bone marrow suppression. Dose adjustments may be necessary in patients with renal impairment.
  - Fluconazole, griseofulvin, terbinafine, and voriconazole: rare, sometimes fatal exfoliative skin disorders have occurred. Monitor for skin rashes and discontinue treatment if rash occurs.
  - Fluconazole: administer with caution to patients with potentially proarrhythmic conditions or those with renal dysfunction. Women of childbearing potential who receive doses of 400 to 800 mg daily should use effective contraception during treatment and for 1 week after the last dose due to the potential for spontaneous abortion and congenital abnormalities with fluconazole exposure during the first trimester. Additionally, caution is advised when driving or operating heavy machinery as fluconazole may cause occasional dizziness or seizures.
  - Griseofulvin: a possibility of cross-sensitivity with penicillin exists. Additionally, lupus-like syndromes or exacerbations of existing lupus have been reported. Patients should avoid exposure to intense or prolonged natural or artificial sunlight.
  - Itraconazole: if neuropathy occurs and can be attributed to itraconazole, treatment should be discontinued. If a cystic fibrosis patient does not respond to treatment with itraconazole capsules, alternative therapy should be considered. Some immunocompromised patients may have decreased bioavailability and require higher doses. Finally, transient and permanent hearing loss have been reported.
  - Ketoconazole: decrease in adrenal corticosteroid secretion can occur at doses of 400 mg and higher.
  - Miconazole: monitor for hypersensitivity reactions and discontinue at the first sign of such reaction.
  - Posaconazole: administer with caution to patients with potentially proarrhythmic conditions
  - Terbinafine: taste and smell disturbances have been reported. Severe neutropenia has been reported. Discontinue treatment if neutrophil count is ≤ 1000 cells/mm^3. Cases of thrombotic microangiopathy (TMA), including thrombotic

thrombocytopenic purpura and hemolytic uremic syndrome, have been reported. Discontinue treatment if clinical symptoms and laboratory measurements are consistent with TMA.
  - Voriconazole: visual disturbances have been reported; galactose intolerance and skeletal disturbances may occur. Voriconazole may increase risk for QT prolongation, hepatic toxicity, and dermatologic reactions.
  - Fetal toxicity may occur with some agents, including fluconazole (use in pregnancy should be avoided unless the benefits outweigh fetal risk), griseofulvin microsize, isavuconazonium sulfate, and voriconazole.
  - In May 2016, the FDA issued a medication safety alert warning health care professionals to avoid prescribing ketoconazole oral tablets to treat skin and nail fungal infections. According to the FDA, the risk of serious liver damage and drug interactions with this agent outweigh the benefits when treating these conditions *(FDA Drug Safety Communication 2016).*
- **Adverse Effects:**
  - A variety of adverse effects from mild to severe may occur with agents in this class. Consult individual package inserts for details.
- **Drug Interactions:**
  - Many drug interactions occur with all of the agents in the class.
  - Drugs metabolized through the cytochrome P450 system increase QT prolongation and may cause torsades de pointes.
  - Consult individual package inserts for details about specific drug interactions and contraindications for concomitant use of certain medications. Agents that have contraindications related to drug interactions include isavuconazole, fluconazole, itraconazole (boxed warning), ketoconazole (boxed warning), posaconazole, and voriconazole.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ancobon (flucytosine)	Capsules	Oral	Every 6 hours	In patients with renal or hepatic dysfunction, use with extreme caution; closely monitor hematologic, renal, and hepatic status.
clotrimazole	Lozenges	Oral	Three to 5 times daily	
Cresemba (isavuconazonium sulfate)	Capsules	Oral	Every 8 hours x 6 doses, then once daily	
Diflucan (fluconazole)	Tablets Suspension	Oral	Once daily	Pediatric weight-based dose equivalency is available. Dosing adjustments based on renal function are necessary. (see prescribing information)
griseofulvin microsize	Tablets Suspension	Oral	Once daily, or in divided doses	Should be taken after a meal with high fat content Pediatric weight-based dosing is available. (see prescribing information) Contraindicated in women who are or may become pregnant.
Gris-PEG (griseofulvin ultramicrosize)	Tablets	Oral	Once daily, or in divided doses	Pediatric weight-based dosing is available. (see prescribing information) Contraindicated in women who are or may become pregnant.
ketoconazole	Tablets	Oral	Once daily	Pediatric weight-based dosing is available. (see prescribing information)
Lamisil (terbinafine)	Tablets	Oral	Once daily	Pediatric (≥ 4 years) weight-based dosing is available. (see prescribing information)

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Use in patients with renal impairment (CrCL ≤ 50 mL/min) has not been studied. Contraindicated in patients with chronic or active liver disease.
Noxafil (posaconazole)	Suspension Tablets, delayed-release	Oral	Once to 3 times daily	The delayed-release tablet and oral suspension are not to be used interchangeably due to the differences in the dosing of each formulation. The suspension must be given with a full meal. The delayed-release tablets should be taken with food.
nystatin	Suspension Tablets	Oral	Three to 4 times daily	Suspension may be used in infants, children, and adults for the treatment of oral candidiasis.
Onmel (itraconazole)	Tablets	Oral	Once daily	Should be given with a full meal.
Oravig (miconazole)	Tablets	Buccal	Once daily	The tablet should be placed against the upper gum just above the incisor tooth. The tablet should not be chewed, crushed, or swallowed.
Sporanox (itraconazole)	Capsules Solution	Oral	Once or twice daily	Capsules should be taken with a full meal. Solution should be taken without food. Only the oral solution should be used for oropharyngeal and esophageal candidiasis; oral solution and capsules should not be used interchangeably. Dose may need to be adjusted to clinical response due to lower bioavailability in some immunocompromised patients.
Vfend (voriconazole)	Tablets Suspension	Oral	Every 12 hours	For Aspergillosis, Scedosporiosis, Fusariosis, and Candidemia, therapy should be initiated with IV voriconazole, then switched to the oral formulation for maintenance therapy.

See the current prescribing information for full details

CONCLUSION

- The oral class of antifungals includes a variety of different agents used to treat many different fungal infections, including aspergillosis, blastomycosis, histoplasmosis, candidiasis, mucormycosis, onychomycosis, ringworm infections, and others.
- Resistant organisms have been reported; thus, it is important to verify susceptibility when resistant organisms are suspected. Current resistance patterns should be monitored for the antifungal agents in order to select the most appropriate therapy. Appropriate guidelines should be referenced often.
- Some patients may require intravenous therapy that is not specifically discussed in this review. Isavuconazonium, fluconazole, voriconazole, and posaconazole are available as oral and intravenous formulations. Some of these antifungal medications are also available in topical formulations.
- Clotrimazole, nystatin, and Oravig (miconazole) are not absorbed systemically. They are not used for systemic infections, but only for the treatment of oropharyngeal candidiasis.
- Onychomycosis can be treated with Onmel (itraconazole), Sporanox (itraconazole), or Lamisil (terbinafine). Griseofulvin is no longer used for this indication.
- The majority of the class is available generically. Cresemba (isavuconazonium sulfate), Noxafil (posaconazole), Onmel (itraconazole), and Oravig (miconazole) are available as brand only.

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Therapeutic Class Overview
Antifungals, Topical

INTRODUCTION

- The topical antifungals are available in multiple dosage forms and are indicated for a number of fungal infections and related conditions. In general, these agents are Food and Drug Administration (FDA)-approved for the treatment of cutaneous candidiasis, onychomycosis, seborrheic dermatitis, tinea corporis, tinea cruris, tinea pedis, and tinea versicolor (*Clinical Pharmacology 2018*).
- The antifungals may be further classified into the following categories based upon their chemical structures: allylamines (naftifine, terbinafine [only available over the counter (OTC)]), azoles (clotrimazole, econazole, efinaconazole, ketoconazole, luliconazole, miconazole, oxiconazole, sertaconazole, sulconazole), benzylamines (butenafine), hydroxypyridones (ciclopirox), oxaborole (tavaborole), polyenes (nystatin), thiocarbamates (tolnaftate [no FDA-approved formulations]), and miscellaneous (undecylenic acid [no FDA-approved formulations]) (*Micromedex 2018*).
- The topical antifungals are available as single entity and/or combination products. Two combination products, nystatin/triamcinolone and Lotrisone (clotrimazole/betamethasone), contain an antifungal and a corticosteroid preparation. The corticosteroid helps to decrease inflammation and indirectly hasten healing time. The other combination product, Vusion (miconazole/zinc oxide/white petrolatum), contains an antifungal and zinc oxide. Zinc oxide acts as a skin protectant and mild astringent with weak antiseptic properties and helps to promote healing.
- Ciclopirox, clotrimazole, clotrimazole/betamethasone, econazole (cream only), ketoconazole, naftifine (cream only), nystatin, nystatin/triamcinolone, and oxyconazole (cream only) are available generically in several dosage forms.
- Ecoza (econazole nitrate 1% foam) and Luzu (luliconazole) cream were approved in 2013.
- Two molecular entities were approved in 2014 for the topical treatment of adult patients with onychomycosis of the toenails due to select strains of *Trichophyton*, Jublia (efinaconazole 10% topical solution) and Kerydin (tavaborole 5% topical solution). Prior to 2014, ciclopirox 8% solution was the only topical agent available for the treatment of onychomycosis (*Rosen et al 2016*).
- This review focuses primarily on topical antifungal products that are available by prescription. Antifungal products that are used for the treatment of oropharyngeal or vulvovaginal candidiasis are not included. There are several topical antifungal products that are available OTC, and some products are available OTC as well as by prescription. Additionally, some agents within this class have been used safely and effectively for many years; however, there are limited published data evaluating the efficacy of these products for their approved indications.
- Medispan class: Antifungals - Topical.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single-entity Products	
clotrimazole	✔ (cream and solution)
Ecoza (econazole)	✔ (cream only)
Ertaczo (sertaconazole)	-
Exelderm (sulconazole)	-
Extina, Nizoral, Xolegel (ketoconazole)	✔ (cream, foam, and shampoo 2%)
Jublia (efinaconazole)	-
Kerydin (tavaborole)	-
Loprox, Penlac (ciclopirox)	✔ (all formulations*)
Luzu (luliconazole)	✔ † (cream)
Mentax (butenafine)	-
Naftin (naftifine)	✔ (cream only)
nystatin	✔ (cream, ointment and powder)
Oxistat (oxiconazole)	✔ (cream only)
Combination Products	
Lotrisone (clotrimazole/betamethasone)	✔ (cream and lotion)
nystatin/triamcinolone	✔ (cream and ointment)
Vusion (miconazole/zinc oxide/white petrolatum)	✔ †

* cream 0.77%, gel 0.77%, shampoo 1%, solution 8%, suspension 0.77%

† Authorized generics for Luzu (luliconazole) cream and Vusion (miconazole/zinc oxide/white petrolatum) ointment are available.

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

INDICATIONS

Table 2. Food and Drug Administration-Approved Indications for Single-Entity Products

Drug	Tinea corporis	Tinea cruris	Tinea pedis	Tinea versicolor	Seborrheic dermatitis	Cutaneous candidiasis	Onychomycosis
clotrimazole				✔		✔	
econazole (cream)	✔	✔	✔	✔		✔	
Ecoza (econazole) foam			✔ *				
Ertaczo (sertaconazole)			✔ *				
Exelderm (sulconazole)	✔	✔	✔ †	✔			
Extina (ketoconazole)					✔ *		
Jublia (efinaconazole)							✔
Kerydin (tavaborole)							✔ ‡
Loprox (ciclopirox)	✔ §	✔ **	✔ ‡	✔ §	✔ ††	✔ §	
Luzu (luliconazole)	✔	✔	✔				
Mentax (butenafine)				✔			
Naftin‡‡ (naftifine)	✔	✔ *	✔ *				
Nizoral (ketoconazole) cream	✔	✔	✔	✔	✔	✔	
Nizoral (ketoconazole) shampoo				✔ §§			
Nystatin						✔	
Oxistat (oxiconazole) ***	✔	✔	✔	✔ †††			
Penlac (ciclopirox lotion)							✔ ‡‡‡
Xolegel (ketoconazole) gel					✔ *		

* Indicated for ≥ 12 years
† The cream is indicated for all tinea infections, but the solution is not indicated for tinea pedis
‡ Safety and efficacy have been established in patients ≥ 6 years of age.
§ Cream, gel, and lotion
** Cream and lotion
†† Gel and shampoo
‡‡ 2% gel only indicated for tinea pedis in patients ≥ 12 years of age. 2% cream may be used for tinea corporis in patients ≥ 2 years of age.
§§ Shampoo 2%
*** The cream is approved for pediatric patients for all indications
††† Cream only
‡‡‡ Indicated as a component of a comprehensive management program, as topical treatment in immunocompetent patients with mild to moderate onychomycosis of fingernails and toenails without lunula involvement.

Table 3. Food and Drug Administration-Approved Indications for Combination Products

Drug	Tinea corporis	Tinea cruris	Tinea pedis	Diaper dermatitis	Cutaneous candidiasis
Lotrisone* (clotrimazole/betamethasone)	✔	✔	✔		
nystatin/triamcinolone					✔
Vusion (miconazole/zinc oxide/white petrolatum)				✔ †	

* Indicated for >17 years for inflammatory conditions

† For the adjunctive treatment of diaper dermatitis only when complicated by documented candidiasis (microscopic evidence of pseudohyphae and/or budding yeast), in immunocompetent pediatric patients 4 weeks and older

(*Prescribing information: ciclopirox gel 2017, ciclopirox lotion 2014, ciclopirox olamine cream 2017, ciclopirox shampoo 2017, ciclopirox solution 2017, clotrimazole cream 2014, clotrimazole solution 2012, clotrimazole/betamethasone 2018, econazole 2018, Ecoza 2016, Ertaczo 2017, Exelderm cream 2018, Exelderm solution 2018, Extina 2018, Jublia 2016, Kerydin 2018, ketoconazole 2016, Lotrisone 2018, Luzu 2018, Mentax 2018, Naftin 1% gel 2018, Naftin 2% cream 2018, Naftin 2% gel 2018, Nizoral 2017, Nizoral A-D 2015, nystatin cream 2017, nystatin ointment 2017, nystatin powder 2017, nystatin/triamcinolone cream 2017, nystatin/triamcinolone ointment 2016, Oxistat 2016, Vusion 2013, Xolegel 2012*)

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

CLINICAL EFFICACY SUMMARY

- Several clinical trials have demonstrated that topical azoles (clotrimazole, miconazole, sulconazole), ciclopirox, and nystatin were effective in the management of cutaneous candidiasis (*Bagatell et al 1985, Beveridge et al 1977, Rajan et al 1983, Tanenbaum et al 1983*). Clinical studies have reported no significant difference in efficacy between sulconazole cream and clotrimazole or miconazole cream for cutaneous candidiasis. Nystatin/triamcinolone was compared to the administration of nystatin monotherapy (*Beveridge et al 1977*). The results of this study demonstrated that nystatin/triamcinolone was as effective as nystatin monotherapy. Also, there was no difference reported in the patient or physician preference for either agent.
- There are limited data evaluating the efficacy of the combination of miconazole/zinc oxide for the treatment of patients with diaper dermatitis complicated by candidiasis. In 2 clinical trials, this combination product was compared to patients receiving zinc oxide monotherapy. In 1 study, miconazole/zinc oxide demonstrated statistically significant reductions in total rash scores in patients with mild-to-moderate diaper dermatitis as compared to zinc oxide monotherapy (*Concannon et al 2001*). A second study determined that miconazole/zinc oxide had a lower incidence of diaper dermatitis and a higher clinical microbiological and overall cure rate as compared to patients treated with zinc oxide alone (*Spraker et al 2006*).
- Topical antifungal agents are the mainstay of treatment for seborrheic dermatitis. During clinical trials, ciclopirox gel and shampoo formulations demonstrated statistically significant improvements in symptom scores and clinical cure compared to placebo vehicles (*Aly et al 2003[a], 2003[b], Vardy et al 2000*). Ketoconazole cream, foam, gel, and shampoo formulations were also associated with statistically significant improvements in symptom scores and clinical cure compared to placebo vehicles (*Carr et al 1987, Cauwenbergh et al 1986, Elewski et al 2006, Elewski et al 2007, Green et al 1987)*. There are limited data comparing ciclopirox to ketoconazole. One study reported significantly higher rates of remission with ciclopirox cream (twice daily for 28 days then once daily for 28 days) than ketoconazole gel (twice weekly for 28 days then once weekly for 28 days) for the treatment of facial seborrheic dermatitis (*Naldi and Rebora 2009*). The results were difficult to interpret because ciclopirox was dosed more frequently than ketoconazole. In a recent systematic review, ciclopirox and ketoconazole were both strongly recommended for facial seborrheic dermatitis due to their consistent effectiveness across multiple high-quality trials (*Gupta and Versteeg 2017*).
- Noninvasive tinea fungal infections may be treated with appropriate skin care and a topical antifungal agent (*Andrews et al 2008, Brown and Dresser 2017, Drake et al 1996[a]*). Based on data obtained from clinical trials on tinea pedis, there was a statistically significant improvement in efficacy (microbiological and clinical cure) in patients treated with the following agents compared to placebo: butenafine, ciclopirox, econazole foam, luliconazole, naftifine, oxiconazole, sertaconazole, and tolnaftate (*Aly et al 1989, Aly et al 2003, Ecoza prescribing information, 2013, Gupta et al 2005, Jarratt et al 2013, Jones et al 2014, Pariser et al 1994, Reyes et al 1997, Stein Gold et al 2013, Tschen et al 1997*). In a

meta-analysis of placebo-controlled trials, the pooled relative risks of failure to cure skin infections of the foot were as follows for the topical antifungal agents: allylamines 0.33, azoles 0.3, butenafine 0.33, ciclopirox 0.27, and tolnaftate 0.19 (*Crawford et al 2007*). No differences were detected between individual azoles and allylamines. Meta-analysis of data collected in 9 trials comparing 4 to 6 weeks of treatment with allylamines and azoles showed a risk ratio for treatment failure of 0.63 in favor of allylamines. In another meta-analysis, allylamines, azoles and other antifungals were found to be more effective in mycological cure and sustained cure vs. placebo (*Rotta et al 2012*). No differences were found between the classes of agents.

- Based on data obtained from clinical trials on various tinea infections (which included patients with tinea pedis, corporis, cruris, and/or versicolor), there was a statistically significant improvement in efficacy (microbiological and clinical cure) in patients treated with the following agents compared to placebo: miconazole, naftifine, oxiconazole, and terbinafine (*Jordan et al 1990, Kagawa et al 1989, Mandy and Garrott 1974, Pariser et al 1994, Ramelet et al 1987*). In a meta-analysis of 27 trials, terbinafine demonstrated 70 to 90% and 70 to 80% efficacy in the treatment of dermatomycoses and tinea versicolor, respectively (*Villars et al 1989*). Most of the head-to-head trials comparing one antifungal to another were conducted in a small number of patients. In general, direct comparative trials did not demonstrate that one antifungal was safer or more efficacious than another.
- The combination product consisting of clotrimazole/betamethasone has been evaluated for the treatment of tinea infections. In 2 double-blind, placebo-controlled trials, patients were randomized to clotrimazole/betamethasone, clotrimazole monotherapy, or betamethasone monotherapy. One trial enrolled patients with only a confirmed diagnosis of tinea cruris (*Wortzel et al 1982*). This study showed that 80, 20, and 13% of patients achieved either complete cure or excellent response to therapy with the combination product, clotrimazole monotherapy, and betamethasone monotherapy, respectively. The other study enrolled patients with a confirmed diagnosis of moderate-to-severe tinea cruris or tinea corporis (*Katz et al 1984*). This study showed that for the treatment of tinea cruris and tinea corporis, patients treated with the combination product had significantly better total sign and symptom reductions compared to each individual component administered as monotherapy.
- A Cochrane review of 129 trials (N = 18,086) assessed the effects of topical antifungal treatments in tinea cruris and tinea corporis (*El Gohary et al 2014*). Mycological cure rates favored naftifine 1% compared to placebo in 3 studies (risk ratio [RR] 2.38, 95% confidence interval [CI] 1.80 to 3.14, number needed to treat [NNT] 3, 95% CI 2 to 4) (low quality evidence). In 1 study, naftifine 1% was more effective than placebo in achieving clinical cure (RR 2.42, 95% CI 1.41 to 4.16, NNT 3, 95% CI 2 to 5) (low quality evidence). Across 2 studies, mycological cure rates were superior for clotrimazole 1% compared to placebo (RR 2.87, 95% CI 2.28 to 3.62, NNT 2, 95% CI 2 to 3). There was no difference in mycological cure between azoles and benzylamines (RR 1.01, 95% CI 0.94 to 1.07) (low quality evidence). There was no evidence for a difference in cure rates between tinea cruris and tinea corporis.
- Ciclopirox solution (lacquer) is a topical antifungal that is FDA-approved for onychomycosis. Two double-blind, placebo-controlled clinical trials reported significantly higher mycologic cure rates for ciclopirox (29 to 36%) compared to vehicle (9 to 11%) (*Katz et al 1984*). Both studies reported significantly higher treatment successes (≤ 10% nail involvement and negative mycology) with ciclopirox (6.5 to 12%) than placebo (0.9%). One of the 2 studies reported a significantly higher treatment cure (clear nail and negative mycology) with ciclopirox (5.5 to 8.5%) vs placebo (0 to 0.9%). A meta-analysis of randomized trials concluded that there was some evidence that ciclopirox was effective for the management of onychomycosis, but ciclopirox had to be applied daily for prolonged periods (1 year) (*Crawford et al 2007*). Oral antifungals are generally recommended for the treatment of onychomycosis (*de Berker 2009, Drake et al 1996[c], Ameen et al 2014*). Topical antifungals should be considered for patients who have contraindications to systemic therapy. There is inconsistent evidence that combining topical and oral antifungals leads to better cure rates than monotherapy with oral antifungals.
- The safety and efficacy of Jublia applied once daily for the treatment of onychomycosis of the toenail were assessed in 2 identical, 52-week prospective, multi-center, randomized, double-blind, vehicle-controlled clinical trials in patients 18 years and older (18 to 70 years of age) with 20% to 50% clinical involvement of the target toenail, without dermatophytomas or lunula (matrix) involvement. The primary endpoint was complete cure rate defined as 0% clinical involvement of target toenail (no clinical evidence of onychomycosis) in addition to mycologic cure (defined as both negative potassium hydroxide [KOH] examination and fungal culture) at week 52. Complete cure was significantly greater for patients treated with Jublia compared to vehicle in both studies (17.8% in study 1 and 15.2% in study 2 compared with 3.3% and 5.5% for vehicle, respectively; $p < 0.001$ for both studies). Similarly, mycologic cure rates were also significantly greater for patients treated with Jublia compared to vehicle in both studies (55.2% in study 1 and

53.4% in study 2 compared with 16.8% and 16.9% for vehicle, respectively; p < 0.001 for both studies). Similar adverse events were reported between the 2 groups (*Elewski et al 2013, Valeant Pharmaceuticals press release 2014*).

- The safety and efficacy of Kerydin were demonstrated in two phase 3, randomized, parallel-group, double-blind, vehicle-controlled trials: Study 301 and 302. Both studies were identically designed and patients (N = 1194) had 20 to 60% of clinical involvement of the target toenail at baseline. Patients were randomized to receive either Kerydin 5% topical solution or a vehicle-control which was applied topically once daily for 48 weeks. The primary endpoint, which was complete cure (defined as 0% clinical involvement of the target nail plus a negative KOH and fungal culture) was observed in 6.5% of Kerydin-treated patients vs 0.5% in the vehicle-controlled group for Study 301, and 9.1% vs 1.5%, respectively, in Study 302 (p ≤ 0.001 for both studies). Mycologic cure (defined as a negative KOH wet mount and a negative fungal culture) was observed in 31.1% of Kerydin-treated patients vs. 7.2% in the vehicle-controlled group for Study 301, and 35.9% vs 12.2%, respectively, in Study 302 (p ≤ 0.001 for both studies). The most common treatment-related adverse events in the Kerydin and vehicle-control groups were application site exfoliation (2.7% and 0.3%, respectively), erythema (1.6% and 0%), and dermatitis (1.3% and 0%) (*Elewski et al 2015*). In a pooled analysis of patients with complete or almost clear nails who completed an additional 8 weeks of post-study follow-up (N = 62), complete cure was maintained in 28.6% of Keridyn-treated patients compared to 7.7% of the vehicle-controlled group (*Gupta et al 2018*).
- In a 2014 evidence-based review of topical therapy for toenail onychomycosis, 28 studies evaluating complete and mycological cure demonstrated that topical amorolfine (not available in the US), ciclopirox, tavaborole, and efinaconazole were effective for patients with less than 50 to 65% toenail involvement. A treatment duration of 48 weeks led to the most successful outcomes. Complete cure (generally defined as mycological cure with no nail involvement) rates were 17.8% with efinaconazole vs 8.5% with ciclopirox (*Gupta et al 2014b*).

Table 4. Results from Phase 3 Trials of FDA-Approved Topical Treatments for Onychomycosis
This table provides an indirect comparison of data collected from different clinical trials. Because study populations and trial methods may vary across trials, this information should not be used to draw conclusions about the relative efficacy or safety of individual treatments.*†

Antifungal	Dosing and Duration	Complete or Clinical Cure	Mycologic Cure
Jublia (efinaconazole) Baseline: 20 to 50% clinical involvement	Once daily applications for 48 weeks of treatment with a 4 week follow-up period	15.2 to 17.8% Difference from vehicle-control, 9.7 to 14.5%	53.5 to 55.2% Difference from vehicle-control, 36.5 to 38.4%
Kerydin (tavaborole) Baseline: 20 to 60% clinical involvement	Once daily applications for 48 weeks of treatment with a 4 week follow-up period	6.5 to 9.1% Difference from vehicle-control, 6 to 7.6%	31.1 to 35.9% Difference from vehicle-control, 23.8%
Penlac (ciclopirox) nail lacquer Baseline: 20 to 65% clinical involvement	Applied for 48 weeks	5.5 to 8.5% Difference from vehicle-control, 4.6 to 8.5%	29 to 36% Difference from vehicle-control, 18 to 27%

*Only first-to-market topical drug formulations are included for comparison.
†According to the Penlac prescribing information, concomitant use of ciclopirox 8% topical solution and systemic antifungal agents for onychomycosis is not recommended because studies have not been conducted to determine whether ciclopirox might reduce the effectiveness of systemic antifungal agents. Some experts support the recommendation of combination therapy; however, this has not been explicitly studied by the manufacturer or evaluated by the FDA.

(*Poulakos et al 2017, Rosen et al 2016, Westerberg et al 2013*)

CLINICAL GUIDELINES

- National and international recommendations which discuss the management of fungal infections focus primarily on superficial mycotic infections. Several recommendations list topical antifungal agents or subclasses, and generally do

not give preference to one agent vs another (*Brown and Dresser 2017, de Berker 2009, Drake et al 1996[a], Drake et al 1996[b], Naldi and Rebora 2009, Ameen et al 2014, Stevens et al 2014*). According to these guidelines, mycological and clinical cure of noninvasive fungal infections are often achieved with topical therapy alone. Oral therapy is preferred for the treatment of extensive or severe infection and those with tinea capitis or onychomycosis.

- New topical antifungal agents Jublia (efinaconazole) and Kerydin (tavaborole) are recommended for mild-moderate toenail fungal infections (*Brown and Dresser 2017*).

SAFETY SUMMARY

- If patients experience hypersensitivity to an agent, therapy should be discontinued. Cross-sensitivity can also occur among the imidazole-containing agents.
- Products containing corticosteroids should be used with caution because systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticoid insufficiency after withdrawal of treatment. Conditions which augment systemic absorption include use over large surface areas, prolonged use, use under occlusive dressings, and use in pediatric patients.
- The use of topical corticosteroids (ie, betamethasone) may increase the risk of posterior subcapsular cataracts and glaucoma.
- The most common adverse events are erythema, stinging, blistering, peeling, edema, pruritus, urticaria, burning, and general irritation of the skin.
- Several products are flammable: Ecoza (econazole), Extina (ketoconazole), Penlac (ciclopirox), Xolegel (ketoconazole), Jublia (efinconazole), and Kerydin (tavaborole). They should not be used near heat or flame.
- Econazole may potentiate the effects of warfarin and increase bleeding risk. Luliconazole may inhibit cytochrome P450 (CYP) 2C19.

DOSING AND ADMINISTRATION

- For all products: enough cream/ointment/lotion should be applied to cover the affected areas and the immediately surrounding skin. If a patient shows no clinical improvement after the treatment period, the diagnosis and therapy should be reviewed.

Table 5. Dosing and Administration

Drug	Available Formulations	Usual Recommended Frequency	Comments
Single-entity products			
clotrimazole	Topical cream, solution	Apply twice daily for up to 4 weeks.	External use only; not for ophthalmic use.
econazole (Ecoza and generics)	Topical cream: (generics) Topical foam: (Ecoza)	**Cream** *Candidiasis:* Apply twice daily for 2 weeks. *Other uses:* Apply once daily for 2 weeks; except pedis, for 4 weeks. **Foam** *Tinea pedis:* Apply once daily for 4 weeks.	Topical use only; not for oral, ophthalmic, or intravaginal use.
Ertaczo (sertaconazole)	Topical cream	Apply twice daily for 4 weeks.	Topical use only; not for oral, ophthalmic, or intravaginal use.
Exelderm (sulconazole)	Topical cream Topical solution	**Cream** *Corporis, cruris, versicolor:* Apply once or twice daily for 3 weeks. *Pedis*: Apply twice daily for 4 weeks. **Solution** *Corporis, cruris, versicolor*: Apply once or twice daily for 3 weeks	Topical use only; not for ophthalmic use.

Drug	Available Formulations	Usual Recommended Frequency	Comments
Extina, Nizoral, Xolegel (ketoconazole)	Topical cream, foam, shampoo, gel	**Cream** *Dermatitis*: Apply twice daily for 4 weeks or until clinical clearing. *Other uses*: Apply once daily for 2 weeks; except for tinea pedis for 6 weeks. **Foam**: Apply twice daily for 4 weeks. **Shampoo 2%:** Apply to damp skin of the affected area. Lather, leave in place for 5 minutes, and then rinse off with water. One application of the shampoo should be sufficient. **Shampoo 1% (OTC):** Apply to wet hair. Generously lather, rinse, and repeat. Use every 3 to 4 days for up to 8 weeks. **Topical Gel:** Apply once daily for 2 weeks.	Topical use only; not for oral, ophthalmic, or intravaginal use.
Jublia (efinaconazole)	Topical solution	Apply to affected toenails once daily for 48 weeks.	Topical use only; not for oral, ophthalmic, or intravaginal use. Ensure the toenail, the toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate, are completely covered.
Kerydin (tavaborole)	Topical solution	Apply to the affected toenails once daily for 48 weeks.	Topical use only; not for oral, ophthalmic, or intravaginal use. Should be applied to the entire toenail surface and under the tip of each toenail being treated.
Loprox, Penlac (ciclopirox)	Topical cream, gel, lotion, shampoo, solution	**Cream and lotion**: Apply twice daily for up to 4 weeks. **Gel**: Apply twice daily for 4 weeks. **Shampoo:** Treatment should be repeated twice per week for 4 weeks, with a minimum of 3 days between applications. **Solution**: Apply once daily (preferably at bedtime or 8 hours before washing) to all affected nails, evenly over the entire nail plate. Do not remove on a daily basis. Daily applications should be made over the previous coat and removed with alcohol every 7 days.	Solution: Should be applied to the nail bed, hyponychium, and under the surface of the nail plate when it is free of the nail bed. Topical use only; not for oral, ophthalmic, or intravaginal use
Luzu (luliconazole)	Topical cream	**Interdigital tinea pedis:** Apply once daily for 2 weeks.	Topical use only; not for oral, ophthalmic, or intravaginal use

Drug	Available Formulations	Usual Recommended Frequency	Comments
		Tinea cruris or tinea corporis: Apply once daily for 1 week.	
Mentax (butenafine)	Topical cream	Apply once daily for 2 weeks.	Topical use only; not for oral, ophthalmic, or intravaginal use
Naftin (naftifine)	Topical cream, gel	**Cream/Gel 2%:** Apply once daily for 2 weeks. **Gel 1%**: Apply twice daily for up to 4 weeks.	Topical use only; not for oral, ophthalmic, or intravaginal use
nystatin	Topical cream, ointment, powder	**Cream and ointment**: Apply twice daily until complete healing. **Powder**: Apply 2 to 3 times daily until complete healing.	Topical use only; not for oral, ophthalmic, or intravaginal use Cream is usually preferred to ointment in candidiasis involving intertriginous areas. Very moist lesions are best treated with topical powder.
Oxistat (oxiconazole)	Topical cream, lotion	**Corporis and cruris**: Apply once or twice daily for 2 weeks. **Versicolor**: Apply once daily for 2 weeks. **Pedis**: Apply once or twice daily for one month.	Shake lotion well before using. Topical use only; not for oral, ophthalmic, or intravaginal use
Combination products			
Lotrisone (clotrimazole/ betamethasone)	Topical cream, lotion	**Corporis, cruris**: Apply twice daily for up to 2 weeks. **Pedis**: Apply twice daily for up to 4 weeks.	Do not use more than 45 grams or 45 mL per week. Shake lotion well before each use. Topical use only; not for oral, ophthalmic, or intravaginal use
nystatin/ triamcinolone	Topical cream, ointment: nystatin 100,000 units/ triamcinolone 1 mg/gram	Apply twice daily for up to 25 days.	For external use only; not for ophthalmic use
Vusion (miconazole/zinc oxide/white petrolatum)	Topical ointment: 0.25% miconazole nitrate/15% zinc oxide/81.35% white petrolatum	Apply with each diaper change for 7 days.	Topical use only; not for oral, ophthalmic, or intravaginal use

See the current prescribing information for full details.

CONCLUSION

- Many of the products are available generically, including ciclopirox, clotrimazole, clotrimazole/betamethasone, econazole cream, ketoconazole, naftifine cream, nystatin, nystatin/triamcinolone, and oxyconazole cream.
- Several topical antifungal products are available OTC and some are available both as prescription and OTC.
- The limited clinical trials available do not differentiate one product from another in terms of mycological and clinical cure.

- Vusion (miconazole/zinc oxide/white petrolatum) is a combination product indicated for diaper dermatitis when complicated by documented candidiasis. It has been shown to be more effective than zinc oxide therapy alone (*Concannon et al 2001, Spraker et al 2006*). Comparative trials to other active agents have not been conducted.
- Jublia is the first FDA-approved triazole antifungal indicated for the topical treatment of adult patients with onychomycosis of the toenails due to *Trichophyton rubrum* and *Trichophyton mentagrophytes.* Jublia is also the first triazole antifungal to be developed for the treatment of distal lateral subungual onychomycosis (DLSO) (*Valeant Pharmaceuticals press release 2014*).
- Kerydin is a first-in-class oxaborole topical antifungal approved for the treatment of toenail onychomycosis (*MarketWatch press release 2014*). Jublia is also approved for this indication.
- National and international recommendations which discuss the management of fungal infections focus primarily on superficial mycotic infections. Several recommendations list topical antifungal agents or subclasses, and generally do not give preference to one agent vs another (*Brown and Dresser 2017, de Berker, 2009, Drake et al 1996[a], Drake et al 1996[b], Naldi and Rebora 2009, Ameen et al 2014, Stevens et al 2014*). According to these guidelines, mycological and clinical cure of noninvasive fungal infections are often achieved with topical therapy alone.
- Dosing and administration of these agents are dependent upon the condition being treated and the patient population.
- Adverse effects for the topical antifungals are primarily dermatological with allergic or contact dermatitis, burning, dry skin, erythema, pruritus, skin irritation, and stinging as the most common reactions reported.

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