OPTUMRx®

Silver State Script Board Meeting

MARCH 26, 2020

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OPTUMRx®

Agenda

NOTICE OF PUBLIC MEETING – SILVER STATE SCRIPTS BOARD

AGENDA

Date of Publication:	**February 13, 2020**
Date and Time of Meeting:	**March 26, 2020 at 1:00 PM**
Name of Organization:	The State of Nevada, Department of Health and Human Services (DHHS), Division of Health Care Financing and Policy (DHCFP)
Place of Meeting:	Springs Preserve 333 S. Valley View Blvd. Las Vegas, Nevada 89107
Webinar Registration:	https://optum.webex.com/optum/onstage/g.php?MTID=e0d8a0d589390e6223ab1a391858b2696 **OR** www.webex.com, select "Join," enter Meeting Number 640 139 985, your name and email and then select, "Join." A Password should not be necessary, but if asked, enter "Medicaid1!" **OR**
Audio Only:	(763) 957-6300 Event Number: 649 127 642 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 five minutes per individual, organization, or agency, but may be extended at the discretion of the Chairperson.

1:00 PM – Closed Executive Session

Pursuant to NRS 422.405(4), as amended by Senate Bill 378 during the 80th Legislative session, the Board intends to hold a closed session for discussions between the DHCFP, OptumRx and the Silver State Scripts Board regarding the methodology and selection of preferred agents on the Nevada Medicaid Preferred Drug List (PDL).

Upon Completion of the Closed Executive Session – 5:00 PM – Public Meeting (Open Session)

AGENDA

1. Call to Order and Roll Call

2. Public Comment

3. Old Business

a. **For Possible Action**: Review and Approve Meeting Minutes from September 26, 2019.

4. New Business

a. Status Update by DHCFP

b. Proposed New Classes

1. Neurological Agents: Anti-Migraine Agents: Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists – Acute

    a. Public Comment
    b. Drug Class Review Presentation – OptumRx
    c. **For Possible Action**: Board Discussion and Action
        1. Approve Clinical/Therapeutic Equivalency of Agents in Class
    d. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
    e. **For Possible Action**: Board Discussion and Action
        1. Approval of drugs for Inclusion on the PDL

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

1. Dermatological Agents: Topical Antipsoriatic Agents

    a. Public Comment
    b. Drug Class Review Presentation – OptumRx
    c. **For Possible Action**: Board Discussion and Action
        1. Approve Clinical/Therapeutic Equivalency of Agents in Class
    d. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
    e. **For Possible Action**: Board Discussion and Action
        1. Approval of drugs for Inclusion on the PDL

2. Hormones and Hormone Modifiers: Antidiabetic Agents – Incretin Mimetics

    a. Public Comment
    b. Drug Class Review Presentation – OptumRx
    c. **For Possible Action**: Board Discussion and Action
        1. Approve Clinical/Therapeutic Equivalency of Agents in Class
    d. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
    e. **For Possible Action**: Board Discussion and Action
        1. Approval of drugs for Inclusion on the PDL

3. Neurological Agents: Anticonvulsants – Benzodiazepines

    a. Public Comment
    b. Drug Class Review Presentation – OptumRx
    c. **For Possible Action**: Board Discussion and Action
        1. Approve Clinical/Therapeutic Equivalency of Agents in Class
    d. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
    e. **For Possible Action**: Board Discussion and Action
        1. Approval of drugs for Inclusion on the PDL

d. Established Drug Classes Being Reviewed Due to the Release of New Generics

1. Cardiovascular Agents: Antihypertensive Agents Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors)

    a. Public Comment
    b. Drug Class Review Presentation – OptumRx
    c. **For Possible Action**: Board Discussion and Action
        1. Approve Clinical/Therapeutic Equivalency of Agents in Class
    d. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
    e. **For Possible Action**: Board Discussion and Action
        1. Approval of drugs for Inclusion on the PDL

e. Established Drug Classes

1. Analgesics: Opiate Agonists (Opiate Agonists, Abuse Deterrent Opiate Agonists)

    a. Public Comment
    b. Drug Class Review Presentation – OptumRx
    c. **For Possible Action**: Board Discussion and Action
        1. Approve Clinical/Therapeutic Equivalency of Agents in Class
    d. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
    e. **For Possible Action**: Board Discussion and Action
        1. Approval of drugs for Inclusion on the PDL

2. Monoclonal Antibodies for the treatment of Respiratory Conditions

    a. Public Comment
    b. Drug Class Review Presentation – OptumRx
    c. **For Possible Action**: Board Discussion and Action
        1. Approve Clinical/Therapeutic Equivalency of Agents in Class

d. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
e. **For Possible Action**: Board Discussion and Action
    1. Approval of drugs for Inclusion on the PDL

3. Respiratory Agents: Nasal Antihistamines

    a. Public Comment
    b. Drug Class Review Presentation – OptumRx
    c. **For Possible Action**: Board Discussion and Action
        1. Approve Clinical/Therapeutic Equivalency of Agents in Class
    d. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
    e. **For Possible Action**: Board Discussion and Action
        1. Approval of drugs for Inclusion on the PDL

4. Toxicology Agents: Agents for the Treatment of Substance Abuse

    a. Public Comment
    b. Drug Class Review Presentation – OptumRx
    c. **For Possible Action**: Board Discussion and Action
        1. Approve Clinical/Therapeutic Equivalency of Agents in Class
    d. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
    e. **For Possible Action**: Board Discussion and Action
        1. Approval of drugs for Inclusion on the PDL

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

g. Closing Discussion

1. Public comments on any subject
2. Date and location of the next meeting
3. Adjournment

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

Notice of this public meeting and draft copies of the changes will be available on or after the date of this notice at the DHCFP Web site at http://dhcfp.nv.gov. The agenda posting of this meeting can be viewed at the follow locations: Carson City Central Office; Las Vegas District Office; Reno District Office; Elko District Office; Nevada State Library; Carson City Library; Churchill County Library; Las Vegas Library; Douglas County Library; Elko County Library; Esmeralda 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 copy of the proposal will be mailed to you. Requests and/or written comments on the proposed changes may be sent to the Division of Health Care Financing and Policy, 1100 E. William Street, Suite 101, Carson City, Nevada 89701 at least three days prior to the public workshop.

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

Note: We are pleased to make reasonable accommodations for members of the public who are physically challenged and wish to attend the meeting. If special arrangements for the meeting are necessary, please notify the Division of Health Care Financing and Policy, in writing, at 1100 East William Street, Suite 101, Carson City, or call Tanya Benitez at (775) 684-3730, as soon as possible, or e-mail at tbenitez@dhcfp.nv.gov

Summary of Silver State Scripts Board

Silver State Scripts Board

By statute (NRS 422.4025), the State of Nevada requires the DHCFP to develop and maintain a Preferred Drug List (PDL) to be used for the Medicaid program and CHIP, and each public or nonprofit health benefit plan that elects to use the PDL. The Silver State Scripts Board (formerly known as the Pharmacy & Therapeutics or P&T Committee) was established to identify prescription drugs to be included on the PDL.

A governing body of a county, school district, municipal corporation, political subdivision, public corporation or other local government agency of the State of Nevada that provides coverage of prescription drugs pursuant to NRS 287.010 or any issuer of a policy health insurance purchased pursuant to NRS 287.010 may use the PDL developed by DHHS as its PDL.

The PDL is not a restricted formulary. Drugs not on the PDL are still available to recipients if they meet the Standard Preferred Drug List Exception criteria.

The Silver State Scripts Board consists of members who are Director-appointed physicians and pharmacists. Members must be licensed to practice in the State of Nevada as either an actively practicing physician or an actively practicing pharmacist.

Meetings are held quarterly and are open to the public. Anyone wishing to address the Silver State Scripts Board 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 Board member and an electronic copy to the DHCFP Coordinator for official record.

For pharmacists and physicians wishing to serve on the Silver State Scripts Board, please email your contact information, NPI and current CV/Resume to rxinfo@dhcfp.nv.gov

Current Board Members:

Mark Decerbo, PharmD (Chairman)

Kate Ward, PharmD (Vice Chairman)

Joseph Adashek, MD

Sapandeep Khurana, MD

Brian Passalacqua, MD

Michael Hautekeet, R.Ph

Evelyn Chu, Pharm.D.

Mark Crumby, Pharm.D.

Aditi Singh, MD

Silver State Scripts Board Meeting scheduled for 2020

Date	Time	South Nevada Location	North Nevada Location
March 26, 2020	1:00 PM	Springs Preserve – Las Vegas	None
June 25, 2020	1:00 PM	Springs Preserve – Las Vegas	None
September 24, 2020	1:00 PM	Springs Preserve – Las Vegas	None
December 10, 2020	1:00 PM	Springs Preserve – Las Vegas	None

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/

Silver State Scripts Board Bylaws:

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

The Division of Health Care Financing and Policy Public Notices:

http://dhcfp.nv.gov/Public/AdminSupport/PublicNotices/

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

OPTUMRx®

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® * LYRICA® CR HORIZANT® QUTENZA®
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® MORPHABOND® XTAMPZA ER® (NEW)		ARYMO® ER HYSINGLA ER® (NEW) OXYCONTIN® QL
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) - Oral		
CELECOXIB CAP DICLOFENAC POTASSIUM DICLOFENAC TAB DR FLURBIPROFEN TAB		CAMBIA ® POWDER DICLOFENAC SODIUM TAB ER

Preferred Products	PA Criteria	Non-Preferred Products
IBUPROFEN SUSP IBUPROFEN TAB INDOMETHACIN CAP KETOROLAC TAB MELOXICAM TAB NABUMETONE TAB NAPROXEN SUSP NAPROXEN TAB NAPROXEN DR TAB PIROXICAM CAP SULINDAC TAB		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 NAPROXEN TAB ER OXAPROZIN TAB SPRIX® SPR 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 TOBRAMYCIN NEBULIZER		TOBI PODHALER® (NEW)
Antivirals		
Alpha Interferons		
PEGASYS® PEGASYS® CONVENIENT PACK PEG-INTRON® and REDIPEN		

Preferred Products	PA Criteria	Non-Preferred Products
Anti-hepatitis Agents		
Polymerase Inhibitors/Combination Products		
EPCLUSA® HARVONI® LEDIPASVIR/ SOFOSBUVIR (NEW) MAVYRET® SOFOSBUVIR/ VELPATASVIR (NEW)	**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® SOVALDI® (NEW) TECHNIVIE® VIEKIRA® PAK VOSEVI® ZEPATIER® (NEW)
Ribavirins		
RIBAVIRIN		RIBASPHERE RIBAPAK® MODERIBA® REBETOL®
Anti-Herpetic Agents		
ACYCLOVIR FAMCICLOVIR VALCYCLOVIR		FAMVIR®
Influenza Agents		
AMANTADINE OSELTAMIVIR CAP/SUSP (NEW) RIMANTADINE RELENZA®		RAPIVAB TAMIFLU® (NEW) XOFLUZA® (NEW)
Cephalosporins		
Second-Generation Cephalosporins		
CEFACLOR CAPS and SUSP CEFACLOR ER CEFUROXIME TABS and SUSP CEFPROZIL SUSP		CEFTIN® CECLOR® CECLOR CD® CEFZIL
Third-Generation Cephalosporins		
CEFDINIR CAPS / SUSP CEFPODOXIME TABS and SUSP		CEDAX® CAPS and SUSP CEFDITOREN OMNICEF® SPECTRACEF® SUPRAX® VANTIN®
Macrolides		
AZITHROMYCIN TABS/SUSP CLARITHROMYCIN TABS/SUSP ERYTHROMYCIN BASE		BIAXIN® DIFICID® ZITHROMAX®

Preferred Products	PA Criteria	Non-Preferred Products
ERYTHROMYCIN ESTOLATE ERYTHROMYCIN ETHYLSUCCINATE ERYTHROMYCIN STEARATE		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® * SYMJEPI®
Biologic Response Modifiers		
Immunomodulators		
Targeted Immunomodulators		
ACTEMRA® CIMZIA® COSENTYX® ENBREL® ENTYVIO® (NEW) HUMIRA® ILUMYA® (NEW) INFLECTRA® KEVZARA® KINERET® OLUMIANT® ORENCIA® OTEZLA® RENFLEXIS® (NEW) SILIQ® (NEW) SIMPONI® XELJANZ®	Prior authorization is required for all drugs in this class https://www.medicaid.nv.gov/Downloads/provider/FA-61.pdf	ILARIS® REMICADE® RINVOQ® (NEW) SKYRIZI® (NEW) STELARA® TALTZ® TREMFYA®
Multiple Sclerosis Agents		
Injectable		
AVONEX® AVONEX® ADMIN PACK BETASERON® COPAXONE® QL	*Trial of only one agent is required before moving to a non-preferred agent*	GLATOPA® GLATIRAMER LEMTRADA® PLEGRIDY®

Preferred Products	PA Criteria	Non-Preferred Products
EXTAVIA® OCREVUS® REBIF® QL TYSABRI®		
Oral		
AUBAGIO® GILENYA® TECFIDERA®		MAVENCLAD® MAYZENT®
Specific Symptomatic Treatment		
DALFAMPRIDINEQL	PA required	AMPYRA® QL
Cardiovascular Agents		
Antihypertensive Agents		
Angiotensin II Receptor Antagonists		
LOSARTAN LOSARTAN HCTZ VALSARTAN (NEW) VALSARTAN HCTZ (NEW)		ATACAND® AVAPRO® BENICAR® CANDESARTAN COZAAR® DIOVAN® (NEW) DIOVAN HCTZ® (NEW) EDARBI® EDARBYCLOR® EPROSARTAN HYZAAR® IRBESARTAN MICARDIS® TELMISARTAN TEVETEN®
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 ‡ NONPREFERRED FOR OVER 10 YEARS OLD	ACCURETIC® EPANED® ‡ 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	*Restricted to ICD-10 codes J40-J48	
METOPROLOL (Reg Release) NADOLOL PINDOLOL PROPRANOLOL PROPRANOLOL/HCTZ SOTALOL TIMOLOL		
Calcium-Channel Blockers		
AFEDITAB CR® AMLODIPINE CARTIA XT® DILTIA XT® DILTIAZEM ER DILTIAZEM HCL EXFORGE® EXFORGE HCT® FELODIPINE ER ISRADIPINE LOTREL® NICARDIPINE NIFEDIPINE ER NISOLDIPINE ER TAZTIA XT® VERAPAMIL VERAPAMIL ER		KATERZIA® (NEW) MATZIM TAB LA (NEW) NORVASC® (NEW)
Vasodilators		
Inhaled		
VENTAVIS® TYVASO®		
Oral		
ORENITRAM® SILDENAFIL TADALAFIL TRACLEER®		ADCIRCA® ADEMPAS® ALYQ® AMBRISENTAN (NEW) 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 LOVASTATIN PRAVASTATIN SIMVASTATIN		ALTOPREV® AMLODIPINE/ATORVASTATIN CADUET® EZALLOR® (NEW) EZETIMIBE-SIMVASTATIN FLUVASTATIN (NEW) FLUVASTATIN XL (NEW) 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		
OMEGA-3-ACID (NEW) VASCEPA®		LOVAZA® (NEW)

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® LICART® LIDODERM® QL LIDAMANTLE® ZTLIDO®
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 Antivirals		
ABREVA® DENAVIR® (NEW) XERESE® CREAM ZOVIRAX®, OINTMENT		ACYCLOVIR OINT

Preferred Products	PA Criteria	Non-Preferred Products
Topical Scabicides		
LINDANE (NEW) NATROBA® * (NEW) NIX® PERMETHRIN RID® ULESFIA®	* PA required	EURAX® MALATHION OVIDE® SKLICE® (NEW) SPINOSAD VANALICE® GEL (NEW)
Topical Anti-inflammatory Agents		
Immunomodulators: Topical		
ELIDEL® QL EUCRISA® PROTOPIC® QL	Prior authorization is required for all drugs in this class	PIMECROLIMUS 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		
Pregnancy-induced Nausea and Vomiting Treatment		
Diclegis® OTC Doxylamine 25mg/Pyridoxine 10mg		BONJESTA® DOXYLAMINE-PYRIDOXINE TAB 10-10 (NEW)
Serotonin-receptor antagonists/Combo		
GRANISETRON QL ONDANSETRON QL	PA required for all medication in this class	AKYNZEO® ANZEMET® QL KYTRIL® QL SANCUSO®

Preferred Products	PA Criteria	Non-Preferred Products
		ZOFRAN® QL ZUPLENZ® QL
Antiulcer Agents		
H2 blockers		
FAMOTIDINE RANITIDINE RANITIDINE SYRUP*	*PA not required for < 12 years	
Proton Pump Inhibitors (PPIs)		
DEXILANT® (NEW) NEXIUM® POWDER FOR SUSP* OMEPRAZOLE (NEW) PANTOPRAZOLE	PA required if exceeding 1 per day *for children ≤ 12 yrs.	ACIPHEX® ESOMEPRAZOLE LANSOPRAZOLE NEXIUM® CAPSULES PREVACID® PRILOSEC® PRILOSEC® OTC TABS PROTONIX® RABEPRAZOLE SODIUM (NEW)
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 CANASA® PENTASA® SULFASALAZINE DR SULFASALAZINE IR		BALSALAZIDE® (NEW) COLAZAL® DELZICOL® (NEW) LIALDA ® (NEW) MESALAMINE ENEMA SUSP (NEW) MESALAMINE (GEN LIALDA) MESALAMINE (GEN ASACOL HD)
Gastrointestinal Enzymes		
CREON® ZENPEP®		PANCREAZE® PANCRELIPASE PERTZYE® ULTRESA® VIOKACE®
Genitourinary Agents		
Benign Prostatic Hyperplasia (BPH) Agents		
5-Alpha Reductase Inhibitors		
DUTASTERIDE FINASTERIDE		AVODART® DUTASTERIDE/TAMSULOSIN

Preferred Products	PA Criteria	Non-Preferred Products
		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®
Erythropoiesis-Stimulating Agents		
ARANESP® QL RETACRIT® (NEW)	PA required Quantity Limit	EPOGEN® QL MIRCERA® QL PROCRIT® QL (NEW)
Platelet Inhibitors		
AGGRENOX® ANAGRELIDE ASPIRIN	* PA required	ASPIRIN/DIPYRIDAMOLE DURLAZA® EFFIENT® * QL

Preferred Products	PA Criteria	Non-Preferred Products
BRILINTA® * QL CILOSTAZOL® CLOPIDOGREL DIPYRIDAMOLE		PLAVIX® PRASUGREL ZONTIVITY® YOSPRALA®
Hormones and Hormone Modifiers		
Androgens		
ANDRODERM®	**PA required** **PA Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-72.pdf	ANDROGEL® (NEW) AXIRON® FORTESTA® NATESTO® STRIANT® TESTIM® TESTOSTERONE GEL TESTOSTERONE SOL (NEW) VOGELXO®
Antidiabetic Agents		
Alpha-Glucosidase Inhibitors/Amylin analogs/Misc.		
ACARBOSE GLYSET® SYMLIN® (PA required)		CYCLOSET® PRECOSE®
Biguanides		
FORTAMET® METFORMIN EXT-REL (Glucophage XR®) METFORMIN EXT-REL (Glucophage XR®) METFORMIN (Glucophage®) METFORMIN ER (GEN GLUMETZA) (NEW) RIOMET®		GLUCOPHAGE® (NEW) GLUCOPHAGE XR® (NEW) GLUMETZA® (NEW) METFORMIN (GEN FORTAMET)
Dipeptidyl Peptidase-4 Inhibitors		
JANUMET® JANUMET XR® JANUVIA® JENTADUETO® KOMBIGLYZE XR® ONGLYZA® TRADJENTA®		ALOGLIPTIN ALOGLIPTIN-METFORMIN ALOGLIPTIN-PIOGLITAZONE KAZANO® NESINA® OSENI®
Incretin Mimetics		
BYDUREON® * BYDUREON® PEN * BYETTA® *	* PA required	ADLYXIN® BYDUREON® BCISE * OZEMPIC®

Preferred Products	PA Criteria	Non-Preferred Products
TRULICITY® VICTOZA® *		SOLIQUA® TANZEUM® XULTOPHY®
Insulins (Vials, Pens and Inhaled)		
APIDRA® HUMALOG® HUMULIN® LANTUS® LEVEMIR ® NOVOLIN® NOVOLOG® TOUJEO SOLO® 300 IU/ML (NEW) TRESIBA FLEX INJ		ADMELOG® AFREZZA® BASAGLAR® FIASP® INSULIN LISPRO INJ 100U/ML HUMALOG® U-200
Meglitinides		
REPAGLINIDE (NEW)		NATEGLINIDE (Starlix®) (NEW) PRANDIN® (NEW) STARLIX® (NEW)
Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors		
FARXIGA® INVOKANA® INVOKAMET® (NEW) JARDIANCE® XIGDUO XR® (NEW)		GLYXAMBI® INVOKAMET® XR QTERN® SEGLUROMET® STEGLATRO® STEGLUJAN™ SYNJARDY® SYNJARDY® XR
Sulfonylureas		
DIABETA® GLIMEPIRIDE (Amaryl®) GLIPIZIDE (Glucotrol®) GLIPIZIDE EXT-REL (Glucotrol XL®) GLYBURIDE MICRONIZED (Glynase®) GLYBURIDE (Diabeta®) METAGLIP®		AMARYL® (NEW) CHLORPROPAMIDE (NEW) GLYNASE® (NEW) GLUCOTROL® (NEW) GLUCOTROL XL® (NEW) GLYBURIDE/METFORMIN (Glucovance®) (NEW) GLUCOVANCE® (NEW) GLIPIZIDE/METFORMIN (Metaglip®) (NEW) TOLAZAMIDE (NEW) TOLBUTAMIDE (NEW)

Preferred Products	PA Criteria	Non-Preferred Products
Thiazolidinediones		
PIOGLITAZONE (NEW)		ACTOPLUS MET XR® (NEW) ACTOPLUS MET® (NEW) ACTOS® (NEW) AVANDAMET® (NEW) AVANDARYL® (NEW) AVANDIA® (NEW) DUETACT® (NEW) PIOGLITAZONE/METFORMIN (NEW) PIOGLITAZONE/GLIMEPR (NEW)
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® DUPIXENT® FASENRA®
Musculoskeletal Agents		
Antigout Agents		
ALLOPURINOL COLCHICINE TAB/CAP PROBENECID PROBENECID/COLCHICINE ULORIC®		COLCRYS® TAB MITIGARE® CAP ZURAMPIC® ZYLOPRIM®
Bone Resorption Inhibitors		
Bisphosphonates		
ALENDRONATE TABS		ACTONEL® ALENDRONATE SOLUTION ATELVIA® BINOSTO® BONIVA® DIDRONEL®

Preferred Products	PA Criteria	Non-Preferred Products
		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® RAZADYNE® RAZADYNE® ER RIVASTIGMINE CAPS RIVASTIGMINE TRANSDERMAL
Anticonvulsants		
APTIOM® BANZEL® BRIVIACT® CARBAMAZEPINE CARBAMAZEPINE XR	PA required for members under 18 years old	DIACOMIT®

Preferred Products	PA Criteria	Non-Preferred Products
CARBATROL ER® CELONTIN® DEPAKENE® DEPAKOTE ER® DEPAKOTE® DIVALPROEX SODIUM DIVALPROEX SODIUM ER EPIDIOLEX® 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® ZARONTIN® ZONEGRAN® ZONISAMIDE		OXTELLAR XR® POTIGA® QUDEXY XR® TROKENDI XR® SPRITAM®
Barbiturates		
LUMINAL® MEBARAL® MEPHOBARBITAL SOLFOTON® PHENOBARBITAL MYSOLINE®	PA required for members under 18 years old	

	Preferred Products	PA Criteria	Non-Preferred Products
	PRIMIDONE		
Benzodiazepines			
	CLOBAZAM 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			
Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists			
	AIMOVIG® AJOVY®	PA required for all products	EMGALITY®
Serotonin-Receptor Agonists			
	RIZATRIPTAN ODT SUMATRIPTAN NASAL SPRAY (NEW) 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® RELPAX® (NEW) RIZATRIPTAN BENZOATE SUMATRIPTAN INJECTION SUMATRIPTAN/NAPROXEN SUMAVEL® TOSYMRA® (NEW) TREXIMET®

Preferred Products	PA Criteria	Non-Preferred Products
		ZEMBRACE SYMTOUCH ZOLMITRIPTAN ZOMIG® ZOMIG® ZMT
Antiparkinsonian Agents		
Dopamine Precursors		
CARBIDOPA/LEVODOPA CARBIDOPA/LEVODOPA ER CARBIDOPA/LEVODOPA ODT STALEVO®	*Trial of only one agent is required before moving to a non-preferred agent*	CARBIDOPA/LEVODOPA/ENTACAPONE DUOPA™ INBRIJA™ (INH) LODOSYN® TAB RYTARY™
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® ROCKLATAN® SIMBRINZA® TIMOLOL DROPS/ GEL SOLN TRAVATAN Z® TRAVATAN®		ALPHAGAN® BETAGAN® BETOPTIC ® BIMATOPROST COSOPT PF® COSOPT® DORZOL/TIMOL SOL PF (NEW) OCUPRESS® OPTIPRANOLOL® TIMOPTIC XE® TIMOPTIC® TRAVOPROST TRUSOPT® VYZULTA® XALATAN® XELPROS® ZIOPTAN®
Ophthalmic Antihistamines		
BEPREVE® KETOTIFEN		ALAWAY® AZELASTINE

Preferred Products	PA Criteria	Non-Preferred Products
PAZEO® ZADITOR OTC®		ALOMIDE ALOCRIL ELESTAT® EMADINE® EPINASTINE LASTACRAFT® OLOPATADINE (drop/sol) OPTIVAR® PATADAY® PATANOL®
Ophthalmic Anti-infectives		
Ophthalmic Macrolides		
ERYTHROMYCIN OINTMENT		
Ophthalmic Quinolones		
BESIVANCE® CIPROFLOXACIN LEVOFLOXACIN MOXEZA® VIGAMOX®		CILOXAN® MOXIFLOXACIN OFLOXACIN® ZYMAXID®
Ophthalmic Anti-infective/Anti-inflammatory Combinations		
NEO/POLY/DEX PRED-G SULF/PRED NA SOL OP TOBRADEX OIN TOBRADEX SUS ZYLET SUS		BLEPHAMIDE MAXITROL NEO/POLY/BAC OIN /HC NEO/POLY/HC SUS OP TOBRA/DEXAME SUS TOBRADEX SUS TOBRADEX ST SUS
Ophthalmic Anti-inflammatory Agents		
Ophthalmic Corticosteroids		
ALREX® DEXAMETHASONE DUREZOL® FLUOROMETHOLONE 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®

Preferred Products	PA Criteria	Non-Preferred Products
		PROLENSA®
Ophthalmics for Dry Eye Disease		
ARTIFICIAL TEARS RESTASIS®		CEQUA® RESTASIS® MULTIDOSE XIIDRA®
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		
AMPHETAMINE SALT COMBO IR AMPHETAMINE SALT COMBO XR (NEW) ATOMOXETINE CONCERTA® (NEW) DEXMETHYLPHENIDATE DEXTROAMPHETAMINE SA TAB DEXTROAMPHETAMINE TAB DAYTRANA® (NEW) DYANAVEL® FOCALIN XR® GUANFACINE ER METADATE CD® METHYLIN® 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® ADDERALL XR® (NEW) ADZENYS® APTENSIO XR® CLONIDINE HCL ER COTEMPLA XR®-ODT DESOXYN® DEXEDRINE® DEXTROAMPHETAMINE SOLUTION EVEKEO® EVEKEO® ODT FOCALIN® INTUNIV® JORNAY PM® (NEW) METADATE ER® METHYLPHENIDATE TAB ER (RELEXXII) (NEW) METHYLPHENIDATE CHEW MYDAYIS® (NEW) RELEXXII® (NEW)

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

Preferred Products	PA Criteria	Non-Preferred Products
RISPERIDONE SAPHRIS® VRAYLAR® ZIPRASIDONE	https://www.medicaid.nv.gov/Downloads/provider/FA-70B.pdf (ages 6-18) *(No PA required Parkinson's related psychosis ICD code on claim)	RISPERDAL® SEROQUEL® SEROQUEL XR® ZYPREXA®
Anxiolytics, Sedatives, and Hypnotics		
ESTAZOLAM FLURAZEPAM ROZEREM® TEMAZEPAM TRIAZOLAM ZALEPLON ZOLPIDEM	No PA required if approved diagnosis code transmitted on claim (All agents in this class) PA required for members under 18 years old	AMBIEN® AMBIEN CR® BELSOMRA® DORAL® ESZOPICLONE EDLUAR® HETLIOZ® INTERMEZZO® LUNESTA® SILENOR® SOMNOTE® SONATA® ZOLPIDEM CR ZOLPIMIST®
Psychostimulants		
Narcolepsy Agents		
NUVIGIL® (NEW) Provigil® *	 * (No PA required for ICD-10 code G47.4)	ARMODAFINIL (NEW) MODAFINIL SUNOSI® (NEW) 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

	Preferred Products	PA Criteria	Non-Preferred Products
			NASACORT AQ® NASONEX® OMNARIS® QNASL® RHINOCORT AQUA® VERAMYST® XHANCE™ ZETONNA®
Phosphodiesterase Type 4 Inhibitors			
	DALIRESP® QL	PA required	
Long-acting/Maintenance Therapy			
	ADVAIR HFA® ANORO ELLIPTA® ARNUITY ELLIPTA® ASMANEX® BEVESPI® BUDESONIDE NEBS* (NEW) DULERA® FLOVENT DISKUS® QL FLOVENT HFA® QL PULMICORT FLEXHALER® RESPULES®* QVAR® SEREVENT DISKUS® QL SPIRIVA® HANDIHALER STIOLTO RESPIMAT® STRIVERDI RESPIMAT® TUDORZA® SYMBICORT®		ADVAIR® DISKUS AEROSPAN HFA® AIRDUO® ALVESCO® ARCAPTA NEOHALER® ARMONAIR® BREO ELLIPTA® BROVANA® INCRUSE ELLIPTA ® LONHALA MAGNAIR® PERFOROMIST NEBULIZER® PULMICORT NEBS (NEW) FLUTICASONE PROPIONATE/SALMETEROL POW (NEW) QVAR® REDIHALER™ SEEBRI NEOHALER® SPIRIVA RESPIMAT® TRELEGY ELLIPTA® UTIBRON NEOHALER ® WIXELA® (NEW)
Short-Acting/Rescue Therapy			
	ALBUTEROL NEB/SOLN ATROVENT® COMBIVENT RESPIMAT®		ALBUTEROL AER HFA LEVALBUTEROL* HFA PROAIR RESPICLICK® PROAIR® HFA

	Preferred Products	PA Criteria	Non-Preferred Products
	IPRATROPIUM NEBS IPRATROPIUM/ALBUTEROL NEBS QL LEVALBUTEROL* NEBS PROVENTIL® HFA XOPENEX® HFA* QL		VENTOLIN HFA® XOPENEX® Solution* QL
Toxicology Agents			
Antidotes			
Opiate Antagonists			
	EVZIO ® NALOXONE NARCAN® NASAL SPRAY		
Substance Abuse Agents			
	SUBLOCADE® SUBOXONE® VIVITROL®		BUNAVAIL® (NEW) BUPRENORPHINE / NALOXONE FILM/TAB ZUBSOLV® (NEW)

Meeting Minutes

SILVER STATE SCRIPTS BOARD

MEETING MINUTES

Date and Time of Meeting: Thursday, September 26, 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: Springs Preserve
333 S Valley View Blvd
Las Vegas, NV 89107

ATTENDEES

Board Members (Present)
Mark Decerbo, Pharm.D., Chair
Joseph Adashek, MD
Evelyn Chu, Pharm.D.
Mark Crumby, Pharm.D.
Michael Hautekeet, RPh
Sapandeep Khurana, MD
Brian Passalacqua, MD
Aditi Singh, MD
Kate Ward, Pharm.D.

Board Members (Absent)
None

DHCFP:
Holly Long, Social Services Program Specialist III
Gabriel Lither, DAG
Beth Slamowitz, Pharm.D., DHHS Senior Advisor on Pharmacy

DXC:
KayLynn Wight, Pharm.D.

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

Public:

Lee Hochner, Amneal
David Freilich, Amneal
Justin Barnes, Ironshore Pharmaceuticals
Deb Profanty, Jazz Pharmaceuticals
Christa Cooper, Lilly
George Yasutake, Actelion
Jeana Colabianchi, Sunovian
Carol Ricciotti, Aimmune
Alen Dezia, Chiesi
Ryan Bitton, Health Plan of NV
Cynthia Albert, Merck
Erin Russell, United Health Group
Karen Meier, Novo Nordisk
Pauline Whelan, Orexo
Joe Cirrinciore, Otsuka
Joel Moerer, Alkermes
Wilson Liu, Sunovion
Jennifer Lauper, BMS
Gary Okamo, BMS
Stephanie Yamamoto, J&J
Scott Burns, J&J
Michael Walker, J&J
Trey Delay, NAMI-South NV
Don Moran, Teva
Melissa Sommers, Novartis
Amy Heidenveich, UT
Nik Seitter, Sunovion
Laura Hill, Abbvie
Bethany Boyd, Pfizer
David Gross, Pfizer
Amy Rodenburg, Allergan
Suzette Figueroa, Lilly
Marcus Conklin, S360
Sucharita Somkuoan, Otsuka

1:00 PM – 2:00 PM – Closed Executive Session

Attendance:

Mark Crumby
Kate Ward
Brian Passalacqua
Aditi Singh
Mark Decerbo
Michael Hautekeet
Joseph Adashek
Sapandeep Khurana
Evelyn Chu
Holly Long, DHCFP
Beth Slamowitz, DHCFP
Gabriel Lither, DHCFP
KayLynn Wight, DXC
Kevin Whittington, OptumRx
Carl Jeffery, OptumRx
Susan McCreight, OptumRx
Robert Earnest, OptumRx

2:00 PM – 5:00 PM – Public Meeting (Open Session)

AGENDA

1. Call to Order and Roll Call

Meeting called to order at 2:25 PM

Mark Decerbo, Chair: Good afternoon. We have a quorum so I'm calling the meeting to order. We are now the Silver State Scripts Board. Most of the committee members are the same with one new member who Holly will introduce. I will start with a roll call.

Michael Hautekeet: Community Pharmacy in Carson City, Nevada.

Brian Passalacqua: Family physician at URN School of Medicine.

Mark Crumby: Pharm.D., Pharmacy Director at Northern Nevada Hopes.

Kate Ward: Pharmacy Clinical Manager at Renown Medical Center in Reno.

Joseph Adashek: Maternal fetal medicine clinical associate professor at University of Nevada School of Medicine and co-owner of Desert Perinatal Associates.

Evelyn Chu: Pharmacy Director of Henderson Hospital.

Gabriel Lither: Senior Deputy Attorney General, counsel to the Board.

Mark Decerbo, Chair: Faculty to the University and School of Medicine.

Sapandeep Khurana: Associate faculty at University School of Medicine

Aditi Singh: Internal Medicine, UNLV School of Medicine, Associate program director for the residency.

Beth Slamowitz: Senior Policy Advisor for Pharmacy with the Department of Health and Human Services.

Holly Long: Policy Specialists for DHCFP Pharmacy Services

Kevin Whittington: Pharmacist with OptumRx

Carl Jeffery: Pharmacist with OptumRx

2. Public Comment

Mark Decerbo, Chair: Do we have any public comment on any class?

Suzette Figueroa, Eli Lilly: I am here as part of an education from the Department of Health and Human Services and Director Whitley. Following a meeting that we had with him a few weeks ago, I would like to share some information with you about our affordability programs for insulins. Over the past several years, our team has had a goal of improving affordability for patients who are on our insulins. We have done that through several programs. One milestone is known today as the Diabetes Solution Center and we opened that helpline about a year ago. The intent is that we want to make sure people could reach Lilly in case they had any questions about how they could better afford their medications. The helpline is putting real people in front of real people. We have the goal of individualizing solutions. We are helping about eight out of ten people on average since opening the help line. We are asking policy makers in the medical field to help spread the word and share this information with their patients.

Trey Delay, Group Six Partners: I'm here on behalf of the National Alliance of Mental Illness (NAMI) of Southern Nevada. Our objective is to work with the State to assure access to medication to treat mental illness. Individuals, families and the public benefit from the proper treatment of serious mental illness both in increased recovery and reduced

public expense. Prior authorization and formulary restrictions to medications are barriers to effective treatment of mental illness. Long acting medications improve patient outcomes, support recovery and reduce expensive admissions and other costs. The Federal Assistance Abuse Mental Health Services Administration has reported that prior authorizations and formulary restrictions are a barrier to treatment. We support increasing access to these medications for Medicaid recipients and is part of the general support for the Governor's desire to increase the number of community center behavioral health clinics which include medical management services.

3. Old Business

a. **For Possible Action**: Review and Approve Meeting Minutes from June 27, 2019.

Mark Decerbo, Chair: Reviewing the meeting minutes from the past meeting, do we have anyone with additions, corrections or divisions to the minutes? Seeing none, this will stand as approved with unanimous consent.

4. New Business

Mark Decerbo, Chair: We move to new business. Holly will give a status update from DHCFP.

a. Status Update by DHCFP

Holly Long: I first want to introduce Dr. Aditi Singh. She received her Doctor of Medicine from UNLV and is currently the associate program director for the internal medicine residency program at UNLV. I wanted to announce that in recognition that the international overdose awareness day Governor Steve Sisolak proclaimed that Saturday August 31 is the overdose awareness day for Nevada. The proclamation is posted on the Governor's website. On September 2, 2019, the Drug Use Review Board proposed changes from the April 25, 2019 meeting became effective. These changes include revisions to the existing policy on agents for the treatment of attention deficit hyperactivity disorder. Most of the criteria for that prior authorization has been removed. What remains is the requirement of the diagnosis. A revision was made to the existing policy on transdermal fentanyl, buprenorphine/naloxone and naltrexone and new prior authorization criteria for Lucemyra and Xyosted have been added.

b. **For Possible Action:** Board Discussion and Approval of Existing Preferred Drug List as Established by the Nevada Medicaid Pharmacy and Therapeutics Committee.

Mark Decerbo, Chair: We need to vote to accept the existing PDL. We need a motion and a second to accept the PDL as it currently exists.

Motion and second to accept the current PDL.

Voting: Ayes are unanimous, the motion carries.

c. **Annual Review - Established Drug Classes Being Reviewed Due to the Release of New Drugs**

i. Cardiovascular Agents: Antihypertensive Agents (Calcium-Channel Blockers), Antilipemics (HMG-CoA Reductase Inhibitors [Statins])

Mark Decerbo, Chair: Do we have any public comment on the calcium channel blockers?

Carl Jeffery: The new medication is Katerzia, it is a liquid amlodipine, it is an easy ready to use medication for the treatment of hypertension in ages six years and older. Nothing special other than it is a pre-mixed amlodipine. The other products are shown on the list here. We have some new generics now. Optum recommends the board consider these clinically and therapeutically equivalent.

Motion and second to accept the class as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum recommends Katerzia be made non-preferred and then remove a couple products that are no longer on the market, Dynacirc CR, Nifediac CC and Nifedical XL, so they would be removed.

Motion and second to accept the PDL as presented.

Voting: Ayes are unanimous, the motion carries.

Mark Decerbo, Chair: The next class is the HMG-CoA reductase inhibitors or Statins. Do we have public comment?

Carl Jeffery: Ezallor is the new agent in this class. It is similar to Crestor, rosuvastatin except it comes in a capsule. Same indication as Crestor. Here is the list of all the products in this class. Optum recommends the board consider this class clinically and therapeutically equivalent.

Motion and second to accept as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: The new medication, Ezallor, Optum recommends be made non-preferred. Advicor is no longer made, so that should be removed and then move the fluvastatin products both extended release and regular release to non-preferred and then more cleanup, Lescol, Liptruzet, Mevacor and Simcor are no longer available, so those will be removed.

Motion and second to accept the PDL as presented.

Voting: Ayes are unanimous, the motion carries.

ii. Psychotropic Agents: ADHD Agents, Psychostimulants (Narcolepsy Agents)

Mark Decerbo, Chair: We move to ADHD agents, do we have any public comment?

Justin Barnes, Senior Medical Liaison with Ironshore Pharmaceuticals. Jornay PM just came to market, it was approved in August 2018. It came to market about three months ago in the middle of June. The important things to note about Jornay PM. Jornay PM is the first and only ADHD medication dosed at night. The importance of that comes with the DELEXIS delivery system. DELEXIS delays release and absorption of methylphenidate for about eight hours post dose which coincides nicely for when most wake up. Then it ramps up to get therapeutic levels after waking. It carries a black box warning for dependence. Jouney PM was originally created because we know parents

reported difficult mornings with kids with ADHD. DELEXIS is a bead with methylphenidate layers and takes 8-10 hours for the whole process. Clinical efficacy trials reviewed demonstrating improvement in the morning and evening. Adverse events are in line with other methylphenidate products.

Carl Jeffery: A few new products, Evekeo ODT. We have Evekeo already, this is an orally disintegrating tablet. Same medication and starting dose, similar to the other products. Mydayis is a little different. It is approved for 13 years of age and older, but it is supposed to last up to 16 hours. We heard about Jornay PM that is dosed in the evening. I have all the available products on the slide here with the new ones. Optum recommends the board consider these clinically and therapeutically equivalent.

Motion and second to accept as clinically and therapeutically equivalent.

Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: Optum recommends swapping brand name Adderall XR to non-preferred but make the generic preferred. Removing Dextrostat and Methylin ER as they are no longer on the market. The new medications, Evekeo ODT, Mydayis and Jornay PM added as non-preferred. There is a product Relexxi and Methylphenidate tab ER, it seems to be a generic Concerta, but we recommend adding it as non-preferred.

Sapandeep Khurana: What about Kapvay?

Carl Jeffery: It is no longer rebatable, so they are not available to Medicaid.

Sapandeep Khurana: The Concerta and the generics, we talked about these before. There are some differences, the generic is preferred, but the brand is non-preferred. And Daytrana, the only non-oral product is non-preferred. The Brand Concerta has a more reliable profile. The Daytrana has a smoother action profile. There is nothing else like it.

Mark Decerbo, Chair: Are there any other restrictions on Daytrana?

Carl Jeffery: There is nothing specific for Daytrana, there is general criteria for the ADHD class.

Mark Decerbo, Chair: We have some discussion for the different delivery.

Sapandeep Khurana: I would like to make a motion to move Daytrana to preferred.

Seconded.

Voting: Ayes are unanimous, the motion carries.

Sapandeep Khurana: I would make a motion to make Concerta brand name preferred along with the generic methylphenidate ER. There are no head-to-head studies comparing the brand to the generic, but the brand is more reliable profile.

Seconded.

Voting: Ayes are unanimous, the motion carries.

Motion to accept the remaining recommendations as presented.

Seconded.

Voting: Ayes are unanimous, the motion carries.

Mark Decerbo, Chair: Our next topic is Narcolepsy agents, do we have public comment?

Deb Profant, Jazz Pharmaceuticals: Provides information on Sunosi including indication, dosage forms, dosage, DEA Schedule, clinical studies demonstrating effectiveness, adverse events and safety. Requests adding Sunosi as preferred.

Mark Decerbo, Chair: Any questions for the speaker? Any other commentary?

Carl Jeffery: We heard about Sunosi already. Discusses different indications for products, dosing for different products. The generics available are Nuvigil and Provigil. Optum recommends the Board consider these clinically and therapeutically equivalent.

Motion and second to accept as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum recommends make brand Nuvigil preferred and the generic armodafinil and Sunosi as non-preferred.

Mark Decerbo, Chair: We have the PDL as presented. Any discussion?

Motion and second to accept the PDL as presented.

Voting: Ayes are unanimous, the motion carries.

d. **Annual Review – Established Drug Classes**

i. Analgesics: Opiate Agonists (Opiate Agonists - Abuse Deterrent)

Mark Decerbo, Chair: Is there any public comment?

Carl Jeffery: This is a challenging class. We have discussed the FDA process for abuse deterrent. We only include products approved by the FDA in this class. This slide shows the different abuse deterrent properties. Most are physical barriers to reduce crushing. None have generics approved. The company that makes Arymo ER is stopping production. Optum recommends the board consider these clinically and therapeutically equivalent.

Motion and second to accept as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Embeda has been preferred for a long time. Optum recommends moving Xtampza ER to preferred and Hysingla ER and Morphabond to non-preferred.

Motion and second to accept the PDL list as presented.

Mark Decerbo, Chair: I will add comment, Morphabond has been well accepted by the community, I think Morphabond may have a place on the preferred list.

Evelyn Chu: Is Morphabond better than Embeda?

Carl Jeffery: There are not any studies comparing them, they both have morphine that is shown equivalent. They have different abuse deterrent properties.

Kate Ward: I withdraw my initial motion.

Brian Passalacqua: I make a motion to include Morphabond as preferred and accept the remaining recommendations.

Second

Voting: Ayes: 5, Nays: 2, the motion carries.

ii. Anti-infective Agents: Aminoglycosides (Inhaled Aminoglycosides), Antivirals, Anti-hepatitis Agents (Polymerase Inhibitors/Combination Products), Antivirals (Influenza Agents), Macrolides

Mark Decerbo, Chair: Any public comment on inhaled aminoglycosides?

Carl Jeffery: This is the aminoglycoside class. All the same active ingredient, same indication. The Tobi Podhaler is the only one that is a little different in that it is administered through a unique device rather than a nebulizer. Optum recommends the board consider these clinically and therapeutically equivalent.

Motion and second to accept the class is clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum recommends moving Tobi Podhaler to non-preferred and keep the rest of the class the same.

Mark Decerbo, Chair: Do we have any discussion?

Motion and second to accept the PDL as presented.

Voting: Ayes are unanimous, the motion carries.

Mark Decerbo, Chair: Hepatitis C agents. Any public comment?

Carl Jeffery: We have seen this class several times before. The current medications have been effective at getting rid of Hep C in Nevada. Optum recommends the board consider the class as clinically and therapeutically equivalent.

Motion and second to accept the class as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: We are moving some products that are not used as much or do not have the wide indication as the other to non-preferred, moving Sovaldi and Zepatier to non-preferred.

Mark Decerbo, Chair: I think Optum is doing a good job at managing this class.

Motion and second to accept the PDL as presented.

Voting: Ayes are unanimous, the motion carries.

Mark Decerbo, Chair: Do we have public comment for the Influenza Antivirals?

Carl Jeffery: The only head-to-head study was the Capstone trial comparing Tamiflu to Xofluza. They had similar outcomes. It comes down to taking one dose vs. taking five doses. Optum recommends the board consider this class clinically and therapeutically equivalent.

Motion and second to accept the class as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum recommends a few changes. Moving generic Tamiflu, Oseltamivir capsules and Suspension to preferred, the brand Tamiflu to non-preferred and moving Xofluza to non-preferred.

Mark Decerbo, Chair: We have the recommendation from Optum. We heard the Xofluza is similar to Tamiflu in efficacy, it is just the different dosing.

Sapandeep Khurana: I think there is some benefit to taking one dose verses the multiple doses.

Mark Decerbo, Chair: Any other comments, I think the one dose Xofluza is worth discussing.

Motion and second to accept the PDL as presented.

Voting: Ayes are unanimous, the motion carries.

Mark Decerbo, Chair: Next is Macrolides, do we have any public comment?

Carl Jeffery: When we brought this up, we thought there would be some changes. I heard there were some challenges in getting erythromycin in the pharmacies, but I have not heard that lately. Optum recommends the board consider the class clinically and therapeutically equivalent.

Motion and second to accept the class as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum does not have any recommended changes to the class.

Motion and second to accept the PDL as presented.

Voting: Ayes are unanimous, the motion carries.

iii. Biologic Response Modifiers: Immunomodulators (Targeted Immunomodulators)

Mark Decerbo, Chair: Next is Targeted Immunomodulators. Do we have public comment?

Laura Hill: My name is Laura Hill, I'm with medical affairs with Abbvie. We have two products that are both new, Rinvoq and Skyrizie. Rinvoq was just approved about a month ago. Discusses indication, safety, clinical trials demonstrating superiority to Humira and methotrexate, remission rates, black box warnings, common adverse events. Covers Skyrizi indication, dosing, clinical trials, superiority to Stelara and Humira, no black box warning. Asks for questions and asks the board to make the products preferred since they are shown superior.

Mark Decerbo, Chair: Any other comment?

Carl Jeffery: Laura gave us a good overview. I have on the slide a brief overview of the two products and the studies. I am showing a graph of the different indications for the different products. The preferred products are highlighted showing we do have all the indications covered. Our exemption criteria does allow a non-preferred product if it has a unique indication. Optum recommends the board consider this class clinically and therapeutically equivalent.

Motion and second to accept the class as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: This is where it gets challenging. Dupixent really should be with the monoclonal antibodies for asthma. Therefore, we will remove it from this class. Optum recommends moving Entyvio, Ilumya, Reflexis and Siliq to preferred and Inflectra to non-preferred and add the two new products Rinvoq and Skyrizi as non-preferred.

Mark Decerbo, Chair: We have the proposed PDL. We have discussed this group and trying to fit them into a single group.

Kate Ward: I would like to have the board make a strong statement about bio-similars being part of the preferred drugs list and make Inflectra staying preferred. I would like to make that motion.

Mark Decerbo, Chair: We have a motion on the floor to keep Inflectra as preferred.

Second.

Joseph Adashek: Can you let me know why you are making that recommendation?

Kate Ward: Inflectra and Renflexis are bio-similars for Remicade and used for multiple indications. I feel they are equivalent and should be used interchangeably and be able to have patients go to where they can get these administered.

Mark Decerbo, Chair: The board really has not addressed the bio-similar.

Kate Ward: It is a balance of not having to infuse one over the other because the patient has Medicaid. The infusion suite may only have one of those products available.

Mark Decerbo, Chair: Is it more of an access or interchangeability?

Kate Ward: It would be both, we would be supporting the use of biosimilars that we should be promoting and the stance that they could receive either. The FDA does not recognize them as interchangeable, but clinically they are. The infusion centers may not have both available. So, the Medicaid population may be limited depending on the infusion location.

Evelyn Chu: The list does support the use of biosimilars, we do have them listed.

Kate Ward: It does not call them out as biosimilars.
Mark Decerbo, Chair: I guess that is the question to the board. We have a motion to move Inflectra to preferred.

Voting: Ayes: 5 Nays: 2, the motion carries.

Mark Decerbo, Chair: We now have the PDL as presented. Any further discussion?

Motion and second to accept the recommendation with the change with Inflectra as preferred.

Voting: Ayes: 5, Nays:2, the motion carries.

iv. Cardiovascular Agents: Antihypertensive Agents (Angiotensin II Receptor Antagonists), Vasodilators (Oral), Antilipemics (Omega-3 Fatty Acids)

Mark Decerbo, Chair: The next class is angiotensin II receptor antagonists. Do we have any public comment?

Carl Jeffery: The list does show the combination products as well as the single-entity agents. Optum recommends the board consider the class clinically and therapeutically equivalent.

Motion and second to accept the class as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum recommends moving the brand Diovan and Diovan HCTZ to non-preferred and no other changes to the class.

Mark Decerbo, Chair: I think losartan is the most widely used. But what are the boards thought about just having a single agent as preferred.

Kate Ward: I am concerned about a single agent. We could move valsartan to preferred to give another option.

Evelyn Chu: We have had some drug shortages with both of these. What happens if these are not available.

Carl Jeffery: That is part of our policy, if there is a drug shortage, we could allow alternatives in the system if it was an extended shortage.

Kate Ward: I make a motion to add Valsartan and valsartan HCTZ as preferred and accept the remaining list.

Second

Voting: Ayes are unanimous, the motion carries.

Mark Decerbo, Chair: The next class is the oral vasodilators. Do we have any public commentary?

George Yasutake, Actelion Pharmaceuticals: Speaks on Opsumit and Uptravi. Discusses indications, progression of disease, patient management, treatment options and benefits, the need for early access to different therapies. Provides benefits of Uptravi on monotherapy and combination. Provides information for Opsumit, disease benefits with treatment, reduces hospitalization and long-term benefits, safety concerns, black box warnings. Summarizes agents and their benefits and indications. Asks the board to add Opsumit and Uptravi as preferred.

Mark Decerbo, Chair: Any other comment?

Carl Jeffery: Ambrisentan, a new generic for Letairis. Nothing really special. There are other generics available for some classes. Optum recommends the board consider this class clinically and therapeutically equivalent.

Motion and second to accept the class as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum recommends the class remain the same with the new generic ambrisentan added as non-preferred.

Motion and second to accept the PDL as presented.

Voting: Ayes are unanimous, the motion carries.

Mark Decerbo, Chair: The next class is Omega-3 Fatty Acids. Any public commentary?

Carl Jeffery: We had more utilization for these than I anticipated. Omtryg is no longer on the market, so we will remove that one. Optum recommends the board consider the class clinically and therapeutically equivalent.

Motion and second to accept as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum recommends making the generic omega-3 acid as preferred and the brands Lovaza and Vascepa as non-preferred.

Motion to have Vascepa remain as preferred on the PDL.

Second

Mark Decerbo, Chair: I support that motion, we have had some failures of other products, but Vascepa has been shown to be more effective.

Voting: Ayes are unanimous, the motion carries.

Mark Decerbo, Chair: Now to vote on the remaing class. We would have now Vascepa and omega-3 as preferred.

Motion and seconded to accept the PDL as presented with Vascepa as preferred.

Voting: Ayes are unanimous, the motion carries.

v. Dermatological Agents: Topical Anti-infectives (Topical Antivirals, Topical Scabicides), Topical Anti-inflammatory Agents (Immunomodulators: Topical)

Mark Decerbo, Chair: The next class is Topical antivirals. Do we have any public commentary?

Carl Jeffery: There is a new generic cream for Zovirax cream. Optum recommends the board consider these clinically and therapeutically equivalent.

Motion and second to accept the class as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum recommends moving Denavir to non-preferred and the new generic cream would be included with the acyclovir as non-preferred.

Motion and second to accept the recommendation as presented.

Voting: Ayes are unanimous, the motion carries.

Mark Decerbo, Chair: Topical scabicides, any public comment?

Carl Jeffery: There are a couple changes here. Vanalice is an OTC that is relatively new, so we want to include that one. What really prompted this review was the limited availability of Sklice. The manufacturer doesn't think it will be

available until late 2020, so the options are pretty limited. Optum recommends the board consider this class clinically and therapeutically equivalent.

Motion and second to accept the class as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum recommends moving Lindane and Natroba to preferred and because of Sklice's limited availability, moving it to non-preferred. The new agent, Vanalice, as non-preferred.

Mark Decerbo, Chair: We have a number of different products available. Any discussion?

Motion and second to accept the PDL as presented.

Voting: Ayes are unanimous, the motion carries.

Mark Decerbo, Chair: The next class Topical Immunomodulators, any public commentary?

Dave Gross, Pfizer Medical Affairs: Provides information on Eucrisa. Discusses classification, indication, application, contraindications, safety and efficacy studies, clinical studies demonstrating improvement in patients with atopic dermatitis vs control vehicle. Speaks to benefits of Eucrisa and long-term safety. Provides information on pruritus treatment. Asks the board to retain Eucrisa on the PDL.

Mark Decerbo, Chair: Any other public commentary?

Holly Long: We have an email that has been provided to the board members and will be available on line. I have also received 11 other emails from providers speaking in support of Eucrisa.

Carl Jeffery: There is a new generic for Elidel. The indications are shown on the screen, they are very similar with Eucrisa having the first-line indication. Optum recommends the board consider this class clinically and therapeutically equivalent.

Motion and second to accept the class as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum recommends moving Eucrisa to non-preferred and the new generic pimecroliums to non-preferred.

Michael Hautekeet: There is a PA requirement for this whole class. Can the prescriber request the Eucrisa at the same time for non-preferred when submitting the PA request?

Carl Jeffery: If the board accepts our recommendation, they need to get a PA and step through Elidel and Protopic.

Joseph Adashek: I make a motion to keep Eucrisa as preferred. I appreciate the doctors have taken the time to write letters, that carries a lot of weight with me.

Second

Mark Decerbo, Chair: We have a motion to accept the PDL as presented except to keep the Eucrisa as preferred. I echo your comments. You look at the label and indication and prescribing, I think that is a good idea.

Voting: Ayes are unanimous, the motion carries.

vi. Gastrointestinal Agents: Antiemetics (Miscellaneous), Antiulcer Agents (Proton Pump Inhibitors [PPIs]), Gastrointestinal Anti-inflammatory Agents

Mark Decerbo, Chair: Miscellaneous antiemetics, any public commentary?

Carl Jeffery: There is a generic for Diclegis available now. Optum recommends the board consider this class clinically and therapeutically equivalent.

Joseph Adashek: I would like to make a motion, I don't know of any other indication for these products to name the class to antiemetics in pregnancy instead of miscellaneous.

Gabriel Lither: This isn't something that is on the agenda, but how are the names of the classes established?

Carl Jeffery: I try to stick with standard names using Clinical Pharmacology therapeutic classes.

Gabriel Lither: So, it is Optum that comes up with the classes. I think you can make the change without a motion.

Motion and second to accept the class as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum recommends the new generic doxylamine/pyridoxine tab be added as non-preferred and the rest of the class remain the same.

Motion and second to accept the PDL as presented.

Voting: Ayes are unanimous, the motion carries.

Mark Decerbo, Chair: Proton Pump Inhibitors, any public commentary?

Carl Jeffery: This is a little busy, there are a lot of similar products available in this class. Optum recommends the board consider the class clinically and therapeutically equivalent.

Motion and second to accept the class as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: I tried to highlight the changes. Optum recommends changing Dexilant to preferred and generic omeprazole to preferred and Nexium to non-preferred and the new generic rabeprazole as non-preferred.

Motion and second to accept the PDL as presented.

Voting: Ayes are unanimous, the motion carries.

Mark Decerbo, Chair: GI Anti-inflammatory agents, any public comment?

Carl Jeffery: The only new one here is a generic for Canasa. Optum recommends the board accept the class as clinically and therapeutically equivalent.

Motion and second to accept the class as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: This looks like a big change, but all the products recommended to move to non-preferred are similar agents. Giazo is no longer available so that would be removed. Then moving Balsalazide, Delzicol, Lialda and mesalamine enema to non-preferred.

Motion and second to accept the PDL as presented.

Voting: Ayes are unanimous, the motion carries.

vii. Hematological Agents: Erythropoiesis-Stimulating Agents

Mark Decerbo, Chair: Erythropoiesis-Stimulating agents. Any public comment?

Carl Jeffery: This class has not been reviewed for a while. Retacrit is a biosimilar to Procrit. Optum recommends the board consider this class clinically and therapeutically equivalent.

Motion and second to accept the class as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum recommends Retacrit be made preferred and Procrit as non-preferred.

Motion and second to accept the PDL as presented.

Voting: Ayes are unanimous, the motion carries.

viii. Hormones and Hormone Modifiers: Antidiabetic Agents (Biguanides, Dipeptidyl Peptidase-4 Inhibitors, Incretin Mimetics, Insulins [Vials, Pens and Inhaled], Meglitinides, Sodium-Glucose Co-Transporter 2 [SGLT2] Inhibitors, Sulfonylureas, Thiazolidinediones)

Mark Decerbo, Chair: Biguanides, any public comments.

Carl Jeffery: This was a class we were limited in discussing, but now we have a little more freedom to discuss. There are not a lot of differences within the class. Optum recommends the board consider this class clinically and therapeutically equivalent.

Motion and second to accept the class as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: We have an opportunity to narrow this class down. Optum recommends moving Glucophage, Glucophage XR and Glumetza to non-preferred and Metformin ER, the generic for Glumetza, as preferred and keep the rest of the class the same.

Motion and second to accept the PDL as presented.

Voting: Ayes are unanimous, the motion carries.

Mark Decerbo, Chair: The dipeptidyl peptidase-4 inhibitors, there are no recommended changes, I think we can move past if there is no public comment. Unanimous consent as voted at the beginning of the meeting.

Mark Decerbo, Chair: Incretin mimetics, one thing that jumps out to me is Ozempic has some superiority outcomes including weight loss, we are starting to see more movement.

Motion and second to accept the PDL as presented.

Voting: Ayes are unanimous, the motion carries.

Mark Decerbo, Chair: Insulin agents, any public comment?

Carl Jeffery: There is an authorized generic for Humalog, Insulin Lispro, made by a Lilly subsidiary. The breakdown is shown on the screen for your reference. Optum recommends the board consider this class clinically and therapeutically equivalent.

Motion and second to accept the class as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum recommends the new insulin product, insulin lispro, be added as non-preferred and keep the rest of the class the same.

Michael Hautekeet: Humalog 100 units are preferred, people on an insulin pump use 200 because you use half as much. Could we make an exception for the 200 if it is being used for an insulin pump?

Beth Slamowitz: Pumps are covered on the DME benefit.

Michael Hautekeet: It would be just the insulin for the pump.

Beth Slamowitz: We don't have many people on a pump.

Carl Jeffery: I think it would qualify for the unique indication if it was indicated.

Mark Decerbo, Chair: So, pumps are never covered?

Beth Slamowitz: They are covered for kids.

Kate Ward: We have Toujeo and Basaglar, I wonder if we put one of them on the preferred list if that would increase the usage over Basaglar. If we made one preferred, then patients who don't want to inject every day would have an option. My proposal is to move Toujeo to the preferred list to have a long-acting insulin option.

Second.

Kate Ward: And also accept the rest of the PDL as presented.

Voting: Ayes are unanimous, the motion carries.

Mark Decerbo, Chair: Meglitinides, any comment?

Carl Jeffery: Optum recommends the drugs in this class be considered clinically and therapeutically equivalent.

Motion and second to accept as therapeutically and clinically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Now that we can make some changes, Optum recommends repaglidide be the only preferred agent and move nateglinide, Prandin and Starlix to non-preferred.

Motion and second to accept the PDL as presented.

Voting: Ayes are unanimous, the motion carries.

Mark Decerbo, Chair: SGLT-2 inhibitors, public comment?

Stephanie Yamamoto, Pharmacist at Janssen Pharmaceuticals: Highlights Invokana changes. Provides indication, and reduction in risk of cardiovascular disease. Discusses clinical trials demonstrating hospitalization reduction.

Holly Long: Is there other information you would like to share outside of the information for Invokana?

Stephanie Yamamoto: No, I'll give my time back to the board, thank you.

Gabriel Lither: We will invite you to speak if the Board has questions.

Carl Jeffery: Similar review as we have seen before. We have some more cardiovascular studies available now. Optum recommends the board consider these clinically and therapeutically equivalent.

Motion and second to accept as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: I think we have a favorable recommendation to move Invokamet and Xigduo XR to preferred and keep the rest of the class the same.

Motion and second to accept the PDL as presented.

Voting: Ayes are unanimous, the motion carries.

Mark Decerbo, Chair: Next is Sulfonylureas, public comment?

Carl Jeffery: I have the different agents broken down by generation. Optum recommends the board consider the medications in this class clinically and therapeutically equivalent.

Motion and second to accept the class as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: We have a lot of changes here, Optum recommends moving Amaryl, Chlorpropamide, Glynase, Glucotrol, Glucotrol XL, Glyburide/metformin, Glucovance, Glipizide/metformin, tolazamide and tolbutamide to non-preferred and keep the rest of the class the same.

Motion and second to accept the PDL as presented.

Voting: Ayes are unanimous, the motion carries.

Mark Decerbo, Chair: The Thiazolidinediones, any public comment?

Carl Jeffery: The list of products is here, Optum recommends the board consider this class clinically and therapeutically equivalent.

Motion and second to accept as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum recommends having the Pioglitazone as the sole preferred product and the rest of the agents be moved to non-preferred.

Motion and second to accept the PDL as presented.

Voting: Ayes are unanimous, the motion carries.

ix. Neurological Agents: Anti-Migraine Agents (Calcitonin Gene-Related Peptide [CGRP] Receptor Antagonists, Serotonin-Receptor Agonists)

Mark Decerbo, Chair: Next is the CGRP class, public commentary?

Don Moran, Teva Pharmaceuticals: At the March meeting, the board elected to make Ajovy preferred. In the monograph, there is a piece of information missing to keep in mind before you make a decision. The monograph was updated as of July 1, there have been critical data that has been updated since then. There was a news release out of the National Health Service, they made a comment on the CGRP. There is paragraph, consider the data and consider keeping Ajovy as preferred. In the paragraph it states there is limited analysis about the CGRP class and trials examining the efficacy and patients who failed two or more prior preventive therapy. However, available data suggests these patients may achieve greater reductions in migraine headaches and frequency further research is warranted. The National Health Service today agreed. They decided to not add one CGRP to their national formulary because patient study in the phase three trials are not reflective of the population in the UK. In addition, Teva, the European Medicines Association agrees with Optum's statement that more research is needed. For that reason, we conducted additional phase three research. That data is published in Lancet on August 16, 2019. It looks at the results of a subset of patients that failed between two and four therapeutic classes of preventive agents and tracked over a 12-week period their response to therapy. Patients were randomized to monthly or quarterly Ajovy or placebo. At the end of that time frame the analysis revealed that those patients who had failed higher coursed including Botox, they had about a 35% reduction in symptoms thereby fulfilling the hypothesis that patients with recalcitrant disease did indeed respond. That was successful enough for us to secure approval for a product in Europe. The last thing, the monograph states that caution should always be exercised for the use of these agents due to the lack of long-term safety data. We have now published and made available 18 months of experience with about 1500 patients revealing there are no signals of liver toxicity, anaphylaxis, severe hypersensitivity and very low rates of drug antibody. I agree with Optum authors. Ajovy is the only agent in the class that can be administered quarterly which may fulfill the niche for patients non-adherent to treatment.

Mark Decerbo, Chair: With the new information, what are the thoughts from the Committee to bring this back at the next meeting? Should we deliberate and vote or have it brought back?

Motion to keep the PDL as previously with two agents preferred and bring back in December. Seconded.

Voting: Ayes are unanimous, the motion carries.

Mark Decerbo, Chair: Triptans, public comment?

David Freilich, Medical Department with Amneal Pharmaceuticals: I'm here to talk to you about Zomig nasal spray. Triptans are the gold standard for treating migraine. Different people respond well to different triptans. It is important to maintain access to multiple options. Papers report between 50 and 90% of patients have nausea and or vomiting and about 30% have nausea. Gastric Stasis and nausea and vomiting are key features in migraine. It is important to have non-oral routes. I would like to request Zomig and sumatriptan as preferred agents in the nasal spray.

Lee Hochner, National Account Manger with Amneal Pharmaceuticals: When the Board reviewed this class last year, I believe the recommendation was to add Zomig nasal spray to non-preferred, but I don't see it listed there. If you want to add a nasal spray as a preferred agent, I ask you add Zomig nasal spray.

Mark Decerbo, Chair: Are you suggesting there might be an error of omission?

Lee Hochner, National Account Manger with Amneal Pharmaceuticals: I believe so.

Mark Decerbo, Chair: I remember having a discussion of alternate sites of administration.

Kate Ward: We did have a discussion of having a nasal spray on the preferred drug list.

Holly Long: We will go back and check on that.

Carl Jeffery: There are two new products, Tosymra and Migranow Kit. Tosymyra is another sumatriptan nasal kit. The Migranow is not actually approved by the FDA, so it will not be included in further discussion. Optum recommend the board consider this class clinically and therapeutically equivalent.

Motion and second to accept as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum recommends adding Relpax and the new product Tosymra as non-preferred.

Mark Decerbo, Chair: We will go back and look at the minutes, I remember talking about a nasal spray and if there is any doubt, we can bring this back for December.

Carl Jeffery: There is another new product coming out, so we will likely see this again at the next meeting anyway.

Motion and second to accept the PDL as presented.

Voting: Ayes are unanimous, the motion carries.

x. Psychotropic Agents: Antipsychotics (Atypical Antipsychotics – Oral)

Mark Decerbo, Chair: Atypical Antipsychotics, public comment?

Sucharita Somkuren, Managed Market Liaison with Otsuka: I'm here to provide information on Abilify Mycite to the Board. The suboptimal response to treatment of patients with serious mental illness and may be due to several factors or alone in combination of under dosing and limited medication effectiveness despite adherence. Covers approval and indication of Abilify Mycite, to track drug ingestion. Covers Mycite app and provider access to data. Provides information on clinical data and offers reasons for use. Indicates how the product will be introduced to providers and patients. Speaks to the Black Box warning for Abilify. Abilify Mycite is a drug and device combination that communicates with a patch and a medical software application.

Carl Jeffery: The new product we have is Abilify Mycite, we just heard about it. Nothing really new or changed otherwise. Optum recommends the board consider the class clinically and therapeutically equivalent.

Sapandeep Khurana: Where do the injectables fall in this list?

Carl Jeffery: We talked about adding the injectable antipsychotics and the board decided not to add it as a class. That is something we can bring back if the board is interested in adding now. If there is no class on the PDL, it is not managed, and everything essentially goes through as preferred.

Motion and second to accept as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum recommends the new Abilify Mycite be added as non-preferred and the rest of the class remain the same.

Motion and second to accept the PDL as presented.

Voting: Ayes are unanimous. The motion carries.

xi. Respiratory Agents: Long-Acting/Maintenance Therapy

Mark Decerbo, Chair: Respiratory agents, long acting/maintenance therapy, any public comment?

Wilson Liu, Medical Science Liaison, Sunovian Pharmaceuticals: Presenting a clinical overview of Utibron Neohaler for COPD. There is a medical need for medical treatment of COPD. About 30% of patients report nighttime symptoms three times per week. Errors in device handling can impact delivery and overtime reduce the clinical benefit. Covers Utibron indication, device and description and instruction for use. Clinical studies discussed and benefit compared to placebo. Please consider adding Utibron Neohaler as preferred.

Carl Jeffery: We just heard about one of the new agents, the other is Wixela is a branded generic for Advair Diskus. There are too many products to fit on a single slide, I have them all listed here. Optum recommends the board consider these clinically and therapeutically equivalent.

Motion and second to accept as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: The biggest change is swapping the generic budesonide nebulizer solution for the brand Pulmicort nebulizers, we will make the budesonide generic preferred and the brand Pulmicort non-preferred and then make the two new products, Utibron and Wixela as non-preferred.

Motion and second to accept the PDL as presented.

Voting: Ayes are unanimous, the motion carries.

xii. Toxicology Agents: Substance Abuse Agents

Mark Decerbo, Chair: Substance abuse agents, public comment?

Carl Jeffery: We don't have anything new in this class. Optum recommends the board consider the class clinically and therapeutically equivalent.

Motion and second to accept as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum recommends moving Bunavail and Zubsolv to non-preferred and leave the rest of the class the same.

Motion and second to accept the PDL as presented.

Voting: Ayes are unanimous, the motion carries.

e. **Annual Review – Drug Classes Without Proposed Changes, For Possible Action**

Carl Jeffery: This meeting is our annual review. The Board is required to review the PDL once per year. The classes listed in the agenda are classes Optum is not making any recommended changes to the current preferred drug list. Unless the Board has any classes they want to call out for discussion, the Board can approve to accept the remaining classes as one motion.

Mark Decerbo, Chair: Do we have any public comment?

Motion and second to accept the remaining classes on the PDL as-is.

Voting: Ayes are unanimous, the motion carries.

f. **Presentation, Discussion and Possible Adoption of Updated Silver State Script Board Bylaws for Possible Action**

Mark Decerbo, Chair: We are a new Board, so we have new bylaws. Can we get a brief overview of changes?

Holly Long: The last page is the most important. These have been approved by the director. We tried to make them look nicer with a table of contents. The main reason behind the change is Senate Bill 378, the changes that impact the name change from P&T to Silver State Scripts Board has been updated throughout the document. There is a change to the terms that I've taken the opportunity to update here which is separate from the Senate Bill. The terms are every two years, that is going to stay the same, we put a limit of three consecutive two-year terms, so a total of six years.

Kate Ward: Does that start from the previous committee?

Holly Long: It is going to start today once these are updated and approved since they will be approved today. Even though your appointment started before today, I won't take that into consideration until today's date. If you have already served two two-year terms, I wouldn't take that into consideration. Some language in green has been reorganized, anything red with a line through it has been removed, red type is new. We do have the cost discussion information included now as well. I did update some of the language related to the open meeting law, I removed public comment requirements. The last part is the disclosure agreement that need to be signed, you don't have to return them to me today, but for the future we ask that you have them completed at every appointment and reappointment. It is pretty basic that other boards have, especially now with our cost discussions and proprietary information shared in the meeting. I need the board to vote to approve it.

Mark Decerbo, Chair: I was looking over some stuff, section 6each of the members constituting a quorum shall vote. So, I guess going forward as the chair, since I am part of the quorum I would vote.

Gabriel Lither: I think the chair can certainly vote. People get caught up with what the chair can and cannot do, but there are not any rules that says the chair cannot vote. Sometimes we need the chair's vote depending on how many members show up to the meeting.

Holly Long: Yes, we would need your vote depending on how many we have for a quorum. I have never heard of this being a problem with other boards.

Mark Decerbo, Chair: Any other comments or questions from the Board?

Motion and second to approve the bylaws as presented.

Voting: Ayes are unanimous, the motion carries.

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

Carl Jeffery: I will be quick here. We talked about the oral CGRP for migraine coming, a new insomnia medication and something for schizophrenia all coming soon. Those are the highlights.

h. **Closing Discussion**

Mark Decerbo, Chair: Do we have any public comment on any topic?

Carl Jeffery: Our next meeting will be back here, December 5th.

Meeting adjourned.

Proposed New 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. Cluster headache is less prevalent than migraine and characterized by attacks of severe, unilateral pain with ipsilateral autonomic symptoms, which occur every other day to multiple times daily during a cluster period (*International Headache Society [IHS] 2018, Starling et al 2015).*
  - The goals for treatment of migraine are to reverse or stop the progression of a migraine attack. The goals for preventive treatment are to reduce the frequency, severity and duration of a migraine (*American Headache Society [AHS] 2019, Katsarava 2012*).
- The International Classification of Headache Disorders (ICHD) includes both cluster headache and migraine as part of a group of primary headache disorders (*IHS 2018*):
  - Chronic migraine is defined as ≥ 15 headache days per month for > 3 months with the features of migraine headache for at least 8 mean 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, < 15 headache days per month) is considered to be episodic migraine, although the condition is not clearly defined in the ICHD.
  - Cluster headache is defined as ≥ 5 attacks lasting 15 to 180 minutes every other day to 8 times a day with severe unilateral orbital, supraorbital, and/or temporal pain. Episodic cluster headache attacks occur for a period of 7 days to 1 year and are separated by pain-free periods lasting at least 3 months. Common symptoms include nasal congestion, rhinorrhea, conjunctival injection and/or lacrimation, eyelid edema, sweating (forehead or face), miosis, ptosis, and/or a sense of restlessness or agitation.
- Cluster headache is more likely to occur in men, whereas migraines are more likely to occur in women. 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. Cluster headache is rare compared to other primary headache disorders. It is estimated to have a prevalence of 0.1% within the general population (*Global Burden of Disease Study [GBD] 2016, Hoffman et al 2018, Lipton et al 2016, Ljubisavljevic et al 2019, Manack et al 2011*).
- Treatments for migraines and cluster headache 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. Oral prophylactic migraine therapies have modest efficacy, and certain oral therapies may not be appropriate for individual patients due to intolerability or eventual lack of efficacy. For the treatment of acute migraine, options include triptans, ergots, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids. For the treatment of cluster headache, subcutaneous sumatriptan, zolmitriptan nasal spray, and oxygen have the most positive evidence for acute therapy, and suboccipital steroid injections are most effective for prevention (*American Migraine Foundation [AMF] 2017, Marmura et al 2015, Robbins et al 2016, Silberstein et al 2012, Simpson et al 2016)*.
- The calcitonin gene-related peptide (CGRP) pathway is important in pain modulation and the Food and Drug Administration (FDA) has approved 4 CGRP inhibitors for prevention or treatment of migraine/headache disorder(s). 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. 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. Ubrogepant is the only oral CGRP inhibitor (*Dodick et al 2018[b], Edvinsson 2017, Goadsby et al 2017, Sun et al 2016, Tepper et al 2017*).
  - Two CGRP inhibitors known as the “gepants,” telcagepant and olcegepant, were previously investigated. In 2009, Merck withdrew the FDA application for telcagepant because of elevated liver enzymes and potential liver toxicity observed with chronic use, which was likely related to the chemical structure of the compound. The manufacturer of

olcegepant also ceased pursuing FDA approval; however, the manufacturer did not explicitly state the rationale. It has been widely speculated that olcegepant development ceased due to limitations associated with administration as an intravenous (IV)-only product (*Edvinsson et al 2017, Walker et al 2013*). No substantial issues with liver toxicity have been observed in trials with the currently marketed CGRP inhibitors.

- Two investigational CGRP inhibitors with near-term anticipated approvals include rimegepant, an oral tablet and oral disintegrating tablet CGRP inhibitor, and eptinezumab, an IV formulation that could be funded under the medical benefit. Additional CGRP inhibitors early in their development include vazegepant, the first intranasally administered CGRP inhibitor, and atogepant, another oral CGRP inhibitor (*Biohaven press release 2019*, *Staines 2019*).
- In April 2019, Teva announced that it would not pursue development of fremanezumab-vfrm for an episodic cluster headache indication due to results from the ENFORCE trial (*Teva Pharmaceuticals press release 2019*). Erenumab-aooe is not currently in early phase studies for the indication of cluster headache (*Clinicaltrials.gov 2019*).

- 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)	−
Ubrelvy (ubrogepant)	−

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Aimovig (erenumab−aooe)	Ajovy (fremanezumab-vfrm)	Emgality (galcanezumab-gnlm)	Ubrelvy (ubrogepant)
Acute treatment of migraine with or without aura in adults	-	-	-	✔ *
Preventive treatment of migraine in adults	✔	✔	✔	-
Treatment of episodic cluster headache in adults	-	-	✔	-

* Limitation of use: Not indicated for the preventive treatment of migraine.

(*Prescribing information: Aimovig 2019, Ajovy 2018, Emgality 2019, Ubrelvy 2019*)

- 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

- Ubrogepant has been studied as acute therapy in approximately 3360 patients across 2 trials in patients with 2 to 8 migraines/month with moderate to severe pain intensity either with or without aura and in 1 open-label extension (OLE) trial in unpublished formats.
- Erenumab-aooe has been studied as preventive therapy in approximately 2500 patients across 4 trials in patients with episodic or chronic migraine subtypes and 1 OLE trial with data from interim analyses in published and unpublished formats.
- Fremanezumab-vfrm has been studied as preventive therapy 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 that required a duration of ≥ 30 minutes.
- Galcanezumab-gnlm has been studied as preventive therapy 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 efficacy and

safety of galcanezumab-gnlm was evaluated for treatment in one 8-week study with 106 adults with episodic cluster headache (maximum of 8 attacks/day).

- 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, and the definitions 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.

Prevention of 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, 5.9% more patients treated with erenumab−aooe 140 mg reported a 100% reduction in MMD, or migraine cessation. Erenumab-aooe 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*).

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]*).

- FOCUS was a DB, PC, Phase 3b trial that evaluated 838 patients with episodic (39%) or chronic migraine (61%) who had previously not responded to 2 to 4 classes of migraine preventive medications. Of the patients enrolled, approximately 40% were classified as having episodic migraines and randomized to fremanezumab-vfrm 225 mg administered monthly with no loading dose (n = 110/283), fremanezumab-vfrm 675 mg administered quarterly (n = 107/276), or placebo (n = 112/279) for 12 weeks. Failure was defined as no clinically meaningful improvement after at least 3 months of therapy at a stable dose, as per the treating physician's judgment, discontinuation because of adverse events that made treatment intolerable, or treatment contraindicated or unsuitable for the preventive treatment of migraine for the patient. At baseline, the MMD as approximately 14.2 days and the MMHD (of at least moderate severity) was 12.6 days. For the overall population, the MMD reduction over 12 weeks was 0.6 (standard error [SE], 0.3) days for placebo, 4.1 (SE, 0.34) days for the monthly fremanezumab-vfrm group (least squares mean difference [LSMD] vs placebo, -3.5; 95% CI, -4.2 to -2.8 days; p < 0.0001), and 3.7 (SE, 0.3) for days for the quarterly fremanezumab-vfrm group (LSMD vs placebo, -3.1; 95% CI, -3.8 to -2.4 days; p < 0.0001). For episodic migraine and compared to placebo, the LSMD in MMD reduction over 12 weeks was 3.1 days for both dose groups (fremanezumab-vfrm monthly: LSMD, -3.1; 95% CI, -4.0 to -2.3 days; fremanezumab-vfrm quarterly: LSMD, -3.1; 95% CI, -3.9 to -2.2 days; p < 0.0001 for both). In the overall population, the proportions of patients with a ≥ 50% response over 12 weeks were 34% in both the quarterly and monthly fremanezumab-vfrm groups vs 9% with placebo (p < 0.0001). Only the monthly fremanezumab-vfrm arm achieved a ≥ 75% sustained responder rate that was statistically different from placebo (OR, 8.6; 95% CI, 2.0 to 37.9; p = 0.0045). Adverse events were similar for placebo and fremanezumab-vfrm. Serious adverse events were reported in 4 (1%) of 277 patients with placebo, 4 (1%) of 285 with monthly fremanezumab-vfrm, and 2 (< 1%) of 276 with quarterly fremanezumab-vfrm (*Ferrari et al 2019*).

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, 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, 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*).
  - In an analysis of persistence for patients with episodic migraine, 41.5 and 41.1% of galcanezumab-gnlm-treated patients (120 mg and 240 mg, respectively) had a ≥ 50% response for ≥ 3 months, which was greater than placebo (21.4%; p < 0.001). Approximately 6% of galcanezumab-gnlm-treated patients maintained ≥ 75% response all 6 months vs 2% of placebo-treated patients. Few galcanezumab-gnlm-treated patients maintained 100% response for all 6 months (< 1.5%) (*Förderreuther et al 2018*).

Prevention of 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*).
  - An analysis of patient reported outcomes found patients with chronic migraine had clinically relevant improvements across a range of measures. Improvements were observed at month 3 for all endpoints regardless of erenumab−aooe dose, and minimally important clinical differences were achieved for certain measures with the erenumab−aooe 140 mg dose (*Lipton et al 2019[b]*).

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; 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*).
- FOCUS was previously described as including 838 patients overall who had not responded to 2 to 4 classes of migraine preventive medications. Of the patients enrolled, 61% were diagnosed with chronic migraine and were randomized to fremanezumab-vfrm 675 mg administered quarterly (n = 169/276), a fremanezumab-vfrm 675 mg loading dose followed by 225 mg administered monthly (n = 173/283), or placebo (n = 167/279). Among patients classified as having chronic migraine and compared to placebo, the LSMD in MMD reduction over 12 weeks was 3.8 days for the fremanezumab-vfrm monthly group and 3.2 days for the fremanezumab-vfrm quarterly group (fremanezumab-vfrm monthly: LSMD, -3.8; 95% CI, -4.8 to -2.8 days; fremanezumab-vfrm quarterly: LSMD, -3.2; 95% CI, -4.2 to -2.2 days; p < 0.0001 for both) (*Ferrari et al 2019*).

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, 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*).
  - In an analysis of persistence for patients with chronic migraine, 29% of galcanezumab-gnlm-treated patients maintained ≥ 30% response all 3 months compared to 16% of placebo-treated patients. A total of 16.8 and 14.6% of galcanezumab-gnlm-treated patients (120 mg and 240 mg, respectively) had a ≥ 50% response for ≥ 3 months, which was greater than placebo (6.3%; p < 0.001). Few patients maintained ≥ 75% response (< 3%) (*Förderreuther et al 2018*).

Treatment of episodic cluster headache

Galcanezumab-gnlm

- Galcanezumab-gnlm was evaluated in an 8-week, DB trial, in which 106 patients with episodic cluster headache were randomized to placebo (n = 57) or galcanezumab-gnlm 300 mg once monthly (n = 49). A total of 90 (85%) patients completed the DB phase. Patients were allowed to use certain specified acute/abortive cluster headache treatments, including triptans, oxygen, acetaminophen (APAP), and NSAIDs during the study. At baseline, patients had a mean of 17.5 headache attacks/week, maximum of 8 attacks/day, minimum of 1 attack every other day, and at least 4 attacks during the prospective 7-day baseline period. For the primary endpoint, galcanezumab-gnlm significantly decreased the mean change from baseline in weekly cluster headache attack frequency during weeks 1 to 3 vs placebo (-8.7 vs -5.2 attacks; p = 0.036). Galcanezumab-gnlm was also associated with a significantly greater proportion of responders (≥ 50% reduction in weekly cluster headache attack frequency) at week 3 (71.4 vs 52.6%; p = 0.046). Adverse events did not differ between groups, except for a significant increase in the incidence of injection-site pain with galcanezumab-gnlm treated patients (8 vs 0%; p = 0.04) (*Clinicaltrials.gov [NCT02397473] 2019, Emgality prescribing information 2019, Goadsby et al 2019*).

Treatment of acute migraine (with or without aura)

Ubrogepant

- Ubrogepant was evaluated in 2 Phase 3, PC, DB trials (ACHIEVE I and II), in which 3358 patients (ACHIEVE I, n = 1672; ACHIEVE II, n =1686) were randomized to take 1 dose of placebo (n = 1122), ubrogepant 50 mg (n = 1118), or ubrogepant 100 mg (n = 557) (100 mg was evaluated in the ACHIEVE I trial only, and a 25 mg group was included in the ACHIEVE II trial only [n = 561]). Patients had 2 to 8 migraines/month with moderate to severe pain intensity in the past 3 months either with or without aura and had a history of migraine for ≥ 1 year. A second dose of study treatment (placebo or ubrogepant), or the patient's usual acute treatment for migraine, was allowed between 2 to 48 hours after the initial treatment for a non-responding or recurrent migraine headache. At baseline, 23% of patients were taking preventive medications for migraine, and approximately 23 to 27% were insufficient triptan responders. In ACHIEVE I, 79% were included in the efficacy analysis and 86% in the safety analysis, and in ACHIEVE II, 91.7% had a qualifying migraine event and 88% were included in the analysis (*Dodick et al 2019, Lipton et al 2019[a], Ubrelvy prescribing information 2019*).
  - Compared to placebo, significant improvements were demonstrated for the co-primary endpoints of pain freedom and the most bothersome symptom (MBS) freedom at 2 hours post-dose in the ubrogepant arms. MBS was a collection of selective, self-identified symptoms (ie, photophobia, phonophobia, or nausea). The following differences from placebo were demonstrated:
    - *Pain-free at 2 hours*: 7.4% (p = 0.002) and 7.5% (p = 0.007) for the ubrogepant 50 mg dose in ACHIEVE I and II trials, respectively, and 9.4% (p < 0.001) for ubrogepant 100 mg dose in ACHIEVE I trial.
    - *MBS-free at 2 hours*: 10.8% and 11.5% (p < 0.001 for both) for the ubrogepant 50 mg dose in ACHIEVE I and II trials, respectively, and 9.9% (p < 0.001) for ubrogepant 100 mg dose in ACHIEVE I trial.
  - The incidence of photo- and phonophobia was reduced following administration. Significantly more patients maintained pain freedom for 2 to 24 hours post dose in the ubrogepant 100 mg arm (difference from placebo, 6.8%; p = 0.002) and the 50 mg arm for ACHIEVE II only (6.2%; p = 0.005).
  - In ACHIEVE I, the most common adverse events included nausea (1.5 to 4.7%), somnolence (0.6 to 2.5%), and dry mouth (0.6 to 2.1%). In ACHIEVE II, the most common adverse events within 48 hours were nausea (≤ 2.5% for all arms) and dizziness (≤ 2.1% for all arms). No serious adverse events or adverse events leading to discontinuation were reported 48 hours after the initial dose. In ACHIEVE II, the serious adverse events at 30 days included appendicitis, spontaneous abortion, pericardial effusion, and seizure.

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, 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, 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.
- The long-term safety of ubrogepant was evaluated in 813 patients with intermittent dosing administered for up to 1 year in an OLE. Of the 813 patients, 421 patients were exposed to ubrogepant 50 mg or 100 mg for ≥ 6 months, and 364 patients were exposed for ≥ 1 year. All patients were treated for ≥ 2 migraine attacks/month, on average. In the OLE, 2.5% of patients withdrew from ubrogepant treatment because of an adverse reaction. The most common adverse reaction resulting in discontinuation in the OLE was nausea (*Clinicaltrials.gov [NCT02873221] 2019, Ubrelvy prescribing information 2019*).
- 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

Acute treatment of migraine

- The American Headache Society (AHS) published updated consensus statement guidelines for migraine in 2018. The AHS recommends the use of APAP, NSAIDs, non-opioid analgesics, or caffeinated analgesic combinations for mild or moderate attacks. The triptans or dihydroergotamine (DHE) are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics. These guidelines do not differentiate the triptans, but recommend that non-oral routes be used when severe nausea or vomiting is present. Overall, the AHS designated the following drugs as having efficacy (*AHS 2019*):
  - Established efficacy:
    - Triptans
    - Ergotamine derivatives
    - NSAIDs (aspirin, diclofenac, ibuprofen, naproxen)
    - Opioids (butorphanol, although use is not recommended)
    - Combination medications
  - Probably effective
    - Ergotamine or other forms of DHE
    - NSAIDs (ketoprofen, ketorolac intramuscular or IV, flurbiprofen)

        - Magnesium IV
        - Isometheptene compounds
        - Combination medications (codeine/APAP, tramadol/APAP)
        - Antiemetics (prochlorperazine, promethazine, droperidol, chlorpromazine, metoclopramide)
    - Ubrogepant was reviewed by the AHS prior to FDA-approval for recommendation. The AHS recommend it may have a role in patients with cardiovascular (CV) conditions or in cases of triptan contraindications. Further recommendations include patients who have contraindications to the use of triptans or who have failed to respond to or tolerate ≥ 2 oral triptans, as determined by either a validated acute treatment patient reported outcome questionnaire or healthcare provider attestation. Coverage should be provided until ≥ 2 attacks are treated to determine efficacy and tolerability.
        - Other agents have had more established efficacy and safety relative to the newly FDA-approved migraine agents.
- There are a number of older guidelines/treatment recommendations for the treatment of migraine but, similar to the 2018 guidelines, they do not state a preference for a particular triptan or therapy (*Evers et al 2009, Francis et al 2010, Marmura et al 2015, Silberstein 2000, Silberstein et al 2012 [guideline reaffirmed in 2015]*).
- In 2019, the American Academy of Neurology (AAN) and the AHS published a guideline on the acute treatment of migraine in children and adolescents. The guideline states that there is evidence to support the efficacy of ibuprofen, APAP (in children and adolescents), and triptans (mainly in adolescents) for migraine relief, although confidence in the evidence varies between agents (*Oskoui et al 2019[a]*).
    - Of note, the CGRP inhibitors have not been adequately studied in children or adolescents and are not currently FDA-approved for use in these populations.

Prevention of migraine

- According to the AAN/AHS evidence−based guideline update on the pharmacologic treatment for episodic migraine prevention in adults, the following medications are effective preventive treatment options (see Appendix A for a definition of classifications) (*Silberstein et al 2012*):
    - 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*).
- In 2019, the AAN/AHS published a guideline on the preventive treatment of migraine in pediatric patients. The guideline states that the majority of preventive medications for pediatric migraine fail to demonstrate superiority to placebo. The guidelines make the following statements and recommendations for initial therapy (see Appendix B for a definition of classifications) (*Oskoui et al 2019[b]*):
    - It is possible that cognitive behavioral therapy (CBT) alone is effective in migraine prevention.
    - There is insufficient evidence to evaluate the effects of flunarizine, nimodipine, valproate, and onabotulinumtoxinA for use in migraine prevention in children and adolescents.
    - Acknowledging the limitations of currently available evidence, use of short-term treatment trials (a minimum of 2 months) may be warranted in those who could benefit from preventive treatment (Level B).

- Consider amitriptyline combined with cognitive behavioral therapy (CBT) (inform of the potential adverse events, including risk of suicide) (Level B).
- Consider topiramate (Level B). Inform of side effects including decreased efficacy when combined with oral contraceptives and the teratogenic effect in patients of childbearing potential (Level A). In patients of childbearing potential, daily folic acid is recommended (Level A).
- Consider propranolol (Level B).
  - Of note, the CGRP inhibitors have not been adequately studied in children or adolescents and are not currently FDA-approved for use in these populations.

Cluster headache

- According to the AHS evidence-based guidelines for the treatment of cluster headache, there are a number of effective treatment options (AAN classifications were used for grading; see Appendix A for definitions) (*Robbins et al 2016*).
- For acute therapy of cluster headache, the following therapy options have positive evidence:
  - Level A (established efficacy and ≥ 2 Class I trials):
    - Certain triptans: sumatriptan subcutaneous and zolmitriptan nasal spray
    - Oxygen
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Certain triptans: sumatriptan nasal spray and zolmitriptan oral
    - Sphenopalatine ganglion stimulation
  - Level C (possibly effective and 1 Class II trial):
    - Cocaine/lidocaine nasal spray
    - Octreotide subcutaneous
- For preventive therapy of cluster headache, the following therapy options have positive evidence:
  - Level A (established efficacy and ≥ 2 Class I trials):
    - Suboccipital steroid injection
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Civamide nasal spray (not marketed in the US)
  - Level C (possibly effective and 1 Class II trial):
    - Lithium
    - Verapamil
    - Warfarin
    - Melatonin

SAFETY SUMMARY

- Ubrogepant is contraindicated with concomitant use of strong CYP3A4 inhibitors.
- Erenumab-aooe, 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, dyspnea, pruritus, urticaria) were reported in trials. Cases of anaphylaxis and angioedema have been reported post-marketing. In cases of serious or severe reactions, treatment should be discontinued.
- Erenumab-aooe has an additional warning and precaution associated with constipation with serious complications noted post-marketing. Some cases have required hospitalization, including surgery. Constipation was a common adverse event reported in up to 3% of patients. Concurrent use of medication associated with decreased gastrointestinal motility may increase the risk for severe constipation.
- For the prevention of migraine, erenumab-aooe, fremanezumab−vfrm, and galcanezumab−gnlm 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 prevention studies included injection site reactions (all agents) and constipation (erenumab-aooe only).
- For the treatment of episodic cluster headache, galcanezumab−gnlm was evaluated for 2 months in trials and the safety profile was similar to those adverse events observed in migraine prevention trials. Two patients discontinued DB treatment due to adverse events.
- For the treatment of acute migraines, the safety of ubrogepant was evaluated for up to 1 year in an OLE in patients who had ≥ 2 attacks/month. The most common adverse events were nausea (2 to 4%) and somnolence (2 to 3%). The most common adverse reaction resulting in discontinuation in the OLE was nausea.

- 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 CV 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. A total of 9 patients reported serious adverse events with ubrogepant 50 mg (sinus tachycardia, intestinal obstruction, gait disturbance, cholelithiasis, acute cholecystitis, allergy, pneumonia, pelvic inflammatory disease, post procedure infection, hypertensive crisis, and a substance-induced mood disorder) and 12 with the 100 mg (colitis, hiatus hernia, acute pancreatitis, non-cardiac chest pain, cholelithiasis, acute cholecystitis, gastroenteritis, pneumonia, sepsis, subdural hematoma, ketoacidosis, hemiparesis, abortion, ectopic pregnancy, suicidal ideation, and acute respiratory failure); however, not all events may be related to treatment. 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, Clinicaltrials.gov [NCT02873221] 2019, 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 (70 mg/mL or 140 mg/mL)	SC	Once monthly (70 or 140 mg)	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 (225 mg/1.5 mL)	SC	Once monthly (225 mg) or once every 3 months (675 mg)	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 (120 mg/mL) Prefilled syringe (100 mg/mL or 120 mg/mL)	SC	*Prevention of migraine*: 2 consecutive injections (120 mg each) as a loading dose, then once monthly	May be self−administered by patients in the abdomen, thigh, back of upper arm or buttocks.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Episodic cluster headache: 3 consecutive injections (100 mg each) at onset, and then once monthly until the end of the cluster period	The cap is not made with natural rubber latex. 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.
Ubrelvy (ubrogepant)	Oral tablets (50 and 100 mg)	PO	*Acute migraine treatment:* As needed. A second dose may be taken at least 2 hours after the initial dose. Max dose: 200 mg in 24 hours.	The safety of treating > 8 migraines in a 30 day period has not been established. Dose adjustments are warranted with certain concomitant drugs or in cases of metabolic impairment. Avoid use in patients with end stage renal disease (CrCL < 15 mL/min). Take with or without food

See the current prescribing information for full details
Abbreviations: CrCL = creatinine clearance; PO = oral; SC = subcutaneous
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. Cluster headache is less prevalent than migraine and characterized by attacks of severe, unilateral pain with ipsilateral autonomic symptoms, which occur every other day to multiple times daily during a cluster period. Cluster headache is more likely to occur in men, whereas migraines are more likely to occur in women.
- Ubrogepant is indicated for acute treatment of migraine with or without aura. Erenumab-aooe, fremanezumab−vfrm, and galcanezumab−gnlm are indicated for the prevention of migraine. Galcanezumab−gnlm has an additional indication for the treatment of episodic cluster headache. No CGRP inhibitor is FDA-approved for use in patients aged < 18 years.
- Guidelines divide treatment recommendations according to age, prevention or treatment, and migraine type:
  - Current evidence−based prophylactic migraine treatment options and guidance are limited for chronic migraine, and oral prophylactic medications prescribed for episodic migraine are often used 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. 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.
  - For the treatment of cluster headache, subcutaneous sumatriptan, zolmitriptan nasal spray, and oxygen have the most positive evidence for acute therapy according to the AHS guidelines. To date, only subcutaneous sumatriptan is FDA-approved for the acute treatment of cluster headache. Additionally, sumatriptan nasal spray, zolmitriptan oral formulations, and sphenopalatine ganglion stimulation are probably effective for acute treatment per guidelines. For prevention of cluster headaches, suboccipital steroid injections are most effective according to the guidelines; however, there is no preventive medication currently FDA-approved for cluster headache.
  - For acute treatment of migraine in adults, guidelines generally recommend the use of APAP, NSAIDs, non-opioid analgesics, or caffeinated analgesic combinations for mild or moderate attacks. The triptans or DHE are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics.

Recent AHS guidelines state that ubrogepant may have a role in patients with CV conditions or in cases of triptan contraindications. It is also noted that other CGRP inhibitors may shortly be FDA-approved for use.

- There are no head-to-head studies with the CGRP inhibitors and no agent is clearly superior to others. Evidence for the CGRP inhibitors have demonstrated efficacy for the respective indications:
  - 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.
    - Compared to placebo, the CGRP inhibitors when prescribed for prophylactic migraine therapy 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.
  - For the treatment of cluster headaches, galcanezumab-gnlm demonstrated efficacy compared to placebo in an 8-week trial, which allowed for acute/abortive treatments during therapy. Galcanezumab-gnlm significantly decreased the mean change from baseline in weekly cluster headache attack frequency by 3.5 during weeks 1 to 3 vs placebo. Additionally, 18.8% more patients were classified as responders (≥ 50% reduction in weekly cluster headache attack frequency) with galcanezumab-gnlm at week 3 vs placebo (p = 0.046).
  - Ubrogepant demonstrated efficacy compared to placebo in 2 DB, RCTs, which reported acute response to migraine treatment after 2 hours. A second dose of study treatment (placebo or ubrogepant), or the patient's usual acute treatment for migraine, was allowed between 2 to 48 hours after the initial treatment for a non-responding or recurrent migraine headache. Compared to placebo, significantly more patients treated with ubrogepant were pain-free at 2 hours when administered the 50 mg (difference vs placebo, 7.4 to 7.5%) or 100 mg (difference vs placebo, 9.4%) dose. For the co-primary endpoint of MBS, significantly more ubrogepant-treated patients reported being MBS-free at 2 hours post dose for the 50 mg (difference vs placebo, 10.8 to 11.5%) and 100 mg (difference vs placebo, 9.9%) dose.
- 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. Furthermore, ubrogepant has a number of drug interactions, and may not be appropriate with other medications. Important co-morbid populations 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 in SC formulations and nausea in oral formulations.
- Overall, erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm 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. Galcanezumab-gnlm is the only CGRP inhibitor indicated for the treatment of episodic cluster headaches and ubrogepant is the only CGRP inhibitor indicated for acute treatment of migraines and also the only oral formulation. The frequency of administration (and route or dose) vary by indication. Further long-term study is warranted.

APPENDICES

- **Appendix A. AAN levels of evidence classification** *(AAN 2017, 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.

Appendix B. AAN/AHS levels of evidence classification *(Oskoui et al 2019[b])*

Level of obligation; magnitude of benefit	
A	Must; large benefit relative to harm
B	Should; moderate benefit relative to harm
C	May; small benefit relative to harm
U	No recommendation supported; too close to call

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

INTRODUCTION

- The goal of treatment for patients with psoriasis is to control the disease. There are 3 main treatment modalities available at present for the treatment of psoriasis: topical agents, phototherapy, and systemic agents. Topical therapies are the mainstay for mild disease either as monotherapy or in combination, and topical therapies are also commonly used in conjunction with phototherapy, traditional systemic agents, or biologic agents for moderate to severe disease. Phototherapy, photochemotherapy, and traditional systemic agents are generally used for moderate or severe disease and in situations in which topical therapy is ineffective or otherwise contraindicated (*Menter et al, 2011, Feldman 2019*).
- Topical corticosteroids (eg, betamethasone, clobetasol, triamcinolone, etc.) are the cornerstone of treatment for the majority of patients with psoriasis. Their effectiveness in treating psoriasis is due to anti-inflammatory, antiproliferative, immunosuppressive, and vasoconstrictive effects. Drawbacks associated with topical corticosteroid treatment are local cutaneous side effects and more serious systemic side effects that are associated with long-term use over a large body surface area (*Menter et al 2011*). Due to these side effects, several agents have been developed and tested as monotherapy or in combination with topical corticosteroids in the hopes of reducing the duration of corticosteroid treatment.
- Other topical antipsoriatic agents include anthralin, calcitriol, calcipotriene, and tazarotene. These agents are available in a variety of vehicles. Early forms of treatment also included coal tar. In the United States, coal tar use has declined due to lack of standardization of available compounds and the development of other agents with less cosmetic issues such as odor and staining.
- Oral antipsoriatic systemic agents are typically reserved for moderate to severe psoriasis and are often combined with other therapies. Acitretin, a topical retinoid, modulates the cellular differentiation of the epidermis and is known to have immunomodulatory and anti-inflammatory activity (*Menter et al 2009[b]).* Acitretin is most effective as a maintenance therapy, usually after the disease has been stabilized, or in combination with other treatments such as phototherapy (*Villasenor-Park et al 2012*). Methoxsalen is a naturally occurring photosensitivity agent (psoralen) that enhances skin reactivity to ultraviolet light A (UVA). The combination of psoralen and UVA is referred to as photochemotherapy or PUVA. PUVA is an option for psoriasis that does not respond to topical medications alone or for lesions that are too extensive for topical treatment (*Menter et al 2010*).
- Agents included in this review are the topical and oral antipsoriatics, which are listed in Table 1. Biologics and targeted agents (ie, adalimumab, adalimumab-adaz, adalimumab-adbm, adalimumab-atto, apremilast, brodalumab, etanercept, etanercept-szzs, etanercept-ykro, guselkumab, infliximab, infliximab-abda, infliximab-dyyb, infliximab-qbtx, ixekizumab, risankizumab-rzaa, secukinumab, tildrakizumab-asmn, and ustekinumab) that are used to treat psoriasis and other inflammatory/immunologic diseases are not included in this review. Topical corticosteroids are also not included in this review.
- Medispan Class: Antipsoriatics, Antipsoriatic – Systemic, and Topical Steroid Combinations

Table 1. Medications Included Within Class Review

Generic	Brand	Generic Availability
Topical Agents		
Anthralin*	Dritho-Creme HP cream	-
	Zithranol shampoo	-
Calcipotriene	Dovonex cream	✔
	Sorliux foam	-
	Topical ointment	✔
	Topical scalp solution	✔
Calcitriol	Vectical ointment	✔
Tazarotene**	Tazorac cream	✔

Generic	Brand	Generic Availability
	Tazorac gel	-
Calcipotriene/ Betamethasone dipropionate	Enstilar foam	-
	Taclonex suspension	-
	Taclonex ointment	✔
Tazarotene/ Halobetasol propionate	Duobrii lotion	-
Oral Systemic Agents		
Acitretin	Soriatane capsules	✔
Methoxsalen	Oxsoralen-Ultra capsules	✔

*Anthralin products are unapproved marketed drugs that have not been formally evaluated by the Food and Drug Administration (FDA) as it was initially marketed before the Federal, Food, Drug, and Cosmetic Act was passed.
**Tazarotene 0.1% topical foam (Fabior) is approved for the treatment of acne. The Avage brand of tazarotene 0.1% topical cream is approved for cosmetic indications.
(*DRUGS@FDA 2019*, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*, *Clinical Pharmacology 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Drugs	Psoriasis (Quiescent or Chronic)	Severe Psoriasis	Plaque Psoriasis	Photo-chemotherapy	Acne Vulgaris
Topical Agents					
Anthralin (Dritho-Creme, Zithranol)	✔				
Calcipotriene (Dovonex, Sorilux, calcipotriene ointment, calcipotriene scalp solution)			✔ *		
Calcitriol (Vectical)			✔ **		
Tazarotene (Tazorac)			✔		✔ †
Calcipotriene/ betamethasone dipropionate (Enstilar foam)			✔ ‖		
Calcipotriene/ betamethasone dipropionate (Taclonex suspension)			✔ ‡		
Calcipotriene/ betamethasone dipropionate (Taclonex ointment)			✔ ‖		
Tazarotene/ halobetasol propionate (Duobrii lotion)			✔		
Oral Systemic Agents					
Acitretin (Soriatane)		✔			
Methoxsalen (Oxsoralen-Ultra)				✔ ¥	

*Sorilux indicated for plaque psoriasis of scalp and body in patients 12 years or older; calcipotriene Topical Solution, 0.005% (Scalp Solution) is indicated for the treatment of chronic, moderately severe psoriasis of the scalp.
**Mild to moderate plaque psoriasis in adults 18 years and older.

†Tazorac 0.1% cream and gel.
‡Taclonex suspension indicated for plaque psoriasis of the scalp and body in patients 12 years and older.
‖Indicated for plaque psoriasis in patients 12 years of age and older.
¥For control of severe, recalcitrant, disabling psoriasis not adequately responsive to other forms of therapy and when the diagnosis has been supported by biopsy.

(Prescribing Information: *Calcipotriene ointment 2017, Calcipotriene solution 2018, Dovonex 2017, Dritho-Creme 2014, Duobrii 2019, Enstilar 2019, Oxsoralen-Ultra 2017, Soriatane 2018, Sorilux 2019, Taclonex ointment 2018, Taclonex suspension 2019, Tazorac cream 2017, Tazorac gel 2018, Vectical 2018, Zithranol 2011*)

- 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

- Various strengths and formulations of anthralin or dithranol have been evaluated (*Fredriksson 1983, Jones et al 1985*). Results from these trials support efficacy of anthralin in the treatment of psoriasis with no significant differences identified between dosage strength, formulation, or administration.
- Topical calcipotriene has demonstrated favorable efficacy in treating psoriasis in several studies with marked improvements in clearing of psoriatic lesions occurring in approximately 50 to 70% of patients (*Highton et al 1995, Dubertret et al 1992, Thaci et al 2001*). Treatment success was reported in patients with psoriasis who were treated with topical calcipotriene foam in two 8-week, multicenter, randomized, double-blind, vehicle-controlled clinical trials (*Feldman et al 2012, Feldman et al 2013*).
- For the treatment of plaque psoriasis, topical calcipotriene has demonstrated favorable efficacy when combined with betamethasone, psoralen plus ultraviolet A (PUVA), and methotrexate (*Buckley et al 2008, De Jong et al 2003, Kragballe et al 2009, Luger et al 2008, Ortonnne et al 2009, Ozkan et al 2012, Torras et al 2014, van de Kerkhof et al 2009*). The combination of calcipotriene plus betamethasone has demonstrated superior efficacy when compared to monotherapy with either calcipotriene or betamethasone or placebo in several clinical trials (*Buckley et al 2008, Douglas et al 2002, Guenther et al 2002, Jemec et al 2008, Kaufman et al 2002, Kragballe et al 2004, Kragballe et al 2009, Luger et al 2008, Ortonne et al 2009, Papp et al 2003, Parslew et al 2005, Singh et al 2000, van de Kerkhof et al 2005, van de Kerkhof et al 2009, van de Kerkhoff et al 2004*).
- The efficacy of calcitriol ointment for the treatment of mild to moderate plaque psoriasis was demonstrated in 2 double-blind, randomized controlled studies involving 839 patients. Calcitriol applied twice daily for 8 weeks was significantly more effective than the vehicle. Additionally, there were no clinically relevant changes in calcium homeostasis or other routine laboratory parameters in calcitriol-treated patients (*Lebwohl et al 2007*).
- Head-to-head trials comparing the vitamin D analogues have been conducted. Ortonne et al found calcitriol to be significantly better tolerated than calcipotriol in sensitive skin fold areas (*Ortonne et al 2003*). In another 12-week, randomized trial in patients with chronic plaque psoriasis, calcitriol demonstrated similar efficacy to calcipotriol and had a significantly better safety profile (*Zhu et al 2007*).
- Head-to-head trials comparing therapies from different medication classes for the treatment of psoriasis also exist. Veronikis et al compared calcipotriene to coal tar and found that both agents were effective in the treatment of plaque psoriasis with no significant differences found between treatment groups (p value not reported) (*Veronikis et al 1999*). Calcipotriol solution has been compared to clobetasol shampoo, with clobetasol being found to be significantly more efficacious in terms of total severity score measures as well as global severity score ($p < 0.05$ for all) (*Reygagne 2005*).
- Tazarotene was shown to be more effective than placebo in treating plaque psoriasis (*Weinstein et al 1997*). Results demonstrated that both tazarotene 0.1% and 0.5% gel were significantly more effective than placebo in reducing the severity of signs and symptoms of target lesions ($p < 0.05$). A second, placebo-controlled trial with the same methodology found similar results (*Weinstein et al 2003*). Topical tazarotene in combination with a low-, medium-, and high-potency topical corticosteroid has been evaluated in patients with mild to moderate plaque psoriasis (*Guenther et al 2000, Lebwohl et al 1998*). While all treatments were effective, the tazarotene and topical corticosteroid combination produced significantly higher treatment success rates at weeks 2, 8, and 12 vs tazarotene monotherapy (all $p < 0.05$). Bowman et al compared the combination of tazarotene gel plus calcipotriene ointment to clobetasol ointment in patients with stable psoriasis and found that both treatments were effective in reducing scaling, plaque elevation, and overall lesion severity with no significant differences between the 2 groups ($p = 0.93$, $p = 0.76$, and $p = 0.29$, respectively) (*Bowman et al 2002*).
- The efficacy of topical tazarotene and halobetasol propionate fixed combination was evaluated in 2 Phase 3, multicenter, double-blind randomized controlled trials in 418 patients with moderate-to-severe plaque psoriasis. More patients treated with topical tazarotene 0.045%/halobetasol propionate 0.01% lotion achieved treatment success at 8 weeks compared to patients who received vehicle in both studies *(Gold et al 2018).* Similarly, in a double-blind,

multicenter Phase 2 trial, more patients who received combination tazarotene/halobetasol propionate achieved treatment success after 8 weeks compared to halobetasol propionate 0.01%, tazarotene 0.045%, or vehicle *(Sugarman et al 2017).* Tazarotene/halobetasol propionate lotion was also compared to halobetasol propionate 0.05% cream and vehicle in patients with moderate-to-severe plaque psoriasis. Treatment success was achieved in 32.8% of patients with tazarotene/halobetasol propionate, 34.0% of patients with halobetasol propionate 0.05%, and 3.3% of patients with vehicle *(Bhatia et al 2018).*

- Acitretin has been shown to be effective in the treatment of patients with moderate to severe psoriasis in open-label studies and controlled clinical trials (*Olsen et al 1989, Tosti et al 2009*). In combination with calcipotriol, acitretin demonstrated improved clinical outcomes compared to acitretin alone or placebo (*Rim et al 2003, van de Kerkhof et al 1998*). Acitretin in combination with phototherapy can enhance treatment efficacy for patients with moderate to severe chronic plaque psoriasis that does not clear using UVB, PUVA, or acitretin alone. Compared with acitretin or UV light monotherapy, the combination regimen enhances efficacy and limits treatment frequency, duration, and cumulative doses (*Lebwohl et al 2001*).
- Several large multicenter trials have demonstrated the efficacy of oral methoxsalen with UVA (PUVA) in psoriasis, indicating clearance of lesions in 70% to 89% of patients (*Henseler et al 1981, Roenigk et al 1979, Melski et al 1977*). Two systematic reviews of the large majority of PUVA studies verified these findings demonstrating that between 70% and 100% of patients treated with PUVA achieved clearing of psoriasis lesions (*Griffiths et al 2000, Spuls et al 1997*).
- The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review of the biologic systemic agents compared to nonbiologic systemic agents or phototherapy on an individual drug level for the treatment of chronic plaque psoriasis. A total of 5 randomized clinical trials and 4 observational studies were identified. In summary, limited data exist that compare agents. Existing data were considered to be low strength of evidence, which in general favored the biological agents over the non-biologic agents (*Lee et al 2012*).
- A Cochrane Review was conducted to compare the effectiveness, tolerability, and safety of topical treatments for chronic plaque psoriasis, relative to placebo, and to similarly compare vitamin D analogues (alone or in combination) with other topical treatments. A total of 177 randomized controlled trials with 34,808 participants were included. When used on the body, most vitamin D analogues were significantly more effective than placebo. Dithranol, combined treatment with vitamin D/corticosteroid, and tazarotene all performed significantly better than placebo. Head-to-head comparisons of vitamin D for psoriasis of the body against potent or very potent corticosteroids had mixed findings. For both the body and scalp psoriasis, combined vitamin D and corticosteroid treatment performed significantly better than vitamin D alone or corticosteroid alone. When applied to psoriasis of the scalp, vitamin D was significantly less effective than both potent corticosteroids and very potent corticosteroids. Vitamin D generally performed better than coal tar, but findings compared to dithranol were mixed. For both body and scalp psoriasis, potent corticosteroids were less likely than vitamin D to cause local adverse events, such as burning or irritation. No comparison of topical agents found a significant difference in systemic adverse effects (*Mason et al 2013*).
- In addition to its FDA approval for the treatment of psoriasis, tazarotene, a topical retinoid agent, is also FDA-approved for the treatment of acne vulgaris. In a placebo-controlled trial by Bershad et al, tazarotene 0.1% gel was compared with tazarotene 0.1% gel plus a vehicle gel, or vehicle gel alone (*Bershad et al 2002*). The primary efficacy endpoint, reduction in acne vulgaris lesions, was significant in both tazarotene treatment groups compared to the vehicle group ($p = 0.002$). Clinical trials comparing tazarotene to other topical retinoid agents have shown conflicting results, with tazarotene being equally or more effective than other topical retinoids (*Pariser et al 2008, Tanghetti et al 2010*).

CLINICAL GUIDELINES

- The current guidelines for the management of psoriasis and psoriatic arthritis from the American Academy of Dermatology (AAD) recommend topical agents for mild to moderate psoriasis. Topical agents are also used adjunctively with ultraviolet light or systemic medications for resistant lesions or more severe disease. Topical corticosteroids are recommended as first-line treatment for most patients. Other topical agents included in the guidelines are vitamin D analogues, tazarotene, tacrolimus, pimecrolimus, anthralin, coal tar, and combination products. Combination products include corticosteroid and salicylic acid, corticosteroid and vitamin D analogue, corticosteroid and tazarotene, and tacrolimus and salicylic acid. When used in conjunction with ultraviolet radiation B or psoralen and UVA phototherapy or biologics, acitretin is effective for psoriasis and the treatment of choice in human immunodeficiency virus-positive patients with severe psoriasis due to its lack of significant immunosuppression (*Menter et al 2009[a], Menter et al 2009[b], Menter et al 2010, Menter et al 2011, Menter et al 2019*).
- In a 2013 position paper published by the AAD, psoriasis patients with moderate to severe psoriasis may avoid stepwise-therapy (ie, first phototherapy, then oral systemic therapies, followed by biologic therapies) and be moved to later line therapy based on disease severity (*AAD 2013*). Treatment needs vary depending on the severity of disease,

body location of disease, characteristics of the psoriasis being treated including lesion thickness, degree of erythema and amount of scaling, as well as patient preferences.

- Topical retinoids such as tazarotene are also effective in the treatment of acne vulgaris. Guidelines do not recommend one retinoid over another but do generally recommend these agents as a first-line combination option (*Thiboutot et al 2009, Eichenfield et al 2013, Zaenglein et al 2016*).
  - According to the AAD, topical retinoids (eg, tretinoin, adapalene, tazarotene) are recommended among the first-line treatment options for the management of acne (strength of recommendation: A [based on consistent and good-quality patient-oriented evidence]; level of evidence I [good-quality patient-oriented evidence, ie, evidence measuring outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life], and II [limited-quality patient-oriented evidence]) (*Zaenglein et al 2016*). Topical retinoids are important in addressing the development and maintenance of acne and are recommended as monotherapy in primarily comedonal acne, or in combination with topical or oral antimicrobials in patients with mixed or primarily inflammatory acne lesions. The guidelines do not prefer one topical retinoid over another.
    - There are several head-to-head studies with retinoid products. Some support greater efficacy of tazarotene over adapalene and tretinoin, and adapalene over tretinoin, but the concentrations and formulations were varied. Overall, the limitations of the existing studies prohibit direct efficacy comparisons of topical retinoids.
  - According to the Medical Letter, topical retinoids can be used alone or in combination with antibiotics to treat both inflamed and noninflamed acne lesions, or for maintenance treatment of acne (*Medical Letter 2016*).

SAFETY SUMMARY

- Topical calcipotriene is contraindicated in individuals with hypersensitivity to any components of the preparation. Additionally, calcipotriene administration in patients with vitamin D toxicity or hypercalcemia is also contraindicated. Calcipotriene should not be used for the treatment of the face, and the scalp solution is contraindicated in acute psoriatic eruptions. The most common adverse effects of calcipotriene are local effects including burning, pruritus, peeling, stinging, dryness, skin irritation, rash, and erythema. Contact dermatitis has been reported to occur with use of topical calcipotriene. Systemic side effects of vitamin D analogs, including hypercalcemia, are rare unless patients apply more than the recommended dosage of 100 g per week (*Clinical Pharmacology 2019*).
- There are no known contraindications to topical calcitriol. Among patients receiving laboratory monitoring, hypercalcemia was observed in 24% (18/74) of patients exposed to active drug and in 16% of (13/79) patients exposed to vehicle. This increase in calcium and albumin-adjusted calcium levels was < 10% above the upper limit of normal. The effects of calcitriol on calcium metabolism have not been evaluated for treatment durations of > 52 weeks. Additionally, increased absorption of calcitriol may occur with the use of occlusive dressings. Avoid exposure of treated areas to artificial or natural sunlight. The safety and efficacy of topical calcitriol in patients with disorders of calcium metabolism and patients with erythrodermic, exfoliative, or pustular psoriasis have not been evaluated. The most common adverse effects include hypercalciuria, pruritus, and lab test abnormalities (not otherwise specified).
- There are no known contraindications to calcipotriene/betamethasone suspension, ointment, or foam. Caution should be used with all formulations in patients with elevated serum calcium levels. Additionally, hypothalamic-pituitary-adrenal axis suppression has occurred due to systemic absorption of the topical corticosteroid. Avoid exposure of treated areas to artificial or natural sunlight. Local adverse reactions such as atrophy, irritation, and allergic contact dermatitis are more likely to occur with occlusive use. Common adverse effects include pruritus, worsening of psoriasis, erythema, and burning sensation.
- Topical tazarotene is contraindicated in patients who are pregnant or who have a documented hypersensitivity reaction to any component of the formulation. Tazarotene should not be used on eczematous skin as severe irritation may occur. Additionally, increased photosensitivity may occur with concurrent administration of fluoroquinolones, phenothiazines, sulfonamides, tetracyclines, and thiazides. Patients should be cautioned to take protective measures (eg, sunscreens, protective clothing) against exposure to sunlight or ultraviolet light (eg, tanning beds) until tolerance is determined. Excessive pruritus, burning, skin redness or peeling may occur. Discontinue tazarotene until skin integrity is restored, or reduce the dosing interval or switch to a lower concentration. The most common adverse effects include burning, erythema, and pruritus.
- Topical tazarotene/halobetasol propionate lotion is contraindicated in pregnancy. Warnings include hypothalamic-pituitary-adrenal axis suppression and photosensitivity. Common adverse effects include contact dermatitis, application site pain, folliculitis, skin atrophy, and excoriation. Local adverse reactions are more likely to occur with occlusive dressings.
- Topical anthralin is contraindicated in acute or actively inflamed psoriatic eruptions. Additionally, the agent should not be used if there is a hypersensitivity to the active ingredient or any of its components. The most common side effects of anthralin are skin irritation and staining of lesional and adjoining skin, nails, and clothing.

- Acitretin is teratogenic and its use, therefore, is limited to male and female patients of nonchildbearing potential. Acitretin should only be considered for women of childbearing potential with severe psoriasis unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments. Other contraindications for acitretin include severe liver or kidney impairment, chronic elevation of lipid profile, and use in combination with methotrexate or tetracyclines. Potential adverse effects of acitretin include dry skin and mucus membranes, alopecia, skin peeling, pruritus, cheilitis, rhinitis, hyperlipidemia, liver toxicity, and teratogenicity. Periodic monitoring of bones, lipid profile, liver function, and eyes is recommended.
- Methoxsalen is contraindicated with a history of light sensitivity, melanoma, invasive squamous cell carcinoma or aphakia. Skin irritation, including severe edema, erythema, blistering, and exfoliative dermatitis, can occur during PUVA therapy. Pruritus and other dermatological effects may occur as well. Nausea occurs in 10% of patients receiving methoxsalen, and central nervous system (CNS) effects including depression, dizziness, and headache have been reported. Patients who have received PUVA therapy should be monitored throughout their lives for the development of cutaneous malignancies.
- Pregnancy and lactation:
  - Anthralin: Pregnancy Category C. It is not known if anthralin is excreted in breast milk. Due to the potential for serious adverse reactions in the nursing infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of treatment to the mother.
  - Calcipotriene: Unclassified in accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR) for Sorilux and Dovonex. It is not known if calcipotriene is excreted in breast milk; caution is advised.
  - Calcitriol: Pregnancy Category C. It is not known if calcitriol is excreted in breast milk; caution is advised.
  - Calcipotriene/betamethasone: Unclassified in accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR) for Taclonex Ointment. Pregnancy Category C for Taclonex suspension and Enstilar foam. It is not known if calcipotriene/betamethasone is excreted in breast milk; caution is advised. It should not be applied to the breast if breast-feeding.
  - Tazarotene and tazarotene/halobetasol: Use in pregnancy is contraindicated. It is not known if tazarotene and/or halobetasol are excreted in breast milk. The decision to continue or discontinue breastfeeding during therapy should take into account the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.
  - Acitretin: Category X. Acitretin is a known teratogen and use is contraindicated in females who are or may become pregnant. Acitretin is excreted in breast milk. Due to the potential for serious adverse reactions in the breastfeeding infant, the manufacturer does not recommend acitretin prior to or during breastfeeding.
  - Methoxalen: Unclassified in accordance with the FDA's PLLR. It is not known if methoxsalen (systemic) is excreted in breast milk; either methoxsalen ingestion or nursing should be discontinued.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Usual Recommended Frequency	Comments
Topical Therapy			
Dritho-Crème (anthralin)	Cream	Apply once a day to psoriatic lesions for 5 to 10 minutes using the lowest strength possible for at least 1 week; may increase contact time up to 30 minutes as tolerated.	Avoid spreading cream onto the forehead; remove by washing or showering. For scalp psoriasis, comb hair to remove scalar debris; wet and part hair; rub cream into lesions.
Zithranol (anthralin)	Shampoo	Apply onto wet scalp 3 to 4 times per week.	Leave on scalp for 3 to 5 minutes and then rinse thoroughly.
Dovonex (calcipotriene)	Cream	Apply a thin layer to affected area 1 to 2 times per day and rub in completely.	

Drug	Available Formulations	Usual Recommended Frequency	Comments
Sorilux (calcipotriene)	Foam	Apply a thin layer twice daily to the affected areas and rub in gently and completely.	Avoid contact with the face and eyes. Not for oral, ophthalmic, or intravaginal use.
Calcipotriene ointment	Ointment	Apply a thin layer to affected area 1 to 2 times per day and rub in gently and completely.	
Calcipotriene scalp solution	Solution	Comb hair to remove scaly debris and apply twice daily, only to lesions, and rub in gently and completely.	Do not spread to forehead. Keep well away from eyes. Avoid applying to uninvolved scalp margins.
Vectical (calcitriol)	Ointment	Apply to affected areas twice daily, morning and evening.	The maximum weekly dose should not exceed 200 g. Not for oral, ophthalmic, or intravaginal use.
Enstilar (calcipotriene/ betamethasone dipropionate)	Foam	Apply to affected area once daily for up to 4 weeks.	Do not use more than 60 g every 4 days. Do not use with occlusive dressings unless directed by a physician. Not for oral, ophthalmic, or intravaginal use. Avoid use on face, groin, axillae, or if skin atrophy is present at treatment site.
Taclonex (calcipotriene/ betamethasone dipropionate)	Ointment, topical Suspension	Ointment: Apply to affected areas once daily for up to 4 weeks. Topical Suspension: Apply to affected areas once daily for up to 8 weeks.	Maximum weekly dose should not exceed 100 g for patients ≥ 18 years of age. For patients 12 to 17 years of age, maximum weekly use should not exceed 60 g. Treatment of > 30% of body surface area is not recommended. Do not use on face, axillae, or groin. Do not use with occlusive dressings unless directed by a physician. Do not use if skin atrophy is present at treatment site. Shake topical suspension before use. Not for oral, ophthalmic, or intravaginal use.
Tazorac (tazarotene)	Cream, gel	Psoriasis for ages ≥ 12 years old (gel) and ≥ 18 years old (cream): Apply a thin film to	Psoriasis: Start with 0.05% cream/gel, then increase to 0.1% if tolerated and medically indicated. Treatment of >

Drug	Available Formulations	Usual Recommended Frequency	Comments
		affected area once daily in the evening. Acne vulgaris for ages ≥ 12 years old: Apply a thin film to affected area once daily in the evening.	20% of body surface area is not recommended (gel only). Not for oral, ophthalmic, or intravaginal use. Avoid contact with eyes, mouth, or other mucous membranes. Apply to dry skin and at least an hour after using emollients.
Duobrii (tazarotene/ halobetasol propionate)	Lotion	Apply a thin layer to affected area once daily.	Maximum weekly dosage should not exceed approximately 50 g. Not for oral, ophthalmic, or intravaginal use. Do not use on face, axillae, or groin. Apply to dry skin.
Oral Therapy			
Soriatane (acitretin)	Capsules	Once daily with the main meal	
Oxsoralen (methoxsalen)	Capsules	Take 1.5 to 2 hours before UVA exposure with low-fat food or milk (see prescribing information for weight-based dosing instructions)	The number of doses per week will be determined by the schedule of UVA exposures.

See the current prescribing information for full details

CONCLUSION

- Numerous topical and systemic therapies are available for the treatment of psoriasis. Topical treatment is considered to be the safest option and is widely used for mild psoriasis, followed by systemic and phototherapies, which are used for moderate to severe psoriasis. Selection of medication must take into account severity of disease, thickness and scaling of the lesions, relevant comorbidities, patient preference, efficacy, and evaluation of individual patient response (*AAD 2013, Hsu et al 2012, Menter et al 2009[b], Menter et al 2019*).
- Topical corticosteroids are the cornerstone of treatment for the majority of patients with psoriasis. Drawbacks associated with topical corticosteroid treatment are local cutaneous side effects and more serious systemic side effects that are associated with long-term use over a large body surface area (*Menter et al 2011*). Several agents have been developed and tested as monotherapy or in combination with topical corticosteroids in the hopes of reducing the duration of corticosteroid treatment.
- The vitamin D analogs, calcipotriene and calcitriol, are other first-line topical agents with proven efficacy in the treatment of psoriasis. Although less effective than topical corticosteroids, they are often used in combination with topical corticosteroids to enhance efficacy and reduce the risk of atrophy, especially over the long term. One potential advantage of calcitriol is that there are no known contraindications for use, whereas calcipotriene (alone, but not in combination with betamethasone) is contraindicated in patients with hypercalcemia and vitamin D toxicity and in acute or actively inflamed psoriatic lesions. Another possible advantage of calcitriol is that it has been shown to be better tolerated in sensitive skin fold areas as well as associated with less stinging, burning, edema and erythema (*Weinstein et al 2003, Zhu et al 2007*).
- The combination of calcipotriene and betamethasone (Enstilar and Taclonex) has been evaluated in several studies for the treatment of psoriasis compared to placebo and to its individual components. Overall, results indicated that the combination product was more effective in reducing psoriasis area and severity index scores, and it increased the percentage of patients with clear or almost clear disease compared to either agent alone or placebo (*Douglas et al 2002, Guenthe et al 2002, Kaufman et al 2002, Kragballe et al 2004, Papp et al 2003, Parslew et al 2005, Singh et al 2000,*

van de Kerkhof et al 2004, van de Kerkhof et al 2005). The combination is available as a suspension, ointment, and foam.

- Tazarotene is the only retinoid agent that is FDA-approved for the treatment of psoriasis. Clinical trials have demonstrated its efficacy alone as well as in combination with other antipsoriatic agents. Guidelines recommend its use as an adjunct to topical corticosteroids (*Menter et al 2009[b]*). No significant differences were observed between calcipotriene or calcitriol and tazarotene in several head-to-head studies (*Guenther et al 2000, Schiener et al 2000, Tzung et al 2005*). Tazarotene is also available in fixed combination with halobetasol propionate. The combination has shown efficacy compared to its individual components *(Sugarman et al 2017).* Other topical preparations, including anthralin, have taken on more secondary roles and are particularly challenging as they stain clothing and skin.
- Of the systemic therapies, acitretin is the least effective as monotherapy and is therefore often used in conjunction with ultraviolet B or psoralen plus UVA phototherapy. Acitretin does not lead to immunosuppression or the associated risk of infection like biologic agents. Guidelines recommend the use of acitretin in combination with phototherapy as first-line treatment for psoriasis when not contraindicated, before resorting to other agents including methotrexate, cyclosporine, or biologic treatments (*Lebwohl 2001, Menter et al 2009, Menter et al 2010*). Acitretin should not be used in women of childbearing potential.
- Methoxsalen and ultraviolet light (PUVA) is an effective method of treating psoriasis. PUVA is indicated in patients with moderate to severe psoriasis that is unresponsive to other forms of therapy or for lesions that are too extensive for topical treatment (*Menter et al 2010*).
- In a position paper published by the AAD, psoriasis patients with moderate to severe psoriasis may avoid stepwise-therapy (i.e., first phototherapy, then oral systemic therapies, followed by biologic therapies) and be moved to later line therapy based on disease severity (*AAD 2013*). Consensus guidelines agree that the decision for treatment should be based on efficacy, potential adverse effects, prior treatments, patient preference, duration and severity of disease, medical risk factors**,** co-morbidities, and potential impact on quality of life (*AAD 2013*).
- Topical retinoids such as tazarotene are also effective in the treatment of acne vulgaris. Guidelines do not recommend one retinoid over another but do generally recommend these agents as a first-line combination option (*Thiboutot et al 2009, Zaenglein et al 2016, Eichenfield et al 2013*).

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Therapeutic Class Overview
Incretin Mimetics & Amylinomimetics

INTRODUCTION

- Diabetes mellitus affects more than 30 million people in the United States (U.S.) (*Centers for Disease Control and Prevention [CDC] 2017*).
- Diabetes mellitus is defined as a group of metabolic disorders characterized by hyperglycemia that result from defects in the secretion and action of insulin (*American Diabetes Association [ADA] Diabetes Basics 2019*).
- The classification of diabetes includes 4 clinical classes: 1) type 1 diabetes mellitus (T1DM) which results from beta-cell (β-cell) destruction, usually leading to absolute insulin deficiency, 2) type 2 diabetes mellitus (T2DM) which results from a progressive insulin secretory defect on the background of insulin resistance, 3) other specific types of diabetes due to other causes, eg, genetic defects in β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced (such as in the treatment of human immunodeficiency virus/acquired immunodeficiency syndrome or after organ transplantation), and 4) gestational diabetes mellitus (GDM) (diabetes diagnosed during pregnancy that is not clearly overt diabetes) (*ADA 2019*).
- Insulin is the standard treatment for T1DM. Pharmacologic options for T2DM include sulfonylureas (SFUs), biguanides, thiazolidinediones (TZDs), meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, amylinomimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, combination products, and insulin.
- The GLP-1 receptor agonists (albiglutide, dulaglutide, exenatide, exenatide extended-release [ER], liraglutide, lixisenatide, and semaglutide) were developed to mimic the effects of endogenous GLP-1 and are Food and Drug Administration (FDA)-approved as adjunctive therapy to diet and exercise to improve glycemic control in adults with T2DM. As of 2018, albiglutide was discontinued by the manufacturer due to limited prescribing of the drug and not because of safety concerns (*Tanzeum Discontinuation FAQ 2017*).
- Pramlintide is the only amylin analog, or amylinomimetic, in the class, and is FDA-approved as an adjunctive treatment with insulin in patients with T1DM or T2DM who have failed to achieve desired glucose control despite optimal insulin therapy. It is a synthetic analog of human amylin, a naturally occurring neuroendocrine hormone synthesized by pancreatic β-cells that contributes to glucose control during the post-prandial period.
- This review will focus on the GLP-1 receptor agonists and pramlintide and their respective FDA-approved indications for treatment of diabetes. Liraglutide (Saxenda) is also indicated as adjunctive therapy for chronic weight management; however, the use of liraglutide for this indication will not be included in this review.
- Medispan class: Endocrine and Metabolic Drugs; Incretin Mimetic Agents (GLP-1 Receptor Agonists) and Amylin Analogs

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Adlyxin (lixisenatide)	-
Bydureon (exenatide ER)	-
Bydureon BCise (exenatide ER)	-
Byetta (exenatide)	-
Ozempic (semaglutide)	-
Symlin (pramlintide)	-
Trulicity (dulaglutide)	-
Victoza (liraglutide)*	-

*As a result of a generic settlement agreement, a generic version of liraglutide may enter the market as early as December 22, 2023 (*Coppock 2019*).

(*DRUGS@FDA 2019*, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. FDA Approved Indications

Indication	Adlyxin (lixisenatide)	Byetta (exenatide)	Bydureon (exenatide ER)	Bydureon BCise (exenatide ER)	Ozempic (semaglutide)	Symlin (pramlintide)	Trulicity (dulaglutide)	Victoza (liraglutide)
T1DM, as an adjunctive treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.						✔		
T2DM, as an adjunctive treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.						✔		
Adjunct to diet and exercise to improve glycemic control in adults with T2DM.	✔	✔	✔	✔	✔		✔	✔
Adjunct to diet and exercise to improve glycemic control in patients 10 years and older with T2DM.								✔
Reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction [MI], or non-fatal stroke) in adults with T2DM and established cardiovascular disease								✔
Limitations of Use								
Not recommended as first-line therapy for patients inadequately controlled on diet and exercise because of the uncertain relevance of the rodent C-cell tumor findings to humans. Prescribe only to patients for whom the potential benefits are considered to outweigh the potential risk.			✔	✔	✔		✔	
Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in these patients.	✔	✔	✔	✔	✔		✔	
Not indicated in treatment of patients with T1DM or for treatment of patients with diabetic ketoacidosis. Not a substitute for insulin in these patients.	✔	✔	✔	✔	✔		✔	✔
Has not been studied in patients with severe gastrointestinal (GI) disease,							✔	

Indication	Adlyxin (lixisenatide)	Byetta (exenatide)	Bydureon (exenatide ER)	Bydureon BCise (exenatide ER)	Ozempic (semaglutide)	Symlin (pramlintide)	Trulicity (dulaglutide)	Victoza (liraglutide)
including severe gastroparesis. Not recommended in patients with pre-existing severe GI disease.								
Has not been studied in patients with gastroparesis. Not recommended in patients with gastroparesis.	✔							
Not studied in combination with prandial/short-acting insulin.	✔	✔	✔	✔				✔

(Prescribing information: *Adlyxin 2019*, *Bydureon 2019, Bydureon BCise 2019, Byetta 2018, Ozempic 2019, Symlin 2016, Trulicity 2019, Victoza 2019*)

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

CLINICAL EFFICACY SUMMARY

Dulaglutide

- The approval of dulaglutide was based on 6 pivotal trials enrolling over 3,000 patients as a part of the AWARD phase 3 program. Trials evaluated the use of dulaglutide 0.75 mg and 1.5 mg strengths. The primary outcome in each trial was the change in HbA1c from baseline to 26 through 52 weeks.
  - AWARD-1 demonstrated that once weekly dulaglutide resulted in significantly larger improvements in HbA1c at 26 weeks compared to placebo and exenatide in patients taking maximally tolerated doses of metformin and pioglitazone (*Wysham et al 2014*).
  - AWARD-2 was an OL study that demonstrated superiority of dulaglutide 1.5 mg once weekly and noninferiority of dulaglutide 0.75 mg once weekly compared to daily insulin glargine in terms of HbA1c reduction from baseline to week 52 (*Giorgino et al 2015*).
  - AWARD-3 was a DB study that demonstrated superiority of dulaglutide 0.75 mg and 1.5 mg once weekly to metformin in patients inadequately treated with diet and exercise with or without submaximal dosing of at least 1 oral antidiabetic drug (OAD). At 26 weeks, changes from baseline HbA1c were 0.78%, 0.71%, and 0.56% for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and metformin, respectively (*Umpierrez et al 2014*).
  - AWARD-4 was an OL, 52-week, noninferiority study which found that dulaglutide once-weekly (both 1.5 mg and 0.75 mg strengths) in combination with insulin lispro resulted in significantly greater improvement in glycemic control than insulin glargine in combination with insulin lispro ($p = 0.005$ and $p = 0.015$ for dulaglutide 1.5 mg and 0.75 mg, respectively) (*Blonde et al 2015*).
  - AWARD-5 was a DB trial that compared placebo, once-weekly dulaglutide (0.75 mg and 1.5 mg), and sitagliptin 100 mg once daily in uncontrolled metformin-treated patients. At weeks 52 and 104, both dulaglutide strengths were superior to sitagliptin in terms of HbA1c reduction from baseline ($p < 0.001$ for all comparisons) (*Nauck et al 2014, Weinstock et al 2015*).
  - AWARD-6 was an OL trial which demonstrated that, in patients taking concurrent metformin, dulaglutide 1.5 mg once weekly was noninferior to liraglutide once daily in HbA1c reduction from baseline to week 26 (*Dungan et al 2014*).
  - The AWARD-7 trial was an OL, non-inferiority study that enrolled patients with T2DM and moderate-to-severe chronic kidney disease (CKD) who were currently on insulin therapy. Patients were randomized to once-weekly dulaglutide (0.75 mg or 1.5 mg) or daily insulin glargine, all in combination with insulin lispro. At week 26, the change in HbA1c with dulaglutide 1.5 mg and 0.75 mg was non-inferior to insulin glargine ($p \leq 0.0001$ for both comparisons) (*Tuttle et al 2018*).

Exenatide

- The efficacy of exenatide as add-on therapy to metformin alone, an SFU alone, or metformin in combination with an SFU was evaluated in 3 placebo-controlled (PC), 30-week, randomized controlled trials (RCTs). In all trials, there were significant decreases in HbA1c with exenatide compared to placebo ($p < 0.001$, $p < 0.002$, and $p < 0.0001$, respectively) (*Buse et al 2004, DeFronzo et al 2005, Kendall et al 2005*). Extensions of these 30-week trials demonstrated that the benefits of exenatide are sustained (*Blonde et al 2006, Buse et al 2007, Klonoff et al 2008, Ratner et al 2006, Riddle et al 2006*).
- A trial evaluating exenatide as add-on therapy in patients currently taking a TZD found that at week 16, exenatide significantly decreased HbA1c ($p < 0.001$), fasting plasma glucose (FPG) ($p < 0.001$), and body weight ($p < 0.001$) compared to placebo (*Zinman et al 2007*).
- When exenatide was compared to glyburide as add-on therapy to metformin, exenatide significantly decreased body weight and body mass index (BMI) ($p < 0.001$ for both), whereas the SFU caused significant increases in both ($p < 0.05$ for both). Both treatments significantly decreased HbA1c, FPG, and postprandial plasma glucose (PPG) (exenatide; $p < 0.001$ for all; glyburide; $p < 0.001$ for all). Only exenatide significantly improved insulin resistance ($p < 0.01$) and β-cell function ($p < 0.05$) (*Derosa et al 2010*).
- The EUREXA study compared the efficacy of exenatide and glimepiride as add-on therapy to metformin. Patients receiving exenatide exhibited greater reductions in HbA1c from baseline (-0.36%), compared to those receiving glimepiride (-0.21%; $p = 0.002$) (*Gallwitz et al 2012*).
- Several trials have compared exenatide to insulin therapy as add-on therapy to metformin and/or an SFU (*Bunck et al 2009, Bunck et al 2010, Davies et al 2009, Heine et al 2005, Nauck et al 2007, Secnik et al 2006*). Similar improvements in HbA1c between treatments were observed in 3 of the trials while mixed results were observed for decreases in FPG. Specifically, in 2 trials, insulin therapy was “superior” in decreasing FPG (p value not reported and $p < 0.0001$), while in another trial there was no difference between the 2 treatments ($p = 0.689$). Insulin therapy was associated with an increase in body weight compared to a decrease with exenatide (*Bunck et al 2009, Heine et al 2005, Nauck et al 2007*). Patient-reported health outcome measures demonstrated no differences between exenatide or insulin therapy; both achieved significant improvements from baseline. However, neither treatment improved Diabetes Treatment Flexibility Scores ($p = 0.93$ for both) (*Secnik et al 2006*).
- Exenatide once weekly was also compared to daily insulin glargine in diabetic patients inadequately controlled with OADs. Following 26 weeks of therapy, exenatide was found to be statistically noninferior to insulin glargine for the change in HbA1c from baseline to endpoint (*Inagaki et al 2012*).

Exenatide ER

- Approval of exenatide ER in the management of T2DM was based on the clinical evidence for safety and efficacy derived from the DURATION trials (1 through 5). Exenatide ER was added to existing antidiabetic regimens in 4 of the 5 trials (1, 2, 3, and 5). In contrast, DURATION-4 compared exenatide ER, metformin, pioglitazone, and sitagliptin all as monotherapy (*Bergenstal et al 2010, Blevins et al 2011, Diamant et al 2010, Drucker et al 2008, Russell-Jones et al 2012*).
  - Overall, exenatide ER as add-on therapy to existing antidiabetic regimens significantly decreased HbA1c compared to exenatide ($p < 0.005$), sitagliptin ($p < 0.0001$), pioglitazone ($p = 0.0165$), and insulin therapy ($p = 0.017$), with no increased risk of hypoglycemia. In terms of decreases in body weight, exenatide ER was superior compared to sitagliptin ($p = 0.0002$) and pioglitazone ($p < 0.0001$), and similar compared to exenatide ($p = 0.89$) (*Bergenstal et al 2010, Blevins et al 2011, Drucker et al 2008*).
  - As expected, GI-related adverse events (AEs) were reported more commonly with the incretin-based therapies. When compared to exenatide, exenatide ER was associated with lower incidences of nausea (14.0% vs 35.0%) and vomiting (4.7% vs 8.9%), and higher incidences of diarrhea (9.3% vs 4.1%) and injection site-related AEs (13% vs 10%) (*Blevins et al 2011*).
  - In the DURATION-4 trial, the decrease in HbA1c achieved with exenatide ER monotherapy was superior compared to sitagliptin ($p < 0.001$) and similar compared to metformin ($p = 0.62$) and pioglitazone ($p = 0.328$). Exenatide ER and metformin were similar in terms of associated decreases in body weight, with exenatide ER achieving superiority compared to sitagliptin and pioglitazone. Overall, exenatide ER was associated with more GI-related AEs, with the exception of diarrhea which occurred at the highest frequency in patients receiving metformin (*Diamant et al 2010*).
  - An OL extension of the DURATION-1 trial demonstrated that treatment with exenatide ER was associated with sustained improvements in glycemic control over a 7-year period with no unexpected safety findings (*Philis-Tsimikas et al 2018*).

- In a post-hoc analysis of 4 clinical trials, patients were treated with weekly exenatide for 52 weeks. Patients had significant lowering of HbA1c, blood pressure and low density lipoprotein (LDL) levels without an increase in weight or hypoglycemia (*Bergenstal et al 2013*).
- The DURATION-6 trial compared HbA1c reductions between liraglutide once daily and exenatide once weekly in patients with T2DM previously treated with lifestyle modifications and oral agents. Both therapies resulted in improvements in glycemic control; however, greater reductions were noted with liraglutide (*Buse et al 2013*).
- Bydureon BCise is a new formulation of Bydureon that is administered via an autoinjector device. It was approved based on the results of two 28-week, OL, AC trials. In the DURATION-NEO-1 trial, Bydureon BCise 2 mg once weekly achieved a statistically significant HbA1c reduction vs Byetta 10 mcg twice daily ($p < 0.05$) in patients with T2DM inadequately controlled with diet and exercise alone or with a stable regimen of metformin, an SFU, a TZD, or a combination of any 2 of these agents. In the DURATION-NEO-2 trial, Bydureon BCise 2 mg once weekly achieved a statistically significant HbA1c reduction vs placebo ($p < 0.05$) in patients with T2DM on metformin. The difference vs sitagliptin was -0.28% (95% CI, -0.62% to -0.02%) (*Bydureon BCise Prescribing Information 2017, Gadde et al 2017, Wysham et al 2017)*.

Liraglutide

- Approval of liraglutide in the management of T2DM was based on the clinical evidence for safety and efficacy derived from the LEAD trials (1 through 6). The LEAD trials evaluated liraglutide monotherapy (LEAD-3); add-on therapy to an SFU (LEAD-1), metformin (LEAD-2), metformin plus a TZD (LEAD-4), metformin plus an SFU (LEAD-5); and monotherapy head-to-head with exenatide (LEAD-6).
  - In LEAD-1, liraglutide was compared to placebo or rosiglitazone as add-on therapy to an SFU. After 26 weeks, liraglutide (0.6, 1.2, and 1.8 mg per day) significantly decreased HbA1c compared to placebo ($p < 0.0001$ for all), with only higher doses achieving superiority compared to rosiglitazone ($p < 0.001$ for both) (*Marre et al 2009*).
  - In LEAD-2, liraglutide was compared to placebo and an SFU as add-on therapy to metformin. Liraglutide significantly decreased HbA1c compared to placebo; however, similar decreases were observed with liraglutide compared to the SFU. Liraglutide was associated with significant decreases in body weight compared to placebo ($p < 0.01$) and the SFU ($p < 0.001$) (*Nauck et al 2009*). Results of an 18-month OL extension trial were consistent with the DB study (*Nauck et al 2013*).
  - In LEAD-3, liraglutide was compared to an SFU as monotherapy, and liraglutide was superior in decreasing HbA1c ($p = 0.0014$ and $p < 0.0001$ for liraglutide 1.2 mg and 1.8 mg, respectively). In addition, increases in body weight were reported with the SFU, while liraglutide significantly decreased body weight ($p = 0.027$) (*Garber et al 2009*). In a 1-year extension trial, patients continuing liraglutide for a total of 2 years maintained significant improvements in HbA1c compared to the SFU (*Garber et al 2011*).
  - In LEAD-4 and LEAD-5, liraglutide was compared to placebo as add-on therapy to metformin plus an SFU and to a TZD. LEAD-5 also had an OL arm of insulin therapy. Results achieved with liraglutide in terms of decreases in HbA1c, body weight, and FPG compared to placebo were similar to those observed in the other LEAD trials (*Russell-Jones et al 2009; Zinman et al 2009*). When compared to insulin therapy, decreases in HbA1c ($p = 0.0015$) and body weight ($p < 0.001$) and improvements in β-cell function ($p = 0.0019$) were significantly greater with liraglutide. It was noted that decreases in PPG were not different between the 2 treatments, and the likelihood of patients achieving FPG goals were also similar (*Russell-Jones et al 2009*).
  - LEAD-6 was a head-to-head trial comparing liraglutide to exenatide as add-on therapy to existing antidiabetic treatment regimens. Liraglutide significantly decreased HbA1c compared to exenatide (1.12% vs 0.79%; $p < 0.0001$), and a significantly greater proportion of patients receiving liraglutide achieved HbA1c goals of < 7%. Significant decreases in FPG were also achieved with liraglutide ($p < 0.0001$); however, exenatide significantly decreased PPG after breakfast and dinner ($p < 0.0001$ and $p = 0.0005$) (*Buse et al 2009*). A 14-week, extension trial revealed that patients who were switched from exenatide to liraglutide achieved additional glycemic control and cardiometabolic benefits (*Buse et al 2010*).
- Liraglutide was studied in children and adolescents aged 10 to less than 17 years with T2DM in the PC Ellipse trial (*Tamborlane et al 2019*). After 26 weeks of DB treatment, liraglutide was associated with a significantly greater decrease in HbA1c vs placebo (mean difference, -1.06%; 95% CI, -1.65 to -0.46; $p < 0.001$), which was maintained over an additional 26-week OL extension (mean difference, -1.30%; 95% CI, -1.89 to -0.70).

Lixisenatide

- The approval of lixisenatide was based on several phase 3 trials as part of the GetGoal clinical trial program. Lixisenatide 20 mcg once daily was evaluated as monotherapy, in combination with OADs, and in combination with basal insulin (with or without OADs). Its efficacy was compared with placebo, exenatide, and insulin glulisine. The

primary endpoint, the difference in change in HbA1c from baseline to trial end between the lixisenatide and comparator groups, was assessed at varying time points ranging between 12 and 26 weeks.

- GetGoal-Mono found that lixisenatide 20 mcg once daily as monotherapy resulted in significantly larger improvements in HbA1c at 12 weeks compared to placebo in patients with T2DM inadequately controlled on diet and exercise ($p < 0.0001$) (*Fonseca et al 2012*).
- GetGoal-F1 was a DB study which found that lixisenatide 20 mcg once daily as add-on therapy to metformin was superior vs placebo in terms of HbA1c reduction from baseline to week 24. The least squares mean change from baseline was -0.26% for the placebo group vs -0.72% for the lixisenatide group. The difference vs placebo was -0.46% ($p < 0.0001$) (*Adlyxin Prescribing Information 2016, Bolli et al 2014*).
- GetGoal-M-Asia demonstrated superiority of lixisenatide 20 mcg once daily as add-on therapy to metformin with or without an SFU compared to placebo in terms of HbA1c reduction from baseline to week 24 (*Yu et al 2014*).
- GetGoal-S was a 24-week, DB study which found that lixisenatide 20 mcg once daily in combination with an SFU with or without metformin resulted in significantly greater improvement in glycemic control than placebo; the difference from placebo in change in HbA1c was -0.58% ($p < 0.0001$) (*Adlyxin Prescribing Information 2016, Rosenstock et al 2014*).
- GetGoal-P was a 24-week, DB study which found that lixisenatide 20 mcg once daily in combination with pioglitazone or without metformin resulted in significantly greater improvement in glycemic control than placebo; the difference from placebo in change in HbA1c was -0.48% ($p < 0.0001$) (*Adlyxin Prescribing Information 2016, Pinget al 2013*).
- In GetGoal-Duo 1, lixisenatide was compared to placebo as add-on therapy to basal insulin and metformin with or without a TZD. Treatment with lixisenatide resulted in a significant reduction in HbA1c at week 24 vs placebo (*Riddle et al 2013a*).
- In GetGoal-L, lixisenatide was compared to placebo as add-on therapy to basal insulin with or without metformin while in Get-Goal-L-Asia, lixisenatide was compared to placebo as add-on therapy to basal insulin with or without an SFU. Both studies found that lixisenatide was superior to placebo in terms of HbA1c reduction from baseline to week 24 (*Riddle et al 2013b, Seino et al 2012*).
- GetGoal-Duo 2 was a 26-week, OL trial that compared lixisenatide to insulin glulisine once daily or 3 times daily for intensification of optimized insulin glargine ± metformin in patients with T2DM uncontrolled on basal insulin ± OADs (ie, an SFU and/or a DPP-4 inhibitor, and/or a glinide). Lixisenatide was found to be noninferior to both insulin glulisine regimens in terms of HbA1c reduction from baseline to week 26. However, lixisenatide provided less HbA1c reduction than insulin glulisine 3 times daily and the difference was statistically significant; the least squares mean difference of lixisenatide vs insulin glulisine 3 times daily was 0.23 ($p = 0.0002$) (*Adlyxin Prescribing Information 2016, Rosenstock et al 2016*).
- GetGoal-X was a 24-week, OL trial that evaluated lixisenatide vs exenatide twice daily as add-on therapy to metformin. Lixisenatide met the pre-specified noninferiority margin vs exenatide twice daily for the difference in HbA1c reduction from baseline to week 24. However, lixisenatide provided less HbA1c reduction than exenatide and the difference was statistically significant; the least squares mean difference vs exenatide was 0.17% ($p = 0.0175$) (*Adlyxin Prescribing Information 2016, Rosenstock et al 2013*).
- A meta-analysis (MA) of 76-week data from 5 trials in the GetGoal clinical trial program (GetGoal-M, GetGoal-F1, GetGoal-S, GetGoal-P, and GetGoal-L) supported the sustained efficacy and tolerability of lixisenatide (*Broglio et al 2017*).

Semaglutide

- The approval of semaglutide was based on several phase 3 trials as part of the SUSTAIN clinical trial program. Semaglutide was evaluated as monotherapy, in combination with OADs, and in combination with basal insulin. Its efficacy was compared with placebo, sitagliptin, exenatide ER, insulin glargine, and dulaglutide. The primary endpoint, the difference in change in HbA1c from baseline to trial end between the semaglutide and comparator groups, was assessed at varying time points ranging between 30 and 56 weeks.
  - SUSTAIN 1 was a 30-week, PC trial which found that semaglutide 0.5 mg and 1 mg weekly significantly improved HbA1c vs placebo ($p < 0.0001$) (*Sorli et al 2017)*.
  - SUSTAIN 2 was a 56-week, OL trial that compared semaglutide 0.5 mg and 1 mg weekly to sitagliptin 100 mg daily in patients on metformin and/or TZDs. Compared with sitagliptin, treatment with semaglutide resulted in statistically significant reductions in HbA1c from baseline to week 56. The mean change from baseline was -1.3% for semaglutide 0.5 mg, -1.5% for semaglutide 1 mg, and -0.7% for sitagliptin. The difference vs sitagliptin was -0.6% ($p < 0.0001$) for semaglutide 0.5 mg and -0.8% ($p < 0.0001$) for semaglutide 1 mg (*Ahrén et al 2017, Ozempic Prescribing Information 2017*).

- SUSTAIN 3 was a 56-week, OL trial that compared semaglutide 1 mg to exenatide ER 2 mg once weekly. At week 56, mean change from baseline in HbA1c was -1.4% in the semaglutide group vs -0.9% in the exenatide ER group (difference: -0.5%, p < 0.0001) (*Ahmann et al 2018, Ozempic Prescribing Information 2017*).
- SUSTAIN 4 was a 30-week OL, AC trial in patients on metformin with or without an SFU that compared semaglutide 0.5 mg and 1 mg to insulin glargine initiated at 10 units once daily. Compared with insulin glargine, treatment with semaglutide resulted in statistically significant reductions in HbA1c from baseline to week 30. The mean change from baseline was -1.2% for semaglutide 0.5 mg, -1.5% for semaglutide 1 mg, and -0.9% for insulin glargine. The difference vs insulin glargine was -0.3% (p < 0.0001) for semaglutide 0.5 mg and -0.6% (p < 0.0001) for semaglutide 1 mg (*Aroda et al 2017*, *Ozempic Prescribing Information 2017*).
- SUSTAIN 5 was a 30-week, DB, PC trial in patients inadequately controlled with basal insulin, with or without metformin, which found that semaglutide 0.5 mg and 1 mg significantly reduced HbA1c vs placebo (p < 0.0001) (*Rodbard et al 2018).*
- SUSTAIN 7 was a 40-week, OL trial that compared semaglutide to dulaglutide once weekly in patients on metformin monotherapy. From a mean baseline HbA1c of 8.2%, semaglutide 0.5 mg achieved a statistically significant reduction of 1.5% vs a reduction of 1.1% with dulaglutide 0.75 mg at week 40, while semaglutide 1.0 mg achieved a statistically significant reduction of 1.8% vs a reduction of 1.4% with dulaglutide 1.5 mg (both p < 0.0001 for noninferiority and superiority) *(Pratley et al 2018).*

Cardiovascular (CV) outcomes

- A MC, DB, PC, RCT (REWIND trial; N = 9901) evaluated the long-term effects of dulaglutide vs placebo in patients with T2DM who had either a previous CV event or CV risk factors. A total of 31.5% of patients reported previous CV disease and 22.2% had baseline estimated glomerular filtration rate (eGFR) < 60 mL/min per 1.73 m^2. The median follow-up was 5.4 years. The primary composite outcome (CV death, non-fatal MI, or non-fatal stroke) occurred 12.0% of patients in the dulaglutide group vs 13.4% in the placebo group (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.79 to 0.99; p = 0.026). All-cause mortality did not differ between groups (10.8% in the dulaglutide group vs 12.0% in the placebo group (HR, 0.90; 95% CI 0.80 to 1.01; p = 0.067). The rates of death from CV causes, nonfatal MI, and hospitalization for heart failure did not differ significantly between groups, while non-fatal MI was statistically significantly different in favor of dulaglutide (*Gerstein et al 2019*).
- A MC, DB, PC, RCT (EXSCEL trial; N = 14,752) was conducted to evaluate the long-term effects of exenatide ER vs placebo, as added to usual care, on CV outcomes in patients with T2DM with or without previous CV disease. A total of 73.1% of patients had previous CV disease, and the median follow-up was 3.2 years. A primary composite outcome event (CV death, non-fatal MI, or non-fatal stroke) occurred in 11.4% of patients in the exenatide ER group vs 12.2% in the placebo group (HR, 0.91; 95% CI, 0.83 to 1.00). Thus, exenatide ER was found to be noninferior to placebo with respect to safety (p < 0.001), but not superior to placebo with respect to efficacy (p = 0.06). The risk of death from any cause was 6.9% vs 7.9% in the exenatide ER and placebo groups, respectively (HR, 0.86; 95% CI, 0.77 to 0.97); the difference was not statistically significant on the basis of the hierarchical testing plan. The rates of death from CV causes, nonfatal MI, nonfatal stroke, and hospitalization for heart failure did not differ significantly between groups (*Holman et al 2017*).
- A MC, DB, PC, RCT (LEADER trial; N = 9340) was conducted to evaluate the long-term effects of liraglutide vs placebo on CV outcomes in patients with T2DM and high CV risk. The median follow-up was 3.8 years. It was found that the primary composite outcome (CV death, non-fatal MI, or non-fatal stroke) occurred in fewer patients in the liraglutide group (13.0%) vs the placebo group (14.9%) (HR, 0.87; 95% CI, 0.78 to 0.97; p < 0.001 for noninferiority; p = 0.01 for superiority). Fewer patients died from CV causes in the liraglutide group (4.7%) vs the placebo group (6.0%) (HR, 0.78; 95% CI, 0.66 to 0.93; p = 0.007). The rate of death from any cause was lower in the liraglutide group (8.2%) vs the placebo group (9.6%) (HR, 0.85; 95% CI, 0.74 to 0.97; p = 0.02). The rates of nonfatal MI, nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group (*Marso et al 2016a*).
  - A prespecified secondary analysis found that the composite renal outcome (new-onset persistent macroalbumineria, persistent doubling of serum creatinine level, end-stage renal disease, and death due to renal disease) occurred in fewer patients in the liraglutide group vs the placebo group (5.7% vs 7.2%; HR, 0.78; 95% CI, 0.67 to 0.92; p = 0.003) (*Mann et al 2017*).
  - Post-hoc analyses of the LEADER trial have reported that the risk reduction in the primary outcome was consistent in patients with CKD (HR, 0.69; 95% CI, 0.57 to 0.85), a history of a MI or stroke (HR, 0.85; 95% CI, 0.73 to 0.99), and established atherosclerotic cardiovascular disease (ASCVD) (without a MI/stroke) (HR, 0.76; 95% CI, 0.62 to 0.94) (*Mann et al 2018, Verma et al 2018*).

- The risk of acute gallbladder or biliary disease was increased with liraglutide vs placebo (HR, 1.60; 95% CI, 1.23 to 2.09) *(Nauck et al 2019)*.

- A MC, DB, PC, RCT (ELIXA trial; N = 6068) evaluated the long-term effects of lixisenatide vs placebo on CV outcomes in patients with T2DM who had a recent acute coronary syndrome (ACS) event within 180 days of screening. The median follow-up was 25 months. It was found that the primary endpoint event (a composite of the first occurrence of any of the following: death from CV causes, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina) occurred in 13.4% of patients in the lixisenatide group and 13.2% in the placebo group (HR, 1.02; 95% CI, 0.89 to 1.17), which demonstrated noninferiority of lixisenatide to placebo ($p < 0.001$), but did not demonstrate superiority ($p = 0.81$). The rates of the individual CV components of the primary endpoint were similar between the lixisenatide and placebo groups (*Pfeffer et al 2015*).
- *Marso et al 2016b* conducted a MC, DB, PC, RCT (SUSTAIN 6 trial; N = 3297) to assess the noninferiority of semaglutide as compared to placebo in terms of CV safety in patients with T2DM, 83.0% of whom had CV disease. Patients were randomized to semaglutide 0.5 mg or 1.0 mg once weekly or placebo. The median observation time was 2.1 years. The primary composite outcome was the first occurrence of CV death, nonfatal MI, or nonfatal stroke. The noninferiority margin was 1.8 for the upper boundary of the 95% CI of the HR.
  - The primary composite outcome occurred in 6.6% of the semaglutide group vs 8.9% of the placebo group (HR: 0.74 [95%CI, 0.58 to 0.95]; $p < 0.001$ for noninferiority). Although a p value of 0.02 for superiority was calculated; testing for superiority was not prespecified. Nonfatal stroke occurred in 1.6% in the semaglutide group vs 2.7% in the placebo group (HR: 0.61 [95% CI, 0.38 to 0.99]; $p = 0.04$). Rates of nonfatal MI, CV death, and all-cause death were not statistically significantly different between groups.
  - Rates of new or worsening nephropathy were lower in the semaglutide group, but rates of retinopathy complications were significantly higher (3.0% for semaglutide vs 1.8% for placebo, HR: 1.76 [95% CI, 1.11 to 2.78]; $p = 0.02$).
- A MC, DB, PC, RCT (Harmony Outcomes trial; N=9463) evaluated the long-term effects of the previously available GLP-1 receptor agonist, albiglutide, vs placebo on CV outcomes in patients with T2DM and established CV disease. The median follow-up was 1.6 years. The primary endpoint (a composite of the first occurrence of any of the following: death from CV causes, MI, or stroke) occurred in 7% of patients in the albiglutide group and 9% in the placebo group (HR, 0.78; 95% CI, 0.68 to 0.90), which demonstrated noninferiority and superiority of albiglutide to placebo ($p < 0.0001$ for noninferiority; $p = 0.0006$ for superiority). The rate of fatal or non-fatal stroke was significantly improved in the albiglutide group, but other individual CV components of the primary endpoint were nonsignificantly lower in the albiglutide group than in the placebo group (*Hernandez et al 2018*).

Meta-analyses

- Meta-analyses and Cochrane Reviews evaluating GLP-1 receptor agonists have found that they lead to decreases in HbA1c of ~1%, with greater decreases in body weight and systolic blood pressure compared to placebo and other antidiabetic agents (*Wang et al 2013, Shyangdan et al 2011, Sun et al 2015*).
- A systematic review and mixed-treatment comparison analysis of GLP-1 receptor agonists found that there were no differences in efficacy within the short-acting (exenatide or lixisenatide) or long-acting (albiglutide, dulaglutide, exenatide ER, liraglutide) groups. However, dulaglutide, liraglutide, and exenatide ER were superior to exenatide and lixisenatide at lowering HbA1c and FPG. There were no clinically meaningful differences between agents in weight loss or hypoglycemia. Albiglutide had the lowest risk of nausea and diarrhea, while exenatide ER had the lowest risk of vomiting (*Htike et al 2016*).
- A systematic review and network meta-analysis sponsored by the manufacturer of semaglutide (Novo Nordisk) found that in patients with T2DM who were inadequately controlled on 1 to 2 OADs, semaglutide 1.0 mg was associated with significantly greater reductions in HbA1c and weight vs all GLP-1 receptor agonist comparators after 6 months of treatment, while the 0.5 mg dose achieved statistically significant reductions in HbA1c and weight vs the majority of other GLP-1 receptor agonists (*Witkowski et al 2018a*). Similar results were found in another Novo Nordisk-sponsored systematic review of trials in patients previously receiving basal insulin (*Witkowski et al 2018b*).
- Meta-analyses have revealed that incretin-based therapies are not associated with an increased risk of pancreatitis and appear to reduce all-cause mortality, CV mortality, and the incidence of MI compared to placebo or other antidiabetic agents. However, treatment with GLP-1 receptor agonists was associated with a significant increase in the incidence of cholelithiasis (*Monami et al 2017a*, *Monami et al 2017b)*.
- A meta-analysis found that overall, GLP-1 receptor agonists did not appear to be associated with an increase in the incidence of retinopathy, and there was a reduction in the incidence of nephropathy vs comparators (*Dicembrini et al 2017*).

- A meta-analysis found that treatment with exenatide ER did not increase the risk of cardiovascular events compared with placebo or active comparators, and may reduce the risk of all-cause mortality *(Bonora et al 2019)*.

Pramlintide

- The safety and efficacy of pramlintide in patients with T1DM have been established in PC, RCTs when administered in addition to existing insulin regimens. In a 52-week, DB, MC, PC study, pramlintide significantly reduced HbA1c from baseline compared to placebo (-0.39% vs -0.12%; p = 0.0071) and was also associated with a significant weight loss compared to placebo (p < 0.001) (*Whitehouse et al 2002*). In a second 52-week study, patients experienced a significant reduction in HbA1c when receiving pramlintide 60 mcg 3 times daily (-0.41 vs -0.18%; p = 0.012) and pramlintide 60 mcg 4 times daily (-0.39 vs -0.18%; p = 0.013) at 26 weeks. Treatment with pramlintide 3 or 4 times daily continued to maintain reductions in HbA1c at 52 weeks compared to treatment with placebo (p = 0.011 and p = 0.001 for the 3- and 4 times daily dosing, respectively) (*Ratner et al 2004*).
- A systematic review and meta-analysis of 10 randomized, PC studies (N = 3297) evaluating the effect of pramlintide as adjunctive therapy to insulin in patients with T1DM found that, compared to placebo, pramlintide resulted in significant reductions in HbA1c (p < 0.001), total daily insulin dose (p = 0.024), mean mealtime insulin dose (p < 0.001), body weight (p < 0.001), and PPG (p = 0.002) (*Qiao et al 2017*).
- A systematic review and meta-analysis of 8 PC, RCTs assessed the effect of pramlintide in patients with T2DM and in obese patients without diabetes. Four T2DM studies (N = 930; 16 to 52 weeks duration) and 4 obesity studies (N = 686; 6 to 24 weeks duration) were included. Of the T2DM studies, 3 studies used meal-time placebo as the comparator while 1 study used rapid-acting insulin as the comparator. When endpoint data from all T2DM studies were combined, pramlintide was associated with a small but significant reduction in HbA1c (mean difference: -0.33% [95% CI, -0.51 to -0.14]; p = 0.0004). In the meta-analysis of the T2DM studies, patients on pramlintide were 1.52 times more likely to reach the HbA1c goal ≤ 7% than patients in the control group; however, this difference was not significant (p = 0.18). Pramlintide was associated with a significant change in body weight in patients with T2DM compared to the control group (-2.57 kg [95% CI, -3.44 to -1.70]; p < 0.00001) (*Singh-Franco et al 2011*).

CLINICAL GUIDELINES

- According to current clinical guidelines, metformin remains the cornerstone of most T2DM treatment regimens. If A1C remains above target with metformin alone and the patient does not have ASCVD or CKD, clinicians should consider combining metformin with any one of the following: a sulfonylurea, TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or basal insulin. The choice of which agent to add is based on drug-specific effects and patient factors. Clinical guidelines note a lower rate of hypoglycemia, established efficacy and safety profile when used in combination with metformin, demonstrated effectiveness in reducing PPG, and the potential for weight loss as advantages associated with the incretin mimetics compared to other antidiabetic agents. The ADA guidelines recommend that lifestyle management and metformin should be initiated in patients with T2DM and established ASCVD. For patients in whom ASCVD, heart failure, or CKD predominates, the best choice for a second agent is a GLP-1 receptor agonist or SGLT2 inhibitor with demonstrated CV risk reduction. The GLP-1 receptor agonist with the strongest evidence for a CV benefit is liraglutide, followed by semaglutide, then exenatide ER. For all patients who require further intensification to injectable agents, a GLP-1 receptor agonist should be the first choice, ahead of insulin. Current clinical guidelines do not support the use of amylinomimetics in the management of T2DM. Among T1DM patients, there is limited evidence available to support the routine use of adjunctive therapies, including pramlintide, to insulin therapy (*ADA 2019, Chiang et al 2018, Davies et al 2018, Garber et al 2019, Inzucchi et al 2015, LeRoith 2019*).
- The American College of Cardiology (ACC) published an expert consensus decision pathway for patients with T2DM and ASCVD (*Das 2018*). It focuses on the use of SGLT2 inhibitors and GLP-1 receptor agonists in appropriate patients to reduce adverse CV outcomes. For the GLP-1 receptor agonists, liraglutide is the only agent in the class with definitive proven benefits of reducing CV events. In contrast, lixisenatide is not associated with a reduction in ASCVD event risk. Thus, both the ACC pathway and ADA guideline consider liraglutide as the preferred GLP-1 receptor agonist in patients with established ASCVD (*ADA 2019, Das 2018*).

SAFETY SUMMARY

- GLP-1 receptor agonists are contraindicated in patients with hypersensitivity to any component of the products. With the exception of exenatide and lixisenatide, they are also contraindicated in those with a personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome, type 2 (MEN 2).

- All GLP-1 receptor agonists, except exenatide and lixisenatide, carry a boxed warning for risk of thyroid C-cell tumors. Other safety risks include pancreatitis (including fatal and non-fatal hemorrhagic or necrotizing pancreatitis), serious hypersensitivity reactions, immunogenicity, serious hypoglycemia when used in combination with SFUs or insulin, and renal impairment. Liraglutide and exenatide ER have a warning for acute gallbladder disease. Semaglutide carries a warning for diabetic retinopathy complications due to the results of the SUSTAIN 6 trial, which found a higher rate of events in patients treated with semaglutide vs placebo; the absolute risk was larger among patients with a history of diabetic retinopathy at baseline compared to those without. Common AEs with these drugs include: nausea, diarrhea, vomiting, headache, and injection site reactions.
- Pramlintide is contraindicated in patients with hypersensitivity to any component of the drug and in those with hypoglycemia unawareness and confirmed gastroparesis. It has a boxed warning for increased risk of hypoglycemia, particularly in patients with T1DM. Common AEs include nausea, headache, anorexia, and vomiting; the incidence of nausea tends to be higher at the beginning of treatment and decreases with time in most patients. Gradual titration of the dose minimizes the incidence and severity of nausea.
- Pramlintide is Pregnancy Category C. Dulaglutide, exenatide, exenatide ER, liraglutide, semaglutide, and lixisenatide are uncategorized in accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR).
  - There are no adequate and well-controlled studies in pregnant women. These drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether these drugs are excreted in human milk.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Adlyxin (lixisenatide)	Injection	SC	Once daily	Inject in the abdomen, thigh, or upper arm. Administer within 1 hour before the first meal of the day, preferably the same meal each day.
Bydureon (exenatide ER)	Injection	SC	Once weekly	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food. Administer immediately after the powder is suspended.
Bydureon BCise (exenatide ER)	Injection	SC	Once weekly	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food. Administer immediately after the autoinjector is prepared.
Byetta (exenatide)	Injection	SC	Twice daily	Inject in the thigh, abdomen, or upper arm. Inject within 60 minutes prior to the morning and evening meals (or before the 2 main meals of the day, approximately 6 hours or more apart).
Ozempic (semaglutide)	Injection	SC	Once weekly	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food.
Symlin (pramlintide)	Injection	SC	Prior to major meals	Inject in the thigh or abdomen. Administer immediately prior to each major meal. Reduce mealtime insulin doses by 50%. Adjust insulin doses to optimize glycemic control once the target dose

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				of pramlintide is achieved and nausea (if experienced) has subsided. The dose should be decreased if significant nausea persists.
Trulicity (dulaglutide)	Injection	SC	Once weekly	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food.
Victoza (liraglutide)	Injection	SC	Once daily	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food.

CONCLUSION

- The GLP-1 receptor agonists exenatide, exenatide ER, dulaglutide, lixisenatide, and semaglutide are incretin-based antidiabetic therapies that are FDA-approved as adjunctive therapy to diet and exercise in adult patients with T2DM; liraglutide is approved for patients 10 years and older. Additionally, liraglutide is indicated to reduce the risk of major adverse CV events in patients with established CV disease. Pramlintide is the only agent within the amylinomimetic medication class and is FDA-approved as adjunctive therapy in patients with T1DM or T2DM who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.
- The incretin mimetics are available as SC injections to be administered in the abdomen, thigh, or upper arm. Exenatide is administered twice daily (60 minutes prior to meals); liraglutide is administered once daily (independent of meals); and lixisenatide is administered once daily (1 hour prior to the first meal of the day). Exenatide ER, dulaglutide, and semaglutide are administered once weekly. Pramlintide is available as a SC injection to be administered immediately prior to each major meal.
- The incretin mimetics have been studied extensively in combination with, and in comparison to, a variety of antidiabetic therapies. The agents are significantly more effective than placebo in reducing HbA1c, FPG, PPG, and body weight. Efficacy data comparing treatment to an SFU, TZD, DPP-4 inhibitor or insulin is mixed, with the GLP-1 agonists achieving significantly greater or comparable benefits in glycemic outcomes.
- Several CV outcomes trials evaluating GLP-1 receptor agonists in patients with T2DM and high CV risk have been published. The LEADER, Harmony Outcomes, and REWIND trials demonstrated a statistically significant CV risk reduction with liraglutide, albiglutide, and dulaglutide, respectively, vs placebo (*Gerstein et al 2019, Hernandez et al 2018, Marso et al 2016a*), whereas the ELIXA trial did not demonstrate a statistically significant difference between lixisenatide vs placebo (*Pfeffer et al 2015*) and the EXSCEL trial did not demonstrate a statistically significant difference between exenatide ER vs placebo (*Holman et al 2017*). Although the risk of MACE was lower with semaglutide vs placebo in the SUSTAIN 6 trial, a superiority analysis was not prespecified (*Marso et al 2016b*).
- Overall, the AE profiles of the GLP-1 receptor agonists are similar. With the exception of lixisenatide and exenatide, all of the agents have a boxed warning regarding the risk of thyroid C-cell tumors. Other warnings include increased risks of pancreatitis (including fatal and non-fatal hemorrhagic or necrotizing pancreatitis), serious hypersensitivity reactions, immunogenicity, serious hypoglycemia when used in combination with SFUs or insulin, and renal impairment. Liraglutide and exenatide ER also have a warning for acute gallbladder disease, while semaglutide has a warning for diabetic retinopathy complications.
- According to current clinical guidelines, metformin remains the cornerstone of most T2DM treatment regimens. If A1C remains above target with metformin alone and the patient does not have ASCVD or CKD, clinicians should consider combining metformin with any one of the following: a sulfonylurea, TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or basal insulin. The choice of which agent to add is based on drug-specific effects and patient factors. Clinical guidelines note a lower rate of hypoglycemia, established efficacy and safety profile when used in combination with metformin, demonstrated effectiveness in reducing PPG, and the potential for weight loss as advantages associated with the incretin mimetics compared to other antidiabetic agents. The ADA guidelines recommend that lifestyle management and metformin should be initiated in patients with T2DM and established ASCVD. For patients in whom ASCVD, heart failure, or CKD predominates, the best choice for a second agent is a GLP-1 receptor agonist or SGLT2 inhibitor with demonstrated CV risk reduction. The GLP-1 receptor agonist with the strongest evidence for a CV benefit is liraglutide, followed by semaglutide, then exenatide ER. For all patients who require further intensification to injectable agents, a GLP-1 receptor agonist should be the first choice, ahead of insulin. Current clinical guidelines do not

support the use of amylinomimetics in the management of T2DM. Among T1DM patients, there is limited evidence available to support the routine use of adjunctive therapies, including pramlintide, to insulin therapy (*ADA 2019, Chiang et al 2018, Davies et al 2018, Garber et al 2019, Inzucchi et al 2015, LeRoith 2019*).

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INTRODUCTION

- Epilepsy is a disease of the brain defined by any of the following (*Fisher et al 2014*):
  - At least 2 unprovoked (or reflex) seizures occurring > 24 hours apart;
  - 1 unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after 2 unprovoked seizures, occurring over the next 10 years;
  - Diagnosis of an epilepsy syndrome.
- Types of seizures include generalized seizures, focal (partial) seizures, and status epilepticus (*Centers for Disease Control and Prevention [CDC] 2018, Epilepsy Foundation 2016*).
  - Generalized seizures affect both sides of the brain and include:
    - Tonic-clonic (grand mal): begin with stiffening of the limbs, followed by jerking of the limbs and face
    - Myoclonic: characterized by rapid, brief contractions of body muscles, usually on both sides of the body at the same time
    - Atonic: characterized by abrupt loss of muscle tone; they are also called drop attacks or akinetic seizures and can result in injury due to falls
    - Absence (petit mal): characterized by brief lapses of awareness, sometimes with staring, that begin and end abruptly; they are more common in children than adults and may be accompanied by brief myoclonic jerking of the eyelids or facial muscles, a loss of muscle tone, or automatisms.
  - Focal seizures are located in just 1 area of the brain and include:
    - Simple: affect a small part of the brain; can affect movement, sensations, and emotion, without a loss of consciousness
    - Complex: affect a larger area of the brain than simple focal seizures and the patient loses awareness; episodes typically begin with a blank stare, followed by chewing movements, picking at or fumbling with clothing, mumbling, and performing repeated unorganized movements or wandering; they may also be called “temporal lobe epilepsy” or “psychomotor epilepsy”
    - Secondarily generalized seizures: begin in 1 part of the brain and spread to both sides
  - Status epilepticus is characterized by prolonged, uninterrupted seizure activity.
- Seizure classifications from the International League against Epilepsy (ILAE) were updated in 2017. The ILAE classification of seizure types is based on whether the seizure has a focal, generalized, or unknown onset; has a motor or non-motor onset; and whether the patient is aware or has impaired awareness during the event (for focal seizures). Additional classification details may also be used (*Fisher et al 2017A, Fisher et al 2017B*).
  - There is variation between the ILAE classifications and many of the Food and Drug Administration (FDA)-approved indications for antiepileptic drugs (AEDs). For example, a “focal aware” seizure corresponds to the prior term “simple partial seizure,” and a “focal impaired awareness” seizure corresponds to the prior term “complex partial seizure.”
- A number of epilepsy syndromes have also been described; these are defined by groups of features that tend to occur together such as having a similar seizure type, age of onset, part of the brain involved, and electroencephalogram (EEG) pattern (*Epilepsy Foundation 2013*). An example is a childhood epilepsy syndrome called Lennox-Gastaut syndrome (LGS), which is characterized by several seizure types including tonic (stiffening) and atonic (drop) seizures. In LGS, there is a classic EEG pattern seen and intellectual development is usually impaired (*Epilepsy Foundation 2014*).
- Epilepsy management is focused on the goals of 1) controlling seizures, 2) avoiding treatment-related adverse effects (AEs), and 3) maintaining or restoring quality of life. Management options vary based on the seizure type. It is usually appropriate to refer patients to a neurologist to establish the epilepsy diagnosis and formulate the management strategy (*Schachter 2019*).
  - A correct diagnosis is essential to proper treatment selection. For example, absence seizures are commonly confused with complex partial seizures. However, drugs that reduce absence seizures are generally ineffective for complex partial seizures, and the most effective drugs for complex partial seizures may be ineffective against or even increase the frequency of absence seizures (*Epilepsy Foundation 2016*).

- When possible, monotherapy with a single AED is the preferred treatment approach. Combination therapy may be associated with decreased patient adherence to therapy and an increased incidence of AEs and drug interactions. When combination therapy is needed, it is recommended to select products with different mechanisms of action and AE profiles. There is little comparative clinical data to support the use of specific combinations (*Schachter et al 2019*).
- Several broad classes of AEDs are available, including barbiturates, benzodiazepines, hydantoins, and miscellaneous agents (see Table 1).
- Cannibidiol (Epidiolex) was FDA-approved in June 2018 for use in pediatric patients 2 years of age and older with LGS or Dravet syndrome (*FDA news release 2018*). It is the first FDA-approved drug for treatment of patients with Dravet syndrome and is the first approved drug that contains a purified substance, cannabidiol, derived from marijuana. Cannabidiol is a schedule V controlled substance (*Epidiolex prescribing information 2018*).
- Stiripentol (Diacomit) capsules and powder for oral suspension were FDA-approved in August 2018 for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam.
- Everolimus tablets for oral suspension (Afinitor Disperz) received an expanded indication in April 2018 for use in partial-onset seizures associated with tuberous sclerosis complex (TSC). This product is a kinase inhibitor that also has several oncology indications.
- Midazolam nasal spray (Nayzilam) was approved in May 2019 for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 12 years of age (*Nayzilam prescribing information 2019*).
- Several of the AEDs are used for additional indications beyond the management of epilepsy, including (but not limited to) bipolar disorder, migraine prophylaxis, and several types of neuropathic pain. These additional indications are listed in Table 2; however, this review primarily focuses on the use of AEDs for the management of epilepsy. Additionally, brands and formulations FDA-approved and marketed only for non-epilepsy indications are not included within this review; these include gabapentin tablets (Gralise), FDA-approved only for the management of postherpetic neuralgia, gabapentin enacarbil extended-release tablets (Horizant), FDA-approved only for management of postherpetic neuralgia and treatment of moderate-to-severe restless leg syndrome, and pregabalin extended-release tablets (Lyrica CR), FDA-approved only for the management of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia.
- Medispan class: Antianxiety agents, benzodiazepines; Anticonvulsants, AMPA glutamate receptor antagonists; Anticonvulsants, anticonvulsants – misc; Anticonvulsants, carbamates; Anticonvulsants, GABA modulators; Anticonvulsants, hydantoins; Anticonvulsants, succinimides; Anticonvulsants, valproic acid; Hypnotics/Sedatives/Sleep Disorder Agents, barbiturate hypnotics

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Barbiturates	
Pentobarbital (Nembutal)	✔
Phenobarbital* (Luminal†, Solfoton†)	✔
Primidone (Mysoline)	✔
Benzodiazepines	
Clobazam (Onfi; Sympazan)	✔ ***
Clonazepam (Klonopin§)	✔
Clorazepate (Tranxene T-Tab§)	✔
Diazepam (Diastat¶, Valium§)	✔ ‖
Midazolam (Nayzilam)	-
Hydantoins	
Ethotoin (Peganone)	-
Fosphenytoin (Cerebyx)	✔
Phenytoin (Dilantin§, Phenytek)	✔ ‖
Miscellaneous	
Brivaracetam (Briviact)	-
Cannabidiol (Epidiolex)	-
Carbamazepine (Carbatrol, Epitol**, Equetro, Tegretol§, Tegretol-XR)	✔

Drug	Generic Availability
Divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)	✔
Eslicarbazepine (Aptiom)	-
Ethosuximide (Zarontin)	✔
Everolimus (Afinitor Disperz)	-
Felbamate (Felbatol)	✔
Gabapentin (Neurontin)	✔
Lacosamide (Vimpat)	-
Lamotrigine (Lamictal, Lamictal ODT, Lamictal XR, Subvenite**)	✔
Levetiracetam (Keppra, Keppra XR, Roweepra**, Roweepra XR**, Spritam, Elepsia XR)	✔ ‖
Methsuximide (Celontin)	-
Oxcarbazepine (Oxtellar XR, Trileptal)	✔ ‖
Perampanel (Fycompa)	-
Pregabalin (Lyrica)	✔
Rufinamide (Banzel)	-
Stiripentol (Diacomit)	-
Tiagabine (Gabitril)	✔ ‖
Topiramate (Topamax, Topamax Sprinkle, Topiragen††, Trokendi XR, Qudexy XR¶)	✔ ‖
Valproic acid (Depacon, Depakene)	✔ ‖
Vigabatrin (Sabril, Vigadrone**)	✔ ‖
Zonisamide (Zonegran§)	✔

* Not FDA approved
† Brand product not currently marketed; generic is available
§ Brand marketing status may vary by strength and/or formulation
‖ Generic availability may vary by strength and/or formulation
¶ Authorized generic available; no A-rated generics approved via abbreviated new drug application
** Branded generic
†† Branded generic; not currently marketed
***Generic available for Onfi tablets and oral suspension; only brand name available for Sympazan oral film.
(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

- Tables 2A and 2B provide an overview of anticonvulsant indications. Except where noted, only FDA-approved products and indications are included. For items marked with an asterisk, there is additional information about the indication provided in the box following the tables.
- Acute-care indications that are not related to convulsive disorders (for example, pre-procedural use of benzodiazepines in hospital settings) are not included.

Table 2A. Indications for anticonvulsants (Part 1 of 2)

Indications	Brivaracetam	Cannabidiol	Carbamazepine	Clobazam	Clonazepam	Clorazepate	Diazepam	Divalproex Sodium	Eslicarbazepine	Ethosuximide	Ethotoin	Everolimus	Felbamate	Fosphenytoin	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam
Partial seizures (simple partial, complex partial and/or secondarily generalized)	✔ *		✔ *			A		✔, A*	✔, A*		✔ *		✔, A*		A*	✔ *	✔, A*	A*
Primary generalized tonic-clonic seizure (grand mal)			✔								✔			✔ *			A*	A*
Absence seizure (petit mal)					✔ *			✔, A*		✔								
Multiple seizure types that include absence seizures								A										
Seizures of Lennox-Gastaut syndrome (LGS)		✔ *		A*	✔, A								A*				A*	
Seizures of Dravet syndrome		✔ *																
Juvenile myoclonic epilepsy (JME)																		A*
Emergency/acute/short-term use for seizure control (see notes)							✔ *							✔ *				
Akinetic and myoclonic seizures					✔, A													
Convulsive disorders (see notes)							A*											
Certain mixed seizure patterns or other partial or generalized seizures			✔ *															
Migraine prophylaxis								✔ *										
Trigeminal neuralgia			✔ *															
Postherpetic neuralgia															✔ *			
Bipolar disorder			✔ *					✔ *									✔ *	
Panic disorder, with or without agoraphobia					✔													
Anxiety disorder; short-term relief of anxiety symptoms						✔	✔											
Symptomatic relief of acute alcohol withdrawal						✔	✔											

Indications	Brivaracetam	Cannabidiol	Carbamazepine	Clobazam	Clonazepam	Clorazepate	Diazepam	Divalproex Sodium	Eslicarbazepine	Ethosuximide	Ethotoin	Everolimus	Felbamate	Fosphenytoin	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam
Relief of skeletal muscle spasm, spasticity, athetosis, and stiff-man syndrome							A											
Partial-onset seizures associated with tuberous sclerosis complex (TSC)												A*						

✓ = monotherapy (or not specified); A = adjunctive therapy

Table 2B. Indications for Anticonvulsants (Part 2 of 2)

Indications	Midazolam	Methsuximide	Oxcarbazepine	Pentobarbital	Perampanel	Phenobarbital†	Phenytoin	Pregabalin	Primidone	Rufinamide	Stiripentol	Tiagabine	Topiramate	Valproic acid	Vigabatrin	Zonisamide
Partial seizures (simple partial, complex partial and/or secondarily generalized)			✓, A*		✓*		✓*	A*	✓, A*			A*	✓, A*	✓, A*	A*	A*
Primary generalized tonic-clonic seizure (grand mal)					A*		✓*		✓, A*				✓, A*			
Absence seizure (petit mal)		✓*												✓, A*		
Multiple seizure types which include absence seizures														A*		
Seizures of LGS										A*			A*			
Seizures of Dravet syndrome											A*					
Emergency/acute/ short-term use for seizure control (see notes)	✓*			✓*			✓*									
Infantile spasms															✓*	
Convulsive disorders (see notes)						✓*										
Migraine prophylaxis													✓*	✓*		

Indications	Midazolam	Methsuximide	Oxcarbazepine	Pentobarbital	Perampanel	Phenobarbital†	Phenytoin	Pregabalin	Primidone	Rufinamide	Stiripentol	Tiagabine	Topiramate	Valproic acid	Vigabatrin	Zonisamide
Postherpetic neuralgia								✔								
Bipolar disorder														✔*		
Sedative for anxiety, tension, and apprehension																
Neuropathic pain associated with diabetic peripheral neuropathy								✔								
Neuropathic pain associated with spinal cord injury								✔								
Fibromyalgia								✔								

✓ = monotherapy (or not specified); A = adjunctive therapy
†Phenobarbital is not approved by the FDA.

***Notes: Additional Detail on Selected Anticonvulsant Indications**

- **Brivaracetam**:
  - Treatment of partial-onset seizures in patients ≥ 4 years of age (oral formulations); ≥ 16 years of age (IV formulation)
- **Cannabidiol**:
  - Treatment of seizures associated with LGS or Dravet syndrome in patients ≥ 2 years of age
- **Carbamazepine**:
  - Partial seizures with complex symptomatology (psychomotor, temporal lobe); patients with these seizures appear to show greater improvement than those with other types; generalized tonic-clonic seizures (grand mal); mixed seizure patterns which include the above, or other partial or generalized seizures
  - Absence seizures do not appear to be controlled; carbamazepine has been associated with increased frequency of generalized convulsions in these patients
  - Treatment of pain associated with true trigeminal neuralgia; beneficial results also reported in glossopharyngeal neuralgia
  - Bipolar indication is for an extended-release capsule formulation (Equetro) only: treatment of patients with acute manic or mixed episodes associated with bipolar I disorder
- **Clobazam**:
  - Seizures associated with LGS in patients aged ≥ 2 years
- **Clonazepam**:
  - In patients with absence seizures who have failed to respond to succinimides, clonazepam may be useful
- **Diazepam**:
  - Oral diazepam may be used adjunctively in convulsive disorders; it has not proved useful as sole therapy.
  - Rectal diazepam is indicated in the management of selected, refractory patients with epilepsy on stable regimens of AEDs who require intermittent use of diazepam to control bouts of increased seizure activity
  - Injectable diazepam is a useful adjunct in status epilepticus and severe recurrent convulsive seizures
- **Divalproex sodium**:
  - Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures (age ≥ 10 years for all formulations)

- Monotherapy and adjunctive therapy in the treatment of simple and complex absence seizures (age ≥ 10 years for extended-release tablets; age not specified for tablets/sprinkle capsules)
- The tablets and extended-release tablets have indications in bipolar disorder and migraine prophylaxis; the sprinkle capsule formulation does not. For bipolar disorder, safety and effectiveness for long-term use (> 3 weeks) has not been demonstrated in controlled clinical trials. Bipolar disorder indications are as follows:
  - Treatment of the manic episodes associated with bipolar disorder (tablets)
  - Treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features (extended-release tablets)

- **Eslicarbazepine**:
  - Treatment of partial-onset seizures in patients ≥ 4 years of age
- **Ethotoin**:
  - Complex partial (psychomotor) seizures
- **Everolimus:**
  - Adjunctive treatment of adult and pediatric patients ≥ 2 years of age with TSC-associated partial-onset seizures (tablets for oral suspension only)
- **Felbamate**:
  - Not first-line; recommended only in patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or renal failure is deemed acceptable
  - Monotherapy or adjunctive therapy in the treatment of partial seizures, with and without generalization, in adults with epilepsy
  - Adjunctive therapy of partial and generalized seizures associated with LGS in children (age not specified)
- **Fosphenytoin**:
  - Treatment of generalized tonic-clonic status epilepticus
  - Prevention and treatment of seizures occurring during neurosurgery
  - Can be substituted short-term for oral phenytoin when oral phenytoin administration is not possible
- **Gabapentin**:
  - Adjunctive therapy in the treatment of partial onset seizures, with and without secondary generalization, in adults and pediatric patients ≥ 3 years of age with epilepsy.
  - Management of postherpetic neuralgia in adults
- **Lacosamide**:
  - Treatment of partial-onset seizures in patients ≥ 4 years of age (tablet and oral solution)
  - Treatment of partial-onset seizures in patients ≥ 17 years of age (injection)
- **Lamotrigine immediate-release formulations**:
  - Age ≥ 2 years for adjunctive therapy for partial-onset seizures, primary generalized tonic-clonic seizures, and generalized seizures of LGS
  - Age ≥ 16 years for conversion to monotherapy in patients with partial-onset seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single AED
  - Maintenance treatment of bipolar disorder to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy (treatment of acute manic or mixed episodes is not recommended)
- **Lamotrigine extended-release tablets**:
  - Age ≥ 13 years for adjunctive therapy for primary generalized tonic-clonic seizures and partial onset seizures with or without secondary generalization, and age ≥13 years for conversion to monotherapy in patients with partial-onset seizures who are receiving treatment with a single AED
  - The extended-release formulation is not FDA-approved for bipolar disorder
- **Levetiracetam**:
  - Adjunctive therapy in the treatment of partial onset seizures in adults and children ≥ 1 month of age with epilepsy (age ≥ 4 years and weighing > 20 kg for the tablets for oral suspension [Spritam])
  - Adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents ≥ 12 years with JME
  - Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and children ≥ 6 years of age with idiopathic generalized epilepsy
  - The extended-release tablets are only indicated for adjunctive therapy in the treatment of partial-onset seizures in patients ≥ 12 years of age with epilepsy
- **Methsuximide**:

- Control of absence (petit mal) seizures that are refractory to other drugs
- **Midazolam nasal spray:**
  - Acute treatment of intermittent, stereotypic episodes of frequent seizure activity (ie, seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 12 years of age.
- **Oxcarbazepine immediate-release formulations**:
  - Monotherapy in the treatment of partial seizures in adults and children 4 to 16 years of age
  - Adjunctive therapy in the treatment of partial seizures in adults and children 2 to 16 years of age
- **Oxcarbazepine extended-release tablets**:
  - Treatment of partial-onset seizures in adults and children ≥ 6 years of age
- **Pentobarbital**:
  - In anesthetic doses in the emergency control of certain acute convulsive episodes, eg, those associated with status epilepticus, cholera, eclampsia, meningitis, tetanus, and toxic reactions to strychnine or local anesthetics
- **Perampanel**:
  - Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy ≥ 4 years of age
  - Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in patients with epilepsy ≥ 12 years of age
- **Phenobarbital (not FDA-approved)**:
  - Phenobarbital tablets are indicated for use as an anticonvulsant; the elixir is indicated for the treatment of generalized and partial seizures; the injection is indicated as an anticonvulsant for the treatment of generalized tonic-clonic and cortical focal seizures, in the emergency control of certain acute convulsive episodes, and in pediatric patients as an anticonvulsant
- **Phenytoin oral formulations**:
  - Treatment of tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery (the oral suspension does not have the neurosurgery indication)
- **Phenytoin injection**:
  - Treatment of generalized tonic-clonic status epilepticus and prevention and treatment of seizures occurring during neurosurgery
  - Can be substituted as short-term use for oral phenytoin when oral phenytoin administration is not possible
- **Pregabalin**:
  - Adjunctive therapy for treatment of partial onset seizures in patients ≥ 1 month of age
- **Primidone**:
  - Control of grand mal, psychomotor, and focal epileptic seizures; may control grand mal seizures refractory to other anticonvulsant therapy
- **Rufinamide**:
  - Adults and pediatric patients ≥ 1 year of age
- **Stiripentol**:
  - Treatment of seizures associated with Dravet syndrome in patients ≥ 2 years of age taking clobazam; no clinical data to support its use as monotherapy
- **Tiagabine**:
  - Adjunctive therapy in adults and children ≥ 12 years of age in the treatment of partial seizures
- **Topiramate**:
  - Initial monotherapy in patients with partial onset or primary generalized tonic-clonic seizures (age ≥ 2 years for tablets, immediate-release sprinkle capsules, and Qudexy XR extended-release capsules; age ≥ 6 years for Trokendi XR extended-release capsules)
  - Adjunctive therapy for adults and pediatric patients with partial onset seizures or primary generalized tonic-clonic seizures and in patients with seizures associated with LGS (age ≥ 2 years for tablets, immediate-release sprinkle capsules, and Qudexy XR extended-release capsules; age ≥ 6 years for Trokendi XR extended-release capsules)
  - Prophylaxis of migraine headache in patients ≥ 12 years of age
- **Valproic acid**:

- Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures (in adults and pediatric patients down 10 years) that occur either in isolation or in association with other types of seizures; sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types which include absence seizures

- **Vigabatrin**:
  - Refractory complex partial seizures as adjunctive therapy in patients ≥ 10 years of age who have responded inadequately to several alternative treatments; not indicated as a first-line agent
  - Infantile spasms as monotherapy in infants 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss
- **Zonisamide**:
  - Adjunctive therapy in the treatment of partial seizures in adults with epilepsy

- 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

- Overall, the anticonvulsants have demonstrated efficacy for their FDA-approved uses. Clinical trial data demonstrating efficacy of the anticonvulsants for the treatment of epilepsy is described in the prescribing information for the individual products, particularly for anticonvulsants more recently approved by the FDA. However, the prescribing information for some older, conventional products (eg, benzodiazepines, carbamazepine, ethotoin, ethosuximide, methsuximide, phenytoin, and primidone) and non-FDA approved products (eg, phenobarbital) do not contain efficacy data in their prescribing information.
- No single AED is clearly the most effective. Comparative efficacy data for the management of epilepsy are limited, and trials have generally not shown significant differences among drugs in terms of efficacy. However, the quality of the data is limited and generally derived from short-term trials (*Karceski 2019*).
- When possible, monotherapy with a single AED is the preferred treatment approach. Combination therapy may be associated with decreased patient adherence to therapy and an increased incidence of AEs and drug interactions. (*Schachter et al 2019*). Most patients with epilepsy are treated with anticonvulsant monotherapy (*Nevitt et al 2017*).
- An evidence review summarized AED efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes (*Glauser et al 2013*). This publication provides conclusions based on a review of 64 randomized trials and 11 meta-analyses. Conclusions include the following:
  - As initial monotherapy for adults with newly diagnosed or untreated partial-onset seizures:
    - Carbamazepine, levetiracetam, phenytoin, and zonisamide are established as efficacious/effective.
    - Valproate is probably efficacious/effective.
    - Gabapentin, lamotrigine, oxcarbazepine, phenobarbital, topiramate, and vigabatrin are possibly efficacious/effective.
    - Clonazepam and primidone are potentially efficacious/effective.
  - As initial monotherapy for children with newly diagnosed or untreated partial-onset seizures:
    - Oxcarbazepine is established as efficacious/effective.
    - Carbamazepine, phenobarbital, phenytoin, topiramate, valproate, and vigabatrin are possibly efficacious/effective.
    - Clobazam, carbamazepine, lamotrigine, and zonisamide are potentially efficacious/effective.
  - As initial monotherapy for elderly adults with newly diagnosed or untreated partial-onset seizures:
    - Gabapentin and lamotrigine are established as efficacious/effective.
    - Carbamazepine is possibly efficacious/effective.
    - Topiramate and valproate are potentially efficacious/effective.
  - As initial monotherapy for adults with newly diagnosed or untreated generalized-onset tonic-clonic seizures:
    - Carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate, and valproate are possibly efficacious/effective.
    - Gabapentin, levetiracetam, and vigabatrin are potentially efficacious/effective.
    - Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures.
  - For children with newly diagnosed or untreated generalized-onset tonic-clonic seizures:
    - Carbamazepine, phenobarbital, phenytoin, topiramate, and valproate are possibly efficacious/effective.

        - Oxcarbazepine is potentially efficacious/effective.
        - Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures.
    - As initial monotherapy for children with newly diagnosed or untreated absence seizures:
        - Ethosuximide and valproate are established as efficacious/effective.
        - Lamotrigine is possibly efficacious/effective.
        - Gabapentin is established as inefficacious/ineffective.
        - Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, tiagabine, and vigabatrin may precipitate or aggravate absence seizures (based on scattered reports).
    - As initial monotherapy for children with benign childhood epilepsy with centrotemporal spikes (BECTS):
        - Carbamazepine and valproate are possibly efficacious/effective.
        - Gabapentin, levetiracetam, oxcarbazepine, and sulthiame (not available in the United States) are potentially efficacious/effective.
    - For patients with newly diagnosed JME:
        - Topiramate and valproate are potentially efficacious/effective.
        - Carbamazepine, gabapentin, oxcarbazepine, phenytoin, tiagabine, and vigabatrin may precipitate or aggravate absence, myoclonic, and in some cases generalized tonic-clonic seizures. There has also been a report that lamotrigine may exacerbate seizures in JME.
    - There is a lack of well-designed randomized trials in epilepsy, particularly for generalized seizures and in the pediatric population.
- A Cochrane systematic review evaluated the efficacy of AED monotherapy for epilepsy (*Nevitt et al 2017*). The review included the use of carbamazepine, phenytoin, valproate, phenobarbital, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, and zonisamide for the treatment of partial onset seizures (simple partial, complex partial or secondarily generalized) or generalized tonic-clonic seizures with or without other generalized seizure types.
    - This network meta-analysis showed that for the primary outcome, the time to withdrawal of allocated treatment:
        - For individuals with partial seizures, levetiracetam performed better than carbamazepine and lamotrigine; lamotrigine performed better than all other treatments (aside from levetiracetam); and carbamazepine performed better than gabapentin and phenobarbital.
        - For individuals with generalized onset seizures, valproate performed better than carbamazepine, topiramate and phenobarbital.
        - For both partial and generalized onset seizures, phenobarbital seems to perform worse than all other treatments.
    - For the secondary outcome, time to first seizure:
        - For individuals with partial seizures, phenobarbital performed better than both carbamazepine and lamotrigine; carbamazepine performed better than valproate, gabapentin, and lamotrigine; and phenytoin performed better than lamotrigine.
        - For both partial and generalized seizure types, phenytoin and phenobarbital generally performed better than other treatments.
    - Few notable differences were shown for either partial or generalized seizure types for the secondary outcomes of time to 6-month or 12-month remission of seizures.
    - Overall, direct evidence and network meta-analysis estimates were numerically similar, and effect sizes had overlapping confidence intervals.
    - Data for individuals with generalized seizures are still limited and additional randomized trials are needed.
- The relative efficacy among valproate, lamotrigine, phenytoin, carbamazepine, ethosuximide, topiramate, levetiracetam, and phenobarbital as monotherapy for generalized (n = 7 studies) or absence seizures (n = 3 studies) was evaluated in a systematic review and network meta-analysis (*Campos et al 2018*). The outcomes analyzed were seizure freedom and withdrawal due to inefficacy. Compared to valproate, phenytoin had a lower odds of seizure freedom (odds ratio, 0.50; 95% credible Interval [CrI] 0.27 to 0.87) in patients with generalized tonic-clonic seizures. Lamotrigine had the highest probability of seizure freedom and valproate had the highest probability of withdrawal due to inefficacy in these patients. For absence seizures, ethosuximide and valproate were found to have a higher probability of seizure freedom compared to lamotrigine.
- A meta-analysis estimated the comparative efficacy of achieving seizure freedom with 22 antiepileptic drugs and placebo in children and adolescents (*Rosati et al 2018*). For the treatment of newly diagnosed focal epilepsy (n = 4 studies), point estimates suggested superiority of carbamazepine and lamotrigine; however, this was not statistically

significant. For refractory focal epilepsy (n = 9 studies), levetiracetam and perampanel were more effective than placebo in mixed comparisons. Ethosuximide and valproic acid were more effective than lamotrigine for absence seizures. The authors concluded that better designed comparative studies with appropriate length of follow-up, well-defined outcomes, and reliable inclusion criteria are needed to validate these results.

- Approximately 20% to 40% of patients with epilepsy can be considered refractory to drug treatment, referred to as drug-resistant epilepsy. Treatment of drug-resistant epilepsy may include additional anticonvulsant drug trials, epilepsy surgery, vagal nerve stimulation, and dietary changes (the ketogenic diet) (*Sirven 2018*).
  - Combination AED regimens are an option for the treatment of drug-resistant epilepsy. However, robust clinical evidence of suitable combinations of AEDs has been difficult to generate due to the large number of possible combinations of drugs and doses. Examples of combinations for which there is some evidence of efficacy include valproate plus lamotrigine for partial-onset and generalized seizures, valproate plus ethosuximide for absence seizures, and lamotrigine plus topiramate for various seizure types; however, even this evidence is fairly limited. In general, when considering combination therapy, it is recommended to combine medications with different mechanisms of action, and to be mindful of the overall drug load to minimize AEs. Two-drug therapy should be attempted before considering addition of a third drug, and higher numbers of drugs should be avoided as they are associated with a very low likelihood of additional seizure reduction (*Kwan et al 2011*).
  - A meta-analysis examined the efficacy of newer AEDs (eslicarbazepine, brivaracetam, perampanel, and lacosamide) versus levetiracetam as adjunctive therapy for uncontrolled partial-onset seizures. Most patients in this meta-analysis were on at least 2 other AEDs at the time of treatment. In this analysis, eslicarbazepine, lacosamide, and brivaracetam were non-inferior to levetiracetam in terms of efficacy, but all newer AEDs except brivaracetam had worse tolerability profiles than levetiracetam at high doses (*Zhu et al 2017*).
  - A network meta-analysis examined the efficacy of AEDs (including brivaracetam, eslicarbazepine acetate, gabapentin, lacosamide, levetiracetam, lamotrigine, oxcarbazepine, pregabalin, perampanel, rufinamide, tiagabine, topiramate, vigabatrin, and zonisamide) for adjunctive use in patients with refractory partial-onset seizures while using monotherapy (*Zhao et al 2017*). The efficacy outcomes studied were 50% responder rate and state of seizure freedom. The authors concluded that topiramate, levetiracetam, pregabalin, and oxcarbazepine were preferable for their relatively high efficacy and low risk of AEs. Rufinamide was the least preferable medication due to its low efficacy and high risk of AEs.
  - A network meta-analysis was conducted to evaluate the efficacy of 17 newer AEDs for treatment of refractory partial-onset epilepsy with or without secondary generalization (*Hu et al 2018*). The primary outcome was seizure freedom, which was defined as a 100% seizure reduction in the maintenance or double-blind treatment period of the trial. Safety was assessed by the withdrawal rate due to treatment-emergent AEs. Based on results of 54 studies that evaluated the efficacy outcome, the most effective agents included tiagabine, brivaracetam, and valproic acid, and the least effective agents included rufinamide, lamotrigine, and zonisamide. Products with favorable safety included levetiracetam, brivaracetam, and perampanel, while those with the least favorable safety included retigabine (not available in the United States), oxcarbazepine, and rufinamide. The authors stated that agents with the best outcomes in terms of efficacy and safety included levetiracetam, vigabatrin, valproic acid, and brivaracetam.
  - Cannibidiol (Epidiolex) was approved in June 2018 for use in pediatric patients 2 years of age and older with LGS or Dravet syndrome (*FDA news release 2018*). It is the first FDA-approved drug for treatment of patients with Dravet syndrome and is the first approved drug that contains a purified substance, cannabidiol, derived from marijuana. Its approval for these 2 indications was based on 3 placebo-controlled trials in patients refractory to other treatments. Epidiolex, along with use of other agents, demonstrated a significant reduction in seizure frequency compared to placebo (*Thiele et al 2018*; *Devinsky et al* 2018; *Devinsky et al* 2017). To date, no comparative trials have been published.
  - Everolimus tablets for oral suspension (Afinitor Disperz) received an expanded indication for adjunctive use in TSC-associated partial-onset seizures in April 2018. Results of a randomized, double-blind, placebo-controlled study of 366 patients with inadequately controlled seizures on 2 or more AEDs demonstrated a significant reduction in seizure frequency compared to placebo (*French et al 2016*).
  - In August 2018, the FDA approved a second drug, stiripentol (Diacomit), for use in the treatment of seizures associated with Dravet syndrome. Two multicenter placebo-controlled studies evaluated the addition of stiripentol to clobazam and valproate therapy in patients 3 years to less than 18 years of age with Dravet syndrome. Responder rates (seizure frequency reduced by 50%) with respect to generalized tonic-clonic seizures were significantly lower with stiripentol compared to placebo (*Diacomit prescribing information 2018).*

- In May 2019, a nasal spray formulation of midazolam (Nayzilam) was approved for the acute treatment of cluster seizures in adults and adolescents. In one randomized controlled trial in patients with seizure clusters while receiving a stable AED regimen, the proportion of patients who experienced treatment success (seizure termination within 10 minutes and no recurrence for the next 6 hours) was significantly higher with midazolam nasal spray compared to placebo (53.7% vs 34.4%, p = 0.0109) with similar tolerability (*Detyniecki et al 2019*).

CLINICAL GUIDELINES

- **Efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy**. American Academy of Neurology and American Epilepsy Society (*French et al 2004A, Kanner et al, 2018A*).
  - A 2018 update to the 2004 guideline focuses on treatment of new-onset epilepsy with second and third generation AEDs. The 2004 publication summarizes the efficacy, tolerability, and safety of gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide for the treatment of children and adults with newly diagnosed partial and generalized epilepsies.
  - The recommendations from the 2004 guideline include the following:
    - Patients with newly diagnosed epilepsy who require treatment can be initially treated with standard AEDs such as carbamazepine, phenytoin, valproic acid, or phenobarbital, or on the newer AEDs lamotrigine, gabapentin, oxcarbazepine, or topiramate. Choice will depend on individual patient characteristics.
    - Lamotrigine can be included in the options for children with newly diagnosed absence seizures.
  - The 2018 recommendations include the following :
    - As monotherapy in adult patients with new-onset focal epilepsy or unclassified generalized tonic-clonic seizures:
      - Lamotrigine use should be considered to decrease seizure frequency.
      - Lamotrigine use should be considered and gabapentin use may be considered to decrease seizure frequency in patients aged ≥ 60 years.
      - Levetiracetam and zonisamide use may be considered to decrease seizure frequency.
      - Vigabatrin appears to be less efficacious than carbamazepine immediate-release and may not be offered; furthermore, the toxicity profile precludes vigabatrin use as first-line therapy.
      - Pregabalin 150 mg per day is possibly less efficacious than lamotrigine 100 mg per day.
      - There is insufficient evidence to consider use of gabapentin, oxcarbazepine, or topiramate over carbamazepine.
      - There is insufficient evidence to consider use of topiramate instead of phenytoin in urgent treatment of new-onset or recurrent focal epilepsy, unclassified generalized tonic-clonic seizures, or generalized epilepsy presenting with generalized tonic-clonic seizures.
      - Data are lacking to support or refute use of third-generation AEDs (eslicarbazepine, ezogabine [no longer marketed], lacosamide, perampanel, pregabalin, and rufinamide), clobazam, felbamate, or vigabatrin for new-onset epilepsy.
      - Data are lacking to support or refute use of newer AEDs in treating unclassified generalized tonic-clonic seizures.
    - Ethosuximide or valproic acid should be considered before lamotrigine to decrease seizure frequency in children with absence epilepsy. An exception would be if there are compelling AE-related concerns with use of ethosuximide or valproic acid.
    - The guideline does not address newly approved agents including cannabidiol, everolimus, or stiripentol.
- **Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy**. American Academy of Neurology and American Epilepsy Society (*Kanner et al 2018B*, *French et al 2004B*).
  - A 2018 update to the 2004 guideline focuses on management of treatment-resistant epilepsy with second and third generation AEDs. The 2004 publication summarizes the efficacy, tolerability, and safety of gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide for the treatment of children and adults with refractory partial and generalized epilepsies.
  - Recommendations from the 2004 guideline include the following:
    - It is appropriate to use gabapentin, lamotrigine, tiagabine, topiramate, oxcarbazepine, levetiracetam, and zonisamide as add-on therapy in patients with refractory epilepsy.

        - Oxcarbazepine, topiramate, and lamotrigine can be used as monotherapy in patients with refractory partial epilepsy.
        - Topiramate may be used for the treatment of refractory generalized tonic-clonic seizures in adults and children.
        - Gabapentin, lamotrigine, oxcarbazepine, and topiramate may be used as adjunctive treatment of children with refractory partial seizures.
        - Topiramate and lamotrigine may be used to treat drop attacks associated with LGS in adults and children.
    - Recommendations from the 2018 guideline include the following:
        - As adjunctive therapy in patients with treatment-resistant adult focal epilepsy (TRAFE):
            - Immediate-release pregabalin and perampanel are established as effective to reduce seizure frequency.
            - Lacosamide, eslicarbazepine, and extended-release topiramate should be considered to decrease seizure frequency.
            - Vigabatrin and rufinamide are effective for decreasing seizure frequency, but are not first-line agents.
            - Ezogabine (no longer marketed) use should be considered to reduce seizure frequency, but carries a serious risk of skin and retinal discoloration.
            - Clobazam and extended-release oxcarbazepine may be considered to decrease seizure frequency.
        - As monotherapy in patients with TRAFE:
            - Eslicarbazepine use may be considered to decrease seizure frequency.
            - Data are insufficient to recommend use of second- and the other third-generation AEDs.
        - For add-on therapy for generalized epilepsy, immediate-release and extended-release lamotrigine should be considered as add-on therapy to decrease seizure frequency in adults with treatment-resistant generalized tonic-clonic seizures secondary to generalized epilepsy. Levetiracetam use should be considered to decrease seizure frequency as add-on therapy for treatment-resistant generalized tonic-clonic seizures and for treatment-resistant juvenile myoclonic epilepsy.
        - Rufinamide is effective to reduce seizure frequency as add-on therapy for LGS. Clobazam use should be considered as add-on therapy for LGS.
        - For add-on therapy in pediatric patients with treatment-resistant focal epilepsy:
            - Levetiracetam use should be considered to decrease seizure frequency (ages 1 month to 16 years).
            - Zonisamide use should be considered to decrease seizure frequency (age 6 to 17 years).
            - Oxcarbazepine use should be considered to decrease seizure frequency (age 1 month to 4 years).
            - Data are unavailable on the efficacy of clobazam, eslicarbazepine, lacosamide, perampanel, rufinamide, tiagabine, or vigabatrin.
        - The guideline does not address newly approved agents including cannabidiol, everolimus, or stiripentol.
- **Evidence-based guideline: management of an unprovoked first seizure in adults.** Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society (*Krumholz et al 2015; reaffirmed in 2018*).
    - This practice guideline makes recommendations based on a consideration of the evidence for prognosis and treatment of adults with an unprovoked first seizure.
    - Recommendations include the following:
        - Adults presenting with an unprovoked first seizure should be informed that the chance for a recurrent seizure is greatest within the first 2 years after a first seizure (21% to 45%).
        - Clinicians should also advise such patients that clinical factors associated with an increased risk of seizure recurrence include a prior brain insult such as a stroke or trauma, an EEG with epileptiform abnormalities, a significant brain-imaging abnormality, or a nocturnal seizure.
        - Clinicians should advise patients that, although immediate AED therapy, as compared with delay of treatment pending a second seizure, is likely to reduce the risk of a seizure recurrence in the 2 years subsequent to a first seizure, it may not improve quality of life.
        - Clinicians should advise patients that over the longer term (> 3 years), immediate AED treatment is unlikely to improve the prognosis for sustained seizure remission.
        - Patients should be advised that their risk for AED AEs ranges from 7% to 31% and that these AEs are predominantly mild and reversible.
    - Immediate AED therapy after an unprovoked first seizure is likely to reduce seizure recurrence risk. A reduction in risk may be important, particularly for adults, for whom seizure recurrences may cause serious psychological and social consequences such as loss of driving privileges and limitations on employment. However, immediate AED treatment

is not well accepted and is debated. Decisions should be based on weighing the risk of recurrence against the AEs of AED therapy, and should take patient preferences into account.
  - It is accepted that when a patient has a second or additional seizures, an AED should be initiated because the risk of subsequent seizures is very high.
- **Evidence-based guideline: treatment of convulsive status epilepticus in children and adults.** Guideline Committee of the American Epilepsy Society (*Glauser et al 2016*).
  - This publication provides conclusions and a treatment algorithm based on a structured literature review of randomized trials of anticonvulsant treatments for seizures lasting longer than 5 minutes. A total of 38 trials were included.
  - For treatment in the adult population, conclusions included the following:
    - Intramuscular (IM) midazolam, intravenous (IV) lorazepam, IV diazepam (with or without phenytoin), and IV phenobarbital are established as efficacious at stopping seizures lasting at least 5 minutes.
    - IV lorazepam is more effective than IV phenytoin in stopping seizures lasting at least 10 minutes.
    - There is no difference in efficacy between IV lorazepam followed by IV phenytoin, IV diazepam plus phenytoin followed by IV lorazepam, and IV phenobarbital followed by IV phenytoin.
    - IV valproic acid has similar efficacy to IV phenytoin or continuous IV diazepam as second therapy after failure of a benzodiazepine.
    - Insufficient data exist in adults about the efficacy of levetiracetam as either initial or second therapy.
    - In adults with status epilepticus without established IV access, IM midazolam is established as more effective compared with IV lorazepam.
    - No significant difference in effectiveness has been demonstrated between lorazepam and diazepam in adults with status epilepticus.
  - For treatment in the pediatric population, conclusions included the following:
    - IV lorazepam and IV diazepam are established as efficacious at stopping seizures lasting at least 5 minutes.
    - Rectal diazepam, IM midazolam, intranasal midazolam, and buccal midazolam are probably effective at stopping seizures lasting at least 5 minutes.
    - Insufficient data exist in children about the efficacy of intranasal lorazepam, sublingual lorazepam, rectal lorazepam, valproic acid, levetiracetam, phenobarbital, and phenytoin as initial therapy.
    - IV valproic acid has similar efficacy but better tolerability than IV phenobarbital as second therapy after failure of a benzodiazepine.
    - Insufficient data exist in children regarding the efficacy of phenytoin or levetiracetam as second therapy after failure of a benzodiazepine.
    - In children with status epilepticus, no significant difference in effectiveness has been established between IV lorazepam and IV diazepam.
    - In children with status epilepticus, non-IV midazolam (IM/intranasal/buccal) is probably more effective than diazepam (IV/rectal).
  - Conclusions included the following (age not specified):
    - Insufficient data exist about the comparative efficacy of phenytoin and fosphenytoin. Fosphenytoin is better tolerated compared with phenytoin. When both are available, fosphenytoin is preferred based on tolerability, but phenytoin is an acceptable alternative.
  - The overall treatment algorithm directs that:
    - A benzodiazepine (IM midazolam, IV lorazepam, or IV diazepam) is recommended as the initial therapy of choice in the first phase of treatment (5 to 20 minutes after the beginning of the seizure). Although IV phenobarbital is established as efficacious and well tolerated as initial therapy, its slower rate of administration positions it as an alternative initial therapy. For prehospital settings or where first-line benzodiazepine options are not available, rectal diazepam, intranasal midazolam, and buccal midazolam are reasonable initial therapy alternatives.
    - In the second phase of treatment (from 20 to 40 minutes after the beginning of the seizure), reasonable options include fosphenytoin, valproic acid, and levetiracetam. There is no clear evidence that any of these options is better than the others. Because of AEs, IV phenobarbital is a reasonable second-therapy alternative if none of the 3 recommended therapies are available.
    - There is no clear evidence to guide therapy in the third phase of therapy (≥ 40 minutes after the beginning of the seizure).

- **Evidence-based guideline update: medical treatment of infantile spasms.** Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (*Go et al 2012*; reaffirmed in 2018)
  - This publication provides updated recommendations for the treatment of infantile spasms. The literature review included an evaluation of 26 published articles on this topic.
  - Recommendations include the following:
    - Evidence is insufficient to recommend the use of prednisolone, dexamethasone, and methylprednisolone as being as effective as adrenocorticotropic hormone (ACTH) for short-term treatment of infantile spasms.
    - Low-dose ACTH should be considered as an alternative to high-dose ACTH for treatment of infantile spasms.
    - ACTH or vigabatrin may be offered for short-term treatment of infantile spasms; evidence suggests that ACTH may be offered over vigabatrin.
    - Evidence is insufficient to recommend other therapies (valproic acid, vitamin B6, nitrazepam [not available in the United States], levetiracetam, zonisamide, topiramate, the ketogenic diet, or novel/combination therapies) for treatment of infantile spasms.
    - Hormonal therapy (ACTH or prednisolone) may be considered for use in preference to vigabatrin in infants with cryptogenic infantile spasms, to possibly improve developmental outcome.
    - A shorter lag time to treatment of infantile spasms with either hormonal therapy or vigabatrin may be considered to improve long-term cognitive outcomes.
  - There is a lack of sufficient randomized trials to provide definitive answers to key questions related to treatment of infantile spams.
- **Practice parameter: treatment of the child with a first unprovoked seizure.** Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (*Hirtz et al 2003*; reaffirmed in 2016)
  - This parameter reviews published literature relevant to the decision to begin treatment after a child or adolescent experiences a first unprovoked seizure and presents evidence-based practice recommendations. Treatment during the neonatal period is not addressed.
  - Recommendations include the following:
    - Treatment with AEDs is not indicated for the prevention of the development of epilepsy.
    - Treatment with AEDs may be considered in circumstances where the benefits of reducing the risk of a second seizure outweigh the risks of pharmacologic and psychosocial AEs.
  - The majority of children who experience a first unprovoked seizure will have few or no recurrences. Treatment with AEDs after a first seizure as opposed to after a second seizure has not been shown to improve prognosis for long-term seizure remission.
  - Treatment has been shown in several studies combining both children and adults to reduce the risk of seizure recurrence; however, there is a relative paucity of data from studies involving only children after a first seizure.
- **Summary of recommendations for the management of infantile seizures**. Task force report for the ILAE Commission of Pediatrics (*Wilmshurst et al 2015*).
  - This publication recommends an approach to the standard and optimal management of infants with seizures. When possible, recommendations are evidence-based; however, when no evidence was available, recommendations are based on expert opinion and standard practice.
  - Recommendations/findings include the following:
    - There is no indication for initiation of chronic AEDs for simple febrile seizures. However, in the acute treatment of febrile seizures, it is important to treat seizures lasting 10 minutes or longer.
    - In an otherwise healthy infant, a policy of “wait and see” is reasonable after the first afebrile seizure. However, this is a rare event and close monitoring is essential.
    - Treatment options with established or probable efficacy include the following:
      - Focal seizures: levetiracetam
      - Epileptic spasms: High-dose or low-dose ACTH
      - Dravet syndrome: stiripentol
    - Treatment options with possible efficacy include the following:
      - Generalized seizures: levetiracetam, valproate, lamotrigine, topiramate, clobazam
      - Epileptic spasms: prednisone, vigabatrin
      - Benign infantile convulsions: carbamazepine, phenobarbital, valproate

- Dravet syndrome: topiramate, zonisamide, valproate
- Benign myoclonic epilepsy of infancy: valproate, topiramate, lamotrigine, clonazepam
- Provoked or situational seizures: carbamazepine

▪ There is no clear evidence supporting an optimal duration of treatment; this is dependent on seizure type.

- **Guidelines on neonatal seizures**. World Health Organization (WHO) (*WHO 2011*).
  - This document was prepared based on a systematic review of the literature and involved cooperation between the WHO, the ILAE, and the International Bureau of Epilepsy (IBE).
  - Recommendations include the following:
    - Phenobarbital should be used as the first-line agent for treatment of neonatal seizures and should be made readily available in all settings.
    - In neonates who continue to have seizures despite administering the maximum tolerated dose of phenobarbital, either a benzodiazepine, phenytoin, or lidocaine may be used as the second-line agent for control of seizures (use of phenytoin or lidocaine requires cardiac monitoring).
    - In neonates with a normal neurological examination and/or normal EEG, stopping AEDs may be considered if the neonate has been seizure-free for > 72 hours; the drug(s) should be reinstituted if seizures recur.
    - In neonates in whom seizure control is achieved with a single AED, the drug can be discontinued abruptly without tapering the dose. In neonates requiring > 1 AED for seizure control, the drugs may be stopped one at a time, with phenobarbital being the last drug to be withdrawn.
- **Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes.** Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society (*Harden et al 2009A*; reaffirmed in 2013; Update in progress)
  - This publication summarizes evidence for selected issues regarding the clinical management of women with epilepsy (WWE) who are pregnant or planning to be pregnant.
  - Recommendations include the following:
    - If possible, avoidance of the use of valproate as part of polytherapy during the first trimester of pregnancy should be considered to decrease the risk of major congenital malformations (MCMs).
    - If possible, avoidance of the use of valproate monotherapy during the first trimester of pregnancy may be considered to decrease the risk of MCMs.
    - To reduce the risk of MCMs, the use of valproate during the first trimester of pregnancy should be avoided, if possible, compared to the use of carbamazepine.
    - To reduce the risk of MCMs, avoidance of the use of polytherapy with valproate during the first trimester of pregnancy, if possible, should be considered, compared to polytherapy without valproate.
    - To reduce the risk of MCMs, avoidance of the use of valproate during the first trimester of pregnancy, if possible, may be considered, compared to the use of phenytoin or lamotrigine.
    - To reduce the risk of MCMs, avoidance of the use of AED polytherapy during the first trimester of pregnancy, if possible, compared to monotherapy should be considered.
    - Limiting the dosage of valproate or lamotrigine during the first trimester, if possible, should be considered to lessen the risk of MCMs.
    - Avoidance of the use of valproate, if possible, should be considered to reduce the risk of neural tube defects and facial clefts, and may be considered to reduce the risk of hypospadias.
    - Avoidance of phenytoin, carbamazepine, and phenobarbital, if possible, may be considered to reduce the risk of specific MCMs: cleft palate for phenytoin use, posterior cleft palate for carbamazepine use, and cardiac malformations for phenobarbital use.
    - Carbamazepine exposure probably does not produce cognitive impairment in offspring of WWE.
    - Avoiding valproate in WWE during pregnancy, if possible, should be considered to reduce the risk of poor cognitive outcomes.
    - Avoiding phenytoin and phenobarbital in WWE during pregnancy, if possible, may be considered to reduce the risk of poor cognitive outcomes.
    - Monotherapy should be considered in place of polytherapy, if possible, for WWE who take AEDs during pregnancy to reduce the risk of poor cognitive outcomes.
    - For WWE who are pregnant, avoidance of valproate, if possible, should be considered compared to carbamazepine to reduce the risk of poor cognitive outcomes.

        - For WWE who are pregnant, avoidance of valproate, if possible, may be considered compared to phenytoin to reduce the risk of poor cognitive outcomes.
    - Valproate has the most data showing an association with risk from in utero exposure. If a change from valproate to another AED is planned, it is prudent to make this change well before pregnancy.
    - Although many of the recommendations in this parameter suggest minimizing AED exposure during pregnancy, for most WWE, discontinuing AEDs is not a reasonable or safe option. Discontinuing AEDs may expose the mother and fetus to physical injury from accidents due to seizure activity.
- **Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding.** Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society (*Harden et al 2009B*; reaffirmed in 2013; Update in progress)
    - This publication summarizes evidence for selected issues regarding the clinical management of WWE who are pregnant or planning to be pregnant.
    - Recommendations include the following:
        - The fact that phenobarbital, primidone, phenytoin, carbamazepine, levetiracetam, valproate, gabapentin, lamotrigine, oxcarbazepine, and topiramate cross the placenta may be factored into the clinical decision regarding the necessity of AED treatment for a woman with epilepsy.
        - Monitoring of lamotrigine, carbamazepine, and phenytoin levels during pregnancy should be considered.
        - Monitoring of levetiracetam and oxcarbazepine (as monohydroxy derivative) levels during pregnancy may be considered.
        - There is insufficient evidence to support or refute a change in phenobarbital, valproate, primidone, or ethosuximide levels related to pregnancy, but this lack of evidence should not discourage monitoring levels of these AEDs during pregnancy.
        - Valproate, phenobarbital, phenytoin, and carbamazepine may not transfer into breast milk to as great an extent as primidone, levetiracetam, gabapentin, lamotrigine, and topiramate.
    - Although many of the AEDs were shown to cross the placenta or enter breast milk, studies were limited in duration and did not systematically evaluate neonatal symptoms.

- Guidelines also support the use of AEDs for several common non-epilepsy indications:
    - The American Academy of Neurology and American Headache Society state that AEDs with established efficacy for migraine prevention include valproate, divalproex sodium, and topiramate; carbamazepine is noted to be possibly effective (*Silberstein et al 2012;* reaffirmed in 2015; Update in progress).
    - The American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation state that, for relief of painful diabetic neuropathy, pregabalin is established as effective, and gabapentin and valproate are probably effective (*Bril et al 2011*; Update in progress).
    - The American Academy of Neurology states that gabapentin and pregabalin are of benefit in reducing pain from postherpetic neuralgia (*Dubinsky et al 2004*).
    - American Psychiatric Association guidelines describe the key role of AEDs in the management of bipolar disorder, including the following (*Hirschfeld et al 2002*):
        - First-line pharmacological treatment for more severe manic or mixed episodes is either lithium plus an antipsychotic or valproate plus an antipsychotic; for less ill patients, monotherapy with lithium, valproate, or an antipsychotic may be sufficient. For mixed episodes, valproate may be preferred over lithium. Carbamazepine and oxcarbazepine are alternatives.
        - First-line pharmacological treatment for bipolar depression is either lithium or lamotrigine. When an acute depressive episode of bipolar disorder does not respond to first-line medication treatment, the next steps include adding lamotrigine, bupropion, or paroxetine.
        - The initial treatment for patients who experience rapid cycling should include lithium or valproate; an alternative is lamotrigine.
        - The medications with the best empirical evidence to support their use in maintenance treatment include lithium and valproate; possible alternatives include lamotrigine, carbamazepine, or oxcarbazepine.

- Note: This guideline was published in 2002 and cannot be assumed to be current; however, AEDs continue to be recommended for both acute (mania or hypomania) and maintenance phases of bipolar disorder *(Post 2017, Stovall 2018).*

SAFETY SUMMARY

- Tolerability and safety are as important as efficacy in determining the overall effectiveness of epilepsy treatment (*Schachter 2019*).
- Common AEs among AEDs include the following (*Schachter 2019*).
  - Systemic AEs:
    - nausea, vomiting, constipation, diarrhea, anorexia
    - rash
    - hyponatremia (carbamazepine, eslicarbazepine, oxcarbazepine)
    - weight gain (pregabalin, perampanel, valproate), weight loss (felbamate, topiramate, stiripentol)
  - Neurologic AEs:
    - headache
    - somnolence, sedation, drowsiness, lethargy, fatigue
    - dizziness, vertigo
    - tremor, anxiety, nervousness, insomnia
    - aggression, irritability, hyperactivity
    - depression, mood alteration
    - confusion
    - ataxia
    - blurred or double vision
- Examples of rare but serious AEs include the following (*Schachter 2019, individual package inserts*):
  - suicidal ideation and behavior (AEDs as a class, except everolimus)
  - neutropenia, leukopenia, pancytopenia, agranulocytosis, thrombocytopenia, and/or aplastic anemia (brivaracetam, carbamazepine, ethosuximide, felbamate, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, phenobarbital, primidone, stiripentol, valproate, vigabatrin, zonisamide)
  - anaphylaxis or angioedema (brivaracetam, fosphenytoin, gabapentin, levetiracetam, phenytoin, pregabalin)
  - severe skin rashes, Stevens-Johnson syndrome (SJS), and/or toxic epidermal necrolysis (TEN) (carbamazepine, clobazam, eslicarbazepine, ethosuximide, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, phenobarbital, primidone, rufinamide, tiagabine, valproate, zonisamide)
  - hepatic failure (carbamazepine, ethosuximide, felbamate, phenytoin, phenobarbital, primidone, valproate)
  - hepatocellular injury (cannabidiol)
  - prolonged PR interval, atrioventricular block, and/or changes in QT interval (eslicarbazepine, lacosamide, rufinamide)
  - serum sickness (carbamazepine, ethosuximide, phenytoin, phenobarbital, primidone, valproate)
  - multiorgan hypersensitivity (carbamazepine, ethosuximide, gabapentin, lacosamide, lamotrigine, oxcarbazepine, perampanel, phenytoin, valproate, zonisamide)
  - severe neuropsychiatric effects/hostility/aggression (brivaracetam, levetiracetam, perampanel)
  - hemophagocytic lymphohistiocytosis (HLH) (lamotrigine)
- A number of AEDs carry boxed warnings related to potentially serious AEs; these include the following:
  - Carbamazepine:
    - Serious and sometimes fatal dermatologic reactions, including TEN and SJS, have been reported. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. Patients with ancestry in genetically at-risk populations (across broad areas of Asia) should be screened for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine.
    - Aplastic anemia and agranulocytosis have been reported. If a patient exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely, and discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.
  - Clobazam, clonazepam, clorazepate, diazepam, and midazolam:
    - Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Concomitant prescribing should be reserved for use in patients for whom alternative

treatment options are inadequate, and patients should be followed for signs and symptoms of respiratory depression and sedation.

- Felbamate:
  - Use is associated with a marked increase in the incidence of aplastic anemia. Felbamate should only be used in patients whose epilepsy is so severe that the risk of aplastic anemia is deemed acceptable. Routine blood testing cannot be reliably used to reduce the incidence of aplastic anemia, but it will in some cases allow detection of hematologic changes before the syndrome declares itself clinically. Felbamate should be discontinued if any evidence of bone marrow depression occurs.
  - Cases of acute liver failure have been reported. Felbamate should not be prescribed for anyone with a history of hepatic dysfunction. Treatment should be initiated only in individuals without active liver disease and with normal baseline serum transaminases. It has not been proven that periodic serum transaminase testing will prevent serious injury, but it is generally believed that early detection of drug-induced hepatic injury along with immediate withdrawal of the suspect drug enhances the likelihood for recovery. Serum transaminases should be monitored at baseline and periodically thereafter. Felbamate should be discontinued if either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) become increased to ≥ 2 times the upper limit of normal, or if clinical signs and symptoms suggest liver failure, and should not be considered for retreatment.
- Fosphenytoin and phenytoin:
  - There is a cardiovascular risk associated with rapid IV infusion rates. The rate of administration should not exceed recommendations, and careful cardiac monitoring is required.
- Lamotrigine:
  - Cases of life-threatening serious skin rashes, including SJS and TEN, and/or rash-related death have been caused by lamotrigine. Benign rashes are also caused by lamotrigine; however, it is not possible to predict which rashes will prove to be serious. Lamotrigine should be discontinued at the first sign of a rash, unless the rash is clearly not drug related.
- Perampanel:
  - Serious or life-threatening psychiatric and behavioral AEs including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported. Patients should be monitored for these reactions and for changes in mood, behavior, or personality. The dose should be reduced if these symptoms occur, and it should be discontinued if symptoms are severe or worsening.
- Valproic acid and divalproex sodium:
  - Hepatotoxicity, including fatalities, have been reported, usually during the first 6 months of treatment. Serum liver tests are required and patients should be monitored closely.
  - There is a risk to fetuses exposed in utero, particularly neural tube defects, other major malformations, and decreased intelligence quotient (IQ). Valproate should not be given to a woman of childbearing potential unless the drug is essential to the management of her medical condition, and women should use effective contraception while using valproate.
  - Pancreatitis, including fatal hemorrhagic cases, has occurred. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation.
- Vigabatrin:
  - Vigabatrin can cause permanent bilateral concentric visual field constriction, including tunnel vision that can result in disability. In some cases, vigabatrin may also damage the central retina and may decrease visual acuity. Baseline and periodic vision assessment are recommended. However, this assessment cannot always prevent vision damage, and once detected, vision loss due to vigabatrin is not reversible. Vigabatrin should be withdrawn from patients who fail to show substantial clinical benefit.
  - Due to the risks of vision loss, vigabatrin is available only through a risk evaluation and mitigation strategy (REMS) program (*FDA REMS 2019*). Healthcare providers who prescribe vigabatrin and pharmacies that dispense the product must be specially certified. Each patient must be enrolled in the REMS program. Prescribers must ensure that periodic visual monitoring is performed and report any AE suggestive of vision loss to the vigabatrin REMS program.

- Everolimus is an antineoplastic, immunosuppressant agent associated with several adverse reactions.
  - The most common AE that occurred in trials for TSC-associated partial-onset seizures was stomatitis.
  - More serious AEs include:

- non-infectious pneumonitis
- infections
- hypersensitivity reactions
- angioedema (when taken with an angiotensin converting enzyme inhibitor)
- renal failure
- impaired wound healing
- myelosuppression
- reduced immune response with vaccination
- hyperglycemia
- hyperlipidemia
- embryo-fetal toxicity

DOSING AND ADMINISTRATION

- General dosing information is provided in Table 3. Dosing may vary based on the specific indication, interacting medications, and the patient's age and renal and hepatic function. Additionally, some medications are recommended to be titrated during initial treatment. Please refer to the prescribing information of the individual products for more detailed information.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Barbiturates				
Pentobarbital (Nembutal)	injection	IV, IM	Single dose	Acute use only. If needed, additional small increments may be given after the initial dose.
Phenobarbital* (Luminal†, Solfoton†)	tablets, elixir, injection	oral, IV, IM	2 to 3 times per day	
Primidone (Mysoline)	tablets	oral	3 to 4 times per day	
Benzodiazepines				
Clobazam (Onfi, Sympazan)	tablets, oral suspension, oral film	oral	1 or 2 times per day	Daily doses > 5 mg should be given in divided doses 2 times per day. Sympazan should be applied on top of the tongue where it adheres and dissolves.
Clonazepam (Klonopin)	tablets, orally disintegrating tablets (wafers)	oral	3 times per day	
Clorazepate (Tranxene T-Tab)	tablets	oral	2 to 3 times per day	
Diazepam (Diastat, Valium)	tablets, oral solution, oral concentrate, rectal gel, injection	oral, rectal, IV, IM	2 to 4 times per day	For the rectal gel (for acute use), a second dose may be given 4 to 12 hours after the initial dose when required. The injection is also for short-term acute use.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Midazolam (Nayzilam)	nasal spray	intranasal	Up to 2 doses per seizure cluster, with the second dose given at least 10 minutes after the first dose	Should be used to treat no more than 1 episode every 3 days and no more than 5 episodes per month.
Hydantoins				
Ethotoin (Peganone)	tablets	oral	4 to 6 times per day	
Fosphenytoin (Cerebyx)	injection	IV, IM	2 times per day or other divided doses based on drug levels	Generally used in acute situations as a loading dose; may be given in divided doses when substituted for oral phenytoin.
Phenytoin (Dilantin, Phenytek)	extended-release capsules, chewable tablets, oral suspension, injection	oral, IV, IM	2 to 4 times per day	Capsules are extended-release and may be suitable for once-daily dosing in some adults.
Miscellaneous				
Brivaracetam (Briviact)	tablets, oral solution, injection	oral, IV	2 times per day	The injection may be used when oral administration is temporarily not feasible.
Cannabidiol (Epidiolex)	oral solution	Oral	2 times per day	The provided oral syringe should be used to measure an accurate dose.
Carbamazepine (Carbatrol, Epitol, Equetro, Tegretol, Tegretol-XR)	tablets, chewable tablets, oral suspension, extended-release tablets, extended-release capsules	oral	2 to 4 times per day	Immediate-release tablets are given 2 to 3 times per day and the suspension is given 4 times per day. Carbatrol and Equetro are twice-daily extended-release capsule formulations; these capsules may be opened and sprinkled on soft food. Tegretol-XR is a twice-daily extended-release tablet formulation; these tablets must be swallowed whole.
Divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)	delayed-release tablets, delayed-release sprinkle capsules, extended-release tablets	oral	2 to 3 times per day (once daily for extended-release tablets)	Delayed-release tablets and extended-release tablets should be swallowed whole. Sprinkle capsules may be opened and sprinkled on soft food. Delayed-release tablet and capsule doses > 250 mg per day should be given in divided doses.
Eslicarbazepine (Aptiom)	tablets	oral	once daily	Tablets may be crushed.
Ethosuximide (Zarontin)	capsules, oral solution/syrup	oral	once daily or in divided doses	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Everolimus (Afinitor Disperz)	tablets for oral suspension	oral	once daily	Should be taken at the same time each day with or without food. Suspension should be prepared using water only and administered immediately after preparation. The suspension should be discarded if not taken within 60 minutes of preparation. Dose adjustments are made based on trough drug concentration.
Felbamate (Felbatol)	tablets, oral suspension	oral	3 or 4 times per day	
Gabapentin (Neurontin)	tablets, capsules, oral solution	oral	3 times per day	Capsules should be swallowed whole.
Lacosamide (Vimpat)	tablets, oral solution, injection	oral, IV	2 times per day	
Lamotrigine (Lamictal, Lamictal ODT, Lamictal XR, Subvenite)	tablets, chewable dispersible tablets, orally disintegrating tablets, extended-release tablets	oral	2 times per day (once daily for extended-release tablets)	Only whole tablets should be administered. Extended-release tablets must not be chewed or crushed.
Levetiracetam (Keppra, Keppra XR, Roweepra, Roweepra XR, Spritam, Elepsia XR)	tablets, tablets for oral suspension, oral solution, extended-release tablets, injection	oral, IV	2 times per day (once daily for extended-release tablets)	Tablets and extended-release tablets should not be chewed or crushed. Tablets for oral suspension (Spritam) can be dissolved in liquid and swallowed or allowed to disintegrate in the mouth.
Methsuximide (Celontin)	capsules	oral	1 to 4 times per day (*Lexicomp 2019*)	
Oxcarbazepine (Oxtellar XR, Trileptal)	tablets, oral suspension, extended-release tablets	oral	2 times per day (once daily for extended-release tablets)	In conversion of oxcarbazepine immediate-release to Oxtellar XR, higher doses of Oxtellar XR may be necessary. Extended-release tablets must not be chewed or crushed.
Perampanel (Fycompa)	tablets, oral suspension	oral	once daily at bedtime	
Pregabalin (Lyrica)	capsules, oral solution	oral	2 to 3 times per day	
Rufinamide (Banzel)	tablets, oral suspension	oral	2 times per day	Tablets can be administered whole, as half tablets, or crushed.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Stiripentol (Diacomit)	capsules, powder for oral suspension	oral	2 to 3 times per day	Capsules must be swallowed whole with a glass of water during a meal. Powder should be mixed with water and taken immediately after mixing during a meal.
Tiagabine (Gabitril)	tablets	oral	2 to 4 times per day	
Topiramate (Topamax, Topamax Sprinkle, Topiragen, Trokendi XR, Qudexy XR)	tablets, sprinkle capsules, extended-release capsules, extended-release sprinkle capsules	oral	2 times per day (once daily for extended-release capsule formulations)	Sprinkle capsules may be opened and sprinkled on soft food. Extended-release capsules (Trokendi XR) must not be chewed or crushed, but extended release sprinkle capsules (Qudexy XR) may be sprinkled on soft food.
Valproic acid (Depakene, Depacon)	capsules, oral solution/ syrup, injection	oral, IV	2 to 4 times per day (*Lexicomp 2019*)	Capsules should be swallowed whole without chewing to avoid local irritation of the mouth and throat. If the total dose exceeds 250 mg, it should be given in divided doses.
Vigabatrin (Sabril, Vigadrone)	tablets, powder for oral solution	oral	2 times per day	Powder for oral solution is supplied in individual dose packets to be mixed with water before administration.
Zonisamide (Zonegran)	capsules	oral	1 or 2 times per day	Capsules must be swallowed whole.

* Not FDA approved
† Brand product not currently marketed; generic is available

CONCLUSION

- Several classes of AEDs are available, including barbiturates, benzodiazepines, hydantoins, and miscellaneous agents. These products vary in terms of their indications for specific seizure types and indications other than epilepsy.
- Overall, the anticonvulsants have demonstrated efficacy for their FDA-approved uses. When possible, monotherapy with a single AED is the preferred treatment approach.
- Patients who are refractory to monotherapy may be treated with combination therapy. When considering combination therapy, it is recommended to combine medications with different mechanisms of action and AE profiles.
- Comparative efficacy data for the management of epilepsy are limited.
- Tolerability and safety are as important as efficacy in determining the overall effectiveness of epilepsy treatment. Both systemic AEs and neurologic AEs commonly occur. Some AEDs are associated with rare but serious AEs, and careful patient selection and monitoring are required.
- Epilepsy management can be complex and is often performed by neurologists. A variety of AEDs should be available to allow clinicians to select the most clinically appropriate agent for individual patients.
- Anticonvulsants are also established as effective for several non-epilepsy indications, including (but not limited to) bipolar disorder, migraine prophylaxis, and neuropathic pain.

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

INTRODUCTION

- Approximately 121.5 million American adults are living with some form of cardiovascular (CV) disease or the after-effects of stroke, according to the American Heart Association (AHA) Heart Disease and Stroke Statistics 2019 update *(Benjamin et al 2019).* CV disease is the number one cause of death in the United States.
- Hypertension (HTN) is an independent risk factor for CV disease and increases the mortality risks of CV disease and other diseases *(Benjamin et al 2019).* The 2017 American College of Cardiology (ACC)/AHA clinical practice guideline defines HTN as blood pressure (BP) ≥ 130/80 mm Hg (*Whelton et al 2018).* Nearly half of American adults (46%) have HTN based on this definition.
- Lowering of BP has been shown to reduce the risk of fatal and nonfatal CV events including stroke and myocardial infarctions (MIs). Lipid control, diabetes mellitus (DM) management, smoking cessation, exercise, weight management, and limiting sodium intake may also reduce CV risk *(Benjamin et al 2019).*
- Numerous classes of antihypertensives are available to reduce BP. Some examples of antihypertensives include diuretics, angiotensin converting enzyme inhibitors (ACE-Is), angiotensin II receptor blockers (ARBs), beta (β)-blockers, and calcium channel blockers (CCBs). Selection of antihypertensive therapy for a specific patient is determined by patient characteristics such as ethnic group, and the presence of compelling indications such as heart failure (HF), DM, chronic kidney disease (CKD), history of stroke or MI, and risk factors for coronary heart disease (CHD). Some patients require 2 or more antihypertensives from different pharmacological classes to achieve BP control *(Go et al 2014, Weber et al 2014, Whelton et al 2018).*
- In general, guideline-recommended BP goals in hypertensive adults range from < 130/80 mm Hg to < 140/90 mm Hg *(American Diabetes Association 2019, de Boer et al 2017, Whelton et al 2018).*
  - BP goals for older patients have long been a point of debate. The SPRINT trial followed patients ≥ 50 years with high BP and increased CV risks under intense hypertensive treatment (systolic blood pressure [SBP] goal of < 120 mm Hg) compared to standard HTN treatment (SBP goal of < 140 mm Hg) over a period of 3.2 years. The trial ended early; however, results demonstrated a reduced primary composite outcome of MI, acute coronary syndrome (ACS), stroke, HF, or CV death driven mainly by reduced HF events and CV death with intense treatment compared to standard treatment. The SPRINT trial pointed to potential clinical benefits associated with more intensive treatment in certain patients, although early termination of the trial and variations in the BP-measurement technique employed have called into question the generalizability of the results *(SPRINT Research Group 2015).*
  - A guideline from the American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP) on treatment of HTN in adults aged ≥ 60 years recommends standard and intense SBP treatment goals of < 150 mm Hg and < 140 mm Hg, respectively, with more intense BP reduction reserved for patients with a history of stroke or transient ischemic attack *(Qaseem et al 2017).*
- This review includes the ACE-Is and the ACE-I combination products.
  - The ACE-Is are Food and Drug Administration (FDA)-approved to treat HTN, HF, left ventricular (LV) dysfunction, diabetic nephropathy, acute myocardial infarction (AMI) to improve survival, and stable coronary artery disease (CAD) to reduce the risk of CV mortality or nonfatal MI.
  - The ACE-I combinations are products that combine an ACE-I with the diuretic hydrochlorothiazide (HCTZ), or a CCB (amlodipine or verapamil) in a fixed-dose formulation. By combining agents from different classes, these combination products are meant to increase the effectiveness of antihypertensive therapy through complementary mechanisms of action while minimizing the potential for dose-related adverse effects. All of the combination ACE-Is are FDA-approved for the treatment of HTN; however, with the exceptions of captopril/HCTZ and perindopril/amlodipine, none are FDA-approved for initial treatment of HTN.
- The single entity and combination ACE-Is included in this review are listed in Table 1.
- Medispan class: Antihypertensives - ACE Inhibitors; ACE Inhibitors & Thiazide/Thiazide-Like; ACE Inhibitor & Calcium Channel Blocker Combinations

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single-Entity ACE-Inhibitors	
Accupril (quinapril)	✔
Altace (ramipril)	✔
captopril*	✔
enalaprilat*	✔
fosinopril*	✔
Lotensin (benazepril)	✔
moexipril*	✔
perindopril*	✔
Prinivil, Qbrelis, Zestril (lisinopril)	✔ (Prinivil and Zestril only)
trandolapril*	✔
Vasotec, Epaned (enalapril)	✔ (Vasotec only)
ACE-I/HCTZ Combinations	
Accuretic (quinapril/HCTZ)	✔
captopril/HCTZ*	✔
fosinopril/HCTZ*	✔
Lotensin HCT (benazepril/HCTZ)	✔
moexipril/HCTZ*	✔
Vaseretic (enalapril/HCTZ)	✔
Zestoretic (lisinopril/HCTZ)†	✔
ACE-I/CCB Combinations	
Lotrel (benazepril/amlodipine)	✔
Prestalia (perindopril/amlodipine)	-
Tarka (trandolapril/verapamil ER)	✔

*Branded Aceon (perindopril), Capoten (captopril), Monopril (fosinopril), Univasc (moexipril), Vasotec (enalaprilat), Mavik (trandolapril), Capozide (captopril/HCTZ), Monopril HCT (fosinopril/HCTZ), and Uniretic (moexipril/HCTZ) are no longer marketed.

†Branded Prinzide (lisinopril/HCTZ) is no longer marketed; however, branded Zestoretic and generic products are available.

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. FDA-Approved Indications for Single-Entity ACE-Is

Indication	benazepril	captopril	enalapril/ enalaprilat	Epaned (enalapril)	fosinopril	lisinopril	moexipril	perindopril	Qbrelis (lisinopril)	quinapril	ramipril	trandolapril
Acute MI to improve survival						✔			✔			
Asymptomatic left ventricular dysfunction			✔ †	✔ §								
Diabetic nephropathy		✔										
Heart failure		✔	✔ †	✔ ‡	✔	✔			✔	✔	✔ *	✔ *
Hypertension in adults	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Hypertension in children aged > 1 month			✔ †	✔ **								
Hypertension in children aged ≥ 6 years	✔				✔	✔			✔			
Left ventricular dysfunction after MI		✔										✔

Indication	benazepril	captopril	enalapril/ enalaprilat	Epaned (enalapril)	fosinopril	lisinopril	moexipril	perindopril	Qbrelis (lisinopril)	quinapril	ramipril	trandolapril
Stable coronary artery disease to reduce the risk of CV mortality or nonfatal MI								✔				
Reduce risk of MI, stroke, and death from CV causes in patients ≥ 55 years of age at high risk for a major CV event											✔	

Abbrv: CV=cardiovascular, MI=myocardial infarction
*Post-MI
** Epaned is not recommended in neonates (ie, infants 1 month of age or less), preterm infants who have not reached a corrected post-conceptual age of 44 weeks, and in pediatric patients with glomerular filtration rate < 30 mL/min/1.73m^2.
†Enalapril oral tablets only
‡For symptomatic heart failure usually in combination with diuretics and digitalis.
§For clinically stable asymptomatic patients with ejection fraction ≤35%.

(Prescribing Information: Accupril 2017, Altace 2018, captopril 2019, enalaprilat 2018, Epaned 2018, fosinopril 2017, Lotensin 2019, moexipril 2015, perindopril 2019, Prinivil 2019, Qbrelis 2018, trandolapril 2018, Vasotec 2018, Zestril 2018)

Table 3. FDA-Approved Indications for Combination ACE-Is

Generic Name	Hypertension; not for initial therapy	Hypertension in patients not adequately controlled on monotherapy with either agent	Hypertension as either initial therapy or substituted for previously titrated doses of the individual products	Hypertension as either initial therapy or in patients not adequately controlled on monotherapy
ACE-I/HCTZ Combinations				
benazepril/HCTZ	✔			
captopril/HCTZ			✔	
enalapril/HCTZ	✔			
fosinopril/HCTZ	✔			
lisinopril/HCTZ	✔			
moexipril/HCTZ	✔			
quinapril/HCTZ	✔			
ACE-I/CCB Combinations				
benazepril/amlodipine		✔		
perindopril/amlodipine*				✔
trandolapril/verapamil ER	✔			

Abbrv: ACE=angiotensin converting enzyme, CCB=calcium channel blocker, ER=extended release, HCTZ=hydrochlorothiazide
*Perindopril/amlodipine may be used as initial therapy in patients likely to need multiple drugs to achieve blood pressure goals.

(Prescribing Information: Accuretic 2017, captopril/HCTZ 2006, fosinopril/HCTZ 2018, Lotensin HCT 2018, Lotrel 2017, moexipril/HCTZ 2017, Prestalia 2019, Tarka 2019, Vaseretic 2017, Zestoretic 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

- ACE-Is have demonstrated efficacy for the treatment of HTN in adults. A Cochrane systematic review of 92 randomized, placebo-controlled trials evaluated the BP-lowering ability of 14 different ACE-Is (N = 12,954). On average, SBP was

lowered by 8 mm Hg and diastolic blood pressure (DBP) by 5 mm Hg. There were no clinically meaningful BP lowering differences among the various ACE-Is *(Heran et al 2008).*
  - Enalapril has demonstrated efficacy for the treatment of HTN in children aged 6 to 16 years *(Wells et al 2002).*
  - Meta-analyses have shown that ACE-Is and ARBs have similar long-term effects on BP *(Sanders et al 2011, Savarese et al 2013).* Additionally, a Cochrane review involving 11,007 subjects with primary HTN found no evidence of a difference in total mortality or CV outcomes for ACE-Is in comparison to ARBs (*Li 2014*).
- ACE-Is have been shown to be effective for CAD and in reducing the risk for CV mortality, MI, and stroke in clinical trials *(ADVANCE Collaborative Group 2007, Blood Pressure Lowering Treatment Trialists' Collaboration 2007, Dahlof et al 2005, Fox et al 2003, Nissen et al 2004, ONTARGET Investigators 2008, Pilote et al 2004, Pitt et al 2003, PREAMI Investigators 2006, PROGRESS Collaborative Group 2001, Sanders et al 2011, Savarese et al 2013, Swedberg et al 1992, The Heart Outcomes Prevention Evaluation Study Investigators 2000, The PEACE Trial Investigators 2004, van Vark et al 2012, Zoungas et al 2014).*
  - Additionally, in a retrospective analysis of patients > 65 years of age, ramipril was associated with significantly lower mortality 1 year after MI compared to captopril, enalapril, fosinopril, lisinopril, and quinapril. There were no significant differences between ramipril and perindopril *(Pilote et al 2004).*
  - In meta-regression analyses of 26 large-scale trials, ACE-Is and ARBs appeared to have similarly beneficial BP-dependent effects for risk reduction of stroke, CHD, and HF *(Blood Pressure Lowering Treatment Trialists' Collaboration 2007).*
  - For patients with mitral regurgitation secondary to MI, both ACE-Is and ARBs have been shown to improve prognosis *(Okura et al 2016).*
- Clinical trials have demonstrated the efficacy of ACE-Is in reducing mortality associated with congestive HF *(Cohn et al 1991, Dickstein et al 2002, Dobre et al 2008, Kober et al 1995, Lee et al 2004, McKelvie et al 1999, Packer et al 1999, Pfeffer et al 1992, Pfeffer et al 2003, Pitt et al 1997, Pitt et al 2000, The Acute Infarction Ramipril Efficacy [AIRE] Study Investigators 1993, The CONSENSUS Trial Study Group 1987, The SOLVD Investigators 1991, The SOLVD Investigators 1992, Tu et al 2005).*
  - No significant differences were noted when ACE-Is and ARBs were compared *(Dickstein et al 2002, Lee et al 2004, McKelvie et al 1999, Pfeffer et al 2003, Pitt et al 1997, Pitt et al 2000).*
- ACE-Is have also shown efficacy for protection against the development of progressive nephropathy in patients with DM *(Barnett et al 2004, Casas et al 2005, Hou et al 2007, Morgensen et al 2000, Ruggenenti et al 2004, The GISEN Group 1997, Wright et al 2002).*
  - In patients with type 2 DM, combination treatment with perindopril and indapamide reduced SBP and significantly decreased micro- and macrovascular events vs placebo *(ADVANCE Collaborative Group 2007, Zoungas et al 2014).*
  - In a meta-analysis comparing ACE-Is to ARBs for preventing the progression of diabetic kidney disease, the effects on renal outcomes were similarly beneficial between the groups *(Strippoli et al 2006).* In a meta-analysis of patients with CKD, including those with diabetic and nondiabetic nephropathy, both ACE-Is and ARBs reduced the risk of kidney failure compared to other active agents and placebo, and reduced CV events compared to placebo *(Xie et al 2016).* However, only ACE-Is reduced the risk of all-cause mortality compared to other active agents.
  - A meta-analysis of randomized antihypertensive trials in patients with DM and microalbuminuria found that reduction in albuminuria among normotensive patients was greatest with trandolapril plus candesartan, followed by trandolapril monotherapy. In hypertensive patients, reduction in albuminuria was greatest with fosinopril plus amlodipine, followed by fosinopril monotherapy. However, the combination therapies had inferior safety profiles when compared to ACE-I monotherapy with respect to dry cough, presyncope, and peripheral edema *(Huang et al 2017).*
  - In a recent trial enrolling adolescents with type 1 DM, the addition of an ACE-I did not change the albumin-to-creatinine ratio over 2 to 4 years of treatment vs placebo. However, the use of an ACE-I was associated with a lower incidence of microalbuminuria. The short duration of the trial was cited as an important limitation, and follow-up to evaluate the potential benefits of early intervention in this population is necessary *(Marcovecchio et al 2017).*
- Clinical trials have demonstrated the effectiveness of some ACE-I combination products compared to other ACE-I combination products or when compared to monotherapy *(Chrysant et al 2004, Chrysant et al 2007, Fogari et al 1997, Hilleman et al 1999, Jamerson et al 2004, Kuschnir et al 1996, Messerli et al 2000, Neutel et al 2005).*
  - Benazepril/amlodipine has demonstrated superior CV outcomes compared to benazepril/HCTZ *(Bakris et al 2010, Jamerson et al 2008, Weber et al 2010)*. In addition, benazepril/amlodipine has demonstrated higher antihypertensive efficacy compared to captopril/HCTZ *(Malacco et al 2002)* and olmesartan/HCTZ *(Kereiakes et al 2007).*

Benazepril/amlodipine also demonstrated noninferiority to valsartan/HCTZ in lowering of DBP over 16 weeks in patients with HTN and DM *(Lee et al 2012).*

- When lisinopril/HCTZ was compared to a combination ARB, candesartan/HCTZ, no significant difference in antihypertensive efficacy was identified; however, the proportion of patients reporting at least 1 adverse event was significantly greater in the lisinopril/HCTZ group *(McInnes et al 2000).*
- Trandolapril/verapamil has been associated with a significantly greater reduction of BP compared to either component as monotherapy *(Brunner et al 2007, Cifkova et al 2000, Karlberg et al 2000, Pepine et al 2003, Pepine et al 2006, Ruggenenti et al 2004).*
- In 728 black patients from sub-Saharan Africa, blood pressure reductions were greater with amlodipine/HCTZ and amplodipine/perindopril than perindopril/HCTZ at 6 months (*Ojji et al 2019*).

- Studies have demonstrated that the combination of 2 renin angiotensin-aldosterone system (RAAS) inhibitors, including an ACE-I combined with an ARB, provides no renal or CV benefits and may lead to significant adverse events, particularly in patients with diabetes and/or renal insufficiency. Most notably, patients receiving combination therapy had increased rates of hyperkalemia, hypotension, and renal dysfunction. All agents in this class have safety warnings against combined use *(Fried et al 2013, ONTARGET Investigators 2008, Parving et al 2012, Pfeffer et al 2003, Sakata et al 2015).*

CLINICAL GUIDELINES

- The 2017 ACC/AHA guideline for the prevention, detection, evaluation, and management of high BP in adults *(Whelton et al 2018)* offers updated classifications of HTN and goals of treatment (see Table 4).

Table 4. Classification of BP measurements

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

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

- In patients with stage 1 HTN, it is reasonable to initiate therapy with a single antihypertensive agent. In patients with stage 2 HTN and BP more than 20/10 mm Hg higher than their target, 2 first-line agents of different classes should be initiated.
  - First-line antihypertensive agents include: thiazide diuretics, CCBs, and ACE-Is or ARBs.
  - Diuretics, ACE-Is, ARBs, CCBs, and β-blockers have been shown to prevent CVD compared with placebo.
    - ACE-Is were notably less effective in preventing HF and stroke compared with CCBs in black patients. ARBs may be better tolerated than ACE-Is in black patients, with less cough and angioedema, but they offer no proven advantage over ACE-Is in preventing stroke or CVD in this population; thiazide diuretics (especially chlorthalidone) or CCBs are the best initial choice for single-drug therapy in this population, or as initial agents in a multidrug regimen.
  - An ACE-I is a preferred drug for treatment of HTN for those with CKD stage 3, or for stage 1 or 2 with albuminuria.

- The American Diabetes Association position statement on DM and HTN recommends that most patients with DM and HTN be treated to a goal BP of < 140/90 mm Hg. Lower BP targets such as < 130/80 mm Hg may be appropriate for individuals at high risk of CVD *(American Diabetes Association 2019, de Boer et al 2017)*.
  - Treatment for HTN should include drug classes demonstrated to reduce CV events in patients with DM: ACE-Is, ARBs, thiazide diuretics, or dihydropyridine CCBs.
  - Patients with BP ≥ 160/100 mm Hg should have prompt initiation of 2 drugs or a single-pill combination of drugs demonstrated to reduce CV events in patients with DM.
  - An ACE-I or ARB, at the maximum tolerated dose indicated for BP treatment, is the recommended first-line treatment for HTN in patients with DM and a urine albumin-to-creatinine ratio ≥ 30 mg/g creatinine.
- The American Academy of Pediatrics clinical practice guideline for high BP in children and adolescents recommends that the treatment goal with nonpharmacologic and pharmacologic therapy should be a reduction in SBP and DBP to < 90th percentile and < 130/80 mm Hg in adolescents ≥ 13 years old *(Flynn et al 2017)*.
  - In hypertensive children and adolescents who have failed lifestyle modifications, clinicians should initiate pharmacologic treatment with an ACE-I, ARB, long-acting CCB, or thiazide diuretic.
  - Children and adolescents with CKD, HTN, and proteinuria should be treated with an ACE-I or ARB.
- Various other guidelines and position statements place ACE-Is as first-line therapy in patients with DM and microalbuminuria; with stable CAD and HTN; with HF; and after an MI. ACE-Is have demonstrated clinical benefit and reductions in morbidity and mortality in these populations *(Amsterdam et al 2014, Go et al 2014, Rosendorff et al 2015, Weber et al 2014, Yancy et al 2017).*
  - Due to differences in the activity of the RAAS, ACE-Is are often less effective as HTN monotherapy in black patients (African or Caribbean descent). Alternative first-line options for these patients include CCBs and thiazide diuretics *(Weber et al 2014).*

SAFETY SUMMARY

Boxed Warnings

- When pregnancy is detected, ACE-Is should be discontinued as soon as possible. Drugs that act directly on the RAAS can cause injury and death to the developing fetus.

Contraindications

- ACE-Is are contraindicated in patients with angioedema or with a history of hereditary or idiopathic angioedema.
- ACE-Is are contraindicated in combination with a neprilysin inhibitor (eg, sacubitril). An ACE-I should not be administered within 36 hours of a neprilysin inhibitor.
- ACE-Is are contraindicated in combination with aliskiren in patients with DM; the combination should also be avoided in patients with renal impairment (glomerular filtration rate [GFR] < 60 mL/min/1.73m^2).
- ACE-I combinations with HCTZ are contraindicated in patients with anuria.
- Due to the verapamil component, trandolapril/verapamil is contraindicated in patients with severe LV dysfunction, hypotension or cardiogenic shock, sick sinus syndrome, second or third degree atrioventricular (AV) block, patients with atrial flutter or fibrillation and an accessory bypass, and patients taking flibanserin.

Warnings and Precautions

- ACE-Is have warnings for anaphylactoid reactions including head and neck angioedema and intestinal angioedema; hypotension; hyperkalemia; and cholestatic jaundice and hepatic failure.
  - Captopril has been shown to cause agranulocytosis and bone marrow depression rarely in patients with uncomplicated HTN, but more frequently in patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Available data from clinical trials are insufficient to show that other ACE-Is do not cause agranulocytosis at similar rates.
- Verapamil has a negative inotropic effect, which is compensated by its afterload reduction (decreased systemic vascular resistance) properties without a net impairment of ventricular performance. However, congestive HF and/or pulmonary edema have been reported. Verapamil-containing products should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%, pulmonary wedge pressure > 20 mm Hg, or severe symptoms of cardiac failure) and in patients with any degree of ventricular dysfunction if they are receiving a β-blocker.
- Perindopril/amlodipine is not recommended in patients with HF. Use caution with amlodipine in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

- HCTZ may alter glucose tolerance and raise levels of cholesterol, triglycerides, and serum uric acid levels (which may precipitate gout). HCTZ may cause elevations of serum calcium and monitoring is recommended in patients with hypercalcemia.

Adverse Effects
- Common adverse effects of ACE-Is include headache, dizziness, cough, and hypotension.
- ACE-Is may cause electrolyte abnormalities and elevations of blood urea nitrogen (BUN) and creatinine.
- Some combination products contain amlodipine, which may cause peripheral edema.

Important Drug Interactions
- Dual blockade of the RAAS with ARBs, ACE-I, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure), compared to monotherapy.
  - Most patients receiving the combination of 2 RAAS inhibitors do not obtain any additional benefit compared to monotherapy.
- In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of non-steroidal anti-inflammatory agents (NSAIDs) with ACE-Is may result in deterioration of renal function, including acute renal failure. The antihypertensive effect of ACE-Is may be attenuated by NSAIDs.
- Concomitant use of ACE-Is and potassium-sparing diuretics (eg, spironolactone, amiloride, triamterene) can increase the risk of hyperkalemia.
- Patients taking mammalian target of rapamycin (mTOR) inhibitors (eg, temsirolimus, sirolimus, everolimus) or a neprilysin inhibitor may be at increased risk for angioedema with concomitant ACE-I use.
- Verapamil has drug interactions with colchicine, digoxin, immunosuppressants, and several others. Consult the prescribing information for trandolapril/verapamil for the full listing and descriptions.

DOSING AND ADMINISTRATION

- All ACE-I-containing products, with the exception of fosinopril, require dosage adjustment in patients with renal impairment.
- The combination ACE-I products are not recommended for use in patients with severe renal impairment and should be used with caution in patients with hepatic impairment.
- Breastfeeding is not recommended while on ACE-I-containing products.

Table 5. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single-Entity ACE-Is				
benazepril	Tablets	Oral	HTN: Once or twice daily	FDA-approved for use in children ≥ 6 years.
captopril	Tablets	Oral	Diabetic nephropathy, HF, LV dysfunction after MI: Three times daily HTN: Twice to 3 times daily	Take 1 hour before meals or 2 hours after meals.
enalapril	Tablets, 1 mg/mL oral solution	Oral	Asymptomatic LV dysfunction, HF: Twice daily HTN: Daily in 1 or 2 divided doses	FDA-approved for use in children aged ≥ 1 month.
enalaprilat	Injection	IV	HTN: Every 6 hours	Administer as a slow IV infusion or as an IV bolus over 5 minutes.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
fosinopril	Tablets	Oral	HF: Once daily HTN: Daily in 1 or 2 divided doses	FDA-approved for use in children ≥ 6 years weighing more than 50 kg.
lisinopril	Tablets, 1 mg/mL solution	Oral	AMI to improve survival, HF, HTN: Once daily	FDA-approved for use in children ≥ 6 years.
moexipril	Tablets	Oral	HTN: Daily in 1 or 2 divided doses	Take 1 hour before meals.
perindopril	Tablets	Oral	HTN: Daily in 1 or 2 divided doses Stable CAD: Once daily	Bioavailability of perindopril is higher with hepatic impairment. Dosage adjustment in elderly patients is required.
quinapril	Tablets	Oral	HF: Twice daily HTN: Daily in 1 or 2 divided doses	Dosage adjustment in elderly patients is required.
ramipril	Capsules	Oral	HF after MI: Twice daily HTN: Daily in 1 or 2 divided doses Reduce risk of MI, stroke, and death from CV causes: Once daily	Capsules should be swallowed whole; capsule contents can be sprinkled on applesauce or mixed in 120 mL of water or apple juice.
trandolapril	Tablets	Oral	HF or LV dysfunction after MI: Once daily HTN: Once to twice daily	Dosage adjustment in hepatic impairment is required.
ACE-I/HCTZ Combinations*				
benazepril/HCTZ	Tablets	Oral	HTN: Once daily	
captopril/HCTZ	Tablets	Oral	HTN: Once daily	Take 1 hour before a meal or 2 hours after meals.
enalapril/HCTZ	Tablets	Oral	HTN: Once daily	
fosinopril/HCTZ	Tablets	Oral	HTN: Once daily	
lisinopril/HCTZ	Tablets	Oral	HTN: Once daily	
moexipril/HCTZ	Tablets	Oral	HTN: Once daily	Take 1 hour before a meal.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
quinapril/HCTZ	Tablets	Oral	HTN: Once daily	
ACE-I/CCB Combinations*				
benazepril/amlodipine	Capsules	Oral	HTN: Once daily	Exposure is increased in elderly patients and in hepatic dysfunction; a lower dosage should be considered.
perindopril/amlodipine	Tablets	Oral	HTN: Once daily	Exposure is increased in elderly patients and in hepatic dysfunction; a lower maximum dosage should be considered in elderly patients.
trandolapril/verapamil	Tablets, extended-release	Oral	HTN: Once daily	Administer with food.

Abbrv: ACE-I=angiotensin converting enzyme inhibitor, AMI=acute myocardial infarction, CAD=coronary artery disease, CCB=calcium channel blocker, CV=cardiovascular, FDA=Food and Drug Administration, HCTZ=hydrochlorothiazide, HF=heart failure, HTN=hypertension, IV=intravenous, LV=left ventricular, MI=myocardial infarction

*Captopril/HCTZ and perindopril/amlodipine are the only combination ACE-Is that are FDA-approved for use as initial HTN therapy. All other agents are recommended for use after the patient has failed to achieve the desired antihypertensive effect and/or experienced unacceptable side effects on monotherapy with one of the principal components. Combination therapy may be initiated after failure on monotherapy or substituted for the titrated individual components.

See the current prescribing information for full details.

CONCLUSION

- The single-entity and combination ACE-I products are FDA-approved for the treatment of HTN, and most are generically available. Most single-entity ACE-Is are also approved for the treatment of HF. With the exception of captopril/HCTZ and perindopril/amlodipine, the combination ACE-Is are not approved for use as initial HTN therapy.
- Evidence-based guidelines recognize the important role ACE-Is play in the treatment of HTN and other CV and renal diseases. There is no consensus on BP goals for certain populations such as older patients and patients with DM. The current ACC/AHA guidelines *(Whelton et al 2018)* recommend a BP goal of < 130/80 mm Hg for most patients.
- ACE-Is have demonstrated efficacy in the treatment of HTN, for protection against progressive nephropathy in patients with DM, for reducing mortality associated with HF, and for reducing the risk of CV mortality, MI, and stroke in patients with CAD.
  - ACE-Is have generally demonstrated comparable efficacy to ARBs across indications.
- Studies have demonstrated that the combination of 2 RAAS inhibitors, including an ACE-I with an ARB, provides no renal or CV benefits and may increase risk of adverse events, including hyperkalemia, hypotension, and renal dysfunction. All agents in this class have safety warnings against combined use.
- All ACE-Is have a boxed warning for use in pregnancy and are contraindicated in patients with a history of angioedema. Other warnings include anaphylactoid reactions including head and neck angioedema, hypotension, hyperkalemia, and cholestatic jaundice and hepatic failure.
- Common adverse effects of ACE-Is include headache, dizziness, cough, and hypotension. ACE-Is may cause electrolyte abnormalities and increases in BUN and creatinine.
- Current guidelines recommend ACE-Is as a first-line therapy for patients with HTN, DM with microalbuminuria, stable CAD with HTN, HF, and post-MI *(American Diabetes Association 2019, Amsterdam et al 2014, de Boer et al 2017, Go et al 2014, Rosendorff et al 2015, Weber et al 2014, Whelton et al 2018, Yancy et al 2017).*
  - Due to differences in the activity of the RAAS, ACE-Is are often less effective as HTN monotherapy in black patients; CCBs and thiazide diuretics should be used as first-line options in these patients.

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Established Drug Classes

Therapeutic Class Overview
Opioids, Long Acting

INTRODUCTION

- Pain originates from somatic or visceral structures. Somatic pain is localized and typically results from injury or disease of the skin, musculoskeletal structures, and joints. Visceral pain arises from internal organ dysfunction or from functional pathology.
- Pain can be acute or chronic. Acute pain often results from injury or inflammation and may have a survival role and assist in the healing process by minimizing re-injury. In contrast, chronic pain, often defined as pain persisting for over three to six months, may be considered a disease in that it serves no useful purpose (*Cohen et al 2016*).
  - A 2016 study estimated that approximately 50 million adults in the United States have chronic pain, and approximately 20 million have high-impact chronic pain (ie, pain that limits life or work activities on most days). Each year, chronic pain contributes to an estimated $560 billion in direct medical costs, lost productivity, and disability programs (*Dahlhamer et al 2018*).
- Pain may be classified as nociceptive and neuropathic pain.
  - Nociceptive pain, including cancer pain, results from an injury or disease affecting somatic structures such as skin, muscle, tendons and ligaments, bone, and joints. It is typically treated with nonopioid analgesics or opioids.
  - Neuropathic pain results from disease or injury to the peripheral or central nervous systems (CNS) and is less responsive to opioids. It is often treated with adjuvant drugs such as antidepressants and antiepileptics. Opioids are recommended as second- or third-line agents (*Cohen et al 2016*).
- Several pharmacologic and nonpharmacologic options are currently available for the management of pain. Treatment options include pharmacologic treatment, physical medicine, behavioral medicine, neuromodulation, interventional, and surgical approaches. Pharmacologic therapy should not be the sole focus of pain treatment; however, it is the most widely utilized option (*Cohen et al 2016*).
  - Major pharmacologic categories used in the management of pain include non-opioid analgesics, tramadol, opioid analgesics (full and partial agonists), alpha-2 (α_2) adrenergic agonists, antidepressants, anticonvulsants, muscle relaxants, N-methyl-d-aspartate (NMDA) receptor antagonists, and topical analgesics. Opioids are available in both short-acting and long-acting or sustained release formulations (*Cohen et al 2016*).
  - Combining different types of treatments, including multiple types of analgesics, may provide an additive analgesic effect without increasing adverse effects (*Cohen et al 2016, The Medical Letter 2013*).
- It is important that patients receive appropriate pain treatment with careful consideration of the benefits and risks of treatment options. The use of opioid analgesics presents serious risks, including overdose and opioid use disorder. From 1999 to 2014, there were more than 165,000 deaths due to opioid analgesic overdoses in the U.S. (*Dowell et al 2016*).
- The long-acting opioids have gained increasing attention regarding overuse, abuse, and diversion. Some manufacturers have addressed concerns about abuse and misuse by developing new formulations designed to help discourage the improper use of opioid medications.
  - In January 2013, the Food and Drug Administration (FDA) released draft guidance for industry regarding abuse deterrent opioids. This document was finalized in April 2015. The guidance explains the FDA's current direction regarding studies conducted to demonstrate that a given formulation has abuse deterrent properties. The guidance also makes recommendations about how those studies should be performed and evaluated (*FDA Industry Guidance 2015*). The 2015 guidance does not address generic opioids. Subsequently in November 2017, the FDA issued a final guidance to support industry in the development of generic versions of abuse-deterrent opioids (*FDA Industry Guidance 2017*).
  - In 2013, reformulated OxyContin (oxycodone) became the first long-acting opioid to be approved with labeling describing the product's abuse deterrent properties consistent with the FDA's guidance for industry (*Hale et al 2016*).
  - Since the approval of reformulated OxyContin, several other long-acting opioids have been approved with abuse deterrent labeling, including, Arymo ER (morphine), Embeda (morphine and naltrexone), Hysingla ER (hydrocodone), Morphabond (morphine), Targiniq ER (oxycodone and naloxone), Troxyca ER (oxycodone and naltrexone), Vantrela ER (hydrocodone), and Xtampza ER (oxycodone) (*Drugs@FDA 2019, Hale et al 2016*). However, Targiniq ER, Troxyca ER, and Vantrela ER were never launched and were recently discontinued. Branded Arymo ER was also discontinued by the manufacturer, Egalet (*Drugs@FDA 2019*).

- A number of federal agencies have implemented measures to combat drug abuse and misuse. The Centers for Medicare & Medicaid Services (CMS) has issued guidance in an effort to improve drug utilization review controls in Part D prescription plans. The U.S. Office of Disease Prevention and Health Promotion offers an interactive training tool, "Pathways to Safer Opioid Use," which teaches healthcare providers how to implement opioid-related recommendations from the adverse events action plan. Additionally, the National Institute on Drug Abuse (NIDA), a component of the National Institutes of Health (NIH), has a number of studies and initiatives to educate providers and patients about opioid addiction and treatment. On July 13, 2017, the National Academies of Science, Engineering, and Medicine (NASAM) also released a consensus report, commissioned by the FDA, which outlined the state of the science regarding prescription opioid abuse and misuse, as well as the evolving role that opioids play in pain management (*CMS 2019, Office of Disease Prevention and Health Promotion 2019, NASAM 2017, NIDA 2015*).
- In December 2018, the U.S. Department of Health & Human Services (HHS) recommended prescribing or co-prescribing naloxone to all patients who are at risk for opioid overdose, including: patients receiving opioids at a dosage of 50 milligram morphine equivalents (MME) per day or greater; patients with respiratory conditions who are prescribed opioids; patients who have been prescribed benzodiazepines along with opioids; and patients prescribed opioids who have a non-opioid substance use disorder, report excessive alcohol use, or have a mental health disorder (*HHS 2018*).
- In March 2016, the Centers for Disease Control and Prevention (CDC) issued a guideline for prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care. The guideline addresses when to initiate or continue opioids for chronic pain; opioid selection, dosage, duration, follow-up, and discontinuation; and assessing risks and addressing harms of opioid use. The guideline encourages prescribers to follow best practices for responsible opioid prescribing due to the risks of opioid use (*Dowell et al 2016*).
- Methadone is FDA-approved for detoxification and maintenance treatment of opioid addiction.
  - Methadone products when used for the treatment of opioid addiction in detoxification or maintenance programs, shall 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 shall dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (42 CFR 8.12) (*Prescribing information: Dolophine 2018, methadone oral solution 2019, Methadose 2018*).
- Included in this review are the long-acting opioids, which are primarily utilized in the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time. Long-acting opioids are available in a variety of different dosage forms, and currently several agents are available generically (*Drugs@FDA 2019*).
  - All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of transdermal and buccal buprenorphine, a partial opioid agonist, which is a Schedule III controlled substance (*Drugs@FDA 2019*).
- Since some agents are available under multiple brand names, many tables in this review are arranged by generic name.
- Medispan class: Opioid Agonists

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single Entity Agents	
Arymo ER†¶, Avinza¶, Kadian, Morphabond†, MS Contin (morphine sulfate)	✔
Belbuca, Butrans (buprenorphine)	✔
Dolophine, Methadose (methadone)	✔
Duragesic (fentanyl)	✔
Exalgo# (hydromorphone)	✔
Hysingla ER†, Zohydro ER§ (hydrocodone bitartrate)	-
levorphanol	✔
Nucynta ER (tapentadol)	-
Opana ER* (oxymorphone)	✔
OxyContin†‡, Xtampza ER† (oxycodone)	✔

Drug	Generic Availability
Combination Products	
Embeda† (morphine sulfate/naltrexone)	-

*Generic products of the pre-reformulated Opana ER are available. The branded versions of Opana ER (pre- and post-reformulation) are no longer available on the market.
†Approved as an abuse deterrent (AD) formulation, which is consistent with the FDA's 2015 guidance for industry, *Abuse-Deterrent Opioids – Evaluation and Labeling.*
‡OxyContin had various patents extending out to 2027. Patent litigation on OxyContin reached an agreement between manufacturers. In late 2014, a number of generic products launched.
§In February 2015, a new formulation of Zohydro ER was FDA-approved with AD properties; however, it has not been deemed to meet the FDA requirements for labeling as an AD opioid.
¶Avinza branded products were discontinued by Pfizer in July 2015. Egalet discontinued the promotion and manufacture of Arymo ER branded products effective September 28, 2018.
#Brand product discontinued, but generic products are available.
(*Drugs@FDA 2019, FDA Industry Guidance 2015, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Single Entity Agents										Combination Products
	buprenorphine	fentanyl	hydrocodone	hydromorphone	levorphanol	methadone	morphine	oxycodone	oxymorphone	tapentadol	morphine sulfate/ naltrexone
Pain Management											
Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in adults.	✔		✔			✔ *	✔	✔	✔	✔	✔
Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in opioid-tolerant pediatric patients ≥ 11 years of age who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent.								✔ †			
Management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.					✔						
Management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.		✔ ‡		✔ ‡							
Management of neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate										✔	
Opioid Addiction											
Detoxification treatment of opioid addiction (heroin or other morphine-like drugs)						✔					
Maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with social and medical services						✔					
Limitations of Use											
Limitations of Use: Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release (ER) opioid formulations, reserve this agent for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔

Indication	Single Entity Agents										Combination Products
	buprenorphine	fentanyl	hydrocodone	hydromorphone	levorphanol	methadone	morphine	oxycodone	oxymorphone	tapentadol	morphine sulfate/ naltrexone
otherwise inadequate to provide sufficient management of pain.											
Limitations of Use: Not indicated as an as-needed (prn) analgesic.	✔	✔	✔	✔		✔	✔	✔	✔	✔	✔

*Methadone tablets and oral solution only
†OxyContin only
‡Patients considered opioid tolerant are those who are receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid.

(Prescribing information: Arymo ER 2018, Belbuca 2018, Butrans 2018, Dolophine 2018, Duragesic 2018, Embeda 2018, Exalgo 2018, Hysingla ER 2018, Kadian 2018, levorphanol 2018, methadone oral solution 2019, Methadose 2018, Morphabond 2018, MS Contin 2018, Nucynta ER 2018, OxyContin 2018, oxymorphone extended-release 2018, Xtampza ER 2018, Zohydro ER 2019)

- 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

- As a class, the long-acting opioids are a well-established therapy for the treatment of moderate to severe pain. In general, opioids are used for the treatment of non-cancer and cancer pain; however, data establishing their effectiveness in the treatment of neuropathic pain are available. Head-to-head trials of long-acting opioids do exist and for the most part the effectiveness of the individual agents, in terms of pain relief, appears to be similar. Small differences between the agents exist in side effect profiles, and associated improvements in quality of life or sleep domains (*Agarwal et al 2007, Aiyer et al 2017, Allan et al 2001, Allan et al 2005, Bao et al 2016, Bekkering et al 2011, Bruera et al 2004, Buynak et al 2010, Caldwell et al 2002, Caraceni et al 2011, Chou et al 2015, Clark et al 2004, Conaghan et al 2011, Felden et al 2011, Finkel et al 2005, Finnerup et al 2015, Gimbel et al 2003, Gordon et al [a], 2010, Gordon et al [b], 2010, Karlsson et al 2009, Hale et al 2007, Hale et al 2010, Katz et al 2010, King et al 2011, Kivitz et al 2006, Langford et al 2006, Ma et al 2008, Melilli et al 2014, Mercadante et al 2010, Mesgarpour et al 2014, Morley et al 2003, Musclow et al 2012, Nicholson et al 2017, Park et al 2011, Pigni et al 2011, Quigley et al 2002, Rauck et al 2014, Schwartz et al 2011, Slatkin et al 2010, Sloan et al 2005, Watson et al 2003, Whittle et al 2011, Wiffen et al 2013, Wild et al 2010*).
- Some systematic reviews and meta-analyses recommend opioids as a potential treatment option for various forms of non-cancer and cancer-related pain; however, other meta-analyses in non-cancer pain have not found a clinically meaningful difference between opioids, other non-opioid pain medications, and placebo. No single opioid is recommended over the others (*Busse et al 2018, Chou et al 2015, Finnerup et al 2015, Mesgarpour et al 2014, Stewart et al 2018*).
  - The Agency for Healthcare Research and Quality (AHRQ) conducted a systematic review (N = 39 studies, 40 publications) of the effectiveness and risks of long-term (>3 months) opioid therapy for chronic pain and included both randomized and observational studies. Findings indicated that three randomized, head-to-head trials of various long-acting opioids found no differences in one-year outcomes related to pain or function. One good-quality case-control study found current opioid use to be associated with increased risk for hip, humerus, or wrist fracture versus non-use (adjusted odds ratio [OR], 1.27; 95% confidence interval [CI], 1.21 to 1.33). The risk was highest with one prescription (OR, 2.7; 95% CI, 2.34 to 3.13) and decreased with higher numbers of prescriptions, with no increased risk with more than 20 cumulative prescriptions. One fair-quality cohort study found that a cumulative opioid supply of at least 180 days over a 3.5-year period was associated with an increased risk for myocardial infarction versus no long-term opioid therapy (adjusted incidence rate ratio, 2.66; 95% CI, 2.3 to 3.08) (*Chou et al 2015*).
  - A systematic review and meta-analysis of 96 randomized controlled trials examined the use of opioids in chronic non-cancer pain. Opioid use was associated with reduced pain compared to placebo (weighted mean difference [WMD], -0.69 cm on a 10-cm visual analog scale; 95% CI, -0.82 to -0.56 cm; $p < 0.001$), as well as improved physical functioning as measured by the 36-item Short Form physical component score (SF-36 PCS; WMD, 2.04 points on a 100-point scale; 95% CI, 1.41 to 2.68 points; $p < 0.001$). However, the minimally important difference (pain, 1 cm; SF-36 PCS, 5 points) was not reached for either parameter. Opioids were also associated with increased vomiting vs placebo (5.9% vs. 2.3%). When opioids were compared to nonsteroidal anti-inflammatory drugs (NSAIDs), similar improvements in pain and physical functioning were observed (pain WMD for opioids vs NSAIDs, -0.60 cm; 95% CI, -1.54 to 0.34; physical functioning WMD for opioids vs NSAIDs, -0.90 points; 95% CI, -2.69 to 0.89) (*Busse et al 2018*). Similarly, another systematic review and meta-analysis of 29 studies found that opioids and other commonly used classes of pain medication produced similar percent reductions in osteoarthritis pain (opioids, 35.4%; oral NSAIDs, 34.3%; topical NSAIDs, 40.9%; acetaminophen, 32.5%; cyclooxygenase-2 [COX-2] inhibitors, 36.9%) (*Stewart et al 2018*).
  - The Special Interest Group on Neuropathic Pain of the International Association for the Study of Pain conducted a systematic review and meta-analysis of randomized, double-blinded studies of oral and topical therapy for neuropathic pain and required a number needed to treat (NNT) for 50% pain relief as the primary measure. For tapentadol ER, the review identified one negative study and one positive enrichment study with a potential bias and a high NNT of 10.2 (95% CI, 5.3 to 185.5) in 67% of the patients responding to the open phase. Thirteen trials were identified with strong opioids, in which oxycodone (10 to 120 mg/day) and morphine (90 to 240 mg/day) were used mainly in peripheral neuropathic pain. The final quality of evidence was moderate. Ten trials were positive with a combined NNT of 4.3 (95% CI, 3.4 to 5.8) and a number needed to harm of 11.7 (95% CI, 8.4 to 19.3). Maximum effectiveness seemed to be associated with 180 mg morphine or equivalent (*Finnerup et al 2015*).
  - Another systematic review evaluated long-acting opioids in the treatment of moderate to severe cancer pain. The review included only double-blinded, randomized controlled trials for efficacy assessments; open-label and controlled

observational studies were allowed for safety assessments. A total of five RCTs and four observational studies met criteria for inclusion. Similar pain intensity improvements were demonstrated for oxycodone ER, oxycodone/naloxone ER, hydromorphone ER, and oxycodone ER. However, the average equivalent dose of oxycodone ER was significantly different from hydromorphone ER. The Morphine ER and hydromorphone ER groups had similar improvements in average cancer pain in the past 24 hours and "current pain in the morning;" however, the "worst pain in the past 24 hours" and "current pain in the evening" were significantly lower in the hydromorphone ER group. The quality of life scores were comparable between oxycodone ER and oxycodone/naloxone ER as well as morphine ER and hydromorphone ER in two trials. The rate of discontinuation due to lack of efficacy was similar among patients treated with morphine ER, hydromorphone ER, oxycodone ER or oxycodone/naloxone ER and ranged from 1.1% (oxycodone/naloxone ER) to 6.5% (hydromorphone ER). The risk of experiencing serious adverse events was comparable in patients treated with morphine ER or hydromorphone ER, morphine ER or fentanyl ER, and morphine ER or oxycodone ER. Overall, the reviewers concluded that there was no difference in efficacy and risk of harms among ER opioids in the treatment of cancer-related pain based on current evidence (*Mesgarpour et al 2014*).

- A recent pragmatic, 12-month, randomized trial (N = 240) compared opioid vs non-opioid medications on pain-related function, pain intensity, and adverse effects in patients with moderate to severe chronic back pain or hip or knee osteoarthritis pain despite analgesic use *(Krebs et al 2018)*.
  - Each intervention had its own prescribing strategy that included multiple medication options in 3 steps. In the opioid group, the first step was immediate-release morphine, oxycodone, or hydrocodone/acetaminophen. For the nonopioid group, the first step was acetaminophen or an NSAID. Medications were changed, added, or adjusted within the assigned treatment group according to individual patient response.
  - Groups did not significantly differ on pain-related function over 12 months (p = 0.58); mean 12-month Brief Pain Inventory (BPI) interference was 3.4 for the opioid group and 3.3 for the nonopioid group (difference, 0.1; 95% CI, −0.5 to 0.7). Pain intensity was significantly better in the nonopioid group over 12 months (p = 0.03); mean 12-month BPI severity was 4.0 for the opioid group and 3.5 for the nonopioid group (difference, 0.5; 95% CI, 0.0 to 1.0). Adverse medication-related symptoms were significantly more common in the opioid group over 12 months (p = 0.03); mean medication-related symptoms at 12 months were 1.8 in the opioid group and 0.9 in the nonopioid group (difference, 0.9; 95% CI, 0.3 to 1.5).
- Arymo ER and Morphabond were approved based on bioequivalence to MS Contin. In lieu of conducting new nonclinical studies and clinical studies of the safety and efficacy, the manufacturers relied on previous findings of efficacy and safety for MS Contin (*FDA Summary Review: Arymo ER 2017, Morphabond 2018*).
- The efficacy of buprenorphine buccal films was evaluated in three 12-week, double-blind (DB), placebo-controlled (PC) trials in opioid-naïve and opioid-experienced patients with moderate-to-severe chronic low back pain. In the trials, the DB treatment phase was preceded by an OL dose titration period. Patients were eligible for randomization into the 12-week DB treatment phase if they were able to titrate to a tolerable and effective buprenorphine dose. The primary efficacy variable was the patients' pain scores (based on a 0 to 10 numeric rating scale). Two of these studies demonstrated efficacy in patients with low back pain. One trial did not show a statistically significant pain reduction for Belbuca compared to placebo, and the results of this trial are not included in the Prescribing Information (*Belbuca Prescribing Information 2018, Gimbel et al 2016, Rauck et al 2016*).
  - In one study of opioid-naïve patients, pain scores increased more in the placebo group vs. the buprenorphine group during the DB phase; mean (standard deviation [SD]) changes from baseline to week 12 were 0.94 (1.85) and 1.59 (2.04) in the buprenorphine and placebo groups, respectively, with a significant between-group difference (-0.67; 95% CI, -1.07 to -0.26; p = 0.0012). A higher proportion of buprenorphine patients (62%) had at least a 30% reduction in pain score from prior to OL titration to study endpoint when compared to patients who received placebo (47%) (*Rauck et al 2016*).
  - In another study, opioid-experienced patients experienced a higher increase in their pain scores in the placebo vs. buprenorphine group after randomization. The difference between groups in the mean change from baseline to week 12 was -0.98 (95% CI, -1.32 to -0.64; p < 0.001). A significantly larger percentage of patients receiving buprenorphine than placebo had pain reductions ≥ 30% and ≥ 50% (p < 0.001 for both) (*Gimbel et al 2016*).

CLINICAL GUIDELINES

- Clinical guidelines do not state a preference for the use of one long-acting opioid over another for the use in moderate to severe pain (*Attal et al 2010, Bril et al 2011, Chou et al 2009, Hochberg et al 2012, Manchikanti et al 2017, Qaseem 2017, Paice et al 2016, The Medical Letter 2013*). However, opioid rotation is recommended if a patient experiences

adverse effects from one agent (*Chou et al 2009*). In addition, methadone safety guidelines from the 2014 American Pain Society recommend buprenorphine as an alternative to methadone for the treatment of opioid addiction in patients with risk factors or known QTc prolongation (*Chou et al 2014*).

- In March 2016, the CDC issued a guideline for prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care. The guideline addresses when to initiate or continue opioids for chronic pain; opioid selection, dosage, duration, follow-up, and discontinuation; and assessing risk and addressing harms of opioid use. Recommendations in the CDC guideline include the following (*Dowell et al 2016*):
  - Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate (category A, evidence 3).
  - Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety (category A, evidence 4).
  - Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy (category A, evidence 3).
  - When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of ER/long-acting opioids (category A, evidence 4).
  - Clinicians should prescribe opioids at the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to ≥ 50 MME/day, and should avoid increasing dosage to ≥ 90 MME/day or carefully justify a decision to titrate dosage to ≥ 90 MME/day (category A, evidence 3).
  - Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed (category A, evidence 4).
  - Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids (category A, evidence 4).
  - Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥ 50 MME/day), or concurrent benzodiazepine use, are present (category A, evidence 4).
  - Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months (category A, evidence 4).
  - When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs (category B, evidence 4).
  - Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible (category A, evidence 3).
  - Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder (category A, evidence 2).

Category of Recommendations:

- Category A: Applies to all persons; most patients should receive the recommended course of action.
- Category B: Individual decision making needed; different choices will be appropriate for different patients. Clinicians help patients arrive at a decision consistent with patient values and preferences and specific clinical situations.

Evidence Type:
- Type 1: Randomized clinical trials or overwhelming evidence from observational studies.
- Type 2: Randomized clinical trials with important limitations, or exceptionally strong evidence from observational studies.
- Type 3: Observational studies or randomized clinical trials with notable limitations.
- Type 4: Clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations.

- In February 2017, the American College of Physicians published clinical practice guidelines for noninvasive treatments of acute, subacute, and chronic low back pain. The guidelines state that clinicians should only consider opioids as an option in patients who have failed other treatments (e.g., non-pharmacological treatment, NSAIDs, tramadol, duloxetine) and only if the potential benefits outweigh the risks for individual patients and after a discussion of known risks and realistic benefits with patients (*Qaseem et al 2017*).
  - There is moderate-quality evidence that show strong opioids (tapentadol, morphine, hydromorphone, and oxymorphone) are associated with a small short-term improvement in pain scores (about 1 point on a pain scale of 0 to 10) and function compared with placebo. There is moderate-quality evidence that show no differences among different long-acting opioids for pain or function, and low-quality evidence shows no clear differences in pain relief between long- and short-acting opioids.
- In February 2017, the American Society of Interventional Pain Physicians (ASIPP) also published new practice guidelines for responsible, safe, and effective prescription opioids for chronic non-cancer pain. Similar to other guidelines, they do not recommend one opioid agent over the others. They do provide the following recommendations and conclusions for long-term opioid therapy (*Manchikanti et al 2017*):
  - Initiate opioid therapy with low dose, short-acting drugs, with appropriate monitoring (Evidence: Level II; Strength of Recommendation: Moderate).
  - Consider up to 40 MME as low dose, 41 to 90 MME as a moderate dose, and greater than 91 MME as high dose (Evidence: Level II; Strength of Recommendation: Moderate).
  - Avoid long-acting opioids for the initiation of opioid therapy (Evidence: Level I; Strength of Recommendation:
  - Strong).
  - Recommend methadone only for use after failure of other opioid therapy and only by clinicians with specific training in its risks and uses, within FDA recommended doses (Evidence: Level I; Strength of Recommendation: Strong).
  - Understand and educate patients of the effectiveness and adverse consequences (Evidence: Level I; Strength of Recommendation: Strong).
  - Similar effectiveness for long-acting and short-acting opioids with increased adverse consequences of long-acting opioids (Evidence: Level I-II; Strength of recommendation: Moderate to strong).
  - Recommend long-acting or high dose opioids only in specific circumstances with severe intractable pain (Evidence: Level I; Strength of Recommendation: Strong).
- The guidelines from the American College of Physicians and the American Society of Interventional Pain Physicians state that buprenorphine has lower quality evidence and is a third-line opioid for the treatment of pain (*Manchikanti et al 2017, Qaseem et al 2017*).
- Guidelines from the Society of Critical Care Medicine do not specifically address the use of long-acting opioids in intensive care unit patients; however, they recommend a multimodal approach to analgesia, using non-opioid medications as adjunctive therapy in order to decrease opioid use and optimize pain control (*Devlin et al 2018*). Similarly, an expert consensus guideline on opioid prescribing in surgical procedures from the American College of Surgeons does not make recommendations on long-acting opioid use in this setting, but recommends the maximization of non-opioid analgesia (ie, ibuprofen). It also provides recommendations on the number of oxycodone 5 mg tablets to prescribe after surgery, depending on the type of surgical procedure performed (*Overton et al 2018*). A guideline from the Orthopaedic Trauma Association provides recommendations for pharmacologic and nonpharmacologic pain management strategies in acute musculoskeletal injury; this guideline recommends avoiding long-acting opioids in the acute setting (*Hsu et al 2019*).

SAFETY SUMMARY

- On July 9, 2012, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) program for ER and long-acting opioids; on September 18, 2018, this REMS was modified to include all immediate-release opioids as well. This program, now known as the Opioid Analgesic REMS program, strongly encourages healthcare providers to complete an

approved training program on opioid analgesics. The goal of the REMS is to ensure that benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse.

- All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of buprenorphine buccal and transdermal systems, which are Schedule III controlled substances.
- Most long-acting opioids are associated with boxed warnings regarding the potential for abuse and misuse, life-threatening respiratory depression, neonatal opioid withdrawal syndrome, an interaction with alcohol, and accidental ingestion risks. Dolophine and methadone products have additional boxed warnings regarding life-threatening QT prolongation. Duragesic, Hysingla ER, OxyContin, Xtampza ER, and Zohydro ER also have a Boxed Warning for an interaction with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers). An additional Boxed Warning for Duragesic cautions against exposure to heat as it may cause increased fentanyl release.
- Key contraindications across the class include acute or severe bronchial asthma, significant respiratory depression, and known or suspected paralytic ileus.
- There are multiple warnings and precautions with each agent. Key safety concerns associated with the opioid analgesics include respiratory depression, driving and operating machinery, hypotension, interactions with other CNS depressants, neonatal opioid withdrawal syndrome, use in special populations, and use in those with gastrointestinal conditions.
- The frequency of adverse reactions varies to some degree with each agent; however, overall adverse reactions are similar within the class. The most common adverse events in adults include nausea, vomiting, constipation, and somnolence.
- OxyContin is approved in patients aged ≥ 11 years. The most frequent adverse events in pediatric patients were vomiting, nausea, headache, pyrexia, and constipation.
- In March 2016, the FDA issued a drug safety communication warning about several safety issues with opioids and describing new class-wide labeling requirements. The warnings include the following (*FDA Drug Safety Communication 2016*):
  - Opioids can interact with antidepressants and migraine medications to cause serotonin syndrome.
  - Taking opioids may rarely lead to adrenal insufficiency.
  - Long-term opioid use may be associated with decreased sex hormone levels and symptoms such as reduced interest in sex, impotence, or infertility.
- In August 2016, the FDA announced that it is requiring class-wide changes to drug labeling, including patient information, in order to help inform health care providers and patients of the serious risks associated with the combined use of certain opioid medications and benzodiazepines (*FDA Drug Safety Communication 2016*).
  - Among the changes, the FDA is requiring boxed warnings and patient-focused Medication Guides for prescription opioid analgesics, opioid-containing cough products, and benzodiazepines – nearly 400 products in total – with information about the serious risks associated with using these medications concomitantly. Risks include extreme sleepiness, respiratory depression, coma, and death.
- On March 14, 2017, the FDA Drug Safety Risk Management and Anesthetic and Analgesic Drug Products Advisory Committees voted 18 to 8, that the benefits of reformulated Opana ER (which did not originally gain the labeling describing potential abuse deterrent properties) no longer outweigh its risks. This vote followed an FDA analysis of epidemiological data that indicated that there was a shift in the pattern of Opana ER abuse from the nasal to the injection route after the product was reformulated (*FDA Advisory Committee 2017*). Following the FDA's official withdrawal request, the manufacturer (Endo) announced the voluntary market withdrawal of reformulated Opana ER (*Endo Press Release 2017*).
- On September 20, 2017, the FDA advised clinicians that opioid addiction medications, such as methadone and buprenorphine, should not be withheld from patients receiving concurrent benzodiazepines or other CNS depressants (*FDA Drug Safety Communication 2017*). Even though combination therapy with these agents increases the risk of serious side effects, the harm caused by untreated opioid addiction can outweigh these risks.
- In April 2019, the FDA issued a drug safety communication regarding the risk of serious harm when opioid medications are suddenly discontinued or doses are rapidly decreased in patients who are physically dependent on opioids. Sudden discontinuation or rapid dose reduction may result in serious withdrawal symptoms, uncontrolled pain, psychological distress, and suicide. Opioid medications should be tapered gradually according to an individualized schedule if discontinuation or dose reduction is necessary (*FDA Drug Safety Communication 2019*).

DOSING AND ADMINISTRATION

- Certain strengths are appropriate only for patients who are considered treatment-experienced. A detailed description is available within the prescribing information for each agent regarding when a patient is considered opioid-tolerant, and which strengths are appropriate in these patients.
- See prescribing information for detailed conversion recommendations as there are no established conversions from other opioid agents. When converting from one agent to another, it is better to underestimate need and monitor for breakthrough pain.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Arymo ER‡, Avinza*, Kadian, Morphabond, MS Contin (morphine sulfate)	ER capsules and tablets	Oral	Arymo ER, Morphabond, MS Contin: Every 8 to 12 hours Avinza: Once daily Kadian: Once daily	• Renal dose adjustment is required. • Hepatic dose adjustment is required.
Butrans, Belbuca (buprenorphine)	Transdermal system (Butrans) Buccal film (Belbuca)	Topical Oral	Administration every 7 days Every 12 hours	• Not evaluated in patients with severe hepatic impairment and should be administered with caution (Butrans). • The maximum dose is 900 mcg every 12 hours. Do not exceed this dose due to the potential for QTc interval prolongation. If pain is not adequately managed on a 900 mcg dose, consider an alternate analgesic (Belbuca). • For severe hepatic impairment, reduce the starting and incremental dose by half (Belbuca).
Dolophine, Methadose (methadone)	Oral solution, dispersible tablet, tablets	Oral	Every 8 to 12 hours (for management of pain)	• Due to the large variability in half-life (eg, 8 to 59 hours), dose adjustments may vary greatly. Dose increases may be no more frequent than every 3 to 5 days; however, some may require up to 12 days. • Due to the metabolism of methadone, patients with liver impairment may be at risk of accumulating methadone after multiple dosing.
Duragesic (fentanyl)	Transdermal system	Topical	Administration every 72 hours (Some patients may not achieve adequate analgesia using this dosing interval and may require systems be applied at 48 hours)	• Avoid use in patients with severe renal impairment. • Avoid use in patients with severe hepatic impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Exalgo§ (hydromorphone)	ER tablets	Oral	Once daily	• Moderate renal impairment: start 50% of the usual dose. • Severe renal impairment: start 25% of the usual dose. • Moderate hepatic impairment: start 25% of the usual dose.
Hysingla ER Zohydro ER (hydrocodone bitartrate)	ER capsules and tablets	Oral	Hysingla ER: Once daily Zohydro ER: Every 12 hours	• For severe hepatic impairment, reduce the Hysingla ER dose to 1/2 the usual initial dose and start Zohydro ER at the lowest dose of 10 mg every 12 hours. • Hysingla ER: In moderate to severe renal impairment (including end stage renal disease), reduce the initial dose to 1/2 the usual initial dose.
Levorphanol	Tablets	Oral	Every 6 to 8 hours	
Nucynta ER (tapentadol)	ER tablets	Oral	Twice daily	• Not recommended in patients with severe renal impairment. • Not recommended in patients with severe hepatic impairment. • In patients with moderate hepatic impairment, initiate at 50 mg every 24 hours and do not exceed 100 mg/day.
Opana ER (oxymorphone)†	ER tablets	Oral	Every 12 hours	• Contraindicated in moderate and severe hepatic impairment.
OxyContin; Xtampza ER (oxycodone)	ER capsules and tablets	Oral	Every 12 hours	• In hepatic impairment, initiate dose at 1/3 to 1/2 the recommended initial dose.
Combination Products				
Embeda (morphine sulfate/ naltrexone)	ER capsules	Oral	Once daily	• Renal dose adjustment may be required in severe renal impairment. • Hepatic dose adjustment may be required in severe hepatic impairment.

*All Avinza branded products have been removed from the market.
†Generic products of the pre-reformulated Opana ER are available. The branded versions of Opana ER (pre- and post-reformulation) are no longer available on the market.
‡Egalet discontinued the promotion and manufacture of Arymo ER branded products effective September 28, 2018.
§Brand product discontinued, but generic products are available.

CONCLUSION

- Opioids have been the mainstay of pain treatment for a number of years, and there is well-documented evidence of their effectiveness. Oral morphine is the standard for comparison for all other opioid agents currently available. There are

several long-acting opioid agents available, which are FDA-approved for the treatment of moderate to severe pain in patients requiring around-the-clock analgesia (*Cohen et al 2016*).
  - Levorphanol is indicated for moderate to severe pain where an opioid analgesic is appropriate; however, the FDA-approved indication does not stipulate that patients require around-the-clock, daily dosing for use.
  - Nucynta ER is the only long-acting agent in this class also indicated for neuropathic pain which requires daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
  - OxyContin has been FDA-approved as an option in pediatric patients, aged ≥ 11 years, for daily, around-the-clock, long term opioid treatment and for which alternative treatment options are inadequate. Unlike adults, pediatric patients must have responded to a minimum opioid daily dose of ≥ 20 mg oxycodone for 5 consecutive days prior to initiating treatment with OxyContin. Although study efficacy and safety data are not rigorous, OxyContin has been prescribed off-label for years within the pediatric population (*FDA Summary: OxyContin 2015*).
- All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of transdermal and buccal buprenorphine, which is a Schedule III controlled substance.
- Since 2013, a number of abuse deterrent formulations have come to the market. Although various manufacturers have introduced formulations with properties to deter misuse potential; there are only a few agents that have completed studies supporting the potential to deter abuse and misuse. The only long-acting opioids that meet all requirements and are currently available include OxyContin (oxycodone hydrochloride extended release), Embeda (morphine sulfate/naltrexone), Hysingla ER (hydrocodone bitartrate extended release), Morphabond (morphine sulfate extended release), and Xtampza ER (oxycodone extended release) (*FDA Industry Guidance 2015*).
- All long-acting opioids are part of the Opioid Analgesic REMS program. In general, all of the long-acting opioids are similar in terms of adverse events, warnings, and contraindications. Methadone-containing products warn of the potential for QTc prolongation and risks associated with an interaction with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) is cited within Duragesic, Hysingla ER, OxyContin, Xtampza ER, and Zohydro ER labeling. The main differences among the individual agents and formulations are due to dosing requirements and generic availability.
  - Several generic long-acting opioids exist, including hydromorphone; oxymorphone; levorphanol; fentanyl transdermal systems; methadone tablets, solution, and concentrate; morphine sulfate ER tablets and capsules; and oxycodone.
- Head-to-head trials demonstrate similar efficacy among the agents in the class. Systematic reviews and treatment guidelines from several professional organizations support and recommend opioids as a potential treatment option for various forms of non-cancer and cancer-related pain; however, some meta-analyses in non-cancer pain have not found a clinically meaningful difference between opioids, other non-opioid pain medications, and placebo. No single opioid is recommended over the others (*Busse et al 2018, Chou et al 2015, Finnerup et al 2015, Mesgarpour et al 2014, Stewart et al 2018*).
- Methadone safety guidelines from the 2014 American Pain Society recommend buprenorphine as an alternative to methadone for the treatment of opioid addiction in patients with risk factors or known QTc prolongation (*Chou et al 2014*). Other current clinical guidelines do not state a preference for the use of one long-acting opioid over another for use in moderate to severe pain (*Attal et al 2010, Bril et al 2011, Chou et al 2009, Hochberg et al 2012, Manchikanti et al 2012, Qaseem et al 2017*). However, opioid rotation is recommended if a patient experiences adverse effects from one agent (*Chou et al 2009*). A guideline from the CDC has been published that addresses the use of chronic pain outside of active cancer treatment, palliative care, and end-of-life care; this guideline emphasizes the use of nonpharmacologic and nonopioid therapies when possible, and notes that clinicians should consider opioid therapy only if the expected benefits for both pain and function are anticipated to outweigh risks to the patient (*Dowell et al 2016*).

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INTRODUCTION

- Asthma is a chronic lung disease that inflames and narrows the airways, making it difficult to breathe. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing (*Centers for Disease Control and Prevention [CDC] 2019*).
- The exact cause(s) of asthma are unknown. A combination of factors such as genetics, certain respiratory infections during childhood, and contact with airborne allergens can contribute to its development (*CDC 2019*).
- The goal of asthma management – asthma control – can be described in the following domains (*National Heart, Lung, and Blood Institute [NHLBI] 2007*):
  - Reduction of impairment
    - Prevent chronic and troublesome symptoms (eg, coughing or breathlessness in the daytime, at night, or after exertion)
    - Require infrequent use (≤ 2 days a week) of short-acting beta-agonist (SABA) for quick relief of symptoms
    - Maintain (near) normal pulmonary function
    - Maintain normal activity levels (including exercise and other physical activity and attendance at work or school)
    - Meet patients' and families' expectations of and satisfaction with asthma care.
  - Reduction of risk
    - Prevent recurrent exacerbations of asthma and minimize the need for emergency department visits or hospitalizations
    - Prevent progressive loss of lung function; for children, prevent reduced lung growth
    - Provide optimal pharmacotherapy with minimal or no adverse effects.
- Current pharmacologic options for asthma management are categorized as: (1) long-term control medications to achieve and maintain control of persistent asthma, and (2) quick-relief medications used to treat acute symptoms and exacerbations.
  - Long-term control medications include:
    - Corticosteroids (inhaled corticosteroids [ICS] for long-term control; short courses of oral corticosteroids to gain prompt control of disease, long-term oral corticosteroids for severe persistent asthma)
    - Cromolyn sodium and nedocromil
    - Immunomodulators (eg, omalizumab)
    - Leukotriene modulators
    - Long-acting beta-agonists (LABAs)
    - Methylxanthines (ie, theophylline)
  - Quick-relief medications include:
    - Anticholinergics (ie, ipratropium bromide), as an alternative bronchodilator for those not tolerating a SABA
    - SABAs (therapy of choice for relief of acute symptoms and prevention of exercise-induced bronchospasm)
    - Systemic corticosteroids (not short-acting, but used for moderate and severe exacerbations) (*NHLBI 2007*)
- Approximately 5 to 10% of asthma patients have severe disease. Severe asthma includes various clinical phenotypes of poorly controlled asthma characterized by frequent use of high-dose ICS and/or oral corticosteroids (*Chung et al 2014*).
- While there are currently no widely accepted definitions of specific asthma phenotypes, several strategies have been proposed to categorize severe asthma phenotypes based on characteristics such as patient age, disease onset, corticosteroid resistance, chronic airflow obstruction, or type of cellular infiltrate in the airway lumen or lung tissue (*Walford et al 2014*). The most recent guideline from the Global Initiative for Asthma (GINA) on severe or difficult-to-treat asthma recommends assessing for Type 2 inflammation through blood and sputum eosinophil levels, exhaled nitric oxide level and allergic triggers to asthma (*GINA 2019b*)
- Chronic idiopathic urticaria (CIU), also called chronic urticaria or spontaneous urticaria, is defined by the presence of hives on most days of the week for a period of 6 weeks or longer, with or without angioedema. The hives are circumscribed, raised, erythematous plaques, often with central pallor, and variable in size. No external allergic cause or contributing disease process can be identified in 80 to 90% of adults and children with CIU (*Khan 2019, Saini 2018*).

- CIU affects up to 1% of the general population in the United States, and the prevalence is believed to be similar in other countries. The condition is more common in adults than children and typically begins in the third to fifth decades of life. CIU is a self-limited disorder in most patients although the condition generally has a prolonged duration of 2 to 5 years (*Saini 2018*).
- Non-sedating H_1-antihistamines are the cornerstone of therapy for CIU. Limited courses of oral glucocorticoids are often used in combination with antihistamines for refractory symptoms. Other pharmacologic options for patients who do not respond to H_1-antihistamines include the use of H_2-antihistamines, leukotriene modifiers, cyclosporine, sulfasalazine, and dapsone (*Khan 2019, Maurer et al 2013*).
- Eosinophilic granulomatosis with polyangiitis (EGPA), previously called Churg-Strauss syndrome, is a systemic necrotizing vasculitis that affects small-to-medium-sized vessels. It is typically associated with eosinophilia and severe asthma (*Groh et al 2015, Padmanabhan et al 2019).*
- EGPA is a rare condition with a prevalence of approximately 13 cases per 1 million persons and an annual incidence of approximately 7 new cases per 1 million persons. It has a higher incidence in patients with asthma (*Groh et al 2015*).
- Systemic glucocorticoids are the mainstay of treatment for EGPA. For refractory EGPA, the addition of cyclophosphamide, azathioprine, methotrexate, rituximab, or intravenous immunoglobulins (IVIG) can be considered *(Groh et al 2015).* In more than 85% of patients with EGPA, remission can be achieved with glucocorticoids with or without an immunosuppressant; however, relapses occur in more than 33% of patients (*Pagnoux and Groh 2016*).
- Atopic dermatitis (AD) is a chronic inflammatory skin condition characterized by dry skin, erythema, oozing, crusting, and severe pruritus exacerbated by various environmental stimuli. It is associated with increased immunoglobulin E (IgE) levels and a history of atopy (asthma, allergic rhinitis, or eczema). A genetic defect that leads to dysfunction of the epidermal skin barrier along with an impaired immune response to microbial entry through the epidermis are believed to be the underlying causes of the condition (*Weston and Howe 2019a*).
- AD affects up to 25% of children and 2 to 3% of adults. It can manifest at different sites depending on the age at onset. The prevalence appears to be increasing especially in Western societies (*Sidbury et al 2014*, *Weston and Howe 2019a*).
- Topical emollients and topical corticosteroids are first-line treatments for AD. Topical calcineurin inhibitors are generally reserved as a second-line treatment option. The use of systemic therapies is reserved for patients with moderate to severe disease and can include phototherapy, oral cyclosporine, or other systemic immunosuppressants (*Weston and Howe 2019b*).
- Chronic rhinosinusitis with nasal polyposis has a prevalence of approximately 2.7% in adults, and peaks in the sixth decade of life. Symptoms include nasal obstruction, reduced sense of smell, and sleep disturbance, all of which can substantially impact quality of life. The majority of cases are idiopathic, but may be due to genetic, metabolic, or immunologic causes, resulting in inflammation characterized by eosinophilia and elevated levels of IL-4, IL-5, and IL-13 *(Hopkins 2019)*.
- Common treatment options for chronic rhinosinusitis with nasal polyposis include saline irrigation and intranasal glucocorticoids in patients with mild symptoms, and short-term systemic glucocorticoids, surgery, and biologic agents in patients with severe symptoms *(Hopkins 2019)*.
- This monograph describes the use of Cinqair (reslizumab), Dupixent (dupilumab), Fasenra (benralizumab), Nucala (mepolizumab), and Xolair (omalizumab).
  - Cinqair, Fasenra, and Nucala are humanized monoclonal antibody interleukin-5 (IL-5) antagonists. The mechanism of action of Fasenra is slightly different, in that it binds to the IL-5 receptor on immune effector cells, whereas Cinqair and Nucala bind to the IL-5 cytokine. Eosinophils play a key role in the pathobiology of airway disorders by contributing to inflammation through release of leukotrienes and pro-inflammatory cytokines. Increases in eosinophils are often correlated with greater asthma severity. IL-5, a cytokine critical to eosinophil differentiation and survival, has been isolated as a potential target in eosinophilic asthma. Nucala is also approved for the treatment of adult patients with EGPA.
  - Xolair is a recombinant DNA-derived monoclonal antibody that selectively binds to human IgE. Xolair, which reduces the allergic response mediators, is useful in a subset of patients with allergic asthma. In addition, Xolair has been shown to improve symptoms in patients with CIU.
  - Dupixent is a human monoclonal antibody that inhibits signaling of IL-4 and IL-13. This results in reduction of release of inflammatory mediators including cytokines, chemokines, nitric oxide and IgE. These actions are useful for eosinophilic asthma, controlling symptoms of moderate to severe AD, and add-on therapy for inadequately controlled chronic rhinosinusitis with nasal polyposis.
- Medispan class: Antiasthmatic – Monoclonal Antibodies

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Cinqair (reslizumab)	--
Dupixent (dupilumab)	--
Fasenra (benralizumab)	--
Nucala (mepolizumab)	--
Xolair (omalizumab)	--

(*Drugs@FDA 2019, Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations 2019*)

INDICATIONS

Table 2: Food and Drug Administration Approved Indications*

Indication	Cinqair† (reslizumab)	Dupixent (dupilumab)	Fasenra† (benralizumab)	Nucala (mepolizumab)	Xolair‡ (omalizumab)
Moderate to severe persistent asthma in patients 6 years of age and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with ICS					✔
Add-on maintenance treatment for patients 12 years of age and older with severe asthma with an eosinophilic phenotype			✔		
Add-on maintenance treatment for patients 6 years of age and older with severe asthma with an eosinophilic phenotype				✔	
Add-on maintenance treatment for patients 12 years of age and older with moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma		✔			
Add-on maintenance treatment for patients 18 years of age and older with severe asthma with an eosinophilic phenotype	✔				
Treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA)				✔	

Indication	Cinqair† (reslizumab)	Dupixent (dupilumab)	Fasenra† (benralizumab)	Nucala (mepolizumab)	Xolair‡ (omalizumab)
The treatment of adults and adolescents 12 years of age and older with CIU who remain symptomatic despite H_1-antihistamine treatment.					✔
Treatment of patients 12 years of age and older with moderate-to-severe AD not adequately controlled with topical prescription therapies or when those therapies are not advisable		✔			
Add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis		✔			

*None of the agents are indicated for the relief of acute bronchospasm or status asthmaticus.
†Not indicated for treatment of other eosinophilic conditions
‡Not indicated for other allergic conditions or other forms of urticaria

(*Prescribing information: Cinqair 2019, Dupixent 2019, Fasenra 2019, Nucala 2019, Xolair 2019*)

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

OMALIZUMAB

Asthma

- The original Food and Drug Administration (FDA) approval of omalizumab was based on the results of 3 randomized, double-blind, placebo-controlled, multicenter trials conducted in patients ≥ 12 years of age with moderate to severe asthma for ≥ 1 year and a positive skin test reaction to a perennial aeroallergen. All patients were required to have a baseline IgE between 30 and 700 international unit (IU)/mL and body weight not more than 150 kg. Patients were treated according to a dosing table to administer at least 0.016 mg/kg/IU (IgE/mL) of omalizumab or placebo over each 4-week period.
  - Each study was comprised of a run-in period to achieve a stable conversion to a common ICS, followed by randomization to omalizumab or placebo. Patients received omalizumab for 16 weeks with an unchanged ICS dose unless an acute exacerbation necessitated an increase. Patients then entered an ICS reduction phase of 12 (*Busse et al 2001, Solèr et al 2001*) and 16 weeks (*Holgate et al 2004*) during which ICS dose reduction was attempted in a stepwise manner.
  - In the 28-week study by Busse et al (N = 525), during the steroid stable phase, patients treated with omalizumab had fewer mean exacerbations/subject (0.28 vs 0.54; p = 0.006) and decreased mean duration of exacerbations (7.8 vs 12.7 days; p < 0.001) compared with placebo-treated patients. Similarly, during the steroid reduction phase, omalizumab was associated with fewer exacerbations/subject (0.39 vs 0.66; p = 0.003), and a shorter mean duration of exacerbations (9.4 vs 12.6 days; p = 0.021) (*Busse et al 2001*).
  - In the 28-week study by Solèr et al (N = 546), asthma exacerbations/patient, the primary endpoint, decreased more in the omalizumab group compared to placebo during both the stable steroid (0.28 vs 0.66; p < 0.001) and steroid reduction phases (0.36 vs 0.75; p < 0.001) (*Solèr et al 2001*).

- In the 32-week study by Holgate et al (N = 246), the percentage reduction in ICS dose, the primary endpoint, was greater among patients treated with omalizumab than among patients treated with placebo (median, 60 vs 50%; p = 0.003). The percentages of patients with ≥ 1 asthma exacerbation were similar between omalizumab and placebo groups during both the stable steroid and steroid reduction phases (p value not reported). The absence of an observed treatment effect may be related to differences in the patient population compared with the first 2 studies, study sample size, or other factors (*Holgate et al 2004*).

- A meta-analysis of 3 of the previously mentioned trials (*Busse et al 2001, Holgate et al 2004, Solèr et al 2001*) and their extension studies assessed the efficacy of omalizumab in a subgroup of 254 patients at high risk of serious asthma-related mortality and morbidity. Patients were defined as high-risk due to asthma histories that included the following: intubation history, emergency room visit within the last year, overnight hospitalization, or intensive care unit treatment. The primary outcome was an annualized rate of acute exacerbation episodes based on data from the initial 16-week stable steroid phase for high-risk patients. Two kinds of acute exacerbation episodes were considered as endpoints: significant acute exacerbation episodes and all acute exacerbation episodes (ie, all episodes recorded by the investigator). Significant acute exacerbation episodes were defined as those requiring a doubling of baseline ICS dose (*Busse et al 2001, Solèr et al 2001*) or use of systemic steroids (all 3 studies). During the stable steroid phase, mean significant acute exacerbation episode rates were 1.56 and 0.69/patient-year, respectively, a reduction of 56% with omalizumab (p = 0.007). Similar reductions in exacerbations in favor of omalizumab were observed for the whole study period and for all acute exacerbation episodes. The authors concluded that 113 significant acute exacerbation episodes were prevented for every 100 patients treated with omalizumab for 1 year (*Holgate et al 2001*).
- A Cochrane Review conducted in 2014 evaluated the efficacy of omalizumab in patients with allergic asthma. Treatment with omalizumab was associated with a significant reduction in the odds of a patient having an asthma exacerbation (odds ratio [OR], 0.55; 95% confidence interval [CI], 0.42 to 0.6; 10 studies; 3261 participants). This represents an absolute reduction from 26% for participants suffering an exacerbation on placebo to 16% on omalizumab, over 16 to 60 weeks. Additionally, in patients with moderate to severe asthma and in those who were receiving background ICS therapy, treatment with omalizumab resulted in a significant reduction in the odds of having an asthma exacerbation (OR, 0.50; 95% CI, 0.42 to 0.6; 7 studies; 1889 participants). A significant benefit was noted for subcutaneous (SC) omalizumab vs placebo with regard to reducing hospitalizations (OR, 0.16, 95% CI, 0.06 to 0.42; 4 studies; 1824 participants), representing an absolute reduction in risk from 3% with placebo to 0.5% with omalizumab over 28 to 60 weeks. The authors concluded that omalizumab was effective in reducing asthma exacerbations and hospitalizations as an adjunctive therapy to ICS and significantly more effective than placebo in increasing the numbers of participants who were able to reduce or withdraw their ICS. Omalizumab was generally well tolerated, although there were more injection site reactions with omalizumab. However, the clinical value of the reduction in steroid consumption has to be considered in light of the high cost of omalizumab (*Normansell et al 2014*).
- A systematic review of 8 randomized, placebo-controlled trials (N = 3429) evaluated the efficacy and safety of SC omalizumab as add-on therapy to corticosteroids in children and adults with moderate to severe allergic asthma. At the end of the steroid reduction phase, patients taking omalizumab were more likely to be able to withdraw corticosteroids completely compared with placebo (relative risk [RR], 1.8; 95% CI, 1.42 to 2.28; p = 0.00001). Omalizumab patients showed a decreased risk for asthma exacerbations at the end of the stable (RR, 0.57; 95% CI, 0.48 to 0.66; p = 0.0001) and adjustable-steroid phases (RR, 0.55; 95% CI, 0.47 to 0.64; p = 0.0001); post-hoc analysis suggests this effect was independent of duration of treatment, age, severity of asthma, and risk of bias. The frequency of serious adverse effects was similar between omalizumab (3.8%) and placebo (5.3%). However, injection site reactions were more frequent in the omalizumab patients (19.9 vs 13.2%). Omalizumab was not associated with an increased risk of hypersensitivity reactions, cardiovascular effects, or malignant neoplasms (*Rodrigo et al 2011*).
- In July 2016, the FDA expanded the indication of omalizumab to patients 6 to 11 years of age with moderate to severe persistent asthma. The approval was based primarily on a 52-week, randomized, double-blind, placebo-controlled, multicenter trial. The study evaluated the safety and efficacy of omalizumab as add-on therapy in 628 pediatric patients 6 to < 12 years of age with moderate to severe asthma inadequately controlled despite the use of an ICS (*Lanier et al 2009*).
  - Over the 24-week fixed-steroid phase, omalizumab reduced the rate of clinically significant asthma exacerbations (worsening symptoms requiring doubling of baseline ICS dose and/or systemic steroids) by 31% vs placebo (0.45 vs 0.64; RR, 0.69; p = 0.007). Over a period of 52 weeks, the exacerbation rate was reduced by 43% (p < 0.001). Other efficacy variables such as nocturnal symptom scores, beta-agonist use, and forced expiratory volume in 1 second (FEV_1) were not significantly different in omalizumab-treated patients compared to placebo.

- A 2017 systematic review of 3 randomized, placebo-controlled trials and 5 observational studies evaluated the safety and efficacy of omalizumab in children and adolescents. Omalizumab reduced exacerbations compared with placebo or baseline in all studies that included this outcome. The randomized controlled trials did not identify significant differences in FEV_1; however, 3 of the 4 observational studies that included this outcome did find significant FEV_1 improvement with omalizumab. Generally, ICS and rescue medication use were reduced with omalizumab in the studies. The authors concluded that the evidence strongly supports omalizumab safety and efficacy in patients 6 to 11 years *(Corren et al 2017)*.
- The EXCELS study was a multicenter, observational cohort study to evaluate the clinical effectiveness and long-term safety of omalizumab in patients with moderate-to-severe allergic asthma. Patients were evaluated as part of 3 groups: non-omalizumab users, those newly starting omalizumab, and those who were established users at study initiation.
  - Interim efficacy results demonstrated that at month 24, the ACT score increased in all 3 patient groups: from 18.4 to 20 in non-omalizumab users, from 15.2 to 19.4 in those newly starting on omalizumab, and from 18.2 to 19.4 in established omalizumab users. For patients newly starting omalizumab treatment, 54% achieved at least a minimally important difference, defined as a ≥ 3 point increase from baseline in ACT. The study demonstrated that established users of omalizumab maintained asthma control during the study period (*Eisner et al 2012*).
  - To investigate the relationship between omalizumab and malignant neoplasms, safety information from the EXCELS trial was analyzed. Similar rates of primary malignancies in omalizumab- and non-omalizumab-treated patients were found. However, study limitations preclude definitively ruling out a malignancy risk with omalizumab (*Long et al 2014*).
  - A higher incidence of overall cardiovascular and cerebrovascular serious adverse events was observed in omalizumab-treated patients compared to non-omalizumab-treated patients (*Iribarren et al 2017*). To further evaluate the risk, a pooled analysis of 25 randomized controlled trials was conducted. An increased risk of cardiovascular and cerebrovascular serious adverse events was not noted, but the low number of events, the young patient population, and the short duration of follow-up prevent a definite conclusion about the absence of a risk (*FDA 2014*).
  - Patients from the EXCELS study were eligible for the XPORT trial, a 52-week, randomized, placebo-controlled trial evaluating the persistence of response to omalizumab in patients who discontinued omalizumab therapy after long-term use. Patients were randomized to continue their omalizumab therapy or to omalizumab discontinuation. More patients who continued omalizumab did not have an exacerbation compared to those who discontinued therapy (67.0% vs 47.7%; absolute difference, 19.3%; 95% CI, 5.0 to 33.6). The authors concluded that continuation of omalizumab after long-term use results in sustained benefit *(Ledford et al 2017)*.

Chronic Idiopathic Urticaria

- The safety and efficacy of omalizumab for the treatment of CIU was assessed in 2 placebo-controlled, multiple-dose clinical studies. Patients received omalizumab 75, 150, or 300 mg or placebo by SC injection every 4 weeks in addition to their baseline level of H_1 antihistamine therapy for 24 or 12 weeks, followed by a 16-week washout observation period. In both studies, patients who received omalizumab 150 mg or 300 mg had greater decreases from baseline in weekly itch severity scores and weekly hive count scores than placebo at week 12. The 75 mg dose did not demonstrate consistent evidence of efficacy and is not approved for use (*Kaplan et al 2013, Maurer et al 2013*).
- Another randomized, double-blind, placebo-controlled study evaluated omalizumab as add-on therapy for 24 weeks in patients with CIU who remained symptomatic despite H_1 antihistamine therapy. Similar to previous studies, patients treated with omalizumab had significantly greater reductions in weekly itch severity score from baseline to week 12 compared to placebo ($p \leq 0.001$) (*Saini et al 2015*).
- A meta-analysis of randomized clinical trials evaluating omalizumab for the treatment of CIU was published in 2016. The analysis included 7 randomized, placebo-controlled studies with 1312 patients with CIU. Patients treated with omalizumab (75 to 600 mg every 4 weeks) had significantly reduced weekly itch and weekly wheal scores compared with the placebo group. The effects of omalizumab were dose dependent, with the strongest reduction in weekly itch and weekly wheal scores observed with 300 mg. Rates of complete response were significantly higher in the omalizumab group ($p < 0.00001$) and dose dependent, with the highest rates in the 300 mg group. Rates of patients with adverse events were similar in the omalizumab and placebo groups (*Zhao et al 2016*). Similar results were identified in a 2019 meta-analysis of 6 trials comparing omalizumab with placebo *(Rubini et al 2019)*.
- A Phase 4 randomized clinical trial evaluated the effect of omalizumab in 205 patients with antihistamine-resistant CIU/chronic spontaneous urticaria. After an initial 24-week period of open-label treatment with omalizumab 300 mg every 4 weeks, patients randomized to continue omalizumab for another 24 weeks of double-blind therapy experienced a significantly lower rate of clinical worsening compared with patients randomized to double-blind placebo (21.0% vs

60.4%; p < 0.0001). No new safety signals were detected over the 48-week omalizumab treatment period *(Maurer et al 2018)*.

BENRALIZUMAB

Asthma

- The safety and efficacy of benralizumab were evaluated in a 52-week dose-ranging exacerbation trial, 3 confirmatory trials, and a 12-week lung function trial (*Bleecker et al 2016, Castro et al 2014, Ferguson et al 2017, Fitzgerald et al 2016, Nair et al 2017*).
  - In a randomized, controlled, double-blind, dose-ranging Phase 2b study, 324 adults with uncontrolled eosinophilic asthma were randomly assigned to placebo (n = 80), benralizumab 2 mg (n = 81), benralizumab 20 mg (n = 81), or benralizumab 100 mg (n = 82) and 285 adults with non-eosinophilic asthma were randomized to benralizumab 100 mg (n = 142) or placebo (n = 143) (*Castro et al 2014*). Treatments were given as 2 SC injections every 4 weeks for the first 3 doses, then every 8 weeks, for 1 year. Among adults with eosinophilic asthma, benralizumab 100 mg reduced exacerbation rates as compared to placebo (0.34 vs 0.57; rate reduction, 41%; 80% CI, 11 to 60; p = 0.096). A significant reduction in exacerbation rates was not seen with benralizumab 2 mg or 20 mg as compared to placebo in these patients. In patients with a baseline blood eosinophil count of ≥ 300 cells/µL, exacerbation rates were lower than in the placebo group for the benralizumab 20 mg (0.30 vs 0.68; rate reduction, 57%; 80% CI, 33 to 72; p = 0.015) and 100 mg (0.38 vs 0.68; rate reduction, 43%; 80% CI, 18 to 60; p = 0.049) groups.
  - SIROCCO was a randomized, multicenter, double-blind, placebo-controlled, 48-week, Phase 3 trial (N = 1205) involving patients with severe asthma with eosinophilia uncontrolled with high-dose ICS and LABAs (*Bleecker et al 2016*). Enrolled patients were randomly assigned to placebo (n = 407), benralizumab 30 mg every 4 weeks (n = 400), or benralizumab 30 mg every 8 weeks (n = 398). Compared with placebo, benralizumab reduced the annual asthma exacerbation rate over 48 weeks when administered every 4 weeks (RR, 0.55; 95% CI, 0.42 to 0.71; p < 0.0001) or every 8 weeks (RR, 0.49; 95% CI, 0.37 to 0.64; p < 0.0001). Both doses of benralizumab also significantly improved pre-bronchodilator FEV_1 in patients at week 48 vs placebo. Asthma symptoms were improved with benralizumab every 8 weeks, but not every 4 weeks, as compared to placebo.
  - CALIMA was a randomized, multicenter, double-blind, placebo-controlled, 56-week, Phase 3 trial that assessed benralizumab as add-on therapy (to high-dose ICS and LABA) for patients with severe, uncontrolled asthma and elevated blood eosinophil counts (*Fitzgerald et al 2016*). A total of 1306 patients were randomly assigned to benralizumab 30 mg every 4 weeks (n = 425), benralizumab 30 mg every 8 weeks (n = 441) or placebo (n = 440). When compared to placebo, significant reductions in annual exacerbation rates were seen with benralizumab every 4 weeks (RR, 0.64; 95% CI, 0.49 to 0.85; p = 0.0018) and every 8 weeks (RR, 0.72; 95% CI, 0.54 to 0.95; p = 0.0188). Benralizumab was also associated with significantly improved pre-bronchodilator FEV_1 and total asthma symptom scores vs placebo.
  - Patients enrolled in the SIROCCO and CALIMA trials who completed treatment were eligible for the BORO Phase 3 safety extension trial. This was a randomized, double-blind study that randomized patients to received benralizumab 30 mg every 4 or 8 weeks. Adult patients received treatment for 52 weeks and adolescents (12 to 17 years of age) were treated for 108 weeks. A total of 1576 patients were included in the full-analysis set with safety assessed at 56 weeks. Treatment discontinuation due to any adverse event occurred in approximately 2% of patients in each group. The most common adverse events were viral upper respiratory tract infections and worsening asthma. Serious adverse events included worsening asthma (3% in the every-8-week dosing group and 4% in the every-4-week dosing group), pneumonia (< 1% in both groups) and pneumonia caused by bacterial infection (< 1% in the every-4-week dosing group and 1% in the every-8-week dosing group). New malignancy occurred in 12 (1%) of the 1,576 patients. Hypersensitivity related to treatment occurred in 3 patients. For the secondary efficacy outcome, patients with elevated blood eosinophil levels had similar exacerbation rates to that observed during the first year of treatment in the SIROCCO and CALIMA trials (*Busse et al 2018*).
  - BISE was a randomized, multicenter, double-blind, placebo-controlled, 12-week, Phase 3 trial that evaluated benralizumab therapy for patients with mild to moderate persistent asthma (*Ferguson et al 2017*). Patients (N = 211) had been receiving either low- to medium-dose ICS or low-dose ICS plus LABA therapy and were randomized to benralizumab 30 mg every 4 weeks (n = 106) or placebo (n = 105). Benralizumab resulted in an 80 mL (95% CI, 0 to 150; p = 0.04) greater improvement in pre-bronchodilator FEV_1 after 12 weeks as compared to placebo. Despite this improvement, this lung function result does not warrant the use of benralizumab in mild to moderate asthma because it did not reach the minimum clinically important improvement of 10%.

- ZONDA was a randomized, multicenter, double-blind, placebo-controlled, 28-week trial that primarily assessed whether or not benralizumab was effective as an oral glucocorticoid-sparing therapy in patients on oral steroids to manage severe asthma associated with eosinophilia (*Nair et al 2017*). Of the enrolled patients, 220 were randomly assigned to benralizumab 30 mg every 4 weeks (n = 72), benralizumab 30 mg every 8 weeks (n = 73), or placebo (n = 75). Results revealed that the 2 benralizumab dosing regimens significantly reduced the median final oral glucocorticoid doses from baseline by 75% vs a 25% reduction seen with placebo ($p < 0.001$ for both comparisons). Additionally, benralizumab administered every 4 weeks resulted in an annual exacerbation rate that was 55% lower than that seen with placebo (marginal rate, 0.83 vs 1.83; $p = 0.003$) and benralizumab administered every 8 weeks resulted in a 70% lower rate than that seen with placebo (marginal rate, 0.54 to 1.83; $p < 0.001$).

- Fitzgerald et al conducted a study exploring the efficacy of benralizumab for patients with different baseline blood eosinophil thresholds and exacerbation histories. This study was a pooled analysis (n = 2295 patients) of the results from the SIROCCO and CALIMA phase 3 studies. The annual exacerbation rate among patients with baseline blood eosinophil counts of ≥ 0 cells/μL was 1.16 (95% CI, 1.05 to 1.28) in patients who received placebo vs 0.75 (0.66 to 0.84) in patients who received benralizumab every 8 weeks (RR, 0.64; 0.55 to 0.75; $p < 0.0001$). In patients who received benralizumab every 4 weeks who had eosinophil counts of ≥ 0 cells/μL, the annual exacerbation rate was 0.73 (0.65 to 0.82); RR vs placebo was 0.63 (0.54 to 0.74; $p < 0.0001$). The extent to which exacerbation rates were reduced increased with increasing blood eosinophil thresholds and with greater exacerbation history in patients in the every-4-week and every-8-week benralizumab groups. Greater improvements in the annual exacerbation rate were seen with benralizumab compared with placebo for patients with a combination of high blood eosinophil thresholds and a history of more frequent exacerbations *(FitzGerald et al 2018).*
- A 2017 meta-analysis evaluated the therapeutic efficacy and safety of benralizumab in patients with eosinophilic asthma. A total of 7 articles (n = 2321) met the inclusion criteria of the systematic review. The pooled analysis found that benralizumab significantly reduced exacerbations (RR, 0.63; 95% CI, 0.52 to 0.76; $p < 0.00001$) compared to placebo. There was no statistical trend for improvement in FEV_1 or asthma control indices such as Quality of Life Assessment (AQLQ) and Asthma Control Questionnaire score in benralizumab-treated patients. In addition, safety data indicated that benralizumab administration resulted no increasing incidence of adverse events and was well tolerated (RR, 1.00; 95% CI, 0.95 to 1.05; $p = 0.96$) *(Tien et al 2017)*.

MEPOLIZUMAB

Asthma

- The safety and efficacy of mepolizumab were evaluated in 3 double-blind, placebo-controlled, multicenter, randomized controlled trials in adolescent and adult patients with severe refractory asthma and signs of eosinophilic inflammation. Generally, patients were eligible for enrollment in the trials if they had eosinophils ≥ 150 cells/μL in the peripheral blood at screening or ≥ 300 cells/μL at some time during the previous year. Patients also were required to be on a high-dose ICS as well as another controller medication (*Bel et al 2014, Ortega et al 2014, Pavord et al 2012*).
  - DREAM was a dose-ranging, 52-week, Phase 2b/3 study (N = 621) that compared annual asthma exacerbation frequency and improvements in clinical symptoms between patients receiving 75 mg, 250 mg, and 750 mg intravenous (IV) mepolizumab and placebo. Mepolizumab decreased clinically significant exacerbation rates across all doses compared to placebo, at a rate of 2.40 per patient per year in the placebo group, 1.24 in the 75 mg mepolizumab group ($p < 0.0001$), 1.46 in the 250 mg mepolizumab group ($p = 0.0005$), and 1.15 in the 750 mg mepolizumab group ($p < 0.0001$). No significant improvements were found for secondary clinical symptom measures, which included change in pre-bronchodilator FEV_1 from baseline, or change in Asthma Control Questionnaire (ACQ) scores *(Pavord et al 2012)*.
  - MENSA was a 32-week Phase 3 trial (N = 576) that compared annual asthma exacerbation frequency and improvements in clinical symptoms between patients receiving SC and IV mepolizumab vs placebo. Patients were selected on the basis of frequent exacerbations, treatment with high doses of ICS, and a defined blood eosinophil count. Both SC and IV mepolizumab significantly decreased clinically significant exacerbation rates compared to placebo, at a rate of 1.74 per patient per year in the placebo group, 0.93 per patient per year in the IV mepolizumab group ($p < 0.001$), and 0.83 per patient per year in the SC mepolizumab group ($p < 0.001$). In both the SC and IV mepolizumab-treated groups, the ACQ scores met thresholds for minimal clinically important change and were significantly improved compared to placebo ($p < 0.001$) *(Ortega et al 2014)*.
  - SIRIUS was a 24-week Phase 3 trial (N = 135) that compared oral corticosteroid requirements between patients receiving SC mepolizumab and placebo. The likelihood of a reduction in the daily oral glucocorticoid dose was 2.39 times higher in the mepolizumab group (95% CI, 1.25 to 4.56; $p = 0.008$). The median reduction in daily oral

corticosteroid dose was 50% (95% CI, 20 to 75) in the mepolizumab-treated group compared to 0% (95% CI, -20 to 33.3) in the placebo group (p = 0.007) *(Bel et al 2014)*.

- A post-hoc analysis of data from DREAM and MENSA was conducted to assess the relationship between baseline blood eosinophil counts and efficacy of mepolizumab. Of 1192 patients, 846 received mepolizumab and 346 received placebo. The overall rate of mean exacerbations per person per year was reduced from 1.91 with placebo to 1.01 with mepolizumab (47% reduction; RR, 0.53; 95% CI, 0.44 to 0.62; p < 0.0001). The exacerbation rate reduction with mepolizumab vs placebo increased progressively from 52% (RR, 0.48; 95% CI, 0.39 to 0.58) in patients with a baseline blood eosinophil count of ≥ 150 cells/µL to 70% (RR, 0.30; 95% CI, 0.23 to 0.40) in patients with a baseline count of ≥ 500 cells/µL. At a baseline count < 150 cells/µL, predicted efficacy of mepolizumab was reduced. The authors concluded that the use of a baseline blood eosinophil count will help to select patients who are likely to achieve important asthma outcomes with mepolizumab (*Ortega et al 2016*).
- COSMOS was a 52-week, open-label extension study in patients who received mepolizumab or placebo in MENSA or SIRIUS. Patients received SC mepolizumab regardless of prior treatment allocation and continued to receive appropriate standard-of-care asthma therapy throughout. In total, 558 (86%; previous mepolizumab: 358; previous placebo: 200) and 94 (14%; previous mepolizumab: 58; previous placebo: 36) patients experienced on-treatment adverse events and serious adverse events, respectively. No fatal adverse events or instances of mepolizumab-related anaphylaxis were reported. Mepolizumab treatment was shown to exert a durable response, with patients who previously received mepolizumab in MENSA or SIRIUS maintaining reductions in exacerbation rate and oral corticosteroid dosing throughout COSMOS. Patients who previously received placebo in MENSA or SIRIUS demonstrated improvements in these endpoints following treatment with mepolizumab (*Lugogo et al 2016*).
- COLUMBA was an open-label extension study of patients enrolled in the DREAM trial who received mepolizumab 100 mg every 4 weeks plus standard of care until criterion for discontinuation was met (safety profile not positive for patient, patient withdrawn by their physician, patient withdrew consent, or drug became commercially available). There were 347 patients enrolled who received treatment for a mean of 3.5 years. Adverse events most frequently reported were respiratory tract infection (67%), headache (29%), bronchitis (21%), and worsening asthma (27%). Although 6 deaths occurred, none were considered related to study treatment. No anaphylaxis reactions were reported. Malignancy was reported in 2% (n = 6) of patients. The exacerbation rate for patients on treatment for 156 weeks or longer was 0.74 events/year, which was a 56% reduction from the off-treatment period between the 2 studies (*Khatri et al 2018*).
- A pharmacokinetic study of SC mepolizumab 40 and 100 mg (for bodyweight < 40 and ≥ 40 kg, respectively) every 4 weeks in 36 children 6 to 11 years of age with severe eosinophilic asthma and ≥ 2 exacerbations in the prior year demonstrated reductions in blood eosinophil count by 89% at week 12 *(Gupta et al 2019a)*. A 52-week safety extension study of 30 children demonstrated no safety or immunogenicity concerns, as well as improvements in blood eosinophil counts and asthma control from baseline *(Gupta et al 2019b)*. Findings of these studies supported FDA approval of mepolizumab for treatment of severe eosinophilic asthma in children (*GlaxoSmithKline 2019*).
- A systematic review and meta-analysis compared hospitalization or hospitalization and/or emergency room visit rates in patients with severe eosinophilic asthma treated with mepolizumab or placebo in addition to standard of care for ≥ 24 weeks. Four studies (N = 1388) were eligible for inclusion. Mepolizumab significantly reduced the rate of exacerbations requiring hospitalization (relative rate, 0.49; 95% CI, 0.30 to 0.80; p = 0.004) and hospitalization/emergency room visit (relative rate, 0.49; 95% CI, 0.33 to 0.73; p < 0.001) vs placebo. Significant reductions of 45% and 38% were also observed for the proportion of patients experiencing 1 or more hospitalization and hospitalization and/or emergency room visit, respectively (*Yancey et al 2017*).

Eosinophilic Granulomatosis with Polyangiitis

- A 52-week, randomized, placebo-controlled, double-blind, parallel-group, multicenter, Phase 3 trial assessed the efficacy and safety of mepolizumab as add-on therapy (to glucocorticoid treatment, with or without immunosuppressive therapy) for patients with relapsing or refractory EGPA (*Wechsler et al 2017*). A total of 136 patients were randomly assigned to mepolizumab 300 mg every 4 weeks (n = 68) or placebo (n = 68). Results demonstrated the following for the mepolizumab and placebo groups, respectively:
  - Percentage of patients with ≥ 24 weeks of accrued remission: 28% vs 3% (OR, 5.91; 95% CI, 2.68 to 13.03; p < 0.001).
  - Percentage of patients in remission at both week 36 and week 48: 32% vs 3% (OR, 16.74; 95% CI, 3.61 to 77.56; p < 0.001).
  - Annualized relapse rate: 1.14 vs 2.27 (RR, 0.50; 95% CI, 0.36 to 0.70; p < 0.001).

- Percentage of patients able to reduce their daily dose of concomitant prednisone or prednisolone to 4 mg or less (average of weeks 48 to 52): 44% vs 7% (OR, 0.20; 95% CI, 0.09 to 0.41; p < 0.001).

RESLIZUMAB

Asthma

- The safety and efficacy of reslizumab were evaluated in 4 double-blind, placebo-controlled, multicenter, randomized controlled trials. In all 4 studies, patients were required to be on at least a medium-dose ICS with or without additional controller medications (*Bjermer et al 2016, Castro et al 2015, Corren et al* 2016).
  - Studies 3082 and 3083 were 52-week studies (N = 953) in patients with asthma who were required to have a blood eosinophil count ≥ 400 cells/µL, and ≥ 1 asthma exacerbation requiring systemic corticosteroid use over the past 12 months. These studies compared the asthma exacerbation rate and improvements in clinical symptoms between patients receiving reslizumab 3 mg/kg IV administered once every 4 weeks and placebo. In both studies, patients receiving reslizumab had a significant reduction in the frequency of asthma exacerbations (Study 3082: RR, 0.50; 95% CI, 0.37 to 0.67; Study 3083: RR, 0.41; 95% CI, 0.28 to 0.59; both p < 0.0001) compared with those receiving placebo. In both trials, an improvement in FEV_1 was evident for reslizumab vs placebo by the first on-treatment assessment at week 4, which was sustained through week 52. Reslizumab treatment also resulted in significant improvements compared with placebo in AQLQ total score, ACQ-7 score, and Asthma Symptom Utility Index (ASUI) score (*Castro et al 2015*).
  - Study 3081 was a 16-week study (N = 315) in patients who were required to have a blood eosinophil count ≥ 400 cells/µL. The study compared the change from baseline in FEV_1 and improvements in clinical symptoms between reslizumab 3 mg/kg vs placebo. Reslizumab 3 mg/kg significantly improved FEV_1 (difference vs placebo: 160 mL; 95% CI, 60 to 259; p = 0.0018). Reslizumab also statistically significantly improved ACQ and AQLQ; however, the minimally important difference was only reached for AQLQ (*Bjermer et al 2016*).
    - Study 3084 was a 16-week study in 496 patients unselected for baseline blood eosinophil levels (approximately 80% of patients had a screening blood eosinophil count < 400 cells/µL). Patients were not allowed to be on maintenance oral corticosteroids. The study compared the change from baseline in FEV_1 and improvements in clinical symptoms between reslizumab 3 mg/kg vs placebo. In the subgroup of patients with baseline eosinophils < 400 cells/µL, patients treated with reslizumab showed no significant improvement in FEV_1 compared with placebo. In the subgroup with eosinophils ≥ 400 cells/µL, however, treatment with reslizumab was associated with much larger improvements in FEV_1, ACQ, and rescue SABA use compared with placebo (*Corren et al 2016*).
  - An open-label, non-randomized extension study of these placebo-controlled trials continued treatment of patients with eosinophilic asthma with reslizumab 3 mg/kg every 4 weeks for up to 24 months to assess the drug's safety. Patients initially randomized to placebo also received active drug. A total of 1051 patients were included (n = 480 reslizumab-naive and n = 571 reslizumab-treated patients). Of these, 740 patients received treatment for 12 months or longer and 249 patients received treatment for 24 months or longer. Worsening asthma and nasopharyngitis were the most common adverse events. Serious adverse events occurred in 7% of patients and treatment discontinuation due to an adverse event occurred in 2% of patients. No deaths (n = 3) were related to treatment. Malignancy occurred in 15 (1%) patients. Patients previously on reslizumab maintained asthma control and those naive to treatment demonstrated improvement in asthma control and lung function. The authors concluded that reslizumab maintained asthma control for up to 2 years in patients with moderate-to-severe eosinophilic asthma (*Murphy et al 2017*).
  - A post hoc analysis of pooled data from 2 randomized, placebo-controlled trials in patients with inadequately controlled asthma and elevated blood eosinophil levels compared the efficacy of reslizumab vs placebo among the subgroup of patients with oral corticosteroid-dependent asthma. Reslizumab was associated with a significant improvement in overall asthma exacerbations (RR, 0.32; 95% CI, 0.18 to 0.55) *(Nair et al 2019)*.
- A 2017 meta-analysis of 5 randomized controlled trials comparing reslizumab to placebo (N = 1366) revealed improvements in exacerbations, FEV_1, and ACQ score with reslizumab. Asthma exacerbations occurred less frequently in reslizumab patients vs placebo (OR, 0.46; 95% CI, 0.35 to 0.59; p < 0.00001). FEV_1 also improved with reslizumab compared to placebo (mean difference, 0.16; 95% CI, 0.10 to 0.23; p < 0.00001). Finally, ACQ score improved with reslizumab compared to placebo (mean difference, -0.26; 95% CI, -0.36 to -0.16; p < 0.00001). All studies included in the meta-analysis were of limited duration of 15 or 16 weeks (*Li et al 2017*).
- A 2019 meta-analysis of 6 randomized controlled trials (5 placebo-controlled trials and 1 open-label extension) evaluated the safety of reslizumab (n = 1028) with placebo (n = 730) in adults with uncontrolled asthma. Compared with placebo, reslizumab was associated with lower proportions of patients with ≥ 1 adverse event (67% vs 81%; RR, 0.83;

95% CI, 0.79 to 0.89) and with ≥ 1 serious adverse event (7% vs 10%; RR, 0.65; 95% CI, 0.48 to 0.89) *(Virchow et al 2019)*.

DUPILUMAB

AD

- The efficacy and safety of dupilumab compared to placebo in adults with moderate-to-severe AD was evaluated in two Phase 3 trials, SOLO 1 (n = 671) and SOLO 2 (n = 708). Adults who did not have an adequate response to topical treatments were included. Patients were randomized to either placebo, dupilumab 300 mg SC weekly or every other week for 16 weeks. The proportion of patients with an Investigator's Global Assessment (IGA) score of 0 or 1 (indicating clear or almost clear skin) and a reduction of 2 points or more in the score from baseline at week 16 was the primary outcome. In both studies between 36% and 38% of patients who received either regimen of dupilumab achieved the primary outcome compared to 8% to 10% of patients who received placebo ($p < 0.001$ for all comparisons). Significantly more patients who received dupilumab had ≥ 75% improvement from baseline on the Eczema Area and Severity Index (EASI-75) compared to those who received placebo ($p < 0.001$). Pruritus and quality of life measures were also significantly improved with dupilumab. The most common adverse effects with dupilumab compared to placebo were conjunctivitis and injection-site reactions (*Simpson et al 2016*).
- The long-term efficacy and safety of dupilumab was compared to placebo in 740 patients with moderate to severe AD not adequately controlled with topical corticosteroids in the LIBERTY AD CHRONOS study. Patients received either dupilumab 300 mg once weekly, once every 2 weeks, or placebo for 52 weeks. The co-primary endpoints were proportion of patients achieving an IGA score of 0 or 1 and ≥ 2 point improvement from baseline and EASI-75 at week 16. At week 16, 39% of patients in both dupilumab groups achieved an IGA score of 0 or 1 compared to 12% of patients who received placebo. EASI-75 was achieved in 64% and 69% of the dupilumab groups vs 23% in the placebo group ($p < 0.0001$). Similar efficacy results were reported at week 52. At 1 year, the most common adverse events associated with dupilumab were injection-site reactions and conjunctivitis. Localized herpes simplex infections were more common with dupilumab while herpes zoster and eczema herpeticum was more common in the placebo group (*Blauvelt et al 2017*).
- The efficacy of dupilumab compared to placebo was evaluated in 251 patients 12 to 17 years of age with moderate-to-severe AD in a double-blind, multicenter, randomized controlled trial. Patients < 60 kg received dupilumab 400 mg initially then 200 mg every 2 weeks and patients ≥ 60 kg received 600 mg initially then 300 mg every 2 weeks for 16 weeks. Compared with placebo, dupilumab resulted in significantly higher proportions of patients achieving EASI-75 at week 16 (41.5% vs 8.2%; $p < 0.001$) and IGA score of 0 or 1 with 2 or more points improvement at week 16 (24.4% vs 2.4%; $p < 0.001$) (*Dupixent prescribing information 2019, Simpson et al 2019*).

Asthma

- A 52-week randomized, double-blind, placebo-controlled study evaluated the efficacy of dupilumab in patients ≥ 12 years of age with moderate-to-severe asthma uncontrolled with a medium-to-high dose ICS plus up to 2 additional controller medications (LABA and/or leukotriene receptor antagonist). Approximately 1900 patients were randomized to add-on therapy with dupilumab (200 mg or 300 mg every 2 weeks) or matching placebo for 52 weeks. The annual rate of severe exacerbations during the 52-week study period and the absolute change in FEV_1 at week 12 were the primary endpoints. A subgroup analysis of patients with an elevated blood eosinophil count of 300/mm^3 was also planned. Both doses of dupilumab resulted in a reduced rate (46% and 47.7%, respectively) of asthma exacerbation compared to placebo ($p < 0.0001$). Patients with higher blood eosinophil levels had greater than 65% reduction in the annual exacerbation rate compared to placebo. The change in FEV_1 was also significantly improved with both doses of dupilumab compared to placebo and even more pronounced in patients with elevated blood eosinophil levels. Adverse events more common with dupilumab compared to placebo included injection-site reactions and eosinophilia (*Castro et al 2018*). In the subgroup of patients with baseline evidence of allergic asthma, dupilumab 200 mg and 300 mg every 2 weeks reduced severe asthma exacerbation rates by 36.9% and 45.5%, respectively (both $p < 0.01$) and improved FEV_1 at week 12 by 0.13 and 0.16 L, respectively (both $p < 0.001$) *(Corren et al 2019)*.
- A total of 210 patients ≥ 12 years of age with oral glucocorticoid-dependent severe asthma were randomized to receive add-on therapy with dupilumab 300 mg or placebo every other week for 24 weeks. Glucocorticoid doses were tapered from week 4 to week 20 and then maintained at a stable dose for 4 weeks. The percentage in glucocorticoid dose reduction at week 24 was the primary outcome. The percentage change in glucocorticoid dose was -70.1% with dupilumab vs -41.9% with placebo ($p < 0.001$). A dose reduction of ≥ 50% was observed in 80% of dupilumab-treated patients compared to 50% of placebo patients. Almost 70% of patients in the dupilumab group achieved a glucocorticoid

dose of less than 5 mg compared to 33% in patients who received placebo. The exacerbation rate was 59% lower with dupilumab compared to placebo. Injection site reactions and eosinophilia were more common with dupilumab compared to placebo (*Rabe et al 2018*).

- A meta-analysis and systematic review of 4 RCTs evaluated the safety and efficacy of dupilumab compared to placebo in approximately 3000 patients with uncontrolled asthma. The rate of severe asthma exacerbation was significantly reduced with dupilumab compared to placebo (RR, 0.44; 95% CI, 0.35 to 0.055; p < 0.01). FEV_1 was also significantly increased with dupilumab with a mean difference of 0.14 L (95% CI, 0.12 to 0.17; p < 0.01). With respect to adverse events, the risk of injection site reactions was higher with dupilumab compared to placebo (RR, 1.91; 95% CI, 1.14 to 2.59; p < 0.01) (*Zayed et al 2018*).

Chronic rhinosinusitis with nasal polyposis

- Two randomized, double-blind, placebo-controlled trials evaluated dupilumab added to standard of care in adults with severe bilateral chronic rhinosinusitis with nasal polyposis (*Bachert et al 2019*). Patients had experienced symptoms despite receiving intranasal corticosteroids, systemic corticosteroids in the previous 2 years, or sinonasal surgery. In both the 24- and 52-week trials, dupilumab resulted in significant improvement as measured by least squares mean differences in nasal polyp score (-2.06; 95% CI, -2.43 to -1.69 and -1.80; 95% CI, -2.10 to -1.51, respectively), nasal congestion or obstruction score (-0.89; 95% CI, -1.07 to -0.71 and -0.87; 95% CI, -1.03 to -0.71, respectively), and Lund-Mackay computed tomography score (-7.44; 95% CI, -8.35 to -6.53 and -5.13; 95% CI, -5.80 to -4.46, respectively). The risk of any adverse event, serious adverse events, and adverse events leading to treatment discontinuation were not significantly different between dupilumab and placebo.

COMPARATIVE REVIEWS

- In 2017, Cockle et al conducted a systematic review and indirect treatment comparison to assess the comparative effectiveness and tolerability of mepolizumab and omalizumab, as add-on therapy to standard of care, in patients with severe asthma. Studies included in the primary analysis were double-blind, randomized controlled trials, ≥12 weeks' duration enrolling patients with severe asthma with a documented exacerbation history and receiving a high-dose ICS plus ≥1 additional controller. Two populations were examined: patients potentially eligible for 1) both treatments (overlap population) and 2) either treatment (trial population) (*Cockle et al 2017*).
  - For the overlap population, no difference was found between mepolizumab and omalizumab. However, trends in favor of mepolizumab were observed, with median estimated RRs of 0.66 (95% credible interval [CrI], 0.37 to 1.19) for the rate of clinically significant exacerbations and 0.19 (95% CrI, 0.02 to 2.32) for the rate of exacerbations requiring hospitalization.
  - Results of the trial population analysis showed that mepolizumab was associated with an estimated median RR of 0.63 (95% CrI, 0.45 to 0.89) corresponding to a reduction of 37% in the rate of clinically significant exacerbations vs omalizumab. No difference between treatments was observed for the rate of exacerbations resulting in hospitalization; however, the median RR of 0.58 (95% CrI, 0.16 to 2.13) demonstrated a trend for mepolizumab over omalizumab.
  - Both treatments had broadly comparable effects on lung function, and similar tolerability profiles.
- Another 2017 systematic review was unable to detect differences in efficacy when comparing add-on therapy with mepolizumab or omalizumab in asthma patients who were not well controlled on ICS therapy. The analysis included both randomized controlled trials and cohort studies with duration of ≥12 weeks. A total of 18 omalizumab studies (N = 4854) and 4 mepolizumab studies (N = 1620) were included. Network meta-analysis did not find a significant difference in FEV_1 between groups (mean difference, 9.3 mL in favor of mepolizumab; 95% CI, -67.7 to 86.3). Both omalizumab and mepolizumab reduced the annualized rates of asthma exacerbations by approximately 50% compared with placebo. Although the authors were unable to identify significant differences in efficacy, there was high heterogeneity among the clinical trials and major differences in study inclusion criteria *(Nachef et al 2018)*.
- A systematic review of the IL-5 antagonists, mepolizumab, reslizumab, and benralizumab, included 13 studies (N = 6000) conducted in patients with asthma poorly controlled by ICS. The majority of patients had severe eosinophilic asthma. All of the IL-5 antagonists reduced asthma exacerbations by approximately 50% and improved FEV_1 by 0.08 L to 0.11 L. Overall, there was not an increase in serious adverse events with any IL-5 antagonist; however, more patients discontinued benralizumab (36/1599) than placebo (9/998) due to adverse events *(Farne et al 2017)*.
- A 2019 network meta-analysis of 11 studies aimed to indirectly compare the efficacy (n = 1855) and safety (n = 3462) of reslizumab with benralizumab in patients with eosinophilic asthma. The efficacy analysis compared a benralizumab subgroup with blood eosinophils ≥ 300 cells/µL (n = 1537) to a reslizumab subgroup in GINA step 4/5 with 2 or more

previous exacerbations and blood eosinophils ≥ 400 cells/µL. Reslizumab was found to have significantly greater improvement in the ACQ and AQLQ scores compared to benralizumab. No significant difference between the groups was observed in clinical asthma exacerbation, but a sensitivity analysis with the overall study population suggested a significantly greater reduction in exacerbations with reslizumab. There were fewer discontinuations due to adverse events with reslizumab; however, the frequency and types of adverse events were not significantly different between treatment groups (*Casale et al 2019).*

- A 2019 network meta-analysis of 11 studies compared efficacy of licensed doses of mepolizumab, benralizumab, and reslizumab in patients with severe eosinophilic asthma based on eosinophil levels. Mepolizumab reduced clinically significant exacerbations compared to benralizumab for patients with blood eosinophils ≥ 150 cells/µL (RR, 0.66; 95% CI, 0.49 to 0.89), ≥ 300 cells/µL (RR, 0.61; 95% CI, 0.37 to 0.99), and ≥ 400 cells/µL (RR, 0.55; 95% CI, 0.35 to 0.87) and with mepolizumab compared to reslizumab for patients with blood eosinophils ≥ 400 cells/µL (RR, 0.55; 95% CI, 0.36 to 0.85). Additionally, change from baseline in ACQ score was greater with mepolizumab compared to benralizumab in patients with baseline blood eosinophils ≥ 150 cells/µL (difference, -0.33; 95% CI, -0.54 to -0.11), ≥ 300 cells/µL (-0.40; 95% CI, -0.76 to -0.03), and ≥ 400 cells/µL (difference, -0.36; 95% CI, -0.66 to -0.05) and compared to reslizumab with blood eosinophils ≥ 400 cells/µL (difference, -0.39; 95% CI, -0.66 to -0.12). There was no difference between reslizumab and benralizumab in clinically significant exacerbations or ACQ scores in patients with blood eosinophils ≥ 400 cells/µL *(Busse et al 2019)*.
- A 2019 systematic review and network meta-analysis of 30 randomized controlled trials compared biologic therapies for treatment of type 2 (ie, eosinophilic) asthma. Mepolizumab, reslizumab, and benralizumab significantly reduced the risk of exacerbations compared with placebo; however, network meta-analysis showed no superiority of any biologic therapy for this outcome among benralizumab, dupilumab, mepolizumab, reslizumab, and other biologics not available in the US (lebrikizumab, tralokinumab, and tezepelumab) *(Edris et al 2019)*.
- Additional meta-analyses have not found significant differences in asthma exacerbation rates between mepolizumab and reslizumab or between benralizumab and mepolizumab *(Bourdin et al 2018, Henriksen et al 2018).*
- The magnitude of treatment effect of biologic agents (including benralizumab, reslizumab, dupilumab, mepolizumab, lebrikizumab [investigational], and tralokinumab [investigational]) in patients with eosinophilic asthma was evaluated in a network meta-analysis. The outcomes evaluated were change in FEV_1, ACQ score and AQLQ score. Event rates for asthma exacerbation and associated RRs were determined for each drug. A total of 26 studies were included in the analysis (n = 7 benralizumab, n = 2 dupilumab, n = 4 lebrikizumab, n = 7 mepolizumab, n = 4 reslizumab, n = 2 tralokinumab) with a total of 8444 patients (n = 4406 on active treatment, n = 4038 in control groups). The duration of treatment ranged from 12 to 56 weeks. Increase in FEV_1, reduction in ACQ score and increase in AQLQ score was observed with all treatments except tralokinumab. Compared to placebo, the greatest FEV_1 increase was with dupilumab (0.16 L; 95% CI, 0.08 to 0.24), followed by reslizumab (0.13 L; 95% CI, 0.10 to 0.17), and benralizumab (0.12 L; 95% CI, 0.08 to 0.17). Mepolizumab and lebrikizumab both had an increase of 0.09 L (95% CI, 0.03 to 0.15 with mepolizumab, 0.04 to 0.15 with lebrikizumab). Reduction in ACQ score (indicating better asthma control) in order of greatest to least reduction was mepolizumab, dupilumab, benralizumab, and reslizumab. The investigational agents had the least impact on the ACQ score. Quality of life scores were similarly increased with the 4 agents while the investigational agents had the least impact on quality of life. Compared to placebo, the calculated RR for annualized asthma exacerbation was significant only for dupilumab (RR, 0.37; 95% CI, 0.17 to 0.80) and reslizumab (RR, 0.64; 95% CI, 0.53 to 0.78). Comparisons between treatments did not show any significant difference for change in FEV_1, asthma control or quality of life except for superiority of mepolizumab to the 2 investigational agents in ACQ score reduction (*Iftikhar et al 2018*).

CLINICAL GUIDELINES

Asthma

- According to guidelines from the NHLBI/National Asthma Education and Prevention Program, pharmacologic therapy is based on a stepwise approach in which medications are increased until asthma is controlled and then decreased when possible to minimize side effects of treatments. The level of asthma control is based on (*NHLBI 2007*):
  - Reported symptoms over the past 2 to 4 weeks
  - Current level of lung function (FEV_1 and FEV_1/forced vital capacity [FVC] values)
  - Number of exacerbations requiring oral corticosteroids per year.

- The NHLBI guidelines state that omalizumab is used as adjunctive therapy in patients 12 years and older who have allergies and severe persistent asthma that is not adequately controlled with the combination of high-dose ICS and LABA therapy (*NHLBI 2007*).
- In 2019, the Global Initiative for Asthma (GINA) published updated guidelines for asthma management and prevention. In April 2019, GINA updated a guideline on diagnosis and management of difficult-to-treat and severe asthma. Criteria for establishing a diagnosis of severe asthma was included, which requires multiple interventions before a diagnosis can be made. For patients with a diagnosis of severe asthma, uncontrolled on Step 4 treatment (eg, 2 or more controllers or taking maintenance oral corticosteroids), phenotyping for Type 2 inflammation into categories such as severe allergic, aspirin-exacerbated, allergic bronchopulmonary aspergillosis, chronic rhinosinusitis and nasal polyposis, atopic dermatitis, or eosinophilic asthma is recommended. Treatment with a biologic agent should be considered in patients who are uncontrolled despite a high-dose ICS/LABA or need maintenance oral corticosteroids. Anti-IgE treatment with omalizumab is recommended for patients ≥ 6 years of age with severe allergic asthma. Similarly, add-on anti-IL-5 therapy (ie, benralizumab, mepolizumab) is recommended for patients ≥ 12 years of age or reslizumab for patients ≥ 18 years of age with severe eosinophilic asthma. Anti-IL4 receptor therapy (ie, dupilumab) is recommended for patients ≥ 12 years of age with severe eosinophilic/Type 2 asthma or patients taking oral corticosteroids. Prior to initiation of these agents, several factors are recommended to consider including cost, insurance eligibility criteria, evaluation of predictors of response, delivery route, dosing frequency and patient preference. (*GINA 2019a, GINA 2019b*).

Chronic Idiopathic Urticaria

- Guidelines developed by the American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma & Immunology, and the Joint Council of Allergy, Asthma & Immunology recommend a stepwise treatment approach for CIU. Treatment with omalizumab is recommended in patients inadequately controlled with antihistamines and a leukotriene receptor antagonist (*Bernstein et al 2014*).
- Joint guidelines by the European Academy of Allergy and Clinical Immunology, the Global Allergy and Asthma European Network, the European Dermatology Forum, and the World Allergy Organization recommend treatment with omalizumab in patients with symptoms despite treatment with a 4-fold dose of modern second generation antihistamines. This is a change from previous guidelines in which use of either omalizumab or cyclosporine after failure of high-dose antihistamines was recommended. However, due to adverse effects and the lack of an approved indication, the new recommendation was that cyclosporine should only be considered if omalizumab does not provide an adequate response. (*Zuberbier et al 2018*).
- Recent guidelines published by the British Society for Allergy and Clinical Immunology similarly recommend omalizumab as a potential second-line agent in patients inadequately controlled on a 4-fold dose of a non-sedating antihistamine (*Powell et al 2015*).

Eosinophilic Granulomatosis with Polyangiitis

- Both the EGPA (Churg-Strauss) Consensus Task Force recommendations and the American Society for Apheresis guideline recommend glucocorticoids alone for patients without life- and/or organ-threatening EGPA. For patients with life- and/or organ-threatening EGPA, both glucocorticoids and an immunosuppressant are recommended, as well as maintenance therapy with azathioprine or methotrexate. Guidelines from the American Society for Apheresis recognized mepolizumab as a future treatment option, and the EGPA Consensus Task Force recommendations noted that mepolizumab held promise for this condition based on the pilot studies available at the time of guideline development. IVIG can be considered for refractory EGPA or for treatment during pregnancy (*Groh et al 2015, Padmanabhan et al 2019*).

AD

  - According to the American Academy of Dermatology, interventions that provide effective control of AD for a majority of patients include non-pharmacologic interventions with emollients, topical treatment with corticosteroids and calcineurin inhibitors, and avoidance of environmental triggers. Phototherapy is the next option for children and adults with moderate to severe AD not controlled with the first-line interventions. A third-line treatment recommended for patients who fail phototherapy is treatment with systemic immunomodulators, such as cyclosporine and methotrexate. The guidelines did not provide a recommendation on use of biologic agents due to limited data available at the time of publication (*Sidbury et al 2014*)

- 2017 guidance from the International Eczema Council provides clinicians with similar guidance as the American Academy of Dermatology as well as additional steps to be taken before initiation of systemic treatment. These include consideration of an alternative diagnosis, ensuring patient compliance with topical treatment, a trial of intensive topical therapy, treatment of infection, identification and avoidance of all potential triggers, and use of phototherapy if possible. The guidance does not comment on use of biologic agents due to limited data (*Simpson et al 2017*). The International Eczema Council also published a position statement on conjunctivitis in atopic dermatitis with and without dupilumab therapy based on an opinion survey and round table discussion of its members. Based on expert opinion, a consensus was reached that patients should be informed about possible conjunctivitis with dupilumab prior to treatment, patients with new-onset conjunctivitis during dupilumab therapy should be referred to ophthalmologists, and treatment should be continued after referral to an ophthalmologist *(Thyssen et al 2019).*
- A 2018 European consensus guideline from a variety of organizations on treatment of atopic eczema includes dupilumab as a treatment option for patients with moderate-to-severe disease in whom an adequate response is not achieved with topical treatments and for whom other systemic treatments are not available. Concomitant use of emollients is recommended and combination with topical agents may be needed. No specific information on use of pediatrics was provided due to lack of data. (*Wollenberg et al 2018*).

Chronic Rhinosinusitis with Nasal Polyposis

- Treatment of chronic rhinosinusitis with nasal polyposis is addressed in guidelines from the American Academy of Otolaryngology-Head and Neck Surgery; American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma & Immunology, and the Joint Council of Allergy, Asthma & Immunology; and the International Forum of Allergy & Rhinology. Routine treatment recommendations include saline irrigation and/or intranasal glucocorticoids in patients with mild symptoms, and short-term systemic glucocorticoids and surgery in patients with severe or refractory symptoms *(Orlandi et al 2016, Peters et al 2014, Rosenfeld et al 2015)*. While not approved at the time of writing, some guidelines acknowledged the demonstration of benefit with IL-5 antagonists *(Orlandi et al 2016, Peters et al 2014)*.

SAFETY SUMMARY

- All agents are contraindicated in patients with a history of hypersensitivity to the specific agent or excipients in its formulation.
- Abrupt discontinuation of systemic, topical or inhaled corticosteroids is not recommended when treatment with any of these agents are initiated. If appropriate, the corticosteroid dosage should be reduced gradually.

Cinqair:

- Boxed warning: Anaphylaxis has been observed with Cinqair infusion in 0.3% of patients in placebo-controlled clinical studies. Anaphylaxis was reported as early as the second dose of Cinqair. Patients should be observed for an appropriate period of time after Cinqair administration by a healthcare professional prepared to manage anaphylaxis.
- Key warnings and precautions:
  - In placebo-controlled clinical studies, 6/1028 (0.6%) patients receiving 3 mg/kg Cinqair had ≥1 malignant neoplasm reported compared to 2/730 (0.3%) patients in the placebo group. The observed malignancies in Cinqair-treated patients were diverse in nature and without clustering of any particular tissue type.
  - Pre-existing helminth infections should be treated before therapy with Cinqair. If patients become infected while receiving Cinqair and do not respond to anti-helminth treatment, Cinqair should be discontinued until the parasitic infection resolves.
- The most common adverse reaction (≥ 2%) included oropharyngeal pain.

Dupixent:

- Key warnings and precautions:
  - Hypersensitivity reactions (eg, anaphylaxis, erythema nodosum, serum sickness, urticaria, and rash) have occurred after administration of Dupixent. Dupixent should be discontinued in the event of a hypersensitivity reaction.
  - For patients with AD, conjunctivitis and keratitis has occurred more often when compared to placebo in clinical trials evaluating Dupixent. New or worsening eye symptoms should be reported to a healthcare provider.
  - For patients with asthma, cases of eosinophilic pneumonia and vasculitis consistent with EGPA have been reported. Occurrence of vasculitic rash, worsening pulmonary symptoms, and/or neuropathy, especially upon reduction of oral corticosteroids should be monitored.

- Pre-existing helminth infections should be treated before therapy with Dupixent. If a patient becomes infected while receiving Dupixent and does not respond to anti-helminth treatment, Dupixent should be discontinued until the parasitic infection resolves.
- Most common adverse reactions in patients with AD included injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye.
- Most common adverse reactions in patients with asthma included injection site reactions, oropharyngeal pain, and eosinophilia.

Fasenra:

- Key warnings and precautions:
  - Hypersensitivity reactions (eg, anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of Fasenra. Fasenra should be discontinued in the event of a hypersensitivity reaction.
  - Pre-existing helminth infections should be treated before therapy with Fasenra. If patients become infected while receiving Fasenra and do not respond to anti-helminth treatment, Fasenra should be discontinued until the parasitic infection resolves.
- The most common adverse reactions (≥ 5%) included headache and pharyngitis.

Nucala:

- Key warnings and precautions:
  - Hypersensitivity reactions (eg, anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of Nucala.
  - Herpes zoster infections have occurred in patients receiving Nucala. Vaccination should be considered if clinically appropriate.
  - Pre-existing helminth infections should be treated before therapy with Nucala. If patients become infected while receiving Nucala and do not respond to anti-helminth treatment, Nucala should be discontinued until the parasitic infection resolves.
- The most common adverse reactions (≥ 5%) included headache, injection site reaction, back pain, and fatigue.

Xolair:

- Boxed warning: Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported. Patients should be observed closely for an appropriate period of time after Xolair administration. Health care providers administering Xolair should be prepared to manage anaphylaxis that can be life-threatening.
  - Patients with a prior history of anaphylactic reactions to other causes may be at an increased risk for anaphylaxis. The frequency of anaphylaxis is reported to be between 0.1 to 0.2% and may occur immediately or up to a year post-treatment.
- Key warnings and precautions:
  - Malignant neoplasms were observed in a higher rate of Xolair-treated patients (0.5%) than control patients (0.2%) in clinical trials. A subsequent 5-year observational cohort study found similar rates of primary malignancies in Xolair- and non-Xolair-treated patients. However, study limitations preclude definitively ruling out a malignancy risk with Xolair (*Long et al 2014*).
  - Rarely, patients on therapy with Xolair may present with serious systemic eosinophilia, which may present with features of vasculitis consistent with Churg-Strauss syndrome. These events usually have been associated with the reduction of oral corticosteroid therapy.
  - Some patients have reported signs and symptoms similar to serum sickness, including arthritis/arthralgia, rash, fever, and lymphadenopathy.
- Adverse reactions in asthma studies: In patients ≥ 12 years of age, the most commonly observed adverse reactions in clinical studies (≥ 1% in Xolair-treated patients and more frequently than reported with placebo) were arthralgia, pain (general), leg pain, fatigue, dizziness, fracture, arm pain, pruritus, dermatitis, and earache. In clinical studies with pediatric patients 6 to < 12 years of age, the most common adverse reactions were nasopharyngitis, headache, pyrexia, upper abdominal pain, streptococcal pharyngitis, otitis media, viral gastroenteritis, arthropod bites, and epistaxis.

- Adverse reactions in CIU studies: Adverse reactions from 3 placebo-controlled, multiple-dose CIU studies that occurred in ≥ 2% of patients receiving Xolair and more frequently than in those receiving placebo included arthralgia, cough, headache, nasopharyngitis, nausea, sinusitis, upper respiratory tract infection, and viral upper respiratory tract infection.
- Cardiovascular and cerebrovascular events in asthma studies: In a 5-year observational cohort study, a higher incidence of overall cardiovascular and cerebrovascular serious adverse events was observed in Xolair-treated patients compared to non-Xolair-treated patients. To further evaluate the risk, a pooled analysis of 25 randomized, controlled, clinical trials was conducted. An increased risk of cardiovascular and cerebrovascular serious adverse events was not noted, but the low number of events, the young patient population, and the short duration of follow-up prevent a definite conclusion about the absence of a risk (*FDA 2014*).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Route	Usual Recommended Frequency	Comments
Cinqair (reslizumab)	IV	Every 4 weeks	• Administered by IV infusion over 20 to 50 minutes. • Safety and effectiveness in pediatric patients ≤ 17 years of age have not been established. • Cinqair should be administered by a healthcare professional.
Dupixent (dupilumab)	SC	AD: every other week Asthma: every other week Chronic rhinosinusitis with nasal polyposis: every other week	• AD and Asthma: Safety and efficacy in pediatric patients < 12 years of age have not been established. • Chronic rhinosinusitis with nasal polyposis: Safety and efficacy in pediatric patients < 18 years of age have not been established. • Dupixent may be administered by a healthcare professional or self-administered via an autoinjector.
Fasenra (benralizumab)	SC	Every 4 weeks for first 3 doses, followed by every 8 weeks	• Safety and efficacy in pediatric patients < 12 years of age have not been established. • Fasenra may be administered by a healthcare professional or self-administered via an autoinjector.
Nucala (mepolizumab)	SC	Asthma: every 4 weeks EGPA: every 4 weeks	• Safety and efficacy in pediatric patients < 6 years of age have not been established. • Nucala may be administered by a healthcare professional or self-administered via an autoinjector.
Xolair (omalizumab)	SC	Allergic asthma: Every 2 or 4 weeks CIU: Every 4 weeks	• Xolair should be administered by a healthcare professional. Allergic asthma: • The dose and frequency is determined by serum total IgE level (IU/mL), measured before the start of treatment, and body weight. • Safety and efficacy in pediatric patients with asthma < 6 years of age have not been established. CIU: • Dosing in CIU is not dependent on serum IgE level or body weight.

Drug	Route	Usual Recommended Frequency	Comments
			• Safety and efficacy in pediatric patients with CIU < 12 years of age have not been established.

See the current prescribing information for full details.

CONCLUSION

- Xolair is a humanized monoclonal antibody that is FDA-approved for patients 6 years of age and older with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with an ICS. Xolair has been shown to decrease the incidence of asthma exacerbations in these patients.
- Although clinical trial results have been mixed and several trials had an open-label design, there is some evidence to indicate that Xolair may decrease asthma-related emergency visits and hospitalizations, as well as decreasing the dose of ICS and rescue medication and increasing symptom-free days (*Buhl et al 2002, Busse et al 2011, Holgate et al 2004, Lanier et al 2003, Solèr et al 2011*).
- Xolair is administered SC in a physician's office every 2 to 4 weeks in a dose that is determined by body weight and the levels of serum IgE. Xolair carries a boxed warning due to the risk of anaphylaxis, and thus must be administered under medical supervision.
- Although Xolair therapy is generally safe, analysis of a 5-year, observational cohort, epidemiological study (EXCELS) showed an increased number of cardiovascular and cerebrovascular adverse events in patients receiving Xolair compared to placebo (*Iribarren et al 2017*). However, a pooled analysis of 25 randomized, double-blind, placebo-controlled clinical trials did not find notable imbalances in the rates of cardiovascular and cerebrovascular serious adverse events (*FDA 2014*).
- Asthma guidelines generally recommend Xolair therapy in patients with severe allergic asthma that is inadequately controlled with a combination of high-dose ICS and LABA (*GINA 2019a, GINA 2019b, NHLBI 2007*). Based on the limited place in therapy and the need for administration under medical supervision, Xolair is appropriate for a small percentage of patients with asthma.
- Xolair received FDA approval for the treatment of adults and adolescents (12 years of age and above) with CIU who remain symptomatic despite H_1-antihistamine treatment. Two randomized, placebo-controlled trials demonstrated its efficacy in reducing weekly itch severity scores and weekly hive count scores significantly greater than placebo at week 12. Xolair was well-tolerated, with a safety profile similar to that observed in asthma patients. In patients with CIU, Xolair is dosed at 150 or 300 mg SC every 4 weeks in a physician's office. Guidelines for the treatment of CIU recommend treatment with Xolair in patients who are inadequately controlled with a 4-fold dose of modern second-generation antihistamines. Although previous guidelines suggested the use of omalizumab after a leukotriene receptor antagonist, the most recent guideline from the European Academy of Allergy and Clinical Immunology, the Global Allergy and Asthma European Network, the European Dermatology Forum, and the World Allergy Organization state that a recommendation regarding use of a leukotriene receptor antagonist cannot be made due to a low level of evidence. Additionally, use of Xolair is recommended before treatment with cyclosporine (*Bernstein et al 2014, Zuberbier et al 2018, Powell et al 2015*).
- Cinqair, Fasenra, and Nucala are IL-5 antagonists approved as add-on treatment options for patients with severe eosinophilic asthma, and have demonstrated effectiveness in reducing asthma exacerbations (*Bel et al 2014, Bjermer et al 2016, Castro et al 2015, Corren et al 2016, Pavord et al 2012, Ortega et al 2014, Bleecker et al 2016, Fitzgerald et al 2016*). The mechanism of action of Fasenra is slightly different, in that it binds to the IL-5 receptor on immune effector cells, whereas Cinqair and Nucala bind to the IL-5 cytokine. All of these agents provide a more targeted treatment option for patients with severe, refractory asthma and should be considered in those with an eosinophilic phenotype uncontrolled on conventional asthma therapy after confirmation of severe disease, along with individual patient factors (*GINA 2019a, GINA 2019b*).
- Dupixent is an IL-4/IL-13 antagonist with 3 FDA-approved indications: treatment of patients ≥ 12 years of age with moderate-to-severe AD, treatment of patients ≥ 12 years of age with severe asthma of the eosinophilic type or dependent on oral corticosteroids, and add-on treatment in adults with inadequately controlled chronic rhinosinusitis with nasal polyposis. Its use in AD should be determined by its approved indication and clinician judgment. According to

the most recent GINA guideline on treatment of severe asthma, the use of Dupixent for severe asthma with an eosinophilic phenotype can be considered for patients with severe eosinophilic/Type 2 asthma or patients taking oral corticosteroids. The approval of Dupixent in chronic rhinosinusitis with nasal polyposis occurred after publication of guidelines, although some acknowledged the potential role for biologic therapies *(Orlandi et al 2016, Peters et al 2014).*

- Nucala is the only antiasthmatic monoclonal antibody approved for the treatment of adult patients with EGPA.
- There are no head-to-head trials comparing Cinqair, Fasenra, Dupixent and Nucala. However, a systematic review of the IL-5 antagonists conducted in patients with asthma poorly controlled by ICS revealed that all of the IL-5 antagonists reduced asthma exacerbations by approximately 50% and improved FEV_1 by 0.08 L to 0.11 L. Overall, there was not an increase in serious adverse events with any IL-5 antagonist; however, more patients discontinued benralizumab (36/1599) than placebo (9/998) due to adverse events *(Farne et al 2017).* One network meta-analysis of IL-4, IL-5 and IL-13 antagonists demonstrated that all agents reduced FEV_1 and improved ACQ and AQLQ scores, except for the investigational agent, tralokinumab; another found mepolizumab, reslizumab, and benralizumab significantly reduced the risk of exacerbations compared with placebo (*Iftikhar et al 2018, Edris et al 2019*)
- Compared to Nucala and Fasenra, Cinqair does have several limitations, including: an indication for patients ≥ 18 years of age (vs ≥ 6 and 12 years of age with Nucala and Fasenra, respectively), IV administration (SC for Nucala and Fasenra), and a boxed warning for anaphylaxis. Dupixent is indicated for treatment of patients ≥ 12 years of age with both severe asthma and AD.
- Subcutaneous autoinjector formulations are available for Dupixent, Fasenra, and Nucala.

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Therapeutic Class Overview
Intranasal Allergic Rhinitis Agents

INTRODUCTION

- Allergic rhinitis (AR) is an inflammatory, immunoglobulin E (IgE)-mediated disease characterized by nasal congestion, rhinorrhea, sneezing, and/or nasal itching. It is generally viewed as either seasonal AR (SAR) or perennial AR (PAR). SAR is caused by seasonal aeroallergens, such as pollens, and PAR is caused by year-round environmental aeroallergens such as dust mites, mold, animal allergens, or occupational allergens (*Seidman et al 2015*). AR is common, affecting 10% to 30% of adults and up to 40% of children in the United States (US) (*Wallace et al 2008*).
- Pharmacologic therapy for AR includes antihistamines (intranasal [IN] and oral), decongestants (IN and oral), corticosteroids (IN and oral), IN cromolyn, IN anticholinergics, and oral leukotriene receptor antagonists (LTRAs) (*Dykewicz et al 2017*).
- IN treatments are often selected over oral therapies based on their high effectiveness and targeted local effects (*Wallace et al 2008, Seidman et al 2015*).
  - IN corticosteroids are generally considered the most effective class of medications for controlling AR symptoms.
  - IN antihistamines are additional options for the treatment of AR and may be considered for first-line use.
  - IN anticholinergics reduce rhinorrhea but are not effective for other AR symptoms.
  - Clinicians may offer combination therapy to patients with an inadequate response to monotherapy.
- Vasomotor rhinitis is a type of nonallergic (non-IgE-mediated) rhinitis (*Wallace et al 2008*). Symptoms are similar to those of AR and include sneezing, congestion, and runny nose. Itchy nose, eyes and throat are typically absent. Symptoms of vasomotor rhinitis can be triggered by airborne pollutants or odors, certain foods and medications, changes in the weather, or underlying health problems (*American Academy of Allergy, Asthma & Immunology [AAAAI] 2019*). IN corticosteroids, IN antihistamines, and IN anticholinergics are effective for vasomotor rhinitis (*Wallace et al 2008*).
- Nasal polyps are soft, painless growths on the lining of nasal passages or sinuses, which result from chronic inflammation due to asthma, infection, allergies, drug sensitivity, or immune disorders (*Mayo Clinic 2018*). Nasal polyps often occur in the setting of chronic rhinosinusitis. Larger polyps may lead to symptoms such as blocked nasal passages, breathing problems, reduced sense of smell, and infections. Medications such as IN corticosteroids can shrink or eliminate nasal polyps; however, surgical removal is sometimes necessary. Nasal polyps often return after treatment.
- Effectiveness is often evaluated with the use of the total nasal symptom score (TNSS). Although there is some variability in specific studies, the TNSS is typically the sum of individual symptom scores for nasal itching, rhinorrhea, sneezing, and nasal congestion. Symptoms are often rated on a scale of 0 (none) to 3 (severe), and twice-daily scores may be summed or averaged, so the score range may be 0 to 12 or 0 to 24 depending on the study design. A minimum clinically important difference in TNSS has not been definitively established (*Glacy et al 2013, Meltzer et al 2016*).
- This therapeutic class overview includes IN corticosteroids, IN antihistamines, and IN anticholinergics. Specific products are listed in Table 1. Note that in some cases, there is more than one brand name for the same chemical entity.
- Most products are formulated as aqueous nasal sprays. One product, Xhance (fluticasone propionate), uses a novel delivery system containing a nosepiece and a mouthpiece; it uses the patient's exhaled breath to facilitate delivery of drug deep into the nasal passages. Two products, Qnasl (beclomethasone dipropionate) and Zetonna (ciclesonide), are formulated as nasal aerosols.
- Several products formerly available by prescription are now available solely as over-the-counter (OTC) products. These products include: fluticasone furoate (Flonase Sensimist, formerly marketed as the prescription product Veramyst), budesonide (Rhinocort Allergy, formerly marketed as the prescription product Rhinocort Aqua), and triamcinolone acetonide (Nasacort Allergy 24HR, formerly marketed as the prescription product Nasacort AQ). Fluticasone propionate is available as a prescription product (generic only; the brand is no longer marketed) and an OTC product (Flonase Allergy Relief).Medispan classes: Nasal Steroids; Nasal Antiallergy; Nasal Agent Combination; Nasal Anticholinergics

Table 1. Medications Included Within Class Review

Drug	Generic Availability
IN corticosteroids	
Beconase AQ (beclomethasone dipropionate monohydrate)	-
Flonase Sensimist (fluticasone furoate)*	-
Flonase Allergy Relief (fluticasone propionate)†‡	✔
Flunisolide†	✔
Nasacort Allergy 24HR (triamcinolone acetonide)*	✔
Nasonex (mometasone furoate monohydrate)	✔
Omnaris (ciclesonide)	-
Qnasl (beclomethasone dipropionate)	-
Rhinocort Allergy (budesonide)*	✔
Xhance (fluticasone propionate)	-
Zetonna (ciclesonide)	-
IN antihistamines	
Astepro (azelastine§)	✔
Azelastine†‖	✔
Patanase (olopatadine hydrochloride)	✔
IN antihistamine/corticosteroid combination	
Dymista (azelastine hydrochloride/fluticasone propionate)	-
IN anticholinergics	
Ipratropium†	✔

*The following products are currently available as nonprescription/OTC products only: fluticasone furoate (Flonase Sensimist, formerly marketed as the prescription product Veramyst), budesonide (Rhinocort Allergy, formerly marketed as the prescription product Rhinocort Aqua), and triamcinolone acetonide (Nasacort Allergy 24HR, formerly marketed as the prescription product Nasacort AQ).
† Brand prescription product no longer marketed, but generic is available. The reference brand names were Astelin (azelastine 0.1%), Atrovent (ipratropium bromide), Flonase (fluticasone propionate), and Nasalide (flunisolide).
‡ Fluticasone propionate is available both as a prescription product (fluticasone propionate) and as an OTC product (Flonase Allergy Relief). Both the prescription and OTC products are available generically.
§ The 0.15% strength of Astepro is available as a brand and a generic; a 0.1% strength was also FDA-approved but is not currently marketed.
‖ Generic Astelin (azelastine 0.1%)
(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

- An overview of the indications for the prescription IN corticosteroids, antihistamines, and anticholinergics is provided in Table 2. Additional detail on the indication(s) for each product is provided in the box following the table. Information from the Pediatric Use section of the prescribing information was included when the recommended age range was not specified in the indication.

Table 2. Indications for IN Corticosteroids, Antihistamines, and Anticholinergics*

Indication	Corticosteroids												Antihistamines			Other	
	Beconase AQ	Flonase Sensimist†	Flunisolide	Flonase Allergy Relief	Fluticasone propionate	Nasacort Allergy 24HR†	Nasonex	Omnaris	Qnasl	Rhinocort Allergy†	Xhance	Zetonna	Astepro	Azelastine	Patanase	Dymista	Ipratropium
Seasonal Allergic Rhinitis (SAR)	✔		✔				✔	✔	✔			✔	✔	✔	✔	✔	✔
Perennial Allergic Rhinitis (PAR)	✔		✔				✔	✔	✔			✔	✔				✔
Vasomotor/Nonallergic Rhinitis	✔				✔									✔			✔
Nasal Polyps (Treatment or Prevention)	✔						✔				✔						
Rhinorrhea Associated with Common Cold																	✔
Relief from symptoms of hay fever or other upper respiratory allergies		✔		✔		✔				✔							

† Available as OTC only

***Notes: Additional Detail on Indications**

- **Beconase AQ (beclomethasone dipropionate monohydrate):**
  - Relief of the symptoms of seasonal or perennial allergic and nonallergic (vasomotor) rhinitis
  - Prevention of recurrence of nasal polyps following surgical removal
  - Safety and effectiveness established in children aged ≥ 6 years
- **Flunisolide:**
  - Treatment of the nasal symptoms of seasonal or perennial rhinitis
  - Not recommended for use in pediatric patients aged < 6 years as safety and efficacy have not been assessed in this age group
- **Flonase Allergy Relief (fluticasone propionate OTC):**
  - Relief of symptoms of hay fever or other upper respiratory allergies
  - Not recommended for use in pediatric patients aged < 4 years
- **Flonase Sensimist (fluticasone furoate OTC):**
  - Relief of symptoms of hay fever or other upper respiratory allergies
  - Not recommended for use in pediatric patients aged < 2 years
- **Fluticasone propionate:**
  - Management of the nasal symptoms of perennial nonallergic rhinitis in adults and pediatric patients aged ≥ 4 years
- **Nasacort Allergy 24HR (triamcinolone acetonide OTC):**
  - Relief of symptoms of hay fever or other upper respiratory allergies
  - Not recommended for use in pediatric patients aged < 2 years
- **Nasonex (mometasone furoate monohydrate):**
  - Treatment of the nasal symptoms of SAR and PAR in adults and pediatric patients aged ≥ 2 years
  - Relief of nasal congestion associated with SAR in adults and pediatric patients aged ≥ 2 years

- Prophylaxis of the nasal symptoms of SAR in adult and adolescent patients aged ≥ 12 years
- Treatment of nasal polyps in patients aged ≥ 18 years

- **Omnaris (ciclesonide):**
  - Treatment of nasal symptoms associated with SAR in adults and children aged ≥ 6 years
  - Treatment of nasal symptoms associated with PAR in adults and adolescents aged ≥ 12 years
- **Qnasl (beclomethasone dipropionate):**
  - Treatment of the nasal symptoms associated with SAR and PAR in patients aged ≥ 4 years
- **Rhinocort Allergy (budesonide OTC):**
  - Relief of symptoms of hay fever or other upper respiratory allergies
  - Not recommended for use in pediatric patients aged < 6 years
- **Xhance (fluticasone propionate):**
  - Treatment of nasal polyps in patients aged ≥ 18 years
- **Zetonna (ciclesonide):**
  - Treatment of symptoms associated with SAR and PAR in adults and adolescents aged ≥ 12 years
- **Astepro (azelastine):**
  - Relief of the symptoms of SAR and PAR in patients aged ≥ 6 years
    - The prescribing information for brand-name Astepro notes that the approved age range is ≥ 2 years for SAR and ≥ 6 months for PAR; however, the lower, 0.1% strength is recommended for patients aged < 6 years and this strength is no longer marked as a brand.
    - An authorized generic for Astepro 0.15% is marketed by Wallace Pharmaceuticals; its indication is for the relief of the symptoms of SAR and PAR in patients aged ≥ 6 years.
- **Azelastine (0.1%; generic Astelin):**
  - Treatment of the symptoms of SAR in adults and pediatric patients aged ≥ 5 years, and for the treatment of the symptoms of vasomotor rhinitis in adults and adolescent patients aged ≥ 12 years
- **Patanase:**
  - Relief of the symptoms of SAR in adults and children aged ≥ 6 years
- **Dymista (azelastine hydrochloride/fluticasone propionate):**
  - Relief of symptoms of SAR in patients aged ≥ 6 years who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief
- **Ipratropium:**
  - **0.03% spray**: Symptomatic relief of rhinorrhea associated with allergic and nonallergic perennial rhinitis in adults and children aged ≥ 6 years
  - **0.06% spray**: Symptomatic relief of rhinorrhea associated with the common cold or SAR for adults and children aged ≥ 5 years

(*Prescribing information: Astepro 2018, Azelastine [Amneal] 2018, Azelastine [Wallace] 2015, Beconase AQ 2019, Dymista 2018, Flonase Allergy Relief 2018, Flonase Sensimist 2018, Flunisolide 2016, Fluticasone propionate 2019, Ipratropium [0.03%] 2016, Ipratropium [0.06%] 2016, Nasacort Allergy 24HR 2018, Nasonex 2018, Omnaris 2018, Patanase 2015, Qnasl 2018,Rhinocort Allergy 2016, Xhance 2018, Zetonna 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

IN Corticosteroids

- Daily administration of IN corticosteroids is associated with statistically significant improvements in allergy-related TNSS and health-related quality of life (QoL) scores. Numerous head-to-head clinical trials comparing the available IN corticosteroids have generally demonstrated no significant clinical differences among the available IN corticosteroids with regard to efficacy. Some studies have reported differences in sensory perceptions and patient preference with 1 agent compared to another. Patients administering the agents noted differences in odor, aftertaste, and severity of irritation; however, these differences were not associated with differences in efficacy between the agents (*Aasand et al 1982, Al-Mohaimeid 1993, Andersson et al 1995, Bachert et al 2002, Berger et al 2003, Day et al 1998, Drouin et al*

1996, Graft et al 1996, Gross et al 2002, Haye et al 1993, Hebert et al 1996, Khanna et al 2005, Karaulov et al 2019, LaForce et al 1994, Langrick 1984, Lumry et al 2003, Mak et al 2013, Mandl et al 1997, McAllen et al 1980, McArthur 1994, Meltzer et al 2005, Meltzer et al 2008, Meltzer et al 2010, Naclerio et al 2003, Ratner et al 1992, Sahay et al 1980, Shah et al 2003, Sipila et al 1983, Small et al 1997, Stern et al 1997, Stokes et al 2004, Svendsen et al 1989, Van As et al 1993, Vanzieleghem et al 1987, Varshney et al 2012, Welsh et al 1987, Winder et al 1993, Yonezaki et al 2016).

- IN corticosteroid aerosol formulations have been demonstrated to be significantly more effective compared to placebo. Aerosol formulations may be associated with increased retention of medication in the nasal cavity and decreased dripping from the nose and deposition in the back of the throat compared to aqueous formulations (*Leach et al 2015*). However, data on effectiveness vs traditional spray formulations are lacking.
  - Beclomethasone:
    - In a 6-week study of patients with PAR, aerosolized beclomethasone significantly improved reflective TNSS compared to placebo (-2.46 vs -1.63; $p < 0.001$). Furthermore, beclomethasone was associated with a statistically significant improvement in QoL score compared to placebo ($p = 0.001$) (*Meltzer et al 2012[a]*).
    - A 2-week study of beclomethasone nasal aerosol 80 mcg daily in pediatric patients 6 to 11 years of age with SAR also demonstrated improvement in reflective TNSS compared to placebo (-1.9 vs -1.2; $p < 0.001$) (*Storms et al 2013*).
    - A 12-week study of beclomethasone nasal aerosol 80 mcg daily in pediatric patients 4 to 11 years of age with PAR demonstrated improvement in both reflective and instantaneous TNSS compared to placebo (mean treatment differences, -0.53 [$p = 0.009$] and -0.52 [$p = 0.008$], respectively) (*Berger et al 2015*).
  - Ciclesonide:
    - A meta-analysis of 8 studies (4,039 patients) evaluating ciclesonide vs placebo for PAR found that ciclesonide was associated with significant reductions in the reflective and instantaneous TNSS,as well as the reflective nasal symptom score (rNSS) subtotal compared to placebo, with no difference in treatment-emergent adverse events (AEs) (*Yang et al 2018*).
    - Ciclesonide administered at a daily dose of 80 mcg or 160 mcg reduced reflective TNSS by 15.1 and 16%, respectively, compared to 3.7% with placebo ($p < 0.001$ for both). In addition, significant improvements were observed with both doses of ciclesonide compared to placebo with regard to ocular symptom scores and QoL ($p < 0.001$ for both) (*Ratner et al 2010*).
    - Similar improvements in outcomes were reported in additional studies of up to 26 weeks duration (*Berger et al 2012, LaForce et al 2009, Mohar et al 2012, Ratner et al 2012*).
- The approval of Xhance (fluticasone propionate) for the treatment of nasal polyps was based on two 16-week, randomized, placebo-controlled trials (*Leopold et al 2019, Sindwani et al 2019*). Adults with nasal polyps and associated moderate to severe nasal congestion showed improvement in nasal congestion/obstruction and bilateral polyp grade when treated with fluticasone propionate using the Xhance delivery device. Published data from 1 of the 2 studies demonstrated that improvements in symptoms and polyp grade continued to increase with an additional 8 weeks of open-label treatment (*Leopold et al 2019*). Use of Xhance was also shown to improve chronic rhinosinusitis symptoms and polyp grade in a 12-month open-label trial, and the product was well tolerated over this time period (*Palmer et al 2018*). However, data are not available comparing Xhance to fluticasone propionate (or other corticosteroids) in a traditional nasal spray formulation.
- Two meta-analyses have reviewed information on the use of IN corticosteroids for treatment of chronic rhinosinusitis with or without nasal polyps.
  - A meta-analysis of 18 randomized trials (N = 2738) reviewed the use of IN corticosteroids vs placebo or no intervention, and demonstrated that IN corticosteroids improved symptoms, including a moderate-sized benefit for nasal blockage and a small benefit for rhinorrhea (*Chong et al 2016[a]*). Little information on QoL was available.
  - A meta-analysis of 9 randomized trials (N = 911) found insufficient evidence to suggest differences in efficacy among different IN corticosteroids or between a spray and an aerosol (*Chong et al 2016[b]*). Lower doses appeared to have similar effectiveness and fewer side effects than higher doses.
- A recent Cochrane systematic review including 34 randomized trials evaluated the effects of intranasal steroids for the management of non-allergic rhinitis. In 2 separate pooled analyses of 4 trials, results found that IN corticosteroids slightly improved patient-reported disease severity (TNSS score) compared to placebo up to week 4 (standard mean difference [SMD], -0.74; 95% CI, -1.15 to -0.33, and SMD, -0.15; 95% CI, -0.25 to -0.05, respectively). However, from 4 weeks to 3 months, data were inconclusive, suggesting that it is unclear whether IN corticosteroids reduced patient

reported TNSS. Additionally, an analysis of 4 studies suggested a higher risk of epistaxis compared to placebo (RR, 2.10; 95% CI, 1.24 to 3.57) (*Segboer et al 2019).*

IN Antihistamines

- IN azelastine has been shown to be safe and effective over 14 days of treatment in placebo-controlled trials (*Howland et al 2011, Lumry et al 2007, van Bavel et al 2009*).
- When azelastine 0.1% and azelastine 0.15% were compared to placebo in a 2-week trial, there was a significantly greater improvement in TNSS for both concentrations vs placebo ($p < 0.001$). In a retrospective analysis, there was a statistically significant difference in favor of azelastine 0.15% compared to azelastine 0.1% ($p = 0.047$) (*Shah et al 2009[a]*).
- IN olopatadine has been proven safe and effective in placebo-controlled trials across a range of doses (*Fairchild et al 2007, Hampel et al 2006, Meltzer et al 2005, Meltzer et al 2011, Patel et al 2007, Ratner et al 2005*).
- Head-to-head studies have not demonstrated any statistically significant differences in efficacy between azelastine and olopatadine (*Lieberman et al 2011, Shah et al 2009[b]*).
  - In patients with SAR, azelastine 0.1% and olopatadine 0.6% reduced symptom scores to a similar extent in a 16-day trial. Tolerability was similar between agents, with the exception of the prevalence and intensity of bitter taste, which were lower with olopatadine (*Shah et al 2009[b]*).
  - In patients with vasomotor rhinitis, both azelastine 0.1% and olopatadine 0.6% significantly reduced symptom scores from baseline in a 2-week clinical trial; the difference between treatments was not statistically significant. The overall incidence of AEs was similar between the 2 groups. The most common AE was taste disturbance, which was reported in 10.3% and 5.3% of patients in the azelastine and olopatadine groups, respectively (*Lieberman et al 2011*).
- In a single-dose crossover study evaluating sensory attributes, 60.6% of patients favored olopatadine, 30.3% favored azelastine, and 9.2% had no preference. Mean patient preference was significantly greater with olopatadine than azelastine for overall aftertaste, overall preference, and likelihood of use (*Meltzer et al 2008*).

IN Anticholinergics

- For the common cold, ipratropium bromide nasal spray has been shown to reduce the severity of rhinorrhea compared to placebo or no treatment, although it had no effect on nasal congestion. Overall, nasal dryness was the most common AE reported (*AlBalawi et al 2013, Diamond et al 1995, Dockhorn et al 1992, Eccles et al 2007, Hayden et al 1996*).
- For the treatment of perennial allergic or nonallergic rhinitis, ipratropium bromide has been shown to significantly reduce the severity and duration of rhinorrhea compared to no treatment or placebo (*Bronsky et al 1995, Dockhorn et al 1999, Georgitis et al 1994, Kaiser et al 1998, Meltzer et al 1997*). Nasal congestion was not significantly improved.

Combination Therapy and Comparisons Among Different Drug Classes

- The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review of pharmacological therapies for the treatment of SAR (*Glacy et al 2013*). A total of 59 randomized controlled trials met inclusion criteria to compare agents of 6 classes for relative efficacy. Agents included oral and IN antihistamines and decongestants, IN corticosteroids, leukotriene modifiers, cromolyn, ipratropium, and normal saline. Overall, there was insufficient evidence to draw a conclusion about relative efficacy among most of the agents used for the treatment of SAR. For a few comparisons, sufficient evidence was available to draw a conclusion. Oral selective antihistamines and montelukast were equivalent for efficacy in reducing nasal and eye symptoms. Montelukast was superior to oral selective antihistamines for controlling asthma symptoms. IN antihistamines and IN corticosteroids had equivalent efficacy for nasal and eye symptoms. Similarly, montelukast was comparable to IN corticosteroids for nasal symptoms. The combination of IN antihistamines and IN corticosteroids demonstrated equivalent efficacy in nasal and eye symptom resolution compared to either monotherapy. For children, conclusions about relative efficacy were not determined due to insufficient evidence.
- A systematic review and meta-analysis evaluated results from 5 randomized trials that compared IN corticosteroids to oral antihistamines in patients with AR (*Juel-Berg et al 2017*). Results demonstrated that IN corticosteroids were superior to oral antihistamines for improving TNSS (difference, -0.70; 95% CI, -0.93 to -0.47). There was no difference in relief of ocular symptoms. Four additional trials were included in a narrative review, and results were consistent with studies in the meta-analysis.
- A meta-analysis compared azelastine hydrochloride nasal spray to other agents used in the management of SAR and PAR which included beclomethasone nasal spray and loratadine combination, terfenadine (not available in the US), oral

cetirizine, budesonide nasal spray, ebastine (not available in the US), levocabastine (not available in the US), and oral loratadine (*Lee et al 2007*). Azelastine was demonstrated to improve symptoms compared to placebo. The analysis did not identify a statistically significant difference in treatment response for azelastine compared to active comparators, despite multiple analyses.

- A meta-analysis of 8 randomized trials in patients with allergic rhinitis found that combination therapy with intranasal fluticasone propionate and azelastine led to significantly greater reductions in TNSS from baseline compared to placebo or monotherapy with either agent (*Debbaneh et al 2019*).
- The combination of azelastine hydrochloride with fluticasone propionate nasal spray was significantly more effective compared to the individual agents in various symptom scores in a 2-week, multicenter, double-blind, randomized trial (*Ratner et al 2008*). The improvement in TNSS from baseline was 37.9% for combination therapy compared to 27.1% and 24.8%, respectively, with single-entity fluticasone and azelastine ($p < 0.05$ for the combination vs either agent alone).
- Other randomized trials comparing the combination of azelastine hydrochloride nasal spray and fluticasone propionate nasal spray have also demonstrated significant improvements in TNSS, individual symptom scores, and QoL ratings compared to each agent administered as monotherapy (*Carr et al 2012, Hampel et al 2010, Meltzer et al 2012[b], Ilyina et al 2019*).
- A randomized, active-controlled, open-label study demonstrated that long-term treatment with combination azelastine hydrochloride and fluticasone propionate nasal spray was well tolerated in adults and adolescents over a 1-year period (*Berger et al 2014*). Another randomized, active-controlled, open-label study demonstrated that this combination was safe and well tolerated in pediatric patients aged 4 to 11 years over a 3-month period (*Berger et al 2018*).

CLINICAL GUIDELINES

- The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) jointly published guidelines on the diagnosis and management of rhinitis in 2008, and a focused update on the treatment of SAR was published by these groups in 2017.
  - The 2008 guidelines note that (*Wallace et al 2008*):
    - IN corticosteroids are the most effective medication class for controlling symptoms of AR. They may also be useful in the treatment of some forms of nonallergic rhinitis.
    - When comparing the available IN corticosteroids, the overall clinical response does not appear to vary significantly between products.
    - IN antihistamines may be considered for use as first-line treatment for allergic and nonallergic rhinitis. However, IN antihistamines are generally less effective than IN corticosteroids for treatment of AR.
    - IN anticholinergics may effectively reduce rhinorrhea but have no effect on other nasal symptoms.
    - The concomitant use of ipratropium bromide nasal spray and an IN corticosteroid is more effective than administration of either drug alone in the treatment of rhinorrhea.
  - The 2017 focused update on treatment of SAR notes that, for the initial treatment of nasal symptoms of SAR (*Dykewicz et al 2017*):
    - For patients aged ≥ 12 years, clinicians should routinely prescribe monotherapy with an IN corticosteroid rather than a combination of an IN corticosteroid with an oral antihistamine.
    - For patients aged ≥ 15 years, clinicians should recommend an IN corticosteroid over an LTRA.
    - For moderate to severe symptoms in patients aged ≥ 12 years, clinicians may recommend the combination of an IN corticosteroid and an IN antihistamine.
- Guidelines on AR from the American Academy of Otolaryngology-Head and Neck Surgery Foundation note that (*Seidman et al 2015*):
  - Clinicians should recommend IN corticosteroids for patients with a clinical diagnosis of AR whose symptoms affect their QoL.
    - There are no significant differences in efficacy between the available agents. Sensory attributes, including aftertaste, nose runout, throat rundown, and smell, are an important factor in patient preference and adherence to therapy. Aerosol preparations may address some of these concerns.
    - Comparative studies have shown that IN corticosteroids are superior to oral antihistamines in controlling nasal symptoms, including nasal congestion, with no significant difference in the relief of ocular symptoms. IN corticosteroids are more effective than LTRAs across the range of allergy symptoms. However, IN antihistamines have a more rapid onset of action than IN corticosteroids in comparison studies.

    - In addition to improving nasal symptoms, IN corticosteroids have beneficial effects on allergic eye symptoms such as itching, tearing, redness, and puffiness.
  - Clinicians should recommend oral second-generation/less-sedating antihistamines for patients with AR and primary complaints of sneezing and itching.
  - Clinicians should not offer oral LTRAs as primary therapy for patients with AR.
  - Clinicians may offer IN antihistamines for patients with seasonal, perennial, or episodic AR.
    - IN antihistamines are effective treatments for AR and can be used as first- or second-line therapy.
    - For the treatment of nasal symptoms, IN antihistamines have shown equality or superiority to oral antihistamines in numerous studies.
    - Azelastine and olopatadine have equal efficacy in head-to-head, placebo-controlled comparison studies.
  - Clinicians may offer combination pharmacologic therapy in patients with AR who have an inadequate response to pharmacologic monotherapy.
    - The most effective addition to an IN corticosteroid is an IN antihistamine.
- According to the International Consensus Statement on Allergy and Rhinitis for AR (*Wise et al 2018*):
  - IN corticosteroids:
    - Benefits: IN corticosteroids are effective in reducing nasal and ocular symptoms of AR. They have superior efficacy compared to oral antihistamines and LTRAs.
    - Harms/disadvantages: IN corticosteroids have undesirable local AEs such as epistaxis with prolonged administration. There might be some negative effects on short-term growth in children, but it is unclear whether these effects translate into long-term growth suppression.
    - Recommendation: IN corticosteroids are strongly recommended and should be used as first-line therapy for AR.
  - IN antihistamines:
    - Benefits: IN antihistamines have a rapid onset, are more effective for nasal congestion than oral antihistamines, are more effective for ocular symptoms than IN corticosteroids, and show consistent reduction in symptoms and improvement in QoL compared to placebo.
    - Harms/disadvantages: There are concerns for patient tolerability, especially due to taste. IN antihistamines are less effective for congestion than IN corticosteroids.
    - Recommendation: IN antihistamines are recommended and may be used as first-line or second-line therapy for AR.
  - IN anticholinergic (ie, ipratropium):
    - Benefits: Use of an IN anticholinergic reduces rhinorrhea.
    - Harms/disadvantages: Local side effects include nasopharyngeal irritation, burning, headache, pharyngitis, epistaxis, nasal dryness, nasal congestion, and dry mouth. Care should be taken to avoid overdosage leading to systemic side effects.
    - Recommendation: An IN anticholinergic is an option for the treatment of AR and may be considered as an adjunct to IN corticosteroids in PAR patients with uncontrolled rhinorrhea.
  - The combination of an IN corticosteroid and an IN antihistamine is strongly recommended when monotherapy fails to control AR symptoms.
  - Combinations of an oral antihistamine and an IN corticosteroid are an option, with the combination equivocal over either drug alone.
- Guidelines from Allergic Rhinitis and its Impact on Asthma (ARIA), a part of the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA), suggest the use of an IN corticosteroid over an IN antihistamine in patients with AR (SAR and PAR). No preference is stated for IN corticosteroid monotherapy vs IN corticosteroid/IN antihistamine combination therapy or for IN antihistamine vs oral antihistamine (*Brozek et al 2017*).
- Joint guidelines on the diagnosis and management of rhinosinusitis are available from the AAAAI, the ACAAI, and the Joint Council of Allergy, Asthma, and Immunology (JCAAI) (*Peters et al 2014*). According to these guidelines:
  - IN corticosteroids (sprays and aerosols) have been extensively studied as a treatment for chronic rhinosinusitis with nasal polyps. Several different IN corticosteroids have been shown to be effective at decreasing nasal polyp size or preventing the regrowth of nasal polyps after surgical removal; however, head-to-head studies comparing different IN corticosteroids are not available.
  - The published studies have consistently shown IN corticosteroids to be superior to placebo for improving nasal patency, lessening nasal symptoms, decreasing polyp size, and improving QoL when used for 1 to 12 months; however, the magnitude of effect is variable.

- The extent to which the use of IN corticosteroids prevents the need for sinus surgery or regrowth of nasal polyps is not well established.

- Joint guidelines from the European Rhinologic Society (ERS) and the European Academy of Allergy and Clinical Immunology (EAACI) also support the use of IN corticosteroids in the management of chronic rhinosinusitis with nasal polyps (*Fokkens et al 2012*). These guidelines state that "modern" IN corticosteroids (mometasone, fluticasone, and ciclesonide) do not have greater efficacy vs "first-generation" IN corticosteroids (budesonide, beclomethasone, betamethasone, triamcinolone, and dexamethasone), although they may have fewer AEs.

SAFETY SUMMARY

- IN corticosteroids
  - Key warnings and precautions among the IN corticosteroids include the following:
    - Local nasal effects, such as epistaxis, nasal ulceration, nasal septal perforation, *Candida albicans* infection of the nose or pharynx, and impaired wound healing
    - Development of glaucoma or cataracts
    - Hypersensitivity reactions, including angioedema, anaphylaxis, urticaria, contact dermatitis, hypotension, bronchospasm, and rash
    - Immunosuppression: potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex; or more serious or even fatal course of chicken pox or measles in susceptible individuals
    - Hypercorticism and adrenal suppression
    - Potential reduction in growth velocity in children
  - Common AEs include cough, pharyngitis, nasal discomfort, headache, and epistaxis.
- IN antihistamines
  - Key warnings and precautions among the IN antihistamines include the following:
    - Local nasal effects, such as epistaxis and nasal ulcerations (olopatadine)
    - Activities requiring mental alertness: somnolence has been reported in some patients using olopatadine or azelastine
  - Common AEs with olopatadine include bitter taste, headache, epistaxis, pharyngolaryngeal pain, post-nasal drip, cough, urinary tract infection, upper respiratory tract infection, pyrexia, and rash.
  - Common AEs with azelastine include bitter taste, pyrexia, dysgeusia, nasal discomfort/burning, epistaxis, headache, sneezing, fatigue, somnolence, upper respiratory infection, cough, pharyngitis, rhinalgia, rhinitis, sinusitis, nausea/vomiting, dry mouth, fatigue, dizziness, otitis media, contact dermatitis, oropharyngeal pain, dysesthesia, and weight gain.
- IN anticholinergics
  - Key warnings and precautions for ipratropium nasal spray include the following:
    - Immediate hypersensitivity reactions, including urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema
    - Anticholinergic effects; should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia, or bladder neck obstruction, particularly if they are receiving an anticholinergic by another route
    - Temporary blurred vision, acute eye pain, and other ophthalmic or vision-related AEs may occur if ipratropium comes into direct contact with the eyes
    - Dizziness, accommodation disorder, mydriasis, and blurred vision may occur with use; patients should be cautioned about engaging in activities requiring balance and visual acuity
    - Has not been studied in patients with hepatic or renal insufficiency; should be used with caution in these populations
  - Common AEs with ipratropium bromide nasal spray include upper respiratory tract infection, epistaxis, pharyngitis, nasal symptoms (including dryness, congestion, and irritation), dry mouth/throat, and nausea.
- Dymista (azelastine hydrochloride and fluticasone propionate) contains an antihistamine and a corticosteroid; safety information for both classes applies to this product. The most common AEs are dysgeusia, epistaxis, and headache.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
IN corticosteroids				
Beconase AQ (beclomethasone dipropionate monohydrate)	Spray	Nasal	Twice daily	42 mcg/actuation
Flonase Sensimist (fluticasone furoate)	Spray	Nasal	Once daily	27.5 mcg/actuation
Flunisolide	Spray	Nasal	2 or 3 times daily	25 mcg/actuation
Flonase Allergy Relief (fluticasone propionate)	Spray	Nasal	Once or twice daily	50 mcg/actuation
Nasacort Allergy 24HR (triamcinolone acetonide)	Spray	Nasal	Once daily	55 mcg/actuation
Nasonex (mometasone furoate monohydrate)	Spray	Nasal	Once or twice daily	50 mcg/actuation
Omnaris (ciclesonide)	Spray	Nasal	Once daily	50 mcg/actuation
Qnasl (beclomethasone dipropionate)	Aerosol	Nasal	Once daily	Available in 2 strengths, 40 mcg/actuation (children aged 4 to 11 years) and 80 mcg/actuation (adults/adolescents)
Rhinocort Allergy (budesonide)	Spray	Nasal	Once daily	32 mcg/actuation
Xhance (fluticasone propionate)	Spray	Nasal	Twice daily	93 mcg/actuation; delivered into the nose by actuating the pump spray into 1 nostril while simultaneously blowing into the mouthpiece of the device
Zetonna (ciclesonide)	Aerosol	Nasal	Once daily	37 mcg/actuation
IN antihistamines				
Astepro (azelastine)	Spray	Nasal	Once or twice daily	Available in a 0.15% strength supplying 205.5 mcg/actuation (0.1% strength is not marketed)
Azelastine*	Spray	Nasal	Twice daily	0.1% strength supplying 137 mcg/actuation
Patanase (olopatadine hydrochloride)	Spray	Nasal	Twice daily	665 mcg/actuation
IN antihistamine/corticosteroid combination				
Dymista (azelastine hydrochloride/fluticasone propionate)	Spray	Nasal	Twice daily	137 mcg azelastine/50 mcg fluticasone propionate/actuation
IN anticholinergic				
Ipratropium	Spray	Nasal	2 to 4 times daily	Available in a 0.03% strength supplying 21 mcg/actuation and a 0.06% strength supplying 42 mcg/actuation; the 0.03% strength is given 2 or 3 times daily and the 0.06% strength is given 3 or 4 times daily

*Generic Astelin
See the current prescribing information for full details

CONCLUSION

- For the management of AR, IN therapies are often selected over oral therapies based on their high effectiveness and targeted local effects (*Seidman et al 2015*). IN corticosteroids are generally considered the most effective class of medications for controlling AR symptoms (*Wallace et al 2008*). IN antihistamines are additional options for the treatment

of AR and may be considered for first-line use. IN anticholinergics reduce rhinorrhea but are not effective for other AR symptoms (*Wallace et al 2008*).

- IN corticosteroids, antihistamines, and anticholinergics have demonstrated efficacy for their respective FDA-approved indications. Patients may have a preference for certain products based on sensory attributes, such as aftertaste, nose runout, throat rundown, and smell. However, available evidence does not suggest that any specific agent is more effective than others within the same therapeutic class.
- Clinicians may offer combination therapy to patients with an inadequate response to monotherapy (*Wallace et al 2008*).

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Therapeutic Class Overview
Opioid Use Disorder Agents

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 2019*).
  - 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 (SAMHSA) 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 (DATA) 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 [CSAT] 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 2019*).
- 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) SC 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.
- On September 7, 2018, a new dosage strength of buprenorphine/naloxone sublingual films was approved by the FDA under the brand name Cassipa. However, the launch of this product has been delayed due to patent infringement claims made by the manufacturer of Suboxone. The current estimated launch date of Cassipa is unknown, but launch may not occur until 2024 (*Fry 2019*).
- 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 (HCl)* tablet	✔
Sublocade (buprenorphine) subcutaneous (SC) injection	-
Subutex (buprenorphine)* sublingual tablet	✔
Vivitrol (naltrexone) intramuscular (IM) injection	-
Combination Products	
Bunavail (buprenorphine/naloxone) buccal film	-
buprenorphine/naloxone* sublingual tablets	✔
Suboxone (buprenorphine/naloxone) sublingual film	✔
Zubsolv (buprenorphine/naloxone) sublingual tablets	- †

*Brand name product was discontinued; however, generic formulations are available.
†Generic version not anticipated until 2032.

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

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 opioids increased to more than 42,000 deaths in 2016 (*SAMHSA 2018)*.
- 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 is usually the cause of overdose deaths *(SAMHSA 2018, 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, most 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 (*Morbidity and Mortality Weekly Report [MMWR] 2012, Coffin 2019*).
- In December 2018, the U.S. Department of Health & Human Services (HHS) recommended prescribing or co-prescribing naloxone to all patients who are at risk for opioid overdose, including: patients receiving opioids at a dosage of 50 milligram morphine equivalents (MME) per day or greater; patients with respiratory conditions who are prescribed opioids; patients who have been prescribed benzodiazepines along with opioids; and patients prescribed opioids who have a non-opioid substance use disorder, report excessive alcohol use, or have a mental health disorder (*HHS 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 IM or 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 2019)*.
- 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 HCl) auto-injector	-
naloxone HCl* injection	✔
Narcan (naloxone HCl) nasal spray	- †

*Brand name product was discontinued; however, generic formulations are available
†Generic product approved by the FDA, but not yet launched

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 3. FDA-Approved Indications for Buprenorphine and Buprenorphine/Naloxone Products

Indication	Single-Entity Agents		Combination Products			
	Sublocade (buprenorphine) SC injection	Subutex (buprenorphine) sublingual tablets	Bunavail (buprenorphine/ naloxone) film	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 2019, buprenorphine/naloxone sublingual tablets 2019, Bunavail 2018, Sublocade 2019, Suboxone film 2018, Zubsolv 2018*)

Table 4. FDA-Approved Indications for Naltrexone Agents Used in Opioid Dependence

Indication	naltrexone HCl tablets	Vivitrol (naltrexone HCl) injection
Blockade of the effects of exogenously administered opioids	✔	
Treatment of alcohol dependence	✔	✔
Prevention of relapse to opioid dependence following opioid detoxification		✔

(*Prescribing information: naltrexone tablets 2017, Vivitrol 2019*)

Table 5. FDA-Approved Indications for Other Agents Used in Opioid Dependence

Indication	Lucemyra (lofexidine) tablets
Mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation	✔

(*Prescribing information: Lucemyra 2018*)

Table 6. FDA-Approved Indications for Naloxone Products

Indication	Evzio (naloxone HCl) auto-injector	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 known 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, Weiss 2011, Woody et al 2008*).
- 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 SC 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 to 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 negative self-reports 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% [300 mg/100 mg], 29% [300 mg/300mg], and 2% [placebo]) ($p < 0.0001$) *(FDA Advisory Committee Briefing Document, Haight et al 2019)*.
- Extended-release IM 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 IM naltrexone; as a result, in the intention-to-treat analysis, relapse-free survival was lower with extended-release IM naltrexone compared to sublingual buprenorphine/naloxone. However, among patients who were able to successfully initiate treatment, extended-release IM 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 IM 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*). A small, randomized, open-label study (N = 60) found that patients receiving extended-release IM naltrexone were twice as likely to remain in treatment for 6 months compared to patients receiving oral naltrexone (*Sullivan et al 2019*).
- 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 results were found in another placebo-controlled trial *(Fishman et al 2019)*. 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 prescribing 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, ASAM, CSAT/U.S. 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, SAMHSA 2019, 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).*
  - Use of tapered 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 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 (*Kampman 2015, WHO 2014*).
  - 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 with 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 SC injection also has several unique warnings and precautions, including: serious harm or death 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 2019*).

- 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 IM 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 IM 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 IM naltrexone has a REMS program due to the risk of severe injection site reactions (*REMS@FDA 2019*).

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 7a. 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	Four 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)	SC 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)	IM 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: 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	• 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
			Zubsolv: Single daily dose (except day 1 of induction: divided into doses of 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 7b. Equivalent Doses of Buprenorphine/Naloxone Combination Products*

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

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

Table 8. 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. *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.	• 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
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.	

See the current prescribing information for full details

CONCLUSION

Products for Treatment of Opioid Dependence

- Buprenorphine sublingual tablets, buprenorphine/naloxone sublingual tablets, Bunavail (buprenorphine/naloxone) buccal film, Sublocade (buprenorphine) SC 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 2019*).
- 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 IM 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 IM 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*). Retention rates with extended-release IM naltrexone are better than those seen with oral naltrexone (*Sullivan et al 2019*).

- 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 IM naltrexone include hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache. Extended-release IM 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, SAMHSA 2019, 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 approvals 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.
- The U.S. HHS has recommended prescribing or co-prescribing naloxone to all patients who are at risk for opioid overdose, including: patients receiving opioids at a dosage of 50 MME per day or greater; patients with respiratory conditions who are prescribed opioids; patients who have been prescribed benzodiazepines along with opioids; and patients prescribed opioids who have a non-opioid substance use disorder, report excessive alcohol use, or have a mental health disorder (*HHS 2018*).

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