Nevada Medicaid Pharmacy and Therapeutics Committee Meeting

June 27, 2019

OPTUMRx®

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NOTICE OF PUBLIC MEETING – PHARMACY AND THERAPEUTICS COMMITTEE

AGENDA

Date of Publication:	May 13, 2019
Date and Time of Meeting:	June 27, 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, Nevada 89107 **Please check with staff to verify room location**
Place of Meeting:	OptumRx Office 9850 Double R Blvd., Suite 200 Reno, Nevada 89521
Webinar Registration:	https://optum.webex.com/optum/onstage/g.php?MTID=e0edf79766bec040e566d3238904e67e7 **OR** www.webex.com, select "Join," enter Meeting Number 646 055 536, 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: 646 055 536

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

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

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

AGENDA

1. Call to Order and Roll Call

2. Public Comment

3. Administrative

a. **For Possible Action**: Review and Approve Meeting Minutes from March 28, 2019

b. Status Update by the DHCFP

1. Public Comment

4. Proposed New Drug Classes

a. Neurological Agents – Antiparkinsonian Agents – Dopamine Precursors

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

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

a. Analgesics – Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

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

b. Biologic Response Modifiers – Multiple Sclerosis Agents – Injectable

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

c. Biologic Response Modifiers – Multiple Sclerosis Agents – Oral

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

d. Dermatological Agents – Topical Analgesics

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

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

e. Neurological Agents – Anticonvulsants

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

f. Ophthalmic Agents – Antiglaucoma Agents

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

g. Psychotropic Agents – ADHD Agents

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

h. Respiratory Agents – Long-acting/Maintenance Therapy

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

6. Established Drug Classes

a. Cardiovascular Agents – Antihypertensive Agents – Vasodilators – Oral

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

b. Dermatological Agents – Topical Anti-inflammatory Agents – Immunomodulators: Topical

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

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

1. Public Comment

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

d. Psychotropic Agents – Antidepressants – Selective Serotonin Reuptake Inhibitors (SSRIs)

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

e. Respiratory Agents – Short-Acting/Rescue Therapy

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

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

8. Closing Discussion

a. Public Comments on Any Subject
b. Date and Location of the Next Meeting
c. Adjournment

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 and notice.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 DHCFP, 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 DHCFP, 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 P&T Committee

Pharmacy and Therapeutics Committee (P&T)

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

The P&T committee consists of at least 9 but not more than 11 members who are Governor-appointed physicians and pharmacists. Members must be licensed to practice in the State of Nevada and either an actively practicing physician or an actively practicing pharmacist. The DHHS Senior Advisor on Pharmacy serves as the Coordinator of the P&T Committee.

Meetings are held quarterly and are open to the public. Anyone wishing to address the P&T Committee may do so. Public comment is limited to 5 minutes per speaker/organization (due to time constraints). Anyone presenting documents for consideration must provide sufficient copies for each committee member and a copy (electronic preferred) for the official record.

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

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

Current Board Members:

Shamim Nagy, MD, Chair

Joseph Adashek, MD

Evelyn Chu, Pharm.D.

Mark Crumby, Pharm.D.

Mark Decerbo, Pharm.D.

Michael Hautekeet, R.Ph

Sapandeep Khurana, MD

Brian Passalacqua, MD

Kate Ward, Pharm.D.

Steven Zuchowski, MD

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

Date	Time	South Nevada Location	North Nevada Location
June 27, 2019	1:00 PM	Springs Preserve – Las Vegas	Optum Office – Reno
September 27, 2019	1:00 PM	Springs Preserve – Las Vegas	Optum Office – Reno
December 5, 2019	1:00 PM	Springs Preserve – Las Vegas	Optum Office – Reno

Web References

Preferred Drug List:

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

Medicaid Services Manual (MSM) Chapter 1200:

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

Pharmacy and Therapeutics Committee Bylaws:

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

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

Current Preferred Drug List

OPTUMRx®

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Meeting Minutes

STEVE SISOLAK
Governor

RICHARD WHITLEY, MS
Director

SUZANNE BIERMAN, JD, MPH
Administrator

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

P&T Meeting – Meeting Minutes

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

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

Place of Meeting:

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

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

Attendees

Board Members (Present – Las Vegas)
Shamim Nagy, MD, Chair
Joseph Adashek, MD
Sapandeep Khurana, MD

Board Members (Absent)
Evelyn Chu, Pharm.D.
Mark Decerbo, Pharm.D.

Board Members (Present – Reno)
Michael Hautekeet, RPh
Steven Zuchowski, MD
Brian Passalacqua, MD
Kate Ward, Pharm.D.

Mark Crumby, Pharm.D.

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

DXC:
Camilla Hauck, RPh

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

Public (Las Vegas)
Kenneth Barry
Georgette Dzwilewski, Indivior
Will Mullen, Indivior
Kelly Barfield, US World Meds
Patti Preston, Paratek
Eric Shaffer, Paratek
Dan Deck, Paratek
Joel Moerer, Alkermes
Deron Grothe, Teva
Don Moran, Teva
Christa Cooper, Lilly
Laura Hill, Abbvie
Lovel Robinson, Abbvie
Leon Ravin, DPBH

Public (Reno)
None

AGENDA

1. Call to Order and Roll Call

Meeting called to order at 1:00 PM

Roll Call:

Joseph Adashek, MD
Sapandeep Khurana, MD
Shamim Nagy, MD, Chair
Gabriel Lither, DAG
Holly Long, DHCFP
Kevin Whittington, OptumRx
Carl Jeffery, OptumRx
Michael Hautekeet, RPh
Mark Crumby, Pharm.D.
Kate Ward, Pharm.D.
Steven Zuchowski, MD
Brian Passalacqua, MD

2. Public Comment

No public comment.

3. Administrative

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

Motion to accept the minutes as submitted. Second. Voting: Ayes are unanimous. The motion carries.

b. Status Update by DHCFP

Holly Long – We are very fortunate to announce the appointment of Suzanne Bierman as the new Administrator for the Division of Healthcare Financing and Policy. She started with us on January 14 and her main office is located in Las Vegas. A little background on Suzanne. She was previously at The Guinn Center in Las Vegas. She has also served as the Assistant Director for the Medicaid Services for the Arkansas Department of Human Services. She earned her Doctorate and Masters in Public Health degrees from the University of Arkansas while working as a Legislative Analyst and Law Clerk for the University of Arkansas Medical Sciences. We are very excited for Susanne to be joining our team. At the January 24, 2019, DUR Board Meeting, it was asked by the board members that we send out what would be the second letter to the top 10 providers of opioids for fee-for-service Medicaid. These letters were sent out on March 15, 2019. We haven't received any feedback related to these so far. The MMIS modernization project was implemented on February 1, 2019. To provide an update on the antibiotic policy that was approved at the July 26 DUR board meeting, it was implemented on March 4, 2019. I would like to announce the resignation of Dr. Adam Zold from the P&T committee. He has been an amazing contributor to this committee. His dedication is greatly appreciated, and his participation will be missed. We are still in the process of recruiting members for the Drug Use Review Board. We are looking for two physicians and two pharmacists that are actively practicing and licensed in the state of Nevada. If you would like to nominate a provider that you think would be a good fit for this position, please feel free to provide your contact information to me.

4. Proposed New Drug Classes

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

Don Moran – Pharmacist and member of the Medical Affairs Team at Teva Pharmaceutical. We manufacture one of the CGRP inhibitors that you'll be discussing today, and that product is fremanezumab marketed under the brand name Ajovy. I realize that you've got a lengthy packet of data to review today looking at the entire class as well as some deliberations to perform. What I'd like to ask you do to, first of all look at this class very critically and add the class in some fashion as an alternative to currently preventative medications and add at least one if not all the agents to your

formulary preferred status. I am very partial to the product Ajovy, of course, and would certainly ask the committee to consider it very favorably as a preferred item. The reason that I suggest that, I guess that there were some bullet points I'd like you to think about in your deliberations today.

Carl Jeffery – Let me just address the audience. What we're displaying is Optum's recommendation and on the left side is preferred products we're recommending and that's Aimovig and Ajovy. The non-preferred we're recommending is Emgality. If you feel like you want to give an overview of the Ajovy…

Don Moran – If there are questions that you might have about the product as a result of your reading the material or you wish of some perspective to balance maybe what Optum has recommended, I'm certainly willing to take a shot at answering your questions the best I can.

Carl Jeffery – This is a new class in our review the CGRPs. They are a novel product for the treatment of migraine headaches. I put a brief description of what the migraine, how they're classified. There are two basic classifications. These are used to treat the episodic migraines and the chronic migraines. The chronic migraines means that the person has 15 or more headache days per month. These are significant suffers of migraines and it's good that we finally have a product that's geared towards these more severe migraine sufferers. A lot of people don't quite meet that definition, though, so these fall into the category of the episodic migraines so that's where we get the differences of the two. There's a newer neurokinin, the CGRP neuropeptide that is thought to result in the pain caused by the migraine so what these do is inhibit the receptor, so it doesn't result in the pain. I didn't explain this well as Don could have but I'll do my best. There are three products we're going to talk about. The first one that was on the market here is the Aimovig and this has been on the market for a few months now maybe since October. Three different studies in the episodic migraines. You can see the numbers, but there are quite a few studies. All shown here, versus placebo, this one still is once a month all shown to have a reduction on migraine headache days compared to placebo. When we get into the migraine studies, it had again another 667 patients, first placebo, again for the same dosing once a month, and it also showed it was effective and reduced number of migraine days. The next one that Don was trying to talk about and we cut him off, is the Ajovy. A couple of studies here, the HALO for the episodic migraine and the chronic migraine. This one's a little bit different in that it has a monthly and a quarterly dosing, so it is kind of nice, so every 3 months they can administer this one. When they did this HALO-EM trial, they were shooting for a 1.6-day migraine headache days reduction. They didn't quite achieve that but did a 1.5 for it and the 1.3 quarterly. Although it didn't hit that significance there, it still numerically improved there. It did significantly increase the proportion of patients that achieved the reduction and the migraine headache days and also a decrease in the number of medication dates that were being used, too. It carries over with the migraine, as well. The last one we have is the Emgality. Again, a couple big studies here and quite a few patients. This one's broken

down in the EVOLVE studies, the EVOLVE 1 and the EVOLVE 2. In the EVOLVE 1, the difference is between the EVOLVE 1 was done just in North America, I think just in the U.S. EVOLVE 2 is more global but you can see again, 9.4% of patients, they looked at a different measure. This is MMHD instead of the MMD's so it's a little bit different measure, so it can't quite compare these apples to apples, but 9.4% of patients reported no headache days and then a little bit lower for the EVOLVE 2. When we get into the chronic migraine, however, though with the REGAINE study here, they had a little bit more trouble getting the significance on here. The primary endpoint was the change which favored the Emgality and it significantly increased the proportion of patients that achieved the 50% reduction but the only 0.2 and 0.8% were reporting the migraines cessation versus placebo so this wasn't statistically significant. So, we looked at the number of claims we've had so far. The Aimovig has been on the market for the longest so it has the most number of claims. The Emgality is the newest one so only two claims we've had. All the utilization numbers I'll be showing today is December, January, February of this year so we tried to get the most recent data we could for the full months. So not a whole lot of utilization of these yet. I will say that the DUR Board has addressed these and have added some prior authorization criteria that will go into effect probably May of this year, so we'll have some PA criteria. But, right now Optum recommends that the Board consider these clinically and therapeutically equivalent.

Shamim Nagy – We need a motion.

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

Carl Jeffery – With this new class, this will be a new class that's included in here, so it will be under the neurological agents, anti-migraine agents and then the calcitonin gene peptide as the CGRP receptor antagonists. This follows in line with the similar, the triptans that are in there already under the anti-migraine agent system, as well, so they'll be in that same category but their own class. Optum recommends that Aimovig, Ajovy be considered preferred and Emgality be non-preferred.

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

b. Toxicology Agents - Substance Abuse Agents - Withdrawal Agents

Shamim Nagy opened this up for public comment.

Kelly Barfield – I'm a corporate account director with US Worlds Meds. Thank you for having me today. Today I'd like to discuss the merits of Lucemyra and the impact it may have by placing it on the Nevada Fee for Service formulary. Lucemyra is the first and only FDA approved non-addictive, non-opioid medication for the mitigation of opioid withdrawal syndrome in adults. Being that

Lucemyra is the first and only nonnarcotic agent to treat opioid withdrawal, compendia has created a new therapeutic class, MediSpan, First Databank, and Elsevier, Gold Standard all have Lucemyra as or the therapeutic category agents for opioid withdrawal. I think it's important to note that the MATs fall under the class of agents for opioid use disorder. This leads me to what Lucemyra is and is not. Lucemyra is not an MAT and not a treatment for opioid use disorder. It's essential alpha 2 adrenergic agonist indicated to mitigate withdrawal symptoms in adults following the abrupt discontinuation of opioids. Lucemyra is not another maintenance therapy for patients with opioid use disorder. Lucemyra is not an opioid-based agent that would treat cravings for addictive patients suffering from opioid use disorder. So, what is Lucemyra and how could it be used based on the label? Lucemyra could be used for patients that developed a physical dependence to opioids and with the aid of their provider, have a need to mitigate their physical symptoms of withdrawal. Lucemyra is an acute 7 to 14-day therapy that may be a single treatment for dependent patients experiencing withdrawal from discontinuation of opioids. Lucemyra can be prescribed by primary care physicians that have not received additional treatment for OUD. The common theme that is continually discussed on national platform is the need to broaden the options and set a care for patients that have developed physical dependence and/or addiction to opioids. With the approval of Lucemyra, primary care physicians now have an agent that they can utilize as a frontline provider to safely treat patients they would like to mitigate the physical symptoms of withdrawal. It is important to note that the treatment of opioids role has a critical time window. Patients are highly sensitive to and fearful of opioid-withdrawal symptoms. The physical symptoms of withdrawal maybe get 8 to 12 hours following discontinuation of opioids with a peak of symptoms at days 2 through 5. For patients and providers to recognize the full utility that Lucemyra may have to offer is essential that patients have unrestricted access without having to wait 24 to 48 hours for the review and approval of a prior authorization. In closing, Lucemyra provides an opportunity to engage a broad range of providers to address and treat opioid dependence where there has been limited options in the past. Thank you.

Shamim Nagy opened up for questions.

Shamim Nagy – Is this for the use in outpatients?

Kelly Barfield – Yeah, it's a good question. This is use for outpatients. Nowhere in the label does the FDA restrict outpatient utilization. Our trials were conducted in an inpatient setting due to the control factor and that variable in recording the results of product, but we have virtually seen very, very limited outpatient utilizations all by an outpatient so far.

Sapandeep Khurana - What's the defensive mechanism of action between Lucemyra and clonidine?

Kelly Barfield – So from an MOA standpoint, there is no difference.

Shamim Nagy opened up for public comment. No public comment.

Carl Jeffery – I'm not going to spend a lot of time, just repeating what Kelly just said, so basically we've got the Lucemyra, there's a caveat with this one. We don't really see any benefit of listing this as a class and so we would be fine of the board not even accepting this class because right now basically the Lucemyra is the only approved agent for it. Clonidine is medically accepted. It doesn't have an FDA-approved indication for it, but it's medically accepted, and it's listed as common compendia so it's not a problem Medicaid covering it for the withdrawal. You can see the number of claims. We don't have any way to tease out that these are just being used for opioid withdrawal so chances are, 99% of these are being used for blood pressure and children for ADHD so three claims in the past quarter with Lucemyra; not a whole lot of utilization yet but unless there's any discussion from the board or some questions, Optum recommends the clonidine and Lucemyra be considered as clinically and therapeutically equivalent.

Shamim Nagy opened up for discussion or questions from the Board. No questions.

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

Carl Jeffery – Like I said, there's really no benefit to having this class on the PDL at this time. There may be more agents in this class coming on; at that time, it may be more of a benefit but right now if the board wanted to have a class, our recommendation would be to have the clonidine and Lucemyra both listed as preferred.

Gabriel Lither – Can you explain the options a little bit more so that everybody understands. The options are to either vote with a class and vote which drugs should be in the class, where the alternative that you're putting forth is the elimination of this class with a PDL and what would it take?

Carl Jeffery – Yeah, this is a new class and so by not having this class put on there. Medicaid has an open formulary, so we cover everything that is FDA approved and rebatable so by not having this class on here, there's no restriction. We just don't advertise it as being preferred but it's not non-preferred, so we just don't add any additional restriction to it by not putting it on there. Chances are this will likely go to the DUR Board meeting where we will add some prior authorization criteria for the DUR Board. I think that's a better way to manage this medication rather than the preferred drug list.

Shamim Nagy – We already have voting on adding this as a new class.

Gabriel Lither – We just have voting for the clinical and therapeutic equivalence.

Multiple Speakers (indiscernible)

Shamim Nagy – Do we have to vote again?

Joseph Adashek – You don't have to. It's up to us if you want to vote again. It doesn't seem like it changes anything anyway so why make it more difficult if we don't have to.

Gabriel Lither – It's not a class right now. It is a proposed new class. Your options are to create new class with whichever medications you want to do, or your second option is to do nothing. And by Dr. Adashek, that you could by simply doing nothing, I was told it was helpful and clearer if you made a motion to do nothing so it's on the record that you are not adopting this new class at this time.

Joseph Adashek – Well I am pretty good at doing nothing. It doesn't change anything that we are doing in terms of this "class," we're not making it a class and it seems like it will work the same. I vote we make no changes to this non-class.

Second. Voting: Ayes are unanimous. The motion carries.

Joseph Adashek – So did we say that they're clinically and therapeutically alternatives, but we have to agree with the fact that it's preferred? Is that correct?

Carl Jeffery – Right, so you agree that they're clinically and therapeutically equivalent. We just didn't create that new class so that class will not exist on the PDL going forward with this update.

Joseph Adashek – So the DUR might decide that…

Holly Long – Right, so maybe we can clarify, too, that if it's not on here, it's not preferred or non-preferred, that's open access to it. It doesn't have to be on the PDL for Medicaid to provide coverage.

Carl Jeffery – Why was it brought forward?

Carl Jeffery – I think it was a request and then I think when this first came out, we weren't sure exactly where it would fit in with the therapies and doesn't really fit in with the other ones with like the Suboxone and those so because we have to work so far out in advance…

Gabriel Lither – I was going to say, sometimes when they're creating the agendas and they're putting together the materials so far in advance that they don't know whether something should really be on the agenda, it's too late and you guys had votes like you just did tonight.

Holly Long – And, sometimes we don't see the utilization that was supported one way or the other and then of course we always are anticipating other drugs that could possibly be coming to that class and if they don't, then we're stuck in that position.

Sapandeep Khurana – As a psychiatrist, I would say, I think would warrant a discussion but right now there's not too much to make a class.

Joseph Adashek – I would hope that DUR would make everything available possible for anything that's in the class of medication for outpatients and for all the opioids and other classes we'll talk about.

Holly Long – Sure, that's for DHCFP, they are in support of that and we're doing everything that we can make sure that the substance abuse treatment is there available for the recipients.

Shamim Nagy – That's a very important issue. We should table this to a future date.

Holly Long – Sure, and I can make note to bring it back to the next P&T meeting if the DUR Board makes any decisions one way or the other.

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

Shamim Nagy opened up for public comment.

Kenneth Barry – My name is Dr. Kenneth Barry, I'm from Alkermes. It's a pleasure to be here to talk to you. I want to present some clinical information and economic information about Vivitrol. We all know that Vivitrol is extended release naltrexone in injectable form and it's used and indicated for opioid use disorder and it should be part of a comprehensive management program that includes psychosocial support. Now SAMHSA government protocol recommendations for medications for OUD. OUD medication should be available to patients across all settings and at all levels of care. All patients considering treatment should be educated about effectiveness, risk, and benefits of each of the three medications used for OUD, which would include methadone, buprenorphine, and naltrexone. Medications from different pharmacological classes are available for OUD as we mentioned. Vivitrol is not associated with the development of tolerance or dependence. It does not cause disulfiram-like reactions resulting from an opiate or alcohol injections and there is no withdrawal syndrome associated with discontinuation of Vivitrol. Opiate-dependent patients including those being treatment for alcohol use disorder should be opiate free for 7 to 10 days prior to initiating Vivitrol. A few clinical studies to consider, one's published in JAMA Psychiatry in 2017. The effect of Vivitrol versus Suboxone for opiate dependence. This was a 12-week clinical trial of 232 opiate-dependent individuals to determine whether treatment with Vivitrol will be as effective as Suboxone and maintaining short-term abstinence from heroin or other illicit drugs. The study found that both drugs were equivalent in maintaining abstinence from heroin and other illicit opiates in the study. Some secondary measures with participants receiving Vivitrol received less craving and thoughts about heroin and had higher patient satisfaction compared to Suboxone patients in the trial. There were no deaths recorded in the study and the one overdose occurred in a Suboxone-treated patient. The next study was published in Lancet 2018. It was better known as XPOT or comparative effectiveness of Vivitrol versus Suboxone for opiate relapse prevention. This was a 24-week study compared to the effectiveness trial of 570

patients with opiate use disorder and had used nonprescription opiates within 30 days prior to the trial. The results show that Vivitrol was as effective as Suboxone treatment in maintaining patients relapse free among participants who were inducted. The 24-week relapse of events were similar across all study groups but the self-reported opiate cravings was initially less with Vivitrol but they did merge at 24 weeks with the Suboxone group, as well. Adverse events including overdose did not differ between the two groups. Overdose fatalities occurred in three participants in the Suboxone arm and two in the Vivitrol arm. Now recent pharmacoeconomic data that was published in the Journal of Medical Economics in 2018 was a 12-month retrospective analysis of insurance claims.

Gabriel Lither - I'm not sure exactly where you're going with the economic data, but it's important to note, this committee does not consider economic factors in its decision. So, it's beneficial for us; we're actually not supposed to hear of documented information.

Kenneth Barry – Okay, I can scratch that.

Gabriel Lither – Just a reminder that you're currently on the approved portion of the diagram up there.

Kenneth Barry – Okay, makes my job even easier, especially when I get home, I like this. So, I just wanted to thank you for your time today and your support for Vivitrol for patients with addiction. Any questions?

Sapandeep Khurana – Is it approved only for opiate disorder or alcohol and opiate abuse disorder?

Kenneth Barry – It's approved for alcohol use disorder and opiate use disorder.

Shamim Nagy opened up for public comment. There were none.

Carl Jeffery – Let me start off by saying that the Board has some decisions to make with this class, as well. This is a new class. We also have on the agenda to discuss the Suboxone, the Zubsolv, and the naloxone and the buprenorphine combinations. These two products would fit nicely into that class and so when we get down a little bit further, I actually have a couple scenarios proposed when we get to that class that this be included in there. Also, we recommended they be added as preferred in that whole class. So if the Board would like to skip this section and wait until we get down with the other buprenorphine-naloxone products, we could discuss adding those with the whole class or if the Board so desires to have this as a separate class, it's totally up to the Board. We have felt that it would fit nicely into the other ones, the buprenorphine-naloxone combination products. We heard about the Vivitrol, but I will just give my spiel about the Sublocade. It's an extended release buprenorphine product. It's dosed at 300 mg monthly for the first 2 months and then the dose is adjusted after that. You can go to 100 mg up to 300 mg dose once a month. They should be stabilized on the sublingual buprenorphine product before adjusting this, but it has been shown to be superior to placebo and achieving the more illicit opioid 3 weeks.

Gabriel Lither – I was just wondering, Carl, can you explain why you think this might feel well in a different class and what change between the time you proposed perhaps the new class and the idea now that it might be better fit in a preexisting class.

Carl Jeffery – Just to give my thunder away here, what we do is change the class so currently the other one is a mixed opioid antagonist for substance abuse agents. What we do is create a single class that would be substance abuse agents and then we would list the Sublocade and the Vivitrol as well as all the buprenorphine-naloxone products in there. What it does is simplify just the class as far as administration and also from the provider standpoint, there is less for them to review I think as far as what is on the preferred drug list. I think it would make it simpler from the provider standpoint as well as having it just under a single class so that was kind of our thought and it's indicated for the same thing. Often times these are interchangeable. As you can see, the Sublocade, they also need to be on the buprenorphine oral product, as well, during initiation.

Shamim Nagy – Should wait to discuss this again when we get to the other class?

Gabriel Lither – To make it clear, just have a motion that would be helpful, a motion to either adopt this new class now or to include these medications in the other class, so would we agree with doing that, would take it to the next class which is similar to this class next or to include it all at once, or would it be better just to make a motion to include them all in the same class, opioid antagonist?

Joseph Adashek – I think if you want to, we can just move the agenda around, as well, we can go to the other class right now, hear what we have to do about them and the class and then make a motion on this class.

Shamim Nagy – I think that would be clearer. Could we do that and move onto the next class?

Carl Jeffery – I think it's a good idea.

Kate Ward – When someone is talking, can they state their name before they make their statement because it's hard to follow you guys back and forth without wondering who's talking.

Joseph Adashek – I move that we talk about the similar class next and then we can decide to whether one category… Do we need a second for that?

Gabriel Lither – The chair controls the agenda so you can move forward with that at this time.

Carl Jeffery – Okay so, I have pulled up here the preferred and non-preferred drugs as we would propose it if the class remains the mixed opioid agonist-antagonists if we decide to update the whole class to just substance abuse agents and include the Sublocade and Vivitrol, this is our proposed class of how it would look. What brought this class back is there is a new generic for the Suboxone and so we would

include the generic as the non-preferred and just still prefer the brand name for now.

Kate Ward – I was wondering as far as the different routes and administration if combining all of them together would be more confusing and would then lead to not choosing the simplest which would be the oral form or if they advocate that it was noncompliant, they would want to (indiscernible), probably be more of a route option rather than them altogether (indiscernible).

Carl Jeffery – I think it's certainly worthy of discussion. I favor the single class and so I think it's just simpler. I think Dr. Ward has a legitimate point there. I think it would be clearer as far as a route of administration injectable versus oral. This is how I think it's simpler.

Shamim Nagy – So I see like an oral class, injectables, single, and combination agents in the same class. There are combinations there, too.

Carl Jeffery – That's why for this class, we would remove the mixed, and you can see that the previous one we have, they are the mixed opioid agonist-antagonists and so we would remove the mixed part of it and just substance abuse agents.

Sapandeep Khurana – Carl I was wondering within the class, is it possible to have orals and injectables list to categories two categories.

Carl Jeffery – It would help just to put a list after them. I'm trying to think how that would look on the preferred drug list, maybe an injectable product or oral. I'm trying to think of how that would look best.

Shamim Nagy – Okay, so you think it's okay?

Carl Jeffery – Yeah, that was our recommendation but certainly I think it's worthy of discussion. I think Dr. Ward raised a good point. I think it's worthy of the Board's consideration and discussion.

Shamim Nagy presented a motion.

Discussion of changing the name of the class to opioid dependency treatment agents.

Joseph Adashek – I move that we include this class of medications all in the same class, at this time just substance abuse agents.

Second. Voting: Ayes are unanimous. Motion carries.

Public comment opened for toxicology/substance abuse agents. There were none.

Carl Jeffery – We have what brought this back is the addition of the Suboxone generic. It's available now and I put it on the utilization statistics here. Suboxone brand is still by far the most used, almost 1000 claims in the past quarter. Optum

recommends the Board consider the medications listed here clinically and therapeutically equivalent.

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

Carl Jeffery – Optum recommends that the Board update this class to include the Bunavail, the Sublocade, the Suboxone, Vivitrol, and Zubsolv as preferred and then the generic buprenorphine-naloxone, both the film and the tablet form as non-preferred. I think we can update renaming the classes well if that's something the Board would like.

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

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

a. Anti-infective Agents - Antivirals - Influenza Agents

Shamim Nagy presented this class and opened up for discussion to the public. There were none.

Carl Jeffery – Xofluza is a new medication, like the Tamiflu agents. It's an endonuclease. Works kind of the same way and just a little bit different. Indicated for patients 12 years and older who have had flu symptoms no more than 48 hours, similar to the Tamiflu. Study was about 1400 patients shown and compared to placebo and Tamiflu, shown to be noninferior or actually about the same similarity between the Tamiflu and the Xofluza. What was a little bit different was the Xofluza was slightly better at not having so many of the side effects that come with the Tamiflu. I don't know when Xofluza was available on the market, but the last quarter we don't have any claims for it. It's right in the flu season so we're looking at December, January, and February so expect to see a good number of claims for these which is not huge. Amantadine I'm guessing, I don't think it's being used a whole lot this year. I've heard it's not real effective this year for the flu virus that's going around this year, so it may be used for other non-flu issues. Still not a huge number of claims here for a quarter but those are our utilization. Optum recommends the drugs in this class be considered clinically and therapeutically equivalent.

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

Carl Jeffery – Optum recommends the new drug, Xofluza, be added to the preferred drug list as non-preferred and keep the rest of the class the same.

Shamim Nagy opened for questions/discussion.

Joseph Adashek – For the medication, Xofluza, what kind of antiviral is that? Is it similar to any of the other agents?

Carl Jeffery – Yeah, it is similar to the Tamiflu. It's a little bit different class but it works the same way as Tamiflu. The difference with the Xofluza as far as the dosing goes, it's just a one-time dose so you get the flu symptoms and it's a one-time dose whereas the Tamiflu 7 to 10 days therapy. It's a little bit different and a little bit easier that way.

Joseph Adashek – A one-time dose, can I ask you, who do you think honestly would be taking much more readily than Tamiflu and less likely to get influenza complications in this one-time dose? If you chose it, usually it's for economic reasons, I know we don't want to discuss that, for reasons that it could be other than the reason I just said.

Carl Jeffery – It's only approved to 12 and older whereas Tamiflu I think is down to 2 I think.

Joseph Adashek – I just don't know enough about it in terms of saying, should it be preferred or… if anyone up north, if they want to make a motion to prefer. Educate me on it other than the fact that it's a one-time dose.

Holly Long – Dr. Crumby or Kate Ward, can you speak to what Dr. Adashek is asking?

Kate Ward – Yeah, it does seem as though it has similar efficacy it obviously doesn't compare to Tamiflu but it does seem to be comparable to Tamiflu in efficacy and needs to be taken over an appropriate period of time with the diagnosis of influenza. Beyond reason, although we cannot discuss it, I believe that they would be able to be chosen interchangeably.

Sapandeep Khurana – I think with one dose, people will not get better any sooner now they're taking 10 doses to 1 dose and the second responses.

Joseph Adashek: If you don't take a full course of Tamiflu, do you have the same risk of resistance as with antibiotics?

Kate Ward – So really you want to take the most effective course and not the entire course that's written so with it, with Tamiflu, there's an amount to whether or not you really need to continue to take the entire course if you're no longer having symptoms. Again, the prescription is going to be filled for the entire course that's written so it doesn't go from a patient standpoint, they're going to get the entire course it's written for. In the form you get, the Tamiflu, you get one dose for treatment.

Joseph Adashek – I understand that, but say the patient feels better and only takes the tablet for 5 days, is there an increased risk of resistance for example than there would be for antibiotics or only takes two days of antibiotics for whatever; for a MRSA infection, there is more resistance if you want to take it two days as opposed to the entire course, would you say that is similar to Tamiflu or not necessarily?

Kate Ward – No, it wouldn't be. It wouldn't be comparable.

Joseph Adashek – My next question is, again, if Tamiflu's for 7 days or 10 days, are you taking 10 times the medication needed than if you were to take the one-time dose in Xofluza. Once you're taking 10 times the medication or say 10 days of Tamiflu, versus 1 day of Xofluza, does that impact the decision?

Kate Ward – No, when I looked at it, as far as average goes, it was well tolerated.

Joseph Adashek - I think that the medication that you take once in one pill would be beneficial, more likely to be taken, more likely tolerated, the side effects grasped, so I would make it a preferred agent. I make a motion that that it would be a preferred agent.

Gabriel Lither – Your motion is to accept the recommendations with the exception of moving Xofluza from non-preferred to preferred correct?

Joseph Adashek – I apologize and that is correct.

Second. Voting: Ayes are unanimous. The motion carries. Xofluza moves to preferred.

b. Autonomic Agents - Sympathomimetics - Self-injectable Epinephrine

Shamim Nagy opened for public comment. There were none.

Carl Jeffery – We have a new product, Symjepi. This one is a little bit different than the other ones that are available. It's a prefilled syringe and not an auto-injector like the Epi-Pens or even the generic epinephrine that's available. It looks like a Lovenox syringe. Right now, we don't have any claims for it in the past quarter. The generic epinephrine, which is our preferred agent, of course, has the bulk of the claims. You have a couple of Epi-Pens, one Epi-Pen prescription, so again seems like it is right in line with what we expected with how our preferred drug list is. We have another one that's on the market, Auvi-Q. This product does not participate in the Federal Drug Rebate Program, which is a requirement from CMS, so we have it up here, even though Medicaid can't cover it. Optum recommends that the Board consider these clinically and therapeutically equivalent.

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

Carl Jeffery – Optum recommends that the new product, the Symjepi, be considered non-preferred in this class and keep the rest of the class the same.

Joseph Adashek – Why was Symjepi invented then? It's such a similar medication to the others. Is there any reason why that is even on the market?

Mark Crumby – Cheaper.

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

c. Hormones and Hormone Modifiers – Androgens

Shamim Nagy opened this class for discussion and public comment. There was none.

Carl Jeffery – This will be a fast one, too. There are two new generic products on the market and that's what prompted us to bring this one back. There's also a new injectable product. It's called Xyosted. It's an injectable testosterone. It didn't make it to our numbers in time to really do a full review, so we may see it on again in the future but right now, we're just talking about the two new generics and that's why we're talking about this one. The testosterone gel is the generic for the AndroGel and the testosterone solution is the generic for the Axiron. Both of those are newly available. The other products with the testosterone gel have already been available for a while and those are out there in the market. You see our utilization. Not a whole lot of utilization on this one. When I show the slide, it's highlighted and the AndroGel. Optum recommends the Board consider adding the AndroGel as the non-preferred. There were 10 claims in the quarter, so I don't think it's going to impact those three members or so that they could either switch to the Androderm or we could grandfather them in with the AndroGel but shouldn't be a big problem to switch over to the Androderm. The two new products, we have one already for the Axiron and the other generic doesn't have any utilization yet. A lot of the other ones don't have utilization, either. Optum recommends the Board consider these clinically and therapeutically equivalent.

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

Carl Jeffery – I think one of the bigger changes since the generics came out, it gave Optum a chance to really review these again. We are going to recommend that the brand AndroGel be removed from preferred and added as non-preferred and then the new testosterone solution and the new testosterone gel which has already been listed on there but the new solution would also be added as non-preferred.

Shamim Nagy presented motion.

Kate Ward – We'll only have a solution available and not the gel available as preferred?

Carl Jeffery – Yes that's right. The advantage of only having a single preferred agent, though, is they just to need to try that one before moving into a non-preferred agent.

Joseph Adashek – I don't prescribe this as all my patients are pregnant, is that a problem with anyone up North, AndroGel is now taken off preferred?

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

d. Ophthalmic Agents – Antiglaucoma Agents

Shamim Nagy opened for public comment. There was no public comment.

Carl Jeffery – We have a new antiglaucoma agent, as the Board may remember, we combined all of the classes into all just one big antiglaucoma agent class a while ago. We have two new products that are on the market, one generic. We have the generic for the Cosopt-PF which is preservative-free, the dorzolamide and Timolol ophthalmic solution. It's just a new generic and nothing real special about that one. The other one is the Xelpros and it's a latanoprost emulsion and what makes it different from the Xalatan or the generic latanoprost that's currently available is that it's the benzalkonium free products. I think the result, there may be some patients who have kind of a sensitivity to the BAK product in there but they won't know that until they try it usually. It has a similar efficacy to Xalatan when it was studied. We have all of the different classes here. You can see the latanoprost generic, by far the most utilized in its class, almost 600 claims in the past quarter. All the other ones are around 100 claims for the most popular like the timolol or the Travatan-Z are 170, 164 claims respectively, so not a huge utilization for outside the latanoprost in the past quarter. This is a slide for the clinically and therapeutically equivalent. I have it broken down by class. There is another ROCK inhibitor that I think did get approved in the last couple of weeks, so we'll probably be seeing this class again, if not the next meeting but the meeting after. Optum recommends the Board consider these clinically and therapeutically equivalent.

Shamim Nagy opened up for discussion.

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

Carl Jeffery – Optum recommends the new generic, the dorzolamide and the timolol be added as non-preferred as well as the new product, the Xelpros be added as non-preferred; keep the rest of the class the same.

Shamim Nagy opened up for discussion.

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

e. Ophthalmic Agents - Ophthalmics for Dry Eye Disease

Shamim Nagy opened for public discussion. No public comment.

Carl Jeffery – Another new drug in its class, Cequa, it's another cyclosporin like the other ones. Its selling point is that it's formulated a little bit different. It's in a solution versus an emulsion with the other ones. It's formulated a little bit

different. They use micro-nano technology, but it's supposed to be absorbed in the eye a little bit better than some of the other ones. I saw and I was on the website this morning reviewing these and even on the website it said that it's not yet available so I'm not sure that the pharmacies have seen this yet but it is available from our clinical team and then for our review. But, it's indicated like the other ones to increase tear production in patients with the keratoconjunctivitis sicca. Similar to the other products, I put all the other indications up here for the Restasis and the Xiidra that are up there. We have about 1000 patients in the trial versus just the vehicle. There's no head-to-head studies versus against the Restasis or the Xiidra but after 84 days, 17% of the Cequa treated patients versus 9% of the vehicle-treated patients achieved their endpoint which is greater than 10 mm from baseline and then the smear wetting test. In my eyes, this doesn't seem all that effective anyway, and I think it's in line with the other ones but that's not great numbers in my mind. You can see the utilization. The Restasis multidose is kind of greyed out there because these numbers, if the Board remembers last time we reviewed this in November, we made the multidose file non-preferred and so the numbers here are from before the Board and it's non-preferred, so the 103 on here likely shifted over to the regular Restasis individual vials. No use for the Cequa yet. As I mentioned, it's probably not available yet and just a few for the Xiidra. Optum recommends the Board consider these clinically and therapeutically equivalent.

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

Carl Jeffery – Optum recommends that the new product, the Cequa, be added as non-preferred and the rest of the class remain the same.

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

6. Established Drug Classes

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

Carl Jeffery – I just was going to mention to the Board, it has nothing to do with the decision, there is a new drug that's another combination of buprenorphine-naloxone product that's supposed to be in the works, the Cassipa is its tradename. They just haven't released it. We may see this class again here soon, but we'll skip ahead to the next class.

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

Shamim Nagy opened up for public comment. No public comment.

Carl Jeffery – We have a new Lyrica-CR. I always find it amazing that these drug companies manage to come out with an extended release product about the time the regular-release product is going to come off patent, so it's incredible how

they're developing these products works. The new Lyrica-CR is once a day instead of 2 or 3 times a day and again the same indication for the Lyrica. Like I said, there's a generic that's in the pipeline, I think we should see it here soon. The other product was new; I don't know how new it is. It just popped up on our clinical review. It's a Qutenza. It's a capsaicin patch and this is the first I'd seen it, but it's indicated for the relief of pain associated with the peripheral neuropathy. It's a little bit different in that it's applied for 60 minutes at a time, up to 4 patches every 3 months and then it can only be administered by a physician or a healthcare professional. This one sounds a little bit weird as far as the administration of it. You can see our utilization, gabapentin is always one of Nevada Medicaid's population's most favorite drugs. It shows up in one of our highest utilization for the non-opioids. The numbers reflect that. The Lyrica is not quite as popular but still quite a few claims, almost 2100 claims for the Lyrica in the last quarter and only 6 claims so far with the Lyrica-CR. Optum recommends the Board consider this class clinically and therapeutically equivalent.

Shamim Nagy presented the topic for discussion. No discussion.

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

Carl Jeffery – Optum recommends that the new Lyrica-CR be added as non-preferred and then since the Qutenza would only be administered in a doctor's office, there won't be any impact here but it would just be a good idea to add it as non-preferred just in case a local pharmacy tries to run it, just so it's a little bit more clearer that way, but the Qutenza be added as non-preferred, as well.

Sapandeep Khurana – Is Savella a preferred drug only for fibromyalgia as it states?

Carl Jeffery – Yes, that's right. It's only indicated for fibromyalgia. I don't think it has the neuropathic pain indication like some of the other ones do so I think that's why it has that caveat.

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

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

Shamim Nagy opened up the discussion for public comment.

Laura Hill – My name is Laura Hill. I'm with Medical Affairs and AbbVie. We're the company that manufacturers Mavyret. I just really wanted to come up in case you had any questions. Thank you.

Carl Jeffery – We have two new authorized generics from Gilead here. There's the generic for the Epclusa and the generic for Harvoni. These were just released a few months ago. The Viekira-XR and Technivie from AbbVie is voluntarily discontinued from the manufacturer. Our plan is not to remove those quite yet

from our preferred drug list, but they probably will be coming but we'll let anybody who's maybe going to continue therapy or maybe if there's some product on the shelf we don't want to be hasty about removing those products. The generics for the Epclusa and the Harvoni are the same and actually made by the same company. No problems with those. You can see the utilization numbers here for the last quarter and so the Epclusa and the Harvoni and the Mavyret actually have quite a few claims on there. Optum makes the recommendation the Board consider this class clinically and therapeutically equivalent.

Shamim Nagy opened up for discussion. No discussion was heard.

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

Carl Jeffery – With the new generics on the market, Optum recommends the new generic for Epclusa and generic for Harvoni be added as preferred and the rest of the class remain the same.

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

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

Shamim Nagy opened the class for public discussion. No public comment.

Carl Jeffery – We brought this back a couple of times because we're trying to figure out what the class should be. This is the last class. The antifungal so, onychomycosis agents, these are only agents that are used to treat toenail fungus. It's generally what they are on infrequently for fingernail fungus. Optum sees no benefit to managing this class on the preferred drug list and so Optum's recommendation is just to eliminate this class from the preferred drug list and as we discussed with the Lucemyra is that it just creates open access. There is prior authorization requirements for a lot of these agents already for like the Jublia and some of the other medications of the topical medications, so it's not like they wouldn't just be uncontrolled but they would be still limited to those who should be best getting them. You can see the utilization of these. The therapy of these agents is a long time for not a whole lot of success rate with these, so still pretty low success and you can see people have to be on these for 48 weeks before they have a moderate reduction or moderate control of their toenail fungus. With the oral agents and I think some of the confusion is because we have it listed as a topical antifungal, I think our intention was that the fungus is topical and not everything is applied topical and I think it was creating some of the confusion because there are oral agents included in there. You can see that the oral agents are proven successful. They're a little bit more successful in treating this than the topical agents but then there are side effects with them, as well. We look at the utilization, the terbinafine can be used for other things, too, although it's probably mostly being used for the toenail fungus and then the ciclopirox is the number one

utilizer as far as the topical treatments go. There's no benefit to having this as a managed class because everything we have on here is generic and so our generic first program would kind of take over from not having this class on there.

Joseph Adashek – I would agree with Optum's recommendations that this is no longer considered a class.

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

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

Carl Jeffery – We've got a couple new nasal spray. I'm sure this is getting a lot of press coverage, the esketamine, the Spravato nasal spray. I don't know if this is going to be on our preferred drug list. Eventually, it is pretty unique on where it fits in and the therapy is really only for treatment-resistant major depressive disorders. From what I hear, it works very rapidly and has been successful for the relatively small group of people and this is really geared towards. It doses twice a week during the induction and then once a week for the maintenance phase. The other two new products are both ADHD medications. I'm not sure why we need more, another methylphenidate product, another amphetamine product, so we'll probably be seeing those in the future. Again, a couple new generics, Advair Diskus is now approved as generic and we'll be seeing those coming up here as well as the Proair, the Ventolin, and I believe the third new one coming out, too, and the Renagel as well as a new generic so these will all be a little foreshadowing where we'll be coming for future meetings.

Joseph Adashek – There's a new postpartum depression, over 60 hours, we'll have to discuss that correct?

Carl Jeffery – Physician-administered drug claims, we call them PAD claims, they're not bound by our preferred drug list and so that one would be given through a physician-administered drug. It's usually given right after the baby is born right?

Joseph Adashek – Well, it's best given for postpartum depression when diagnosed. It could be a couple weeks later, a month later.

Kate Ward – It requires the healthcare facility to administer because of the adverse effects that we're seeing so, it is given in the hospital.

Joseph Adashek – If there's 2 people out of 250, they got out of bed too fast to go to the bathroom, I read those where to the two adverse events. That was the reason it is given in a healthcare facility.

Sapandeep Khurana – For the esketamine, if the pharmacy has claimed now, what's the status that it would go through?

Carl Jeffery – Yeah, this is not restricted right now so you have to take out a claim for it. I can't think of anything that would stop it. I don't know that it's been loaded yet, though, I don't know if it's in the system yet.

Sapandeep Khurana – So would it come through or not?

Carl Jeffery – There wouldn't be any approval. The claim would just go through without any kind of restrictions so there is no approval process. It is on our list. We will bring it to the DUR Board. I think it merits restriction. I don't think it should be open access to everybody. There's some monitoring that needs to go along with it, and not everybody has treatment for major depressive disorder, so I think from what they're saying, there's certainly a limited number of people who have tried and failed other more traditional therapies before they moved to this product.

Sapandeep Khurana – You are correct, treatment is the definition of TRD and this is the study of indication of failure of two antidepressants.

Carl Jeffery – And so, two SSRI failures, probably a lot of people. A couple of new drugs coming out of the pipeline. I don't know what's with the nasal spray focus but metoclopramide nasal spray, this is interesting as it is only for adult women for acute and recurrent diabetic gastroparesis, so it would be interesting to see how this one comes out and if we'll address it. Dosed at 4 times a day so still frequent with this one. New medication that's coming out for the plaque psoriasis. I thought this one looked promising. It's a new subQ IL-23. This one is dosed every 12 weeks, so I think it's promising that it's not having to be given very frequently. Superior to Humira and Stelara which may have some promise to and then this other new one, the last one on here, is a new one for the SMA, which is muscular atrophy type 1. We've got a couple of other products that are on the market. It's a novel gene therapy which I think this one looks promising. A one-time infusion and I think we can discuss cost with this one since we're not deciding about covering it or not but 2 million dollars for the administration of this one-time infusion. A lot of money with this one coming out but I think if it's effective, and so they studied it in 12 patients, all 12 of them after 2 years, haven't declined at all, so I think it shows a lot of promise and if we're going to get that much effect out of it, maybe it's worthwhile, but I think we're just getting the tip of this new gene therapy with these other medications coming out.

Shamim Nagy opened for public comment.

Daniel Deck – Hello my name is Daniel Deck. I'm a clinical pharmacist by training. I work with the medical affairs division at Paratek Pharmaceuticals and I just wanted to take 2 or 3 minutes of your time to introduce you to a new antibiotic that helps address the challenge of antibiotic resistance. Omadacycline is a modernized tetracycline antibiotic that is FDA approved for the treatment of adult patients with community-acquired pneumonia and acute bacterial skin and skin structure infections. It's available in both an IV and oral formulation which will help facilitate discharge from the hospital on the same antibiotic and really focused on the resistance piece. It's structurally distinct from other tetracyclines and allows it to

overcome the common tetracycline-resistant mechanisms that we see that affect the older tetracycline antibiotics. As we know in the disease states of skin and soft tissue infection and community-acquired pneumonia, resistance is a growing challenger and as we know, some of the other options there are growing safety concerns with the fluoroquinolones and the black box warning. Omadacycline has activity against all the common community-acquired pneumonia pathogens including strep pneumo, Haemophilus, including islets that are resistant to other antibiotics and in the skin and soft tissue infection world, we're active against MRSA and group A strep. Notably older tetracyclines are not active against many islets of strep. We also have invitro activity against E coli including islets that are multidrug resistant. What those produce, extend the spectrum beta-lactomases, VRE, the safety and efficacy of omadacycline against these microorganisms has not been established. The tetracycline class also has a much lower incidence of C. diff which is a growing problem. It contributes the burden of cost in the hospital and so we look forward to coming back at some point when we're being considered for review to talk to you at greater length about that.

8. Closing Discussion

a. Public comments on any subject. There were none.
b. Date and location of the next meeting –

Carl Jeffery - June 27, 2019, and you can provide some feedback on how the meeting room was up there and if there's something we can improve.

c. Adjournment

Meeting adjourned at 2:36 PM

Proposed New Drug Classes

INTRODUCTION

- Parkinson's disease (PD) is a neurodegenerative disorder caused by progressive dopamine depletion in the nigrostriatal pathway of the brain and characterized by the cardinal manifestations of tremor, bradykinesia, and rigidity. Although traditionally recognized as a motor disorder, PD is a complex multifactorial condition that also includes neuropsychiatric and other non-motor manifestations. Approximately 500,000 people in the United States have PD and an estimated 50,000 new cases are diagnosed annually *(Chou 2018, National Institute of Health [NIH] 2010).*
- Current treatment options for PD include levodopa, dopamine agonists (DAs) (eg, bromocriptine, pramipexole, ropinirole), monoamine oxidase (MAO)-B inhibitors, anticholinergic agents, amantadine, and catechol-O-methyl transferase (COMT) inhibitors *(Tarsy 2018b)*.
- The dopamine precursor levodopa is the most effective drug for the symptomatic treatment of PD and is the first choice if symptoms, especially bradykinesia, become troublesome. Levodopa is combined with the peripheral decarboxylase inhibitor carbidopa to block its conversion to dopamine in the systemic circulation and liver prior to crossing the blood-brain barrier. This prevents nausea, vomiting, and orthostatic hypotension *(Tarsy 2018b).*
- Levodopa-induced complications develop within several years of starting levodopa in a substantial number of patients; complications include motor fluctuations ("wearing off" phenomenon), dyskinesia, and dystonia. It is estimated that these motor complications occur in at least 50% of patients after 5 to 10 years of levodopa treatment. The risk of motor complications increases with higher levodopa doses and younger age of PD onset *(Tarsy 2018b).*
- Treatment strategies for managing levodopa-induced dyskinesia include adjusting the levodopa doses and dosing schedule or adding an additional antiparkinson medication. For patients who fail oral and transdermal medical therapies, other options include deep brain stimulation, continuous carbidopa-levodopa intestinal gel infusion, and continuous subcutaneous apomorphine infusion *(Tarsy 2018a).*
- Levodopa combination products are available in several formulations. Immediate-release (IR) tablets, orally disintegrating tablets (ODT), and controlled-release (CR) tablets are available in multiple strengths. Rytary, an extended-release (ER) capsule, contains microbeads of carbidopa and levodopa that, after dissolving, are absorbed at different rates. Stalevo tablets include entacapone, a COMT inhibitor, to prolong and potentiate the levodopa effect; this may be useful for patients experiencing end-of-dose "wearing off" periods. Duopa, an enteral suspension, is given as a continuous infusion for patients with motor fluctuations in advanced PD *(Tarsy 2018b)*. The newest levodopa product, Inbrija, is an inhalation powder intended to be used as an adjunct to oral carbidopa/levodopa therapy for the intermittent treatment of OFF episodes.
- Medispan Class: Antiparkinson Dopaminergics; Levodopa Combinations

Table 1. Medications Included Within Class Review

Drug	Generic Availability
carbidopa/levodopa ODT	✔
Duopa (carbidopa/levodopa) enteral suspension	-
Inbrija (levodopa) inhalation powder	-
Rytary (carbidopa/levodopa) ER capsules	-
Sinemet (carbidopa/levodopa) tablets	✔
Sinemet CR (carbidopa/levodopa) ER tablets	✔
Stalevo (carbidopa/levodopa/entacapone) tablets	✔

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	carbidopa/levodopa ODT	Duopa (carbidopa/levodopa)	Inbrija (levodopa)	Rytary (carbidopa/levodopa)	Sinemet/Sinemet CR (carbidopa/levodopa)	Stalevo (carbidopa/levodopa/ entacapone)
Treatment of PD, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication	✔			✔	✔	
Treatment of motor fluctuations in patients with advanced PD		✔				
Intermittent treatment of OFF episodes in patients with PD treated with carbidopa/levodopa			✔			
Treatment of PD • Stalevo can be used: ○ To substitute (with equivalent strengths of each of the 3 components) carbidopa/levodopa and entacapone previously administered as individual products ○ To replace carbidopa/levodopa therapy (without entacapone) when patients experience the signs and symptoms of end-of-dose "wearing-off" and when they have been taking a total daily dose of levodopa ≤ 600 mg and have not been experiencing dyskinesias						✔

(*Prescribing information: carbidopa/levodopa ODT 2016, Duopa 2018, Inbrija 2018, Rytary 2016, Sinemet 2018, Sinemet CR 2018, Stalevo 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

Carbidopa/levodopa

- Although the efficacy of levodopa in PD has been widely established in clinical practice, there have been few placebo-controlled (PC) studies evaluating its effects. A systematic review of the available evidence concluded that levodopa is clinically efficacious as monotherapy for symptomatic PD *(Fox et al 2018)*. A Cochrane Review of trials comparing DAs (with or without levodopa) vs placebo and/or levodopa in patients with early PD demonstrated that while patients on a DA were less likely to develop dyskinesia, dystonia, or motor fluctuations, symptomatic control of PD was better with levodopa. Adverse effects (AEs) such as edema, somnolence, constipation, dizziness, and hallucinations were also increased in DA-treated patients vs levodopa-treated patients *(Stowe et al 2008)*.
- ELLDOPA, a multicenter (MC), double-blind (DB), PC, dose-ranging, randomized controlled trial (RCT), evaluated the effect of levodopa on the rate of progression of PD in 361 patients with early PD for 42 weeks. Patients were randomized to either carbidopa/levodopa (3 different doses) or placebo therapy. The primary outcomes were the change in Unified Parkinson Disease Rating Scale (UPDRS) scores and the percent change in the ratio of the specific striatal [^{123}I]β-CIT uptake to the nondisplaceable striatal [^{123}I]β-CIT uptake between the two images (prior to baseline and at week 40). The mean difference between the total score on the UPDRS was 7.8 units in the placebo group, 1.9 units in the groups receiving levodopa at a dose of 150 mg/day and 300 mg/day, and -1.4 units in those receiving 600 mg/day ($p < 0.001$). The mean percent decline in the [^{123}I]β-CIT uptake was significantly greater with levodopa than placebo (-6%, -

4%, and -7.2% among those receiving levodopa at 150 mg/day, 300 mg/day, and 600 mg/day, respectively vs -1.4% among those receiving placebo) (p = 0.036). The patients receiving the highest dose of levodopa had significantly more dyskinesia, hypertonia, infection, headache, and nausea than those receiving placebo. The authors concluded that from a clinical perspective, the ELLDOPA study did not find that levodopa hastens the progression of PD. Small doses were found to be effective, although less so than higher doses *(The Parkinson Study Group 2004)*.

- A 5-year, MC, DB, parallel-group, RCT compared the long-term clinical and safety effects of IR and CR carbidopa/levodopa in 618 levodopa-naïve PD patients. The mean dose of IR medication after 5 years was 426 ± 205 mg/day and 510 ± 224 mg/day for the bioavailable dose of CR medication (p = 0.02). After 5 years, 20.6% of the IR group and 21.8% of the CR group had motor fluctuations or dyskinesia (not statistically significant). The prevalence of AEs did not differ between the treatment arms. The authors concluded that despite the progressive nature of PD, both the IR and CR formulations of carbidopa/levodopa maintained similar control in PD after 5 years. The low incidence of motor fluctuations or dyskinesia was not significantly different between treatment groups and may be partly attributed to the relatively low doses of levodopa used throughout the trial *(Koller et al 1999).*

Carbidopa/levodopa + entacapone

- The efficacy and safety of adjuvant COMT inhibitor therapy (entacapone or tolcapone) to carbidopa/levodopa therapy were examined in a Cochrane Review of 14 RCTS of PD patients with motor fluctuations (N = 2566). Eight trials examined entacapone 200 mg added to each levodopa dose vs placebo in 1560 patients. Compared with placebo, entacapone significantly reduced levodopa dose (weighted mean difference: 55 mg/day; p < 0.00001), reduced OFF-time (difference: 41 minutes; p = 0.004), and improved UPDRS activities of daily living and motor scores (p < 0.05 for both). Entacapone also significantly increased the risk of dyskinesia, nausea, vomiting, diarrhea, constipation, and dizziness (p ≤ 0.01 for all). Tolcapone was shown to provide similar benefits in relieving levodopa-induced complications, but also raised liver enzyme levels in some patients *(Deane et al 2004).*
  - Due to risk of liver toxicity, tolcapone should only be used in PD patients who are not responding satisfactorily to or are not appropriate candidates for other adjunctive therapies *(Tolcapone prescribing information 2018).*

Duopa

- The efficacy and safety of Duopa were evaluated in 3 clinical trials of patients with advanced PD who had persistent motor fluctuations despite optimized treatment with oral carbidopa/levodopa. The primary efficacy measure was mean change in OFF-time from baseline to the end of the study. ON-times with and without dyskinesias were also measured.
  - In a 12-week, DB, PC, RCT, patients (N = 71) were randomized to receive Duopa or placebo per percutaneous endoscopic gastrostomy with jejunal tube (PEG-J). Those who were in the Duopa group received placebo IR carbidopa/levodopa and those in the placebo intestinal gel infusion group received active IR carbidopa/levodopa. Duopa demonstrated a statistically significant reduction in OFF-time compared with IR carbidopa/levodopa (-4.04 hours vs -2.14 hours, respectively; treatment difference: -1.91 hours; p = 0.0015). Duopa was associated with a statistically significantly greater improvement than IR carbidopa/levodopa in ON-time without troublesome dyskinesia (4.11 hours vs 2.24 hours, respectively; treatment difference: 1.86 hours; p = 0.0059) and in ON-time without dyskinesia (3.37 hours vs 1.09 hours, respectively; treatment difference: 2.28 hours; p = 0.0142). Significant improvements in the UPDRS II (ability to engage in activities of daily living) score and health-related quality of life (HRQoL), as measured by the Parkinson's Disease Questionnaire (PDQ-39), were also reported in patients receiving Duopa vs IR carbidopa/levodopa *(Olanow et al 2014).*
  - In a 52-week, open-label extension study, all patients received Duopa (N = 62). Those continuing Duopa maintained their improved OFF-time; however, this value was not statistically significant compared to the mean OFF-time at the start of the extension study (mean change in hours/day: -0.42; p = 0.377). Duopa-naïve patients showed a statistically significant improvement in OFF-time from the start of the extension study (mean change in hours/day: −2.34; p < 0.001). Statistically significant improvements in ON-time without troublesome dyskinesia from the start of the extension study were demonstrated in both Duopa-naïve (mean change in hours/day: 2.19; p = 0.005) and Duopa-continuing patients (mean change in hours/day: 1.00; p = 0.036, respectively). In regard to HRQoL, both the Duopa-continuing and Duopa-naïve groups demonstrated statistically significant improvements in the overall UPDRS Part IV score, a measure of motor complications associated with PD *(Slevin et al 2015).*
  - In a 54-week open-label study, all patients received Duopa (N = 354). OFF-time was significantly decreased from baseline to last visit by 4.4 hours/day (p < 0.001). This improvement was sustained throughout all visits from weeks 4 to 54. Similarly, ON-time without troublesome dyskinesia increased by 4.8 hours/day (p < 0.001), and ON-time with troublesome dyskinesia decreased by 0.4 hours/day (p = 0.023). These improvements were sustained at all visits. Statistically significant improvements in UPDRS Parts II and III (activities of daily living and motor examination),

UPDRS Part IV dyskinesia items, and HRQoL were observed at the study end compared with baseline *(Fernandez et al 2015).*

Inbrija

- The efficacy and safety of Inbrija for the treatment of OFF episodes in patients with PD treated with oral carbidopa/levodopa were evaluated in a 12-week, DB, PC, RCT. Patients with at least 2 hours of OFF time per day were randomized to receive Inbrija inhalation powder 60 mg (n = 113), 84 mg (n = 114), or placebo (n = 112) as needed for OFF episodes. The average use of Inbrija or placebo was approximately 2 doses per day. Change in UPDRS Part III (motor) score from pre-dose (OFF state) to 30 minutes post-dose was significantly greater in the Inbrija 84 mg group vs placebo at week 12 (least squares mean change in Inbrija group: -9.83 vs -5.91 in placebo; between-group difference: -3.92; 95% CI, -6.84 to -1.00; p = 0.0088). The proportion of patients who returned to an ON state and sustained the ON state through 60 minutes post-dose was 58% for Inbrija 84 mg and 36% for placebo (p = 0.003) *(LeWitt et al 2019).*
- The effect of Inbrija on pulmonary function was evaluated in PD patients treated with oral carbidopa/levodopa in a 12-month, open-label, RCT. Patients were randomized to receive Inbrija 84 mg (n = 278) or to an observational cohort receiving oral standard of care therapy (n = 130). There was no significant difference in pulmonary function as assessed by spirometry parameters between the Inbrija and observational cohort groups at 52 weeks. Exploratory endpoints in the Inbrija group included improvements in UPDRS Part III scores, as well as patient-reported measures such as daily OFF time *(Grosset et al 2018a [poster], Grosset et al 2018b [poster], Inbrija prescribing information 2018).*

Rytary

- The efficacy and safety of Rytary were evaluated in 3 DB, RCTs; 2 trials were conducted in advanced PD patients vs carbidopa/levodopa IR and carbidopa/levodopa + entacapone, and 1 trial was conducted in early PD patients vs placebo.
  - In comparison to IR carbidopa/levodopa (n = 192), Rytary (n = 201) demonstrated a statistically significant improvement in the percentage of OFF-time in advanced PD patients, from a baseline of 36.9% to 23.8% for the Rytary group and from a baseline of 36.0% to 29.8% for the IR carbidopa/levodopa group (p < 0.0001). This translated to the Rytary group experiencing an additional reduction of 1 hour in OFF-time compared to the IR carbidopa/levodopa group (p < 0.0001) *(Hauser et al 2013)*.
  - In a crossover study of advanced PD patients, all patients received either Rytary or carbidopa/levodopa + entacapone (n = 91). Rytary demonstrated a statistically significant improvement in the percentage of OFF-time, from a baseline of 36.3% (both Rytary and carbidopa/levodopa + entacapone patients) to 24.0% vs 32.5% in the carbidopa/levodopa + entacapone group (p < 0.0001). Hence, compared with carbidopa/levodopa + entacapone treatment, Rytary reduced OFF-time by 1.4 hours *(Stocchi et al 2014)*.
  - The PC study randomized 381 levodopa-naïve patients to 3 strengths of Rytary (145 mg, 245 mg, or 390 mg) given 3 times daily or placebo. All dosages demonstrated a statistically significant improvement in UPDRS measures vs placebo throughout the study and at 30 weeks (p < 0.0001). Rytary was well tolerated, with the most commonly reported AEs being nausea, dizziness, and headache; the authors concluded that Rytary 145 mg 3 times daily appeared to provide the best overall balance between efficacy and safety *(Pahwa et al 2014)*.

CLINICAL GUIDELINES

- The American Academy of Neurology (AAN) practice parameter on initiation of treatment for PD recommends that in patients who require the initiation of dopaminergic treatment, levodopa or a DA may be used; the choice depends on the relative impact of improving motor disability (better with levodopa) compared with the lessening of motor complications (better with DAs). Either an IR or an ER product may be considered, as there appears to be no difference in the rate of motor complications *(Miyasaki et al 2002)*.
- The AAN practice parameter on treatment of PD with motor fluctuations and dyskinesia recommends entacapone and rasagiline to reduce OFF-time *(Pahwa et al 2006).*
- The International Parkinson and Movement Disorder Society provides recommendations for treatment of motor symptoms of PD. For monotherapy in early PD, DAs, oral levodopa preparations, selegiline, and rasagiline are clinically useful. For treating motor fluctuations, clinically useful options include most DAs, levodopa ER, levodopa intestinal infusion, entacapone, rasagiline, safinamide, and deep brain stimulation, which is more invasive *(Fox et al 2018).*
- The European Federation of Neurological Societies (EFNS) and Movement Disorders Society (MDS) provide recommendations for motor fluctuations and dyskinesias in late PD. For motor fluctuations, the levodopa dose may be adjusted to attenuate any “wearing-off” syndromes. Dyskinesias may be managed by reducing the individual levodopa dose at the risk of increasing OFF-time. Increased OFF-time can be attenuated by increasing the number of daily doses of levodopa or increasing the dose of a DA (eg, apomorphine, bromocriptine, pramipexole, ropinirole). Additional doses

of levodopa or a DA at night might be effective for control of dystonia appearing during night or early morning *(Oertel et al 2011)*.

SAFETY SUMMARY

Contraindications

- All levodopa products are contraindicated in patients currently taking a nonselective MAO inhibitor or who have recently (within 2 weeks) taken a nonselective MAO inhibitor. Hypertension can occur if these drugs are used concurrently.

Warnings and Precautions

- Warnings and precautions for all of the levodopa products include falling asleep during activities of daily living, hallucinations/exacerbations of psychosis, impulse control disorders, causation or exacerbation of dyskinesia, and increased intraocular pressure in patients with glaucoma.
- Sudden discontinuation or rapid dose reduction should be avoided to reduce the risk of withdrawal-emergent hyperpyrexia and confusion resembling neuroleptic malignant syndrome (NMS).
- Cardiovascular ischemic events and arrhythmia have been reported in patients taking carbidopa/levodopa.
- Patients should be observed carefully for the development of depression with concomitant suicidal tendencies.
- Duopa has warnings for neuropathy and gastrointestinal or gastrointestinal procedure-related risks.
- Inbrija has a warning for bronchospasm in patients with lung disease; use in patients with asthma, chronic obstructive pulmonary disease (COPD), or other chronic underlying lung disease is not recommended.
- Due to the entacapone component, Stalevo has addition warnings for diarrhea, colitis, and rhabdomyolysis.
- Epidemiological studies have shown that patients with PD have a higher risk of developing melanoma than the general population. Whether the increased risk observed is due to PD or other factors, such as drugs used to treat PD, is unclear.

Key Adverse Effects

- The most common AEs for the carbidopa/levodopa oral formulations include dyskinesias and nausea. Orthostatic hypotension, confusion, dizziness, and hallucinations also occur.
- The most common AEs for Duopa (incidence at least 7% greater than oral carbidopa/levodopa) are complication of device insertion, nausea, depression, peripheral edema, hypertension, upper respiratory tract infection, oropharyngeal pain, atelectasis, and incision site erythema.
- The most common AEs for Inbrija are cough, nausea, upper respiratory tract infection, and discolored sputum.
- The most common AEs for Stalevo are dyskinesias, urine discoloration, diarrhea, nausea, abdominal pain, vomiting, and dry mouth.

DOSING AND ADMINISTRATION

General dosing information

- The optimum daily dosage of the levodopa combination products must be determined by careful titration in each patient.
- Because PD is progressive, periodic clinical evaluations are recommended; adjustment of the carbidopa/levodopa dosage regimen may be required.
- Other antiparkinson medications (eg, anticholinergic agents, dopamine agonists, and amantadine) can be given with the carbidopa/levodopa products. Dosage adjustment of carbidopa/levodopa may be necessary when these agents are added.
- Studies show that peripheral dopa decarboxylase is saturated by carbidopa at approximately 70 to 100 mg a day. Patients receiving less than this amount of carbidopa are more likely to experience nausea and vomiting. Experience with total daily dosages of carbidopa greater than 200 mg is limited.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
carbidopa/levodopa	ODT	Oral	Usual initial dosage: 3 times daily; dosage may be increased by 1 tablet daily or every other day, as necessary, until a dosage of 8 tablets per day is reached	The ODT should be allowed to dissolve on top of the tongue, then swallowed with saliva; administration with liquid is not necessary.
Duopa (carbidopa/levodopa)	Enteral suspension	PEG-J	Continuous 16-hour infusion period composed of a morning dose, a continuous dose, and extra doses	Duopa must be administered with the CADD-Legacy 1400 portable infusion pump. At the end of the 16-hour infusion, patients will disconnect pump from the PEG-J and take their nighttime dose of oral IR carbidopa-levodopa tablets
Inbrija (levodopa)	Inhalation powder	Inhalation	Inhale 2 capsules as needed for OFF symptoms up to 5 times daily	Capsules for inhalation must be administered with the Inbrija inhaler.
Rytary (carbidopa/levodopa)	ER capsule	Oral	Patients naïve to levodopa therapy: 3 times daily; titrate as needed Converting from IR carbidopa/levodopa to Rytary: follow conversion based on total levodopa dose in prescribing information	
Sinemet (carbidopa/levodopa)	Tablet	Oral	Usual initial dosage: 3 times daily Dosage may be increased by 1 tablet every day or every other day, as necessary, until a dosage of 8 tablets per day is reached	
Sinemet CR (carbidopa/levodopa)	ER tablet	Oral	Initial dose in patients not receiving levodopa: twice daily Initial dosage in patients treated with conventional carbidopa/levodopa preparations: Sinemet CR should be substituted at an amount that provides ~10% more levodopa per day; the interval between doses should be 4 to 8 hours during the waking day	An interval of at least 3 days between dosage adjustments is recommended.
Stalevo (carbidopa/levodopa/ entacapone)	Tablet	Oral	Converting patients from carbidopa, levodopa, and entacapone to Stalevo: patients taking entacapone 200 mg with each dose of non-ER carbidopa/levodopa, can switch to the corresponding strength of Stalevo	Tablets should not be split or fractionated. Patients with hepatic impairment should be treated with caution.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			containing the same amounts of levodopa and carbidopa Converting patients from carbidopa/levodopa products to Stalevo: there is no experience in transferring patients treated with ER formulations of carbidopa/levodopa	

See the current prescribing information for full details

CONCLUSION

- The efficacy of levodopa in the treatment of symptomatic PD has been well established. It is generally the first choice for treatment if symptoms, especially bradykinesia, become troublesome. Levodopa is combined with the peripheral decarboxylase inhibitor carbidopa to block its conversion to dopamine in the systemic circulation and liver prior to crossing the blood-brain barrier. This prevents nausea, vomiting, and orthostatic hypotension *(Tarsy 2018a, Tarsy 2018b).*
  - Although highly effective in the treatment of PD symptoms, levodopa-induced complications develop within several years of starting levodopa in a substantial number of patients; complications include motor fluctuations ("wearing off" phenomenon), dyskinesia, and dystonia. Treatment strategies for managing levodopa-induced dyskinesia include adjusting the levodopa dose and dosing schedule or adding an additional antiparkinson medication.
- Carbidopa/levodopa combination products are available as IR tablets, ER tablets and capsules, and ODTs. Stalevo tablets include entacapone, a COMT inhibitor, to prolong and potentiate the levodopa effect in patients who experience "wearing off". Duopa, an enteral carbidopa/levodopa suspension, is given as a continuous PEG-J infusion for patients with motor fluctuations in advanced PD. Inbrija is a levodopa inhalation powder intended to be used as an adjunct to carbidopa/levodopa therapy for the intermittent treatment of OFF episodes.
- The optimum daily dosage of the levodopa combination products must be determined by careful titration in each patient.
- Warnings and precautions for all of the levodopa products include falling asleep during activities of daily living, hallucinations/exacerbations of psychosis, impulse control disorders, and causation or exacerbation of dyskinesia. Duopa has additional warnings for gastrointestinal risk and neuropathy. Inbrija has a warning for bronchospasm in patients with lung disease. Due to the entacapone component, Stalevo has additional warnings for diarrhea, colitis, and rhabdomyolysis. Common AEs for the levodopa products include dyskinesias and nausea.
- Guidelines for the treatment of PD recommend initiation of either a DA or carbidopa/levodopa product; either an IR or an ER product may be considered, as there appears to be no difference in the rate of motor complications. In late PD, motor fluctuations or dyskinesias can be managed by modifying the levodopa dose/schedule or adding an additional antiparkinson medication such as entacapone *(Fox et al 2018, Miyasaki et al 2002, Oertel et al 2011, Pahwa et al 2006).*

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

Therapeutic Class Overview
Oral nonsteroidal anti-inflammatory drugs (NSAIDs)

INTRODUCTION

- Nonsteroidal anti-inflammatory drugs (NSAIDs) are a large class of medications with analgesic, anti-inflammatory, and anti-pyretic properties used for a wide variety of conditions including pain, rheumatoid arthritis (RA), osteoarthritis (OA), primary dysmenorrhea, ankylosing spondylitis (AS), juvenile idiopathic arthritis (JIA), acute migraine, and acute gout *(Conaghan 2012).*
  - RA is an autoimmune inflammatory arthritis that can be treated with conventional or biologic disease-modifying antirheumatic drugs (DMARDs) such as Trexall (methotrexate) or Humira (adalimumab), systemic or intraarticular (IA) corticosteroids, and/or oral or topical analgesics including NSAIDs *(Singh et al 2015).*
  - OA is the most common form of arthritis, and is a degenerative inflammatory disease that can be treated with oral or topical analgesics including NSAIDs, IA corticosteroid or hyaluronate injections, Cymbalta (duloxetine), and physical therapy *(Hochberg et al 2012, Loeser 2018).*
  - Primary dysmenorrhea is menstrual pain in the absence of other pelvic pathology, and represents one of the most common causes of pelvic pain. It can be treated with oral NSAIDs, hormonal contraceptives, topical heat, and exercise *(Osayande et al 2013).*
  - AS is a chronic inflammatory arthritis characterized by sacro-iliac joint involvement that can be treated with oral or topical NSAIDs, tumor necrosis factor inhibitors, slow acting antirheumatic drugs including Plaquenil (hydroxychloroquine), locally administered parenteral glucocorticoids, physical therapy, or surgery *(Ward et al 2016).*
  - JIA is a chronic idiopathic inflammatory disorder that affects pediatric patients. JIA encompasses multiple forms of arthritis in childhood, including what was previously described as juvenile rheumatoid arthritis before being supplanted by the newer term. Treatment for JIA includes conventional or biologic DMARDs, intravenous immunoglobulin, calcineurin inhibitors, and NSAIDs *(Grom 2018, Ringold et al 2013).*
  - Migraine is a disorder associated with severe headaches worsened by activity, light, and/or sounds, and can be treated with oral analgesics including NSAIDs and opioids, ergot derivative medications, triptans, antiemetics, and antiepileptics *(Marmura et al 2015).*
  - Gout is the most common cause of inflammatory arthritis in adults, and typically presents acutely as synovitis due to tissue deposition of monosodium urate crystals. Acute gout can be treated with Colcrys (colchicine), systemic corticosteroids, and/or NSAIDs *(Khanna et al 2012).*
- Some NSAIDs including ibuprofen and naproxen are available at lower strengths as over-the-counter (OTC) formulations, which do not require a prescription. The same compounds are also available in higher strengths as a prescription-only product. Other NSAIDs are available only by prescription regardless of strength.
- Both prescription-strength and OTC NSAIDs are widely utilized, accounting for over 111 million prescriptions annually and 60% of the OTC analgesic market in the United States (U.S.). The use of NSAIDs has been increasing over time and utilization is highest in individuals over 60 years of age *(Conaghan 2012, Davis et al 2017).*
- The therapeutic effects of NSAIDs are primarily attributed to inhibition of cyclooxygenase (COX) enzymes, which participate in the formation of mediators associated with inflammation and pain. Most NSAIDs block both related isoforms of the COX enzyme: COX-1 and COX-2 *(Solomon 2017).*
  - COX-1 regulates normal cellular processes such as gastric cytoprotection, vascular homeostasis, platelet aggregation, and kidney function. Inhibition of COX-1 is theorized to contribute to some adverse events associated with NSAID use *(Solomon 2017).*
  - COX-2 is usually undetectable in most tissues, but its expression is increased during states of inflammation *(Solomon 2017).*
- In 2005, the Food and Drug Administration (FDA) began requiring all prescription NSAIDs to carry a boxed warning highlighting the potential for increased risk of cardiovascular (CV) events such as myocardial infarction (MI) and stroke, as well as gastrointestinal (GI) bleeding. OTC NSAIDs were also required to have labeling providing more specific information about these risks *(FDA Drug Safety Communication).*
  - In 2015, following an advisory committee review of additional evidence, the FDA required revisions to existing warnings for both prescription and OTC NSAIDs to strengthen messaging regarding potential risks of use. Statements were included regarding the risk potentially increasing with duration of use *(FDA Drug Safety Communication).*

- Most NSAIDs on the market have been generic for some time. In fact, many of the originator brand products have been discontinued, leaving only generic versions on the market. The newer patented NSAIDs Cambia (diclofenac potassium), Durlaza (aspirin ER), Tivorbex (indomethacin), Vivlodex (meloxicam), and Zorvolex (diclofenac) are new formulations of previously approved molecular entities manufactured at a new strength, dosage form, and/or delivery system.
- This review includes an evaluation of orally-administered, single-agent, prescription NSAIDs. Products that are available OTC are included if they are also available in a prescription-only strength or formulation.
- Medispan class: Nonsteroidal Anti-inflammatory Drug (NSAID), Oral

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Anaprox (naproxen sodium)	✔
Anaprox DS (naproxen sodium)	✔
Cambia (diclofenac potassium)	-
Daypro (oxaprozin)	✔
diclofenac potassium	✔
diclofenac sodium DR	✔
diclofenac sodium ER	✔
diflunisal	✔
Durlaza (aspirin ER)	-
EC-Naprosyn (naproxen DR)	✔
etodolac	✔
etodolac ER	✔
Feldene (piroxicam)	✔
flurbiprofen	✔
ibuprofen	✔
Indocin (indomethacin)	✔ *
indomethacin ER	✔
ketoprofen	✔
ketoprofen ER	✔
ketorolac	✔
meclofenamate	✔ †
Mobic (meloxicam)	✔
nabumetone	✔
Nalfon (fenoprofen)	✔
Naprelan (naproxen sodium SR)	✔
Naprosyn (naproxen)	✔
Ponstel (mefenamic acid)	✔
ProFeno (fenoprofen)	✔
sulindac	✔
Tivorbex (indomethacin)	-
tolmetin	✔
Vivlodex (meloxicam)	-
Zipsor (diclofenac potassium)	✔
Zorvolex (diclofenac)	-

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)
*Only capsule formulation is available generically; the oral suspension and rectal suppository are branded products only.
†Available as a single-source generic product.

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Drug	Mild to moderate pain	RA	OA	Primary dysmenorrhea	AS	Other indication(s)
Anaprox (naproxen sodium)	✔ *	✔	✔	✔ *	✔	• Juvenile RA • Tendonitis or bursitis* • Acute gout*
Anaprox DS (naproxen sodium)	✔ *	✔	✔	✔ *	✔	• Juvenile RA • Tendonitis or bursitis* • Acute gout*
Cambia (diclofenac potassium)						• Acute migraine
Daypro (oxaprozin)		✔	✔			• Juvenile RA
diclofenac potassium	✔	✔	✔	✔		
diclofenac sodium DR		✔	✔		✔	
diclofenac sodium ER		✔	✔			
diflunisal	✔	✔	✔			
Durlaza (aspirin ER)						• Reduce risk of death and MI • Reduce risk of death and recurrent stroke
EC-Naprosyn (naproxen DR)		✔	✔		✔	• Juvenile RA
etodolac	✔ †	✔	✔			
etodolac ER		✔	✔			• Juvenile RA
Feldene (piroxicam)		✔	✔			
flurbiprofen		✔	✔			
ibuprofen	✔	✔	✔	✔		
Indocin (indomethacin)		✔	✔		✔	• Acute painful shoulder • Acute gouty arthritis
indomethacin ER		✔	✔		✔	• Acute painful shoulder • Acute gouty arthritis
ketoprofen	✔	✔	✔	✔		
ketoprofen ER		✔	✔			
ketorolac	✔ ‡					
meclofenamate	✔	✔	✔	✔	✔	• Reduction of fever • Juvenile RA • Acute painful shoulder • Acute gouty arthritis
Mobic (meloxicam)		✔	✔			• Juvenile RA
nabumetone		✔	✔			
Nalfon (fenoprofen)	✔	✔	✔			

Drug	Mild to moderate pain	RA	OA	Primary dysmenorrhea	AS	Other indication(s)
Naprelan (naproxen sodium SR)	✔	✔	✔	✔	✔	• Tendonitis or bursitis • Acute gout
Naprosyn (naproxen)	✔ *	✔	✔	✔ *	✔	• Juvenile RA • Tendonitis or bursitis* • Acute gout*
Ponstel (mefenamic acid)	✔ §			✔		
Profeno (fenoprofen)	✔	✔	✔			
sulindac		✔	✔		✔	• Acute painful shoulder • Acute gouty arthritis
Tivorbex (indomethacin)	✔ †					
tolmetin		✔	✔			• Juvenile RA
Vivlodex (meloxicam)			✔			
Zipsor (diclofenac potassium)	✔					
Zorvolex (diclofenac)	✔ †		✔			

*Suspension formulation only
†Acute pain only
‡Acute pain only, treatment limited to 5 days of total therapy
§Acute pain only, when therapy will not exceed 7 days
(*Prescribing information: Anaprox/Anaprox DS, EC-Naprosyn, Naprosyn 2018, Cambia 2017, Daypro 2017, diclofenac potassium 2017, diclofenac sodium DR 2017, diclofenac sodium ER 2017, diflunisal 2017, Durlaza 2015, etodolac 2017, etodolac ER 2017, Feldene 2017, flurbiprofen 2017, ibuprofen 2014, Indocin 2018, indomethacin ER 2017, ketoprofen, ketoprofen ER 2015, ketorolac 2016, meclofenamate 2015, Mobic 2018, nabumetone 2016, Nalfon 2017, Naprelan 2017, Naprosyn 2018, Ponstel 2017, Profeno 2017, sulindac 2016, Tivorbex 2018, tolmetin 2015, Vivlodex 2015, Zipsor 2017, Zorvolex 2016*)

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

CLINICAL EFFICACY SUMMARY

- Generally, the NSAID class has well-established efficacy as analgesic and anti-inflammatory medications. In addition to placebo-controlled pivotal trials for individual agents, several systematic reviews and meta-analyses have shown that NSAIDs compare favorably to placebo for pain reduction for various conditions. Most have also concluded that there is insufficient evidence that any one NSAID is more effective than any other *(Derry et al 2012, Enthoven et al 2016, Kroon et al 2015, Marjoribanks et al 2015, Wang et al 2016).*
  - A Cochrane review of NSAIDs for treatment of chronic low back pain evaluated 13 trials (N = 1354), and concluded that there is evidence that NSAIDs are more effective than placebo at reducing pain and disability. No difference in efficacy was seen between individual NSAIDs *(Enthoven et al 2016).*
  - A systematic review (N = 68 trials) of NSAID use in various types of chronic pain including OA, RA, soft-tissue pain, back pain, and AS found that there are no significant differences in pain relief between nonselective NSAIDs, partially selective NSAIDs (defined in the trial as meloxicam, nabumetone, and etodolac), and celecoxib. Comparisons between nonselective NSAIDs also found no clear differences in efficacy *(Peterson et al 2010).*
  - In a comparative effectiveness review, the Agency for Healthcare Research and Quality (AHRQ) assessed the efficacy of selective and non-selective NSAIDs, aspirin, acetaminophen, and topical NSAIDs and rubefacients for long-term improvements in OA symptoms. The review found that good evidence exists that nonselective and partially

selective NSAIDs do not differ significantly in efficacy for pain relief or symptom improvement as compared to each other or to COX-2 selective NSAIDs. However, the review concluded that no evidence exists comparing the efficacy of aspirin to NSAIDs for treatment of pain. Oral NSAIDs were found to have similar efficacy to topical NSAIDs for OA of the knee *(Chou et al 2006).*

- A Cochrane review including 80 trials (N = 5820) concluded that NSAIDs are a very effective treatment for primary dysmenorrhea. Insufficient evidence was found to determine if any individual NSAID is more effective than another NSAID, including comparisons between COX-2 selective and nonselective NSAIDs *(Marjoribanks et al 2015).*
- A network meta-analysis of 26 trials (N = 3410) for treatment of pain due to AS found that there were no significant differences in efficacy between NSAIDs. Etoricoxib (an NSAID not available in the U.S.) was found to be superior to celecoxib, ketoprofen, and tenoxicam (also not available in the U.S.). No other significant differences between NSAIDs were found. All 20 evaluated NSAIDs reduced pain as compared to placebo *(Wang et al 2016).*
- A systematic review of 39 studies (N = 4356) evaluating the use of NSAIDs for axial spondyloarthritis determined that there is high to moderate quality evidence that NSAIDs are efficacious for treatment of axial spondyloarthritis. NSAIDs were more beneficial than placebo and there was no difference in efficacy between the various evaluated NSAIDs, including COX-2 selective agents *(Kroon et al 2015).*
- A Cochrane review of NSAIDs for treatment of acute gout including 23 trials (N = 2200) determined that while data is insufficient to draw firm conclusions, they do not conflict with guideline recommendations for the use of NSAIDs as first-line treatment. Additionally, moderate-quality evidence was found to support the claim that COX-2 selective NSAIDs and nonselective NSAIDs are probably equally beneficial *(van Durme et al 2014).*

- Comparative reviews have also been conducted evaluating the efficacy of oral NSAIDs as compared to topical NSAIDs and other non-NSAID agents for the treatment of various types of pain.
  - A Cochrane review of 34 studies (N = 7688) evaluated oral NSAIDs and topical diclofenac for treatment of OA pain. The review found that while both were significantly more effective than placebo, there appeared to be no difference in efficacy between the two treatment modalities for knee or hand OA *(Derry et al 2012).*
  - A network meta-analysis of 137 studies (N = 33,243) comparing acetaminophen, oral NSAIDs, and IA injections of corticosteroids or hyaluronic acid concluded that IA treatments were clinically superior to oral NSAIDs after 3 months of treatment. Oral NSAIDs were in turn clinically superior to acetaminophen for treatment of OA pain after the same duration of treatment *(Bannuru et al 2015).*
  - For treatment of OA, AHRQ has stated that there is good evidence that acetaminophen is modestly inferior in efficacy compared to NSAIDs, although with a lower risk of GI complications *(Chou et al 2006).*
  - A network meta-analysis found that select NSAIDs (celecoxib, diclofenac, naproxen, and piroxicam) and opioids are similarly effective in reduction of pain for the treatment of knee OA *(Smith et al 2016).*
  - A network meta-analysis comparing ibuprofen, diclofenac potassium, aspirin, and multiple triptans (including a combination of naproxen and sumatriptan) for treatment of migraine found that ibuprofen and aspirin were inferior to eletriptan and rizatriptan with respect to pain relief, but that diclofenac potassium was more effective than any other intervention for pain relief at 2 hours. However, diclofenac did have the largest rate of migraine recurrence requiring rescue therapy. Addition of naproxen to sumatriptan significantly reduced the rate of migraine recurrence as compared to sumatriptan alone. Overall tolerability was similar between the NSAIDs, which as a class was superior to that of the triptans *(Xu et al 2016).*
  - A Cochrane review concluded that for primary dysmenorrhea, the NSAID class appears to be more effective than acetaminophen. However, this analysis was based on only 3 trials that compared NSAIDs with acetaminophen, and the quality of evidence was low *(Marjoribanks et al 2015).*
- Studies were conducted evaluating the efficacy of Tivorbex (indomethacin), Vivlodex (meloxicam), and Zorvolex (diclofenac) as compared to placebo. All 3 products were found to be superior to placebo for the treatment of pain in individual randomized controlled trials. Studies were not conducted comparing efficacy or safety of these products vs existing higher-dose generic formulations of indomethacin, meloxicam, or diclofenac. Systemic exposure of Tivorbex, Vivlodex, and Zorvolex has not been shown to be equivalent to other formulations of oral indomethacin, meloxicam, and diclofenac, respectively.
- Several large systematic reviews and meta-analyses have analyzed the risk of adverse events with use of NSAIDs, including comparisons between the nonselective NSAIDs and between nonselective and COX-2 selective NSAIDs.
  - A large meta-analysis of 280 trials (N = 124,513) evaluating the CV and GI risk of various NSAIDs concluded that the vascular risk of high-dose diclofenac (150 mg daily or greater) and possibly ibuprofen are comparable to that of COX-2 selective NSAIDs. By contrast, high-dose naproxen (100 mg daily or greater) is associated with less vascular risk than other NSAIDs. All NSAIDs increased risk of upper GI complications by a factor of 2 to 4, although the lowest

incidence was seen with COX-2 selective NSAIDs. None of the evaluated NSAIDs were found to increase risk of stroke *(Coxib and traditional NSAID Trialists' [CNT] Collaboration 2013).*
  - A Bayesian meta-analysis of MI risk with NSAID use in a cohort of 446,763 individuals found that all NSAIDs, including naproxen and celecoxib, were associated with an increased risk of acute MI. Risk was greatest with use of higher doses as well as during the first month of NSAID use. Risk did not appear to increase beyond the first 30 days of use *(Bally et al 2017).*
  - A comparative effectiveness review found that all NSAIDs can cause or aggravate hypertension, congestive heart failure, edema, and impaired renal function. Although no clear differences were seen between selective or nonselective NSAIDs in incidence of these adverse events, weak evidence was noted for a lower hypertensive effect with aspirin and sulindac than other NSAIDs. Overall tolerability was similar between the NSAIDs. Aspirin was less well tolerated than the oral NSAIDs *(Chou et al 2006).*

CLINICAL GUIDELINES

- **OA:** The American College of Rheumatology (ACR) conditionally recommends the use of oral NSAIDs as a class for the treatment of hand, hip, and knee OA. Within the NSAID class, no specific agents were identified as being more or less effective or safe as compared to other members of the class. Additional pharmacologic recommendations included acetaminophen, topical NSAIDs, and tramadol *(Hochberg et al 2012).*
  - A conditional recommendation was defined as one based on absence of high-quality evidence and/or evidence of only a small gradient of difference between desirable and undesirable effects of treatment.
  - For patients ≥ 75 years of age, an additional conditional recommendation was made for the use of topical rather than oral NSAIDs for treatment of hand OA. For patients < 75 years old, the technical expert panel expressed no preference for topical rather than oral NSAIDs.
- **Primary dysmenorrhea:** Based upon a Cochrane review of 73 randomized controlled trials, the American Academy of Family Physician recommends oral NSAIDs as first-line treatment for primary dysmenorrhea. Specifically, guidelines support the use of celecoxib, ibuprofen, mefenamic acid, and naproxen. Choice of NSAID should be based on individual patient characteristics as no NSAID has been shown to be more effective than any other *(Osayande et al 2014).*
  - Treatment initiation is recommended 1 to 2 days before expected onset of menses, with treatment duration of 2 to 3 days.
- **AS:** A joint guideline by the ACR, Spondylitis Association of America, and the Spondyloarthritis Research and Treatment Network strongly recommends treatment of active AS with oral NSAIDs. Additionally, a conditional recommendation was provided for continuous treatment with NSAIDs over on-demand treatment. As no formal comparative effectiveness studies of NSAIDs were available, the guideline recommended against designating any particular NSAID as the preferred treatment option. Instead, choice of NSAID should be determined by each patient's history, risk factors, and comorbidities *(Ward et al 2016).*
- **JIA:** ACR recommendations for JIA include initiation of NSAID monotherapy in patients without prior treatment for a maximum of 1 month. The guideline specifically states that continuation of NSAID monotherapy for longer than 2 months in patients with continued disease activity is inappropriate. Both recommendations were based on expert opinion *(Ringold et al 2013).*
- **Acute migraine:** The American Headache Society guidelines for acute treatment of migraine include various degrees of recommendations for use of oral NSAIDs depending on the specific agent. Aspirin, diclofenac, ibuprofen, and naproxen are recommended as having established efficacy. Additional NSAIDs including flurbiprofen and ketoprofen are recommended as probably effective, while celecoxib was deemed to have conflicting or inadequate evidence to support or refute use (*Marmura et al 2015).*
- **Gout:** Oral NSAIDs are recommended by the ACR as an appropriate first-line treatment option for acute gout, either as monotherapy or in combination with systemic corticosteroids and/or oral colchicine. However, the task force did not recommend any specific NSAID over the others *(Khanna et al 2012).*
  - The ACR also supports use of low-dose NSAID therapy as an appropriate first-line method of prophylaxis for acute gout attacks.
  - No consensus was reached on the use of intramuscular ketorolac or topical NSAIDs for the treatment of acute gout.

SAFETY SUMMARY

- **Boxed warnings:**
  - All oral NSAID products with the exception of Durlaza (aspirin ER) share the 2 boxed warnings below for CV and GI risk:
    - Serious CV thrombotic events: NSAIDs cause an increased risk of serious CV thrombotic events, including MI and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use. NSAIDs are contraindicated in the setting of coronary artery bypass graft (CABG) surgery.
    - Serious GI bleeding, ulcerations and perforation: NSAIDs cause an increased risk of serious GI adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.
  - Ketorolac carries additional boxed warnings for the following:
    - Renal risk: Ketorolac is contraindicated in patients with advanced renal function impairment and in patients at risk for renal failure due to volume depletion.
    - Risk of bleeding: Ketorolac inhibits platelet function and is, therefore, contraindicated in patients with suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, or incomplete hemostasis, and in those at high risk of bleeding. Ketorolac is contraindicated as a prophylactic analgesic before any major surgery.
    - Risk during labor and delivery: The use of ketorolac tromethamine in labor and delivery is contraindicated because it may adversely affect fetal circulation and inhibit uterine contractions.
    - Concomitant use with NSAIDs: Ketorolac is contraindicated in patients currently receiving aspirin or NSAIDs because of the cumulative risks of inducing serious NSAID-related side effects.
    - Special populations: Dosage should be adjusted for patients 65 years or older, for patients under 50 kg (110 lbs) of body weight, and for patients with moderately elevated serum creatinine.
- **Contraindications:**
  - Most oral NSAID products share a contraindication for use in the setting of CABG surgery, as well as in patients with a history of asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Additional contraindications specific to individual compounds are listed below.
  - Fenoprofen (Profeno only):
    - History of significantly impaired renal function
  - Ketorolac:
    - Active or history of peptic ulcer disease; recent or history of GI bleeding or perforation
    - Prophylactic analgesic before any major surgery
    - Advanced renal impairment or patients at risk for renal failure because of volume depletion
    - Labor and delivery
    - Suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis and those at high risk of bleeding
    - Patients currently receiving aspirin or NSAIDs
    - Concomitant use with probenecid or pentoxifylline.
- **Warnings and precautions:**
  - Most oral NSAID products share similar warnings and precautions for:
    - Increased risk of CV thrombotic events
    - New onset or worsening of hypertension
    - Increased risk of hospitalization due to heart failure and increased edema
    - Risk of GI effects including ulceration, bleeding, and perforation
    - Risk of renal injury and toxicity
    - Potential for skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis
    - Risk of premature closure of the ductus arteriosus when used in late pregnancy
    - Borderline elevations of one or more liver tests
    - Potential for anemia
    - Risk of severe bronchospasm in patients with preexisting aspirin-sensitive asthma
    - Risk of Reye's syndrome

- Ketorolac:
  - The total combined duration of use of ketorolac tromethamine tablets and IV or IM dosing of ketorolac tromethamine is not to exceed 5 days in adults. Ketorolac tromethamine tablets are not indicated for use in pediatric patients.

- **Adverse events:**
  - Adverse events were similar among products and commonly included GI complaints (abdominal pain, constipation, diarrhea, dyspepsia, flatulence, gross bleeding/perforation, heartburn, nausea, gastric/duodenal GI ulcers, and vomiting), abnormal renal function, anemia, dizziness, edema, elevated liver enzymes, headaches, increased bleeding time, pruritus, rashes, and tinnitus.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency
Anaprox (naproxen sodium)	Tablets	Oral	Twice daily
Anaprox DS (naproxen sodium)	Tablets	Oral	Twice daily
Cambia (diclofenac potassium)	Powder for oral solution	Oral	Once as needed
Daypro (oxaprozin)	Tablets	Oral	Once daily
diclofenac potassium	Tablets	Oral	Three times daily
diclofenac sodium DR	Tablets	Oral	Three times daily
diclofenac sodium ER	Tablets	Oral	Three times daily
diflunisal	Tablets	Oral	Twice daily
Durlaza (aspirin ER)	Capsules	Oral	Once daily
EC-Naprosyn (naproxen DR)	Tablets	Oral	Twice daily
etodolac	Capsules, Tablets	Oral	Two to four times daily
etodolac ER	Tablets	Oral	Once daily
Feldene (piroxicam)	Capsules	Oral	Once daily
flurbiprofen	Tablets	Oral	Two to four times daily
ibuprofen	Capsules, Tablets	Oral	Four to six times daily
Indocin (indomethacin)	Suspension, Tablets	Oral	Two to three times daily
indomethacin ER	Capsules	Oral	Once to twice daily
ketoprofen	Capsules	Oral	Three to four times daily
ketoprofen ER	Capsules	Oral	Once daily
ketorolac	Tablets	Oral	Four to six times daily
meclofenamate	Capsules	Oral	Three to four times daily
Mobic (meloxicam)	Capsules, Suspension, Tablets	Oral	Once daily
nabumetone	Tablets	Oral	Once to twice daily
Nalfon (fenoprofen)	Capsules, Tablets	Oral	Three to four times daily
Naprelan (naproxen sodium SR)	Tablets	Oral	Once daily
Naprosyn (naproxen)	Suspension, Tablets	Oral	Twice daily
Ponstel (mefenamic acid)	Capsules	Oral	Four times daily
ProFeno (fenoprofen)	Tablets	Oral	Three to four times daily
sulindac	Tablets	Oral	Twice daily
Tivorbex (indomethacin)	Capsules	Oral	Two to three times daily
tolmetin	Capsules, Tablets	Oral	Three times daily
Vivlodex (meloxicam)	Capsules	Oral	Once daily
Zipsor (diclofenac potassium)	Capsules	Oral	Four times daily
Zorvolex (diclofenac)	Capsules	Oral	Three times daily

See the current prescribing information for full details

CONCLUSION

- Oral NSAIDs are efficacious for the treatment of pain, RA, OA, primary dysmenorrhea, AS, acute migraine, and acute gout. Multiple systematic reviews and meta-analyses have shown that NSAIDs are superior to placebo for these indications. Furthermore, practice guidelines for these conditions recommend NSAIDs as a first-line treatment option.
- The totality of currently available evidence on relative efficacy between the available NSAIDs suggests that in general, there does not appear to be a significant difference in efficacy among the NSAIDs. Clinical practice guidelines for the aforementioned conditions support this finding and either recommend the use of NSAIDs as a class or recommend a list of NSAIDs for potential use without specifying a preference between listed agents.
- All NSAIDs carry some degree of risk for adverse events including CV thrombotic events and GI bleeding, ulceration, and perforation. Available evidence for the relative risk of these adverse events amongst NSAIDs is conflicting and inconclusive at this time. All reviewed NSAIDs with the exception of Durlaza (aspirin ER) carry the same boxed warnings for CV and GI risk. Contraindications, warnings/precautions, and adverse effects are similar among products.
- Differences between oral NSAIDs include FDA-labeled indications, available dosage formulations and strengths, and dosing frequency.

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INTRODUCTION

- Multiple Sclerosis (MS), a chronic, immune-mediated disease of the central nervous system (CNS), is the leading cause of disability in young and middle-aged people in developed areas of the world *(MS Coalition 2018)*. MS is characterized by repeated episodes of inflammation within the brain and spinal cord, resulting in injury to the myelin sheaths that surround and insulate nerves, and subsequently the nerve cell axons *(Goodin et al 2002)*. There are 4 clinical subtypes of MS:
  - Relapsing-remitting MS (RRMS), which is characterized by acute attacks followed by partial or full recovery. This is the most common form of MS, accounting for 80 to 85% of cases.
  - Secondary progressive MS (SPMS) begins as RRMS; however, the attack rate declines over time. Patients experience a gradual deterioration. Patients with RRMS for more than 10 years may transition to SPMS.
  - Primary progressive MS (PPMS) occurs in approximately 10% of patients with MS. Patients have a continuous and gradual decline in function without evidence of acute attacks.
  - Clinically isolated syndrome (CIS) refers to the first episode of neurologic symptoms that lasts at least 24 hours and is caused by inflammation or demyelination in the CNS *(Goodin et al 2002, Sanvito et al 2011, National MS Society 2019[a])*.
- A more recent revision of the MS clinical course descriptions recommended that the core MS phenotype descriptions of relapsing and progressive disease be retained with some of the following modifications: (1) an important modifier of these core phenotypes is an assessment of disease activity, as defined by clinical assessment of relapse occurrence or lesion activity detected by CNS imaging; (2) the second important modifier of these phenotypes is a determination of whether progression of disability has occurred over a given time period; and (3) the prior category of PRMS can be eliminated since subjects so categorized would now be classified as PPMS patients with disease activity *(Lublin et al 2014)*.
- An estimated 1 million adults in the United States have been diagnosed with MS. Most patients are diagnosed between the ages of 20 and 50 years, and MS is reported more frequently in women than in men *(National MS Society 2019[b])*.
- Diagnosis of MS requires evidence of damage in at least 2 separate areas of the CNS, evidence of damage that occurred at 2 separate time points at least 1 month apart, and that other possible diagnoses have been ruled out. The clinically isolated syndrome (CIS) includes 1 attack and objective evidence of 1 lesion *(Thompson et al 2018)*. Following CIS, the course of MS is variable. The inclusion of CIS in the spectrum of MS phenotypes with prospective follow-up of most such patients determining their subsequent disease phenotype was also recommended in the recent revision of the MS clinical course descriptions *(Lublin et al 2014)*.
- Disease-modifying therapies (DMTs) delay the development from CIS to clinically definite MS (CDMS) *(Miller et al 2012, Armoiry et al 2018)*. Evaluation includes an extensive patient history, neurological examination, laboratory tests to rule out other possible causes, magnetic resonance imaging (MRI) to evaluate for new disease and signs of more chronic damage, and possibly lumbar puncture (*Thompson et al 2018*).
- Exacerbations, also known as flares, relapses, or attacks of MS are caused by inflammation in the CNS that leads to damage to the myelin and slows or blocks transmission of nerve impulses. An exacerbation must last at least 24 hours and be separated from a previous exacerbation by at least 30 days. Exacerbations can be mild or severe. Intravenous (IV) corticosteroids may be used to treat severe exacerbations of MS. Corticosteroids decrease acute inflammation in the CNS but do not provide any long-term benefits *(Frohman et al 2007)*.
- The approach to treating MS includes the management of symptoms, treatment of acute relapses and utilization of DMTs to reduce the frequency and severity of relapses, reduce lesions on MRI scans, and possibly delay disease and disability progression *(Rae-Grant et al 2018[b])*. The American Academy of Neurology (AAN), the European Committee for Research and Treatment of Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) recently updated their guidelines on MS. Both guidelines recommend initiation of DMTs treatment early on in the patient's disease course (*Rae Grant et al 2018[b], Montalban et al 2018*). The MS Coalition, the AAN, and the Association of British Neurologists guidelines support access to the available DMTs for patients with MS. While there are no precise algorithms to determine the order of product selection, therapy should be individualized and patients'

clinical response and tolerability to medications should be monitored (Corboy et al 2015, Goodin et al 2002, MS Coalition 2017, Scolding et al 2015).

- Pediatric-onset MS is rare, with the vast majority of cases demonstrating a relapsing remitting disease course (*Otallah et al 2018*). Gilenya (fingolimod) is the first FDA-approved agent for pediatric patients. Its approval was based on the PARADIGMS trial (*Chitnis et al 2018*). Tecfidera (dimethyl fumarate), Aubagio (teriflunomide), and Lemtrada (alemtuzumab) are all currently being evaluated in pediatric patients in Phase 3 trials.
- Cladribine injection is indicated for the treatment of active hairy-cell leukemia (*Clinical Pharmacology 2019*). This oncology indication is not related to the treatment of MS and will not be discussed in this review.
- All agents in this class review are listed as Multiple Sclerosis Agents in Medispan; the exceptions are mitoxantrone (listed as an antineoplastic antibiotic) and Ampyra (dalfampridine) (listed as a potassium channel blocker).

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Ampyra (dalfampridine)	✔
Aubagio (teriflunomide)	✔ *
Avonex (interferon β-1a)	-
Betaseron (interferon β-1b)	-
Copaxone, Glatopa† (glatiramer acetate)	✔
Extavia (interferon β-1b)	-
Gilenya (fingolimod)	-
Lemtrada (alemtuzumab)	-
Mavenclad (cladribine)	-
Mayzent (siponimod)	-
mitoxantrone‡	✔
Ocrevus (ocrelizumab)	-
Plegridy (peginterferon β-1a)	-
Rebif (interferon β-1a)	-
Tecfidera (dimethyl fumarate)	-
Tysabri (natalizumab)	-

*A generic of teriflunomide received FDA-approval in 2018; however, a settlement agreement will delay launch.
†Glatopa by Sandoz is an FDA-approved generic for Copaxone (glatiramer acetate); it is available in 20 mg/mL and 40 mg/mL injections. Mylan launched generic versions of the 20 mg/mL and the 40 mg/mL strengths of Copaxone on October 5, 2017.
‡Although brand Novantrone has been discontinued, generic mitoxantrone remains available.
§As of April 30, 2018, Zinbryta (daclizumab) has been voluntarily withdrawn from the market by the manufacturer; cases of encephalitis and meningoencephalitis have been reported in patients treated with Zinbryta. All references to the drug have been removed from this document.

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Drug	Improve walking in MS‡	Relapsing forms of MS	Slow accumulation of physical disability	Decrease frequency of clinical exacerbations	First clinical episode	Progressive forms of MS
Ampyra (dalfampridine)	✔ *	-	-	-	-	-
Aubagio (teriflunomide)	-	✔	-	-	-	-
Avonex (IM interferon β-1a)	-	✔	✔	✔	✔	-
Betaseron/Extavia (interferon β-1b)	-	✔	-	✔	✔	-
Copaxone/Glatopa	-	✔	-	-	-	-

Drug	Improve walking in MS‡	Relapsing forms of MS	Slow accumulation of physical disability	Decrease frequency of clinical exacerbations	First clinical episode	Progressive forms of MS
(glatiramer acetate)						
Gilenya (fingolimod)	-	✔ †	-	-	-	-
Lemtrada (alemtuzumab)	-	✔ ‡ (3rd line)	-	-	-	-
Mavenclad (cladribine)		✔				✔ §
Mayzent (siponimod)		✔			✔ ‖	✔ ‖
mitoxantrone	-	✔ (2nd line)	✔ (neurologic disability)	✔	-	✔ ¶
Ocrevus (ocrelizumab)	-	✔	-	-	-	✔ #
Plegridy (peginterferon β-1a)	-	✔	-	-	-	-
Rebif (interferon β-1a)	-	✔	✔	✔	-	-
Tecfidera (dimethyl fumarate)	-	✔	-	-	-	-
Tysabri (natalizumab)	-	✔ **	-	-	-	-

IM=intramuscular; SC=subcutaneous
*Ampyra is indicated as a treatment to improve walking in patients with MS. This was demonstrated by an increase in walking speed.
†Approved in patients 10 years of age and older.
‡Because of its safety profile, Lemtrada should generally be reserved for patients who have had an inadequate response to 2 or more drugs indicated for the treatment of MS
§ Because of its safety profile, use of Mavenclad is generally recommended for patients who have had an inadequate response, or are unable to tolerate, an alternate drug indicated for the treatment of MS. Mavenclad is not recommended for use in patients with CIS because of its safety profile.
‖ Mayzent is a sphingosine-phosphate receptor modulator indicated for the treatment of relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease in adults.
¶Mitoxantrone is indicated for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening RRMS (ie, patients whose neurologic status is significantly abnormal between relapses). Mitoxantrone is not indicated for the treatment of patients with PPMS. The product has additionally been approved for several cancer indications.
#Ocrevus is approved for PPMS.
**Tysabri increases the risk of Progressive Multifocal Leukoencephalopathy (PML) (a rare, but often fatal demyelinating disease of the central nervous system caused by the John Cunningham virus [JCV]). When initiating and continuing treatment with Tysabri in patients with MS, physicians should consider whether the expected benefit of Tysabri is sufficient to offset this risk. Tysabri is also indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease (CD) with evidence of inflammation that have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α. In CD, Tysabri should not be used in combination with immunosuppressants or inhibitors of TNF- α.

(Prescribing information: Ampyra 2017, Aubagio 2016, Avonex 2016, Betaseron 2018, Copaxone 2018, Extavia 2016, Gilenya 2018, Glatopa 2018, Lemtrada 2017, Mavenclad 2019, Mayzent 2019, mitoxantrone 2018, Novantrone 2012, Ocrevus 2017, Plegridy 2018, Rebif 2015, Tecfidera 2018, Tysabri 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 the management of MS, numerous clinical trials have established the safety and efficacy of the biologic response modifiers in reducing the frequency of relapses lesions on MRI scans, and possibly delaying disease progression and disability.

Interferons and glatiramer acetate

- Pivotal clinical trials demonstrating efficacy in reducing the rate of relapses, burden of disease on MRI, and disability progression for the interferons and glatiramer acetate were published in the 1990's *(Jacobs et al 1996, Johnson et al,*

1995, The interferon beta [IFNβ] Multiple Sclerosis Study Group 1993, The IFNβ Multiple Sclerosis Study Group 1995). Long-term follow-up data for IFN β-1b show that overall survival in MS is improved *(Goodin et al 2012)*.

- Head-to-head trials have found Copaxone (glatiramer acetate), Rebif (IFNβ-1a SC), and Betaseron (IFNβ-1b) to be comparable in terms of relapse rate reduction and disease and disability progression *(PRISMS 1998, Kappos et al 2006, Mikol et al 2008, Flechter et al 2002, Cadavid et al 2009, O'Connor et al 2009)*. The results of several studies suggest that lower dose Avonex (IFNβ-1a 30 mcg intramuscular [IM] once weekly) may be less efficacious while being more tolerable compared to higher dose Rebif (IFNβ-1a subcutaneous [SC] 3 times weekly or every other day) or glatiramer acetate *(Khan et al 2001[a], Khan et al 2001[b], Barbero et al 2006, Durelli et al 2002, Panitch et al 2002, Panitch et al 2005, Schwid et al 2005, Schwid et al 2007, Traboulsee et al 2008)*.
- In a meta-analysis of 5 randomized studies comparing IFNs with glatiramer acetate, there were no significant differences between IFNs and glatiramer acetate in terms of the number of patients with relapses, confirmed progression, or discontinuation due to adverse events at 24 months *(La Mantia et al 2016)*.
  - At 36 months, however, evidence from a single study suggested that relapse rates were higher in the group given IFNs than in the glatiramer acetate group (risk ratio [RR] 1.40, 95% confidence interval [CI]: 1.13 to 1.74; p = 0.002). While MRI outcomes analysis showed that effects on newer enlarging T2 or new contrast-enhancing T1 lesions at 24 months were similar, the reduction in T2- and T1-weighted lesion volume was significantly greater in the groups given IFNs than in the glatiramer acetate groups (mean difference [MD] −0.58, 95% CI: −0.99 to −0.18; p = 0.004, and MD −0.20, 95% CI: −0.33 to −0.07; p = 0.003, respectively).
- In a network meta-analysis of 24 studies comparing IFNs and glatiramer acetate, both drugs were found to reduce the annualized relapse rate (ARR) as compared to placebo but did not differ statistically from each other (*Melendez-Torres et al 2018*). Ranking of the drugs based on SUCRA (surface under the cumulative ranking curve) indicated that glatiramer acetate 20 mg once daily had the highest probability for superiority, followed by peginterferon β-1a 125 mcg every 2 weeks.
- A meta-analysis of 6 placebo-controlled trials failed to find a significant advantage of Avonex (IFNβ-1a) 30 mcg IM once weekly compared to placebo in the number of relapse-free patients after 1 year of therapy (*Freedman et al 2008*). In contrast, other studies found Avonex (IFNβ-1a) 30 mcg IM once weekly to be comparable to the other IFNβ products in terms of relapse rate reduction, disability progression, and SPMS development *(Carra et al 2008, Limmroth et al 2007, Minagara et al 2008, Rio et al 2005, Trojano et al 2003, Trojano et al 2007)*. Moreover, IFN therapy, especially the higher dose products, is associated with the production of neutralizing antibodies (NAb), which may result in decreased radiographic and clinical effectiveness of treatment *(Goodin et al 2007, Sorensen et al 2005)*. Exploratory post-hoc analyses of the PRISMS trial linked the development of NAb with reduced efficacy *(Alsop et al 2005)*. Development of NAb among patients (N = 368) randomized to receive Rebif (IFNβ-1a) 44 or 22 mcg SC 3 times weekly for 4 years was associated with higher relapse rates (adjusted relapse rate ratio, 1.41; 95% CI: 1.12 to 1.78; p = 0.004), a greater number of active lesions, and percentage change in T2 lesion burden from baseline on MRI scan (p < 0.001). In a systematic review of 40 studies of MS agents including IFNβ-1a and IFNβ-1b, the primary outcome measure was the frequency of IFN NAb *(Govindappa et al 2015)*. NAb development was most frequent with IFN β-1b, followed by IFN β-1a SC, and lowest with IFN β-1a IM. Higher doses were associated with a higher rate of NAb development.
- The CombiRx trial evaluated the combination of Copaxone (glatiramer acetate) and Avonex (IFNβ-1a IM) over 3 years. The ARR for the combination therapy (IFNβ-1a + glatiramer) was not statistically superior to the better of the 2 single treatment arms (glatiramer) (p = 0.27). The ARRs were 0.12 for the combination therapy, 0.16 for IFNβ-1a, and 0.11 for glatiramer acetate. Glatiramer acetate performed significantly better than IFNβ-1a, reducing the risk of exacerbation by 31% (p = 0.027), and IFNβ-1a + glatiramer acetate performed significantly better than IFNβ-1a, reducing the risk of exacerbation by 25% (p = 0.022). The 3 treatment groups did not show a significant difference in disability progression over 6 months. Combination therapy was superior to either monotherapy in reducing new lesion activity and accumulation of total lesion volume *(Lublin et al 2013)*.
- It is estimated that within a few years of initiating treatment, at least 30 and 15% of patients discontinue MS biological response modifiers due to perceived lack of efficacy or side effects, respectively *(Coyle 2008, Portaccio et al 2008)*. According to several observational studies, switching patients who have failed to adequately respond to initial treatment to another first-line therapy is safe and effective *(Caon et al 2006, Zwibel 2006, Carra et al 2008)*. Patients switching to glatiramer acetate after experiencing inadequate response to IFNβ-1a therapy experienced a reduction in relapse rates and disability progression. Likewise, switching to IFNβ-1a therapy after suboptimal efficacy with glatiramer acetate increased the number of relapse-free patients in 1 study *(Carra et al 2008)*. The smallest reduction in the ARR was seen in patients who had switched from one IFNβ-1a preparation to another.

- The GALA study evaluated glatiramer acetate SC 40 mg 3 times weekly compared to placebo in 1404 patients with relapsing MS over 12 months. Results demonstrated that glatiramer acetate 40 mg 3 times weekly, compared to placebo, reduced the ARR and MRI endpoints *(Khan et al 2013)*.
- Glatiramer acetate 20 mg daily and 40 mg 3 times weekly have not been directly compared for efficacy. A Phase 3 dose comparison study evaluated glatiramer acetate 20 mg and 40 mg each given daily in 1155 patients with MS. The primary endpoint, mean ARR, was similar in both groups: ARR = 0.33 (20 mg group) vs ARR = 0.35 (40 mg group). For patients from both groups who completed the entire 1-year treatment period, the mean ARR = 0.27 *(Comi et al 2011)*.
- The efficacy and safety of Plegridy (peginterferon β-1a) in adult patients with MS (N = 1516) were evaluated in ADVANCE, a Phase 3, multicenter, randomized, placebo-controlled trial. Eligible adult patients had RRMS with baseline Expanded Disability Status Scale (EDSS) score ≤ 5 and 2 clinically documented relapses in the previous 3 years with at least 1 relapse in the previous 12 months. Patients were randomized to placebo or SC peginterferon β-1a 125 mcg every 2 weeks or every 4 weeks for 48 weeks. Approximately 81% of patients were treatment naïve.
  - At week 48, ARRs were significantly lower in the peginterferon β-1a every 2 week group (ARR = 0.256; p = 0.0007) and peginterferon β-1a every 4 week group (ARR = 0.288; p = 0.0114) compared to placebo (ARR = 0.397).
  - There were also significant differences between the peginterferon β-1a every 2 weeks and every 4 weeks groups compared to placebo in the proportion of patients with relapse at week 48 (p = 0.0003 and p = 0.02, respectively). The proportions of patients with 12 weeks of sustained disability progression at the end of the 48 week study period were significantly lower in the peginterferon β-1a groups (both 6.8%; p = 0.0383 for every 2 weeks group; p = 0.038 for every 4 weeks group) compared to placebo (10.5%).
  - The mean number of new or newly enlarging T2 hyperintense lesions on MRI were significantly reduced in the peginterferon β-1a every 2 weeks group compared to placebo (3.6 lesions vs 10.9 lesions, respectively; p < 0.0001). Significant beneficial effects on the mean number of Gadolinium (Gd)-enhancing lesions were also observed with peginterferon β-1a every 2 weeks compared to placebo (p < 0.0001).
  - During the 48 weeks of treatment, the most commonly reported adverse effects included influenza-like illness and injection site erythema. Discontinuations due to adverse effects were higher in the peginterferon β-1a groups compared to placebo *(Calabresi et al 2014b)*.
  - NAb to interferon β-1a were identified in < 1% of all groups after 1 year (peginterferon β-1a every 2 weeks, 4 patients; peginterferon β-1a every 4 weeks, 2 patients; placebo, 2 patients) *(Calabresi et al 2014b)*. Preliminary data on NAb development to peginterferon β-1a over 2 years showed < 1% for all groups *(White et al 2014)*.
- The ADVANCE study continued into a second year. Patients originally randomized to placebo were re-randomized to peginterferon β-1a (the “placebo-switch group”). Peginterferon β-1a patients were continued on their original assigned therapy. A total of 1332 patients entered the second year of the study. After 96 weeks, the ARR was significantly lower in the peginterferon β-1a every 2 weeks group (ARR 0.221; p = 0.0001 vs placebo-switch group; p = 0.0209 vs every 4 week regimen) compared to both the placebo-switch group (ARR 0.351) and the peginterferon β-1a every 4 week group (ARR 0.291). The peginterferon β-1a every 4 week group (ARR 0.291; p = NS vs placebo-switch group) was not significantly different than the placebo-switch group (ARR 0.351) after 96 weeks based on the intent-to-treat (ITT) analysis. Peginterferon β-1a every 2 weeks was also associated with a lower proportion of patients who had relapse and a lower proportion of patients who had disability progression. Mean number of new or newly enlarging T2-weight hyperintense MRI lesions over 2 years was numerically lower with the peginterferon β-1a every 2 weeks group compared to the placebo-switch group *(Calabresi et al 2014b, Kieseier et al 2015)*.
- The ATTAIN study was an open-label extension of the ADVANCE study, where patients were followed for an additional 2 years (*Newsome et al 2018*). Of the original ADVANCE patients, 71% continued into the ATTAIN study, and 78% of those patients completed the extension study. The primary objective of the study was to evaluate the long-term safety of peginterferon β-1a. During the study, the common adverse events were influenza-like illness (43%), injection site erythema (41%), and headache (29%). The rate of treatment-related serious adverse events was 1%. The adjusted ARR and risk of relapse was reduced significantly with the every 2 weeks compared to the every 4 weeks dosing group (0.188 vs 0.263 and 36% vs 49%, respectively).

Gilenya (fingolimod)

- Gilenya (fingolimod) has been evaluated in 2 large, randomized controlled trials (RCTs) in adults against placebo and against Avonex (IFNβ-1a IM). In FREEDOMS, a 24-month placebo-controlled trial, fingolimod (0.5 and 1.25 mg once daily) was associated with significant reductions in ARR compared to placebo (54 and 60%, respectively; p < 0.001 for both). Moreover, fingolimod was associated with reductions in disability progression and a prolonged time to first relapse compared to placebo *(Kappos et al 2010)*. In the 12-month TRANSFORMS trial, fingolimod 0.5 and 1.25 mg once daily

significantly reduced ARR by 52 and 40%, respectively, compared to IFNβ-1a 30 mcg IM once weekly ($p < 0.001$ for both) *(Cohen et al 2010)*. In a 12-month extension of TRANSFORMS, patients initially randomized to IFNβ-1a IM were switched to either dose of fingolimod for 12 additional months and experienced significant reductions in ARR compared to initial treatment with IFNβ-1a IM. Patients switched from IFNβ-1a IM to fingolimod experienced fewer adverse events compared to treatment with IFNβ-1a IM in the core study (86 vs 91% and 91 vs 94% for the 0.5 and 1.25 mg groups, respectively; p values not reported). Fewer patients continuing fingolimod from the core study reported adverse events in the extension period compared to the core study (72 vs 86% and 71 vs 90% for the 0.5 and 1.25 mg doses, respectively; p values not reported) *(Khatri et al 2011)*. The TRANSFORMS extension study followed patients for up to 4.5 years with results consistent with those observed in the first 12 months of the extension study; however, there was significant attrition bias with very few patients enrolled past 36 months *(Cohen et al 2015)*.

- In the FREEDOMS II study, a 24-month placebo-controlled study, fingolimod (0.5 mg and 1.25 mg) significantly reduced ARR compared to placebo (48 and 50%, respectively; both $p < 0.0001$) *(Calabresi et al 2014a)*. Mean percentage brain volume change was lower with both fingolimod doses compared to placebo. Fingolimod did not show a significant effect on time to disability progression at 3 months compared to placebo.
- Fingolimod has also been evaluated in pediatric patients with relapsing MS (*Chitnis et al 2018*). The PARADIGMS trial randomized patients between 10 and 17 years of age to fingolimod 0.5 mg daily (0.25 mg for patients ≤ 40 kg) or IFNβ-1a IM 30 mcg weekly for up to 2 years. Fingolimod significantly reduced ARR compared to IFNβ-1a IM (adjusted rates, 0.12 vs 0.67; relative difference of 82%; $p < 0.001$). Fingolimod was also associated with a 53% relative reduction in the annualized rate of new or newly enlarged lesions. However, serious adverse events occurred more frequently with fingolimod than IFNβ-1a IM (16.8% vs 6.5%).

Aubagio (teriflunomide)

- Efficacy and safety of Aubagio were evaluated in two Phase 3, randomized, double-blind, placebo-controlled trials – the TEMSO trial (*O'Connor et al, 2011*) and the TOWER trial *(Confavreux et al 2014)*. In the TEMSO trial, 1088 patients with relapsing MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for a total of 108 weeks. Results demonstrated that compared to placebo, teriflunomide at both doses, reduced the ARR.
  - The percentage of patients with confirmed disability progression (CDP) was significantly lower only in the teriflunomide 14 mg group (20.2%) compared to placebo (27.3%; $p = 0.03$) *(O'Connor et al 2011)*.
- Teriflunomide has demonstrated beneficial effects on MRI scans in a Phase 2, randomized, double-blind, clinical trial. A total of 179 patients with MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for 36 weeks and were followed every 6 weeks with MRI scans during the treatment period. The teriflunomide groups had significant reductions in the average number of unique active lesions per MRI scan *(O'Connor et al 2006)*.
- In the TOWER trial, 1165 patients with relapsing MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for at least 48 weeks of therapy. The study ended 48 weeks after the last patient was randomized. Results demonstrated that, compared to placebo, teriflunomide 14 mg significantly reduced the ARR and the risk of sustained accumulation of disability *(Confavreux et al 2014)*.
- Teriflunomide and Rebif were compared in the 48-week TENERE study evaluating 324 patients with relapsing MS. The primary outcome, time to failure defined as a confirmed relapse or permanent discontinuation for any cause, was comparable for teriflunomide 7 mg and 14 mg and Rebif *(Vermersch et al 2014)*.

Tecfidera (dimethyl fumarate)

- Tecfidera (dimethyl fumarate) was evaluated in two Phase 3 studies: DEFINE and CONFIRM *(Gold et al 2012, Fox et al 2012, Xu et al 2015)*. DEFINE was a multicenter RCT that compared 2 dosing regimens of dimethyl fumarate (240 mg twice daily and 240 mg 3 times daily) to placebo in patients with RRMS. There were 1237 patients enrolled, and the trial duration was 96 weeks. Results demonstrated that, compared to placebo, treatment with both doses of dimethyl fumarate reduced the proportion of patients with a relapse within 2 years, the ARR, the number of lesions on MRI, and the proportion of patients with disability progression *(Gold et al 2012)*.
- CONFIRM was a multicenter RCT that compared 2 dosing regimens of dimethyl fumarate (240 mg twice daily and 240 mg 3 times daily) to placebo, with an additional, open-label study arm evaluating glatiramer acetate 20 mg SC daily. Glatiramer acetate was included as a reference comparator, but the study was not designed to test the superiority or non-inferiority of dimethyl fumarate vs glatiramer acetate. There were 1430 patients enrolled, and the trial duration was 96 weeks. Results of CONFIRM were similar to DEFINE, with the exception that there was no significant difference between groups in the likelihood of disability progression. The CONFIRM trial demonstrated that, compared to placebo,

treatment with both doses of dimethyl fumarate reduced the proportion of patients with a relapse within 2 years, the ARR, and the number of lesions on MRI *(Fox et al 2012)*.

Tysabri (natalizumab)

- Tysabri (natalizumab) reduced the risk of experiencing at least 1 new exacerbation at 2 years and reduced the risk of experiencing progression at 2 years *(Polman et al 2006, Pucci et al 2011, Rudick et al 2006)*. The AFFIRM trial compared natalizumab to placebo in patients with MS with less than 6 months of treatment experience with any DMT. Natalizumab reduced the ARR at 1 and 2 years compared to placebo. The cumulative probability of sustained disability progression and lesion burden on MRI were significantly reduced with natalizumab compared to placebo *(Polman et al 2006)*. In the SENTINEL trial, natalizumab was compared to placebo in patients who were receiving IFNβ-1a IM 30 mcg once weekly for at least 1 year. The combination of natalizumab plus IFNβ-1a IM resulted in a significant reduction in ARR at year 1 and 2 and significant reduction in cumulative probability of sustained disability progression at year 2. Lesion burden on MRI was also significantly reduced with the combination therapy. Two cases of PML were reported in the SENTINEL patient population resulting in the early termination of the trial *(Rudick et al 2006)*.

Lemtrada (alemtuzumab)

- The efficacy and safety of alemtuzumab were compared to Rebif (IFNβ-1a SC) in two randomized, Phase 3, open-label trials in patients with relapsing forms of MS – CARE-MS I and CARE-MS II (*Cohen et al 2012, Coles et al 2012)*. In the 2-year studies, patients were randomized to alemtuzumab infused for 5 consecutive days followed by a 3 consecutive day treatment course 12 months later or to Rebif (IFNβ-1a SC) 44 mcg 3 times weekly after an initial dosage titration. All patients received methylprednisolone 1 g IV for 3 consecutive days at the initiation of treatment and at month 12.
  - The CARE-MS I trial enrolled treatment-naïve patients with MS (n = 581) who were high functioning based on the requirement of a score of 3 or lower on the EDSS.
  - Patients (n = 840) enrolled in the CARE-MS II trial had experienced at least 1 relapse while on IFNβ or glatiramer acetate after at least 6 months of treatment. Patients were required to have an EDSS score of ≤ 5.
  - The co-primary endpoints for both trials were the relapse rate and the time to 6-month sustained accumulation of disability.
  - In the CARE-MS I trial, alemtuzumab reduced the risk of relapse by 55% compared to IFNβ-1a SC ($p < 0.0001$). Relapses were reported in 22% of alemtuzumab-treated patients and 40% of IFNβ-1a SC patients over 2 years. The proportion of patients having sustained accumulation of disability over 6 months was not significantly different between alemtuzumab (8%) vs IFNβ-1a SC (11%) ($p = 0.22$).
  - In the CARE-MS II trial, alemtuzumab significantly reduced relapse rate and sustained accumulation of disability compared to IFNβ-1a SC. The relapse rate at 2 years was reduced by 49% with alemtuzumab ($p < 0.0001$). The percent of patients with sustained accumulation of disability confirmed over 6 months was 13% with alemtuzumab and 20% with IFNβ-1a SC, representing a 42% risk reduction with alemtuzumab ($p = 0.0084$).
  - Both studies evaluated MRI outcomes, specifically the median percent change in T2 hyperintense lesion volume from baseline. Neither study found a significant difference between the 2 drugs for this measure.
  - During extension studies of CARE-MS I and CARE-MS II, approximately 80% of patients previously treated with alemtuzumab did not require additional treatment during the first year *(Garnock-Jones 2014)*.
- A Cochrane review by Zhang et al (2017) that compared the efficacy, tolerability, and safety of alemtuzumab vs IFNβ-1a in the treatment of RRMS identified 3 RCTs in 1694 total patients from the CARE-MS I, CARE-MS II, and CAMMS223 studies. In the alemtuzumab 12 mg/day group, the results showed statistically significant differences in reducing relapses (RR = 0.60, 95% CI: 0.52 to 0.70); preventing disease progression (RR = 0.60, 95% CI: 0.45 to 0.79); and developing new T2 lesions on MRI (RR = 0.75, 95% CI: 0.61 to 0.93) after 24 and 36 months' follow-up, but found no statistically significant difference in the changes of EDSS score (MD = -0.35, 95% CI: -0.73 to 0.03). In the alemtuzumab 24 mg/day group, the results showed statistically significant differences in reducing relapses (RR = 0.38, 95% CI: 0.23 to 0.62); preventing disease progression (RR = 0.42, 95% CI: 0.21 to 0.84); and the changes of EDSS score (MD = -0.83, 95% CI: -1.17 to -0.49) after 36 months' follow-up. The most frequently reported adverse effects with alemtuzumab were infusion-associated reactions, infections, and autoimmune events.

Ocrevus (ocrelizumab)

- The Phase 3 clinical development program for ocrelizumab (ORCHESTRA) included 3 studies: OPERA I, OPERA II, and ORATORIO *(Hauser et al 2017[a], Montalban et al 2017)*.

- OPERA I and OPERA II were 2 identically-designed, 96-week, Phase 3, active-controlled, double-blind, double-dummy, multicenter, parallel-group, RCTs that evaluated the efficacy and safety of ocrelizumab (600 mg administered as an IV infusion given as 2-300 mg infusions separated by 2 weeks for dose 1 and then as a single 600 mg infusion every 6 months for subsequent doses) compared with Rebif (IFNβ-1a; 44 mcg administered by SC injection 3 times per week) in 1656 patients with RMS *(Hauser et al 2017, ClinicalTrials.gov Web site, Ocrevus Formulary Submission Dossier 2017)*.
  - Across both studies, the majority of patients had not been treated with a DMT in the 2 years before screening (range: 71.4% to 75.3%); of those patients that had received a previous DMT as allowed by the protocol, most received IFN (18.0% to 21.0%) or glatiramer acetate (9.0% to 10.6%). Two patients previously treated with natalizumab for < 1 year were included, while 5 patients previously treated with fingolimod and 1 patient previously treated with dimethyl fumarate (both not within 6 months of screening) were also included.
  - Ocrelizumab achieved statistically significant reductions in the ARR vs Rebif across both trials (primary endpoint).
    - OPERA I (0.16 vs 0.29; 46% lower rate with ocrelizumab; $p < 0.001$)
    - OPERA II (0.16 vs 0.29; 47% lower rate; $p < 0.001$)
  - In pre-specified pooled analyses (secondary endpoints), the percentage of patients with disability progression confirmed at 12 weeks was statistically significantly lower with ocrelizumab vs Rebif (9.1% vs 13.6%; hazard ratio [HR] = 0.60, 95% CI: 0.45 to 0.81; $p < 0.001$). The results were similar for disability progression confirmed at 24 weeks: 6.9% vs 10.5%; HR = 0.60, 95% CI: 0.43 to 0.84; $p = 0.003$. The percentages of patients with disability improvement confirmed at 12 weeks were 20.7% in the ocrelizumab group vs 15.6% in the Rebif group (33% higher rate of improvement with ocrelizumab; $p = 0.02$).
  - The mean numbers of Gd-enhancing lesions per T1-weighted MRI scan were statistically significantly reduced with ocrelizumab vs Rebif (secondary endpoint).
    - OPERA I: 0.02 vs 0.29 (rate ratio = 0.06, 95% CI: 0.03 to 0.10; 94% lower number of lesions with ocrelizumab; $p < 0.001$)
    - OPERA II: 0.02 vs 0.42 (rate ratio = 0.05, 95% CI: 0.03 to 0.09; 95% lower number of lesions; $p < 0.001$)
  - The most common adverse events were infusion-related reactions and infections.
- No opportunistic infections, including PML, were reported in any group over the duration of either trial.
  - An imbalance of malignancies was observed with ocrelizumab; across both studies and through 96 weeks, neoplasms occurred in 0.5% (4/825) of ocrelizumab-treated patients vs 0.2% (2/826) of Rebif-treated patients.
  - Among the ocrelizumab-treated patients that developed neoplasms, there were 2 cases of invasive ductal breast carcinoma, 1 case of renal-cell carcinoma, and 1 case of malignant melanoma. Rebif-treated patients with neoplasms included 1 case of mantle-cell lymphoma and 1 case of squamous-cell carcinoma in the chest.
    - Between the clinical cutoff dates of the 2 trials (April 2, 2015 [OPERA I] and May 12, 2015 [OPERA II]) and June 30, 2016, 5 additional cases of neoplasm (2 cases of breast cancer, 2 cases of basal-cell skin carcinoma, and 1 case of malignant melanoma) were observed during the OL extension phase in which all continuing patients received ocrelizumab.
- ORATORIO was an event-driven, Phase 3, double-blind, multicenter, placebo-controlled, RCT evaluating the efficacy and safety of ocrelizumab (600 mg administered by IV infusion every 6 months; given as 2-300 mg infusions 2 weeks apart for each dose) compared with placebo in 732 people with PPMS *(Montalban et al 2017, ClinicalTrials.gov Web site, Ocrevus Formulary Submission Dossier 2017)*. Double-blind treatment was administered for a minimum of 5 doses (120 weeks) until the occurrence of ~253 events of disability progression in the trial cohort that was confirmed for at least 12 weeks.
  - The majority of patients (~88%) reported no previous use of DMTs within 2 years of trial entry. The proportion of patients with Gd-enhancing lesions was similar (27.5% in the ocrelizumab group vs 24.7% in the placebo group); however, there was an imbalance in the mean number of Gd-enhancing lesions at baseline, with nearly 50% fewer lesions in the placebo group (1.21 vs 0.6) (*FDA Medical and Summary Reviews 2017*).
  - The percentages of patients with 12-week confirmed disability progression (primary endpoint) were 32.9% with ocrelizumab vs 39.3% with placebo (HR = 0.76, 95% CI: 0.59 to 0.98; relative risk reduction of 24%; $p = 0.03$).
  - The percentages of patients with 24-week CDP (secondary endpoint) were 29.6% with ocrelizumab vs 35.7% with placebo (HR=0.75, 95% CI: 0.58 to 0.98; relative risk reduction of 25%; $p = 0.04$).
  - Additional secondary endpoints included changes in the timed 25-foot walk, the total volume of hyperintense brain lesions on T2-weighted MRI, and brain volume loss.

- The proportion of patients with 20% worsening of the timed 25-foot walk confirmed at 12 weeks was 49% in ocrelizumab-treated patients compared to 59% in placebo-treated patients (25% risk reduction).
- From baseline to Week 120, the total volume of hyperintense brain lesions on T2-weighted MRI decreased by 3.37% in ocrelizumab-treated patients and increased by 7.43% in placebo-treated patients ($p < 0.001$).
- From Weeks 24 to 120, the percentage of brain volume loss was 0.90% with ocrelizumab vs 1.09% with placebo ($p = 0.02$).

- Infusion-related reactions, upper respiratory tract infections, and oral herpes infections occurred more frequently with ocrelizumab vs placebo.
- Neoplasms occurred in 2.3% (11/486) of patients treated with ocrelizumab vs 0.8% (2/239) of patients who received placebo. Among the ocrelizumab-treated patients that developed neoplasms, there were 4 cases of breast cancer, 3 cases of basal-cell carcinoma, and 1 case in each of the following: endometrial adenocarcinoma, anaplastic large-cell lymphoma (mainly T cells), malignant fibrous histiocytoma, and pancreatic carcinoma. In the placebo group, 1 patient developed cervical adenocarcinoma in situ and 1 patient developed basal-cell carcinoma.
  - Between the clinical cutoff date (July 24, 2015) and June 30, 2016, 2 additional cases of neoplasm (1 case of basal-cell skin carcinoma and 1 case of squamous-cell carcinoma) were detected during the open-label extension phase in which all patients received ocrelizumab.

Mayzent (siponimod)

- The Phase 3 trial, EXPAND was a double-blind, randomized, parallel-group, placebo-controlled, time-to-event study in patients with SPMS who had evidence of disability progression in the previous 2 years (*Bar-Or et al 2018, Fox et al 2015, Kappos et al 2018*).
  - A total of 1651 patients were randomized to treatment with either siponimod 2 mg (n = 1105) or placebo (n = 546).
  - A total of 82% of the siponimod-treated patients and 78% of placebo-treated patients completed the study.
    - The median age of patients was 49.0 years, 95% of patients were white, and 60% were female.
  - For the primary endpoint, 288 (26%) of 1096 patients receiving siponimod and 173 (32%) of 545 patients receiving placebo had a 3-month CDP (HR 0.79: 95% CI: 0.65 to 0.95: RR reduction, 21%; $p = 0.013$).
  - Key secondary endpoints included time to 3-month confirmed worsening of at least 20% from baseline in T25FW and change from baseline in T2 lesion volume on MRI. Siponimod did not show a significant difference in T25FW. Patients treated with siponimod had a 55% relative reduction in ARR (0.071 vs 0.16), compared to placebo (nominal $p < 0.01$). The absolute reduction in the ARR was 0.089 with siponimod.

Mavenclad (cladribine)

- The 96-week Phase 3 trial, CLARITY, was a double-blind, 3-arm, placebo-controlled, multicenter trial to evaluate the safety and efficacy of oral cladribine in 1326 patients with RRMS (*Giovannoni et al 2010*, *Giovannoni 2017*).
  - Patients were required to have at least 1 relapse in the previous 12 months. The median patient age was 39 years and the female-to-male ratio was 2:1. The mean duration of MS prior to study reenrollment was 8.7 years.
  - Patients were randomized to receive either placebo (n = 437), or a cumulative oral dose of cladribine 3.5 mg/kg (n = 433) or 5.25 mg/kg (n = 456) over the 96-week study period in 2 treatment courses.
  - The primary outcome was ARR.
  - ARRs at 96 weeks were reduced in both cladribine treatment groups vs placebo (0.14, 0.15, and 0.33 in the 3.5 mg/kg, 5.25 mg/kg and placebo groups, respectively; each $p < 0.001$).
  - A significantly higher percentage of patients remained relapse-free at 96 weeks both in the cladribine treatment groups vs placebo; a total of 79.7% and 78.9% of patients in the 3.5 mg/kg and 5.25 mg/kg groups, respectively, were relapse free vs 60.9% in the placebo group (each $p < 0.001$ vs placebo).
  - Cladribine 3.5 mg/kg significantly lowered the ARR vs the 5.25 mg/kg treatment group.

Symptomatic MS

- Despite the demonstrated efficacy of DMTs, for many patients there is little evidence of their effect on quality of life (QOL) in general or symptom management in particular. Impaired mobility contributes to direct and indirect costs *(Miravelle et al 2011)*.
  - Ampyra (dalfampridine) is the only FDA-approved agent for the symptomatic treatment of impaired mobility in patients with MS. Improvement of walking ability with dalfampridine was demonstrated in two 14-week, double-blind, Phase 3, RCTs of 540 patients of all MS types. Compared to placebo, dalfampridine significantly improved the

walking speed by about 25% in approximately one-third of MS patients as measured by the timed 25-foot walk (T25FW) *(Goodman et al 2009, Jensen et al 2014, Ruck et al 2014)*.
  - However, questions have been raised regarding the cost-effectiveness of dalfampridine, and whether treatment leads to a long-term clinically meaningful therapeutic benefit. To address the benefit of long-term therapy with dalfampridine, an open-label, observational study of 52 MS patients with impaired mobility was conducted. Results demonstrated that about 60% of patients were still on treatment after 9 to 12 months. Two weeks after treatment initiation, significant ameliorations could be found for T25FW, maximum walking distance, as well as motoric and cognitive fatigue, which persisted after 9 to 12 months *(Ruck et al 2014)*.

Clinically Isolated Syndrome (CIS)

- Avonex (IFNβ-1a IM) and Betaseron (IFNβ-1b) are FDA-approved for the treatment of the first clinical episode with MRI features consistent with MS. Copaxone (glatiramer acetate) and Aubagio (teriflunomide) have evidence supporting a significant delay in the time to development of a second exacerbation, compared to placebo, in patients with an isolated demyelinating event.
- In the PRECISE trial, glatiramer acetate significantly reduced the risk of converting to a CDMS diagnosis by 45% compared to placebo in patients with CIS (p = 0.005). In addition, the time for 25% of patients to convert to CDMS was significantly prolonged with glatiramer acetate compared to placebo (722 vs 336 days; p = 0.0041) *(Comi et al 2009)*. In the 2 year, open-label extension phase of PRECISE, early initiation of glatiramer acetate demonstrated a 41% reduced risk of CDMS compared to delayed glatiramer acetate (HR: 0.59; 95% CI: 0.44 to 0.8; p = 0.0005). Over the 2 year extension, the baseline-adjusted proportions of patients who developed CDMS were 29.4% and 46.5% for the early and late initiation treatment groups (odds ratio [OR]: 0.48; 95% CI: 0.33 to 0.7; p = 0.0002) *(Comi et al 2012)*.
- A meta-analysis of randomized, double-blind, placebo-controlled trials in patients with CIS found a significantly lower risk of CDMS with IFN therapy compared to placebo (p < 0.0001) *(Clerico et al 2008)*. A 10-year, multicenter, randomized clinical trial with IFNβ-1a IM demonstrated that immediate initiation of therapy in patients with CIS reduced the risk for relapses over 10 years, but it was not associated with improved disability outcomes compared to a control group that also initiated therapy relatively early in the disease *(Kinkel et al 2012)*. Over the 10-year study, the drop-out rate was significant. Similar results were observed with IFNβ-1b (BENEFIT study) over an 8-year observation period. Patients who received treatment early had a lower overall ARR compared to those patients who delayed treatment *(Kappos et al 2007, Edan et al 2014)*. In the first 3 years of BENEFIT, early treatment with IFNβ-1b reduced the risk for progression of disability by 40% compared to delayed treatment (16% vs 25%, respectively; HR = 0.6; 95% CI: 0.39 to 0.92; p = 0.022).
- A 2018 systematic review and network meta-analysis of RCTs was conducted to assess the potential short- and long-term benefits of treatment with IFN-β or glatiramer acetate in patients with CIS (*Armoiry et al 2018)*. The review identified 5 primary RCTs that assessed the time to clinically definite multiple sclerosis (CDMS) in patients with CIS treated with IFN-β or glatiramer acetate vs placebo. They found that all drugs reduced the time to CDMS when compared with placebo, with a pooled HR of 0.51 (95% CI: 0.44 to 0.61) and low heterogeneity, and there was no evidence that indicated that 1 active treatment was superior to another when compared indirectly. The authors noted that there was insufficient information to rate the risk of selection bias, 4 of the 5 studies were at high risk of performance bias, and 1 study was rated to have a high risk for attrition bias. Four of the trials had open-label extension studies performed over 5 to 10 years, all of which indicated that early DMT therapy (regardless of agent) led to an increase in time to CDMS when compared with placebo (HR = 0.64, 95% CI: 0.55 to 0.74; low heterogeneity). These results should be taken with caution; however, as all of the open-label extension arms were at a high risk for attrition bias and had large losses to follow-up noted.
- The TOPIC study enrolled 618 patients with CIS and found teriflunomide 7 and 14 mg doses reduced the risk of relapse defining CDMS compared to placebo *(Miller et al 2014)*. Teriflunomide 14 mg reduced the risk of conversion to CDMS by 42.6% compared to placebo (HR, 0.574; 95% CI: 0.379 to 0.869; p = 0.0087) whereas teriflunomide 7 mg reduced the conversion to CDMS by 37.2% compared to placebo (HR, 0.628; 95% CI: 0.416 to 0.949; p = 0.0271).

Progressive MS

- Limited treatment options are available for patients with non-active SPMS and PPMS. Mitoxantrone is FDA-approved for treating SPMS, while ocrelizumab has been specifically approved for the treatment of PPMS (and relapsing forms of MS).
- Mitoxantrone was shown to reduce the clinical relapse rate and disease progression in aggressive RRMS, SPMS, and progressive-relapsing MS *(Hartung et al 2002, Krapf et al 2005)*. For MRI outcome measures, mitoxantrone was not statistically significantly different than placebo at month 12 or 24 for the total number of MRI scans with positive Gd

enhancement or at month 12 for the number of lesions on T2 weighted MRI. However, the baseline MRI lesion number and characteristics were different among the groups *(Krapf et al 2005)*. In 2010, Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology evaluated all published data including cohort data for mitoxantrone. Evaluation of efficacy found that mitoxantrone is probably effective in modestly reducing clinical attack rate, MRI activity, and disease progression. A confirmatory trial is necessary before widespread adoption of mitoxantrone for DMT for MS can be made in light of the risks of cardiotoxicity and treatment-related leukemia *(Marriott et al 2010)*.

- The results of studies with the other agents for MS have failed to consistently demonstrate a benefit in progressive forms of MS, and due to being off-label, these uses are not included in Table 2. In the PROMISE trial, glatiramer acetate was no more effective than placebo in delaying the time to accumulated disability for patients with PPMS *(Wolinsky et al 2007)*. The ASCEND trial evaluated natalizumab in SPMS was found to have no significant difference in the rate of confirmed disability progression compared to placebo (*Kapoor et al 2018*).
- Several IFN trials in this population have yielded conflicting results *(Rizvi et al 2004)*. A systematic analysis evaluated 5 clinical trials (N = 3082) of IFNβ compared to placebo in the treatment of SPMS. In 4 trials with the primary outcome of sustained disability progression at 3 or 6 months, IFNβ demonstrated no benefit. The risk ratio for sustained progression with IFNβ was 0.98 (95% CI: 0.82 to 1.16; p = 0.79); however, between-study heterogeneity was high (I^2 = 57%) *(La Mantia et al 2013)*.

Timing of DMT initiation

- A 2017 systematic review by Merkel et al (2017) evaluated the effect of high-efficacy immunotherapies (ie, fingolimod, natalizumab, alemtuzumab) at different stages of MS. Twelve publications (9 RCTs + 3 observational studies) were identified as reporting information relevant to the outcomes of early vs delayed initiation of high-efficacy DMTs for RRMS. A number of these studies suggested that earlier commencement of high-efficacy DMTs resulted in more effective control of relapse activity than their later initiation. The evidence regarding the effect of the timing of high-efficacy therapies on disability outcomes was conflicting; additional data are required to answer this question.

Decisions to discontinue DMTs in MS

- Patient with RRMS eventually progress to SPMS. Patients experience worsening disability with or without relapses. Current therapies focus on relapsing forms of MS and are not indicated for non-active SPMS. The decision to discontinue DMTs has not been well studied. The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review evaluating the decision dilemmas surrounding discontinuation of MS therapies in the setting of progressive disease and pregnancy *(Butler et al 2015)*. No studies directly assess continued therapy vs discontinued therapy for MS in comparable populations. Based on low strength of evidence, long-term all-cause survival is higher for treatment-naïve MS patients who did not delay starting IFNβ-1b by 2 years and used DMT for a longer duration than those who delayed therapy. Very little evidence is available about the benefits and risks of discontinuation of therapy for MS in women who desire pregnancy (*Rae-Grant et al 2018[b]*).

Meta-Analyses

- A 2017 systematic review conducted by the Institute for Clinical and Economic Review (ICER) included ocrelizumab in a comparative efficacy analysis with other DMTs used in the treatment of MS.
  - Network meta-analyses demonstrated that for the treatment of RRMS, alemtuzumab, natalizumab, and ocrelizumab (in that order) were the most effective DMTs for reducing ARRs (~70% reduction vs placebo).
  - Ocrelizumab and alemtuzumab had the greatest reductions in disability progression (53% to 58% reduction vs placebo, respectively), closely followed by natalizumab (44%).
- A systematic review that identified 28 RCTs found that the magnitude of ARR reduction varied between 15 to 36% for all IFNβ products, glatiramer acetate, and teriflunomide; and from 50 to 69% for alemtuzumab, dimethyl fumarate, fingolimod, and natalizumab. The risk of 3-month disability progression was reduced by 19 to 28% with IFNβ products, glatiramer acetate, fingolimod, and teriflunomide; by 38 to 45% for peginterferon IFNβ, dimethyl fumarate, and natalizumab; and by 68% with alemtuzumab *(Fogarty et al 2016)*.
- RCTs (n = 39) evaluating 1 of 15 treatments for MS were analyzed for benefits and acceptability in 25,113 patients with RRMS *(Tramacere et al 2015)*. Drugs included were IFNβ-1b, IFNβ-1a (IM and SC), glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, peginterferon IFNβ-1a, azathioprine, and immunoglobulins. Investigational agents, daclizumab and laquinimod, were also included. The studies had a median

duration of 24 months with 60% of studies being placebo-controlled. The network meta-analysis evaluated the recurrence of relapses and disability progression.
  - Relapses: alemtuzumab, mitoxantrone, natalizumab, and fingolimod were reported to have greater treatment benefit compared to placebo. Over 12 months (29 studies; N = 17,897):
    - alemtuzumab: RR = 0.40, 95% CI: 0.31 to 0.51; moderate quality evidence
    - mitoxantrone: RR = 0.40, 95% CI: 0.20 to 0.76; low quality evidence
    - natalizumab: RR = 0.56, 95% CI: 0.43 to 0.73; high quality evidence
    - fingolimod: RR = 0.63, 95% CI: 0.53 to 0.74; low quality evidence
    - dimethyl fumarate: RR = 0.78, 95% CI: 0.65 to 0.93; moderate quality evidence
    - daclizumab (no longer on the market): RR = 0.79, 95% CI: 0.61 to 1.02; moderate quality evidence
    - glatiramer acetate: RR = 0.80, 95% CI: 0.68 to 0.93; moderate quality evidence
  - Relapses over 24 months vs placebo (26 studies; N = 16,800):
    - alemtuzumab: RR = 0.46, 95% CI: 0.38 to 0.55; moderate quality evidence
    - mitoxantrone: RR = 0.47, 95% CI: 0.27 to 0.81; very low quality evidence
    - natalizumab: RR = 0.56, 95% CI: 0.47 to 0.66; high quality evidence
    - fingolimod: RR = 0.72, 95% CI: 0.64 to 0.81; moderate quality evidence
  - Disability worsening over 24 months vs placebo (26 studies; N = 16,800):
    - mitoxantrone: RR = 0.20, 95% CI: 0.05 to 0.84; low quality evidence
    - alemtuzumab: RR = 0.35, 95% CI: 0.26 to 0.48; low quality evidence
    - natalizumab: RR = 0.64, 95% CI: 0.49 to 0.85; moderate quality evidence
  - Relapses and disability worsening over 36 months were only tested in 2 studies (CombiRx and CAMMS223). Both studies had a high risk of bias.
  - Acceptability: Higher rates of withdrawal due to adverse events compared to placebo over 12 months were reported for teriflunomide (RR = 2.24, 95% CI: 1.5 to 3.34); peginterferon beta-1a (RR = 2.8, 95% CI: 1.39 to 5.64); Avonex (RR = 4.36, 95% CI: 1.98 to 9.6); Rebif (RR = 4.83, 95% CI: 2.59 to 9); and fingolimod (RR = 8.26, 95% CI: 3.25 to 20.97).
  - Over 24 months, only fingolimod had a significantly higher proportion of participants who withdrew due to any adverse event (RR vs placebo = 1.69, 95% CI: 1.32 to 2.17).
    - mitoxantrone: RR = 9.82, 95% CI: 0.54 to 168.84
    - natalizumab: RR = 1.53, 95% CI: 0.93 to 2.53
    - alemtuzumab: RR = 0.72, 95% CI: 0.32 to 1.61
- Filippini et al (2013) conducted a Cochrane review of 44 RCTs on the relative effectiveness and acceptability of DMTs and immunosuppressants in patients with either RRMS or progressive MS (N = 17,401).
  - On the basis of high quality evidence, natalizumab and Rebif were superior to all other treatments for preventing clinical relapses in the short-term (24 months) in RRMS compared to placebo (OR = 0.32, 95% CI: 0.24 to 0.43; OR = 0.45, 95% CI: 0.28 to 0.71, respectively); they were also more effective than Avonex (OR = 0.28, 95% CI: 0.22 to 0.36; OR = 0.19, 95% CI: 0.06 to 0.6, respectively).
  - Based on moderate quality evidence, natalizumab and Rebif decreased the odds of patients with RRMS having disability progression in the short-term, with an absolute reduction of 14% and 10%, respectively, vs placebo.
  - Natalizumab and Betaseron were significantly more effective (OR = 0.62, 95% CI: 0.49 to 0.78; OR = 0.35, 95% CI: 0.17 to 0.7, respectively) than Avonex in reducing the number of patients with RRMS who had progression at 2 years of follow-up, and confidence in this result was graded as moderate.
  - The lack of convincing efficacy data showed that Avonex, IV immunoglobulins (IVIG), cyclophosphamide, and long-term corticosteroids have an unfavorable benefit-risk balance in RRMS.
- The Canadian Agency for Drugs and Technologies in Health (CADTH) conducted a systematic review of 30 RCTs to assess the comparative clinical- and cost-effectiveness of drug therapies for the treatment of RRMS (N,= 16,998) (*CADTH, 2013).* Results suggested that all active treatments produce statistically significant reductions in ARR compared with no treatment, and that there were clear between-treatment differences.
  - Compared with no treatment, reductions in the ARR were approximately 70% for natalizumab and alemtuzumab, 50% for fingolimod or dimethyl fumarate, and 30% for SC IFNs, glatiramer acetate, or teriflunomide.
  - Among active comparisons, ARRs were lower for Betaseron (0.69, 95% CI: 0.54 to 0.87); Rebif (0.76, 95% CI: 0.59 to 0.98); and fingolimod (0.49, 95% CI: 0.38 to 0.63) compared with Avonex. In addition, ARRs were statistically lower for dimethyl fumarate (0.76, 95% CI: 0.62 to 0.93) compared with glatiramer acetate.

- Compared with placebo, all active treatments exhibited a lower risk of sustained disability progression, but results were only statistically significant for Avonex, Rebif, natalizumab, fingolimod, teriflunomide, and dimethyl fumarate; RR (95% CI) for these agents ranged from 0.59 (95% CI: 0.46 to 0.75) for natalizumab to 0.74 (95% CI: 0.57 to 0.96) for teriflunomide. Between-treatment differences were less apparent.
- Among active comparisons, the risk of sustained disability progression was statistically lower for alemtuzumab (0.59, 95% CI: 0.40 to 0.86) compared with Rebif, and for Betaseron (0.44, 95% CI: 0.2 to 0.80) compared with Avonex.
- Among active comparisons, MRI findings were more favorable for alemtuzumab compared with Rebif, and more favorable for all 3 of fingolimod, Betaseron, and Rebif compared with Avonex. Compared with glatiramer acetate, Tecfidera resulted in a lower mean number of T2 lesions, but the mean number of Gd-enhancing lesions was not statistically different between these 2 treatments.
- The incidence of serious adverse events and treatment discontinuations did not differ significantly between treatments in the majority of trials, except for a higher incidence of treatment discontinuation for Rebif compared to placebo and alemtuzumab.

- Hamidi et al (2018) conducted a systematic review and network meta-analysis of 37 studies including 26 RCTs from a health technology assessment (HTA) report and 11 supplemental RCTs published after the HTA. Eleven agents, including dimethyl fumarate, teriflunomide, IFNs, peginterferon, glatiramer acetate, natalizumab, fingolimod, and alemtuzumab were included and were compared to either placebo or any drug treatment in patients of varying treatment experience levels. Key findings from the network meta-analysis include:
  - Alemtuzumab 12 mg had the highest probability of preventing annual relapses (RR = 0.29, 95% CI: 0.23 to 0.35; high quality evidence).
  - Alemtuzumab 24 mg (RR = 0.36, 95% CI: 0.16 to 0.7; low quality evidence) and alemtuzumab 12 mg (RR = 0.40, 95% CI: 0.27 to 0.60; very low quality evidence) were the most effective against progression of disability.
  - Dimethyl fumarate 240 mg and fingolimod 0.5 mg and 1.25 mg were more effective treatments when considering annual relapse and disability progression:
    - Annual relapse:
      - Dimethyl fumarate 240 mg twice daily: RR = 0.5, 95% CI: 0.42 to 0.6; high quality evidence
      - Fingolimod 0.5 mg: RR = 0.46, 95% CI: 0.39 to 0.54; high quality evidence
      - Fingolimod 1.25 mg: RR = 0.45, 95% CI: 0.39 to 0.53; high quality evidence
    - Disability progression:
      - Dimethyl fumarate 240 mg twice daily: RR = 0.65, 95% CI: 0.49 to 0.85; high quality evidence
      - Fingolimod 0.5 mg: RR = 0.71, 95% CI: 0.55 to 0.90; high quality evidence
      - Fingolimod 1.25 mg: RR = 0.71, 95% CI: 0.56 to 0.90; high quality evidence
  - Withdrawal due to adverse events was difficult to assess due to the low quality of available evidence, however, the authors determined that:
    - Fingolimod 1.25 mg (RR = 2.21, 95% CI: 1.42 to 2.5; moderate quality evidence), and Rebif 44 mcg (RR = 2.21, 95% CI: 1.29 to 3.97; low quality evidence) were associated with higher withdrawals due to adverse events when compared with other treatment options.
  - Alemtuzumab 24 mg (mean difference = -0.91; 95% CI: -1.48 to -0.40), and 12 mg (mean difference = -0.6; 95% CI: -1.02 to -0.24) were more effective than other therapies in lowering the EDSS.
  - No treatments were found to significantly increase serious adverse events; peginterferon β-1a was associated with more adverse events overall when compared with other medications (RR = 1.66, 95% CI: 1.21 to 2.28).
  - None of the 11 agents studied were associated with a statistically significantly higher risk of mortality when compared to placebo.
- A Bayesian network meta-analysis evaluating DMTs for RRMS ranked the most effective therapies based on SUCRA analysis (*Lucchetta et al 2018*). A total of 33 studies were included in the analysis. For the ARR, alemtuzumab (96% probability), natalizumab (96%), and ocrelizumab (85%) were determined to be the most effective therapies (high-quality evidence).
- A meta-analysis of randomized controlled trials was conducted to evaluate the efficacy and safety of teriflunomide in reducing the frequency of relapses and progression of physical disability in patients with relapsing multiple sclerosis (*Xu et al 2016*). The results showed that teriflunomide (7 and 14 mg) reduced the ARR and teriflunomide 14 mg decreased the disability progression in comparison to placebo (RR = 0.69, 95% CI: 0.55 to 0.87).

CLINICAL GUIDELINES

- The European Committee for Research and Treatment of Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) published updated guidelines in 2018 (*Montalban et al 2018*).
- The main recommendations reported were the following:
  - The entire spectrum of disease-modifying drugs should be prescribed only in centers with adequate infrastructure to provide proper monitoring of patients, comprehensive assessment, detection of side effects, and capacity to address them properly. (Consensus statement)
  - Offer IFN or glatiramer acetate to patients with CIS and abnormal MRI findings with lesions suggesting MS who do not fulfill full criteria for MS. (Strong)
  - Offer early treatment with disease-modifying drugs in patients with active RRMS, as defined by clinical relapses and/or MRI activity (active lesions: contrast-enhancing lesions; new or unequivocally enlarging T2 lesions assessed at least annually). (Strong)
  - For active RRMS, choosing among the wide range of available drugs from the modestly effective to the highly effective will depend on patient characteristics and comorbidity, disease severity/activity, drug safety profile, and accessibility of the drug. (Consensus statement)
  - Consider treatment with IFN in patients with active SPMS, taking into account, in discussion with the patient, the dubious efficacy, as well as safety and tolerability profile. (Weak)
  - Consider treatment with mitoxantrone in patients with active SPMS, taking into account the efficacy and specifically the safety and tolerability profile of this agent. (Weak)
  - Consider ocrelizumab for patients with active SPMS. (Weak)
  - Consider ocrelizumab for patients with PPMS. (Weak)
  - Always consult the summary of product characteristics for dosage, special warnings, and precautions of use, contraindications, and monitoring of side effects and potential harms. (Consensus statement)
  - Consider combining MRI with clinical measures when evaluating disease evolution in treated patients. (Weak)
  - When monitoring treatment response in patients treated with disease-modifying drugs, perform standardized reference brain MRI within 6 months of treatment onset and compare the results with those of further brain MRI, typically performed 12 months after starting treatment. Adjust the timing of both MRIs, taking into account the drug's mechanism and speed of action and disease activity, including clinical and MRI measures. (Consensus statement)
  - When monitoring treatment response in patients treated with disease-modifying drugs, the measurement of new or unequivocally enlarging T2 lesions is the preferred MRI method, supplemented by Gd-enhancing lesions for monitoring treatment response. Evaluation of these parameters requires high-quality standardized MRI scans and interpretation by highly qualified readers with experience in MS. (Consensus statement)
  - When monitoring treatment safety in patients treated with disease-modifying drugs, perform standard reference MRI every year in patients at low risk for PML, and more frequently (3 to 6 months) in patients at high risk for PML (JC virus positivity, natalizumab treatment duration over 18 months) and in patients at high risk for PML who switch drugs at the time the current treatment is discontinued and the new treatment is started. (Consensus statement)
  - Offer a more efficacious drug to patients treated with IFN or glatiramer acetate who show evidence of disease activity, assessed as recommended above. (Strong)
  - When deciding on which drug to switch to, in consultation with the patient, consider patient characteristics and comorbidities, drug safety profile, and disease severity/activity. (Consensus statement)
  - When treatment with a highly efficacious drug is stopped, whether due to inefficacy or safety, consider starting another highly efficacious drug. When starting the new drug, take into account disease activity (clinical and MRI; the greater the disease activity, the greater the urgency to start new treatment), the half-life and biological activity of the previous drug, and the potential for resumed disease activity or even rebound (particularly with natalizumab). (Consensus statement)
  - In treatment decisions, consider the possibility of resumed disease activity or even rebound when stopping treatment, particularly with natalizumab. (Weak)
  - Consider continuing a disease-modifying drug if the patient is stable (clinically and on MRI) and shows no safety or tolerability issues. (Weak)
  - Advise all women of childbearing potential that disease-modifying drugs are not licensed during pregnancy, except glatiramer acetate 20 mg/mL. (Consensus statement)

- For women planning a pregnancy, if there is a high risk for disease reactivation, consider using IFN or glatiramer acetate until pregnancy is confirmed. In some very specific (active) cases, continuing this treatment during pregnancy could also be considered. (Weak)
- For women with persistent high disease activity, it would generally be advised to delay pregnancy. For those who still decide to become pregnant or have an unplanned pregnancy, treatment with natalizumab throughout pregnancy may be considered after full discussion of potential implications; or treatment with alemtuzumab could be an alternative for planned pregnancy in very active cases provided that a 4-month interval is strictly observed from the latest infusion until conception. (Weak)

- The American Academy of Neurology (AAN) performed a systematic review that included 20 Cochrane reviews and 73 additional articles in order to assess the available evidence on initiation, switching, and stopping DMTs in patients with MS (*Rae Grant et al 2018[a]*). The results of the systematic review were used to assist in formulating updated AAN treatment guidelines (*Rae Grant et al 2018[b]*). The main recommendations were as follows:
  - Starting DMT
    - Clinicians should discuss the benefits and risks of DMTs for people with a single clinical demyelinating event with 2 or more brain lesions that have imaging characteristics consistent with MS (Level B). After discussing the risks and benefits, clinicians should prescribe DMTs to people with a single clinical demyelinating event and 2 or more brain lesions characteristic of MS who decide they want this therapy. (Level B)
    - Clinicians should offer DMTs to people with relapsing forms of MS with recent clinical relapses or MRI activity. (Level B)
    - Clinicians should monitor the reproductive plans of women with MS and counsel regarding reproductive risks and use of birth control during DMT use in women of childbearing potential who have MS. (Level B)
    - Clinicians should counsel men with MS on their reproductive plans regarding treatment implications before initiating treatment with teriflunomide. (Level B)
    - Because of the high frequency of severe adverse events, clinicians should not prescribe mitoxantrone to people with MS unless the potential therapeutic benefits greatly outweigh the risks. (Level B)
    - Clinicians should prescribe alemtuzumab, fingolimod, or natalizumab for people with highly active MS. (Level B)
    - Clinicians may initiate natalizumab treatment in people with MS with positive anti-JCV antibody indices above 0.9 only when there is a reasonable chance of benefit compared with the low but serious risk of PML. (Level C)
    - Clinicians should offer ocrelizumab to people with PPMS who are likely to benefit from this therapy unless there are risks of treatment that outweigh the benefits. (Level B)
  - Switching DMTs
    - Clinicians should discuss switching from one DMT to another in people with MS who have been using a DMT long enough for the treatment to take full effect and are adherent to their therapy when they experience 1 or more relapses, 2 or more unequivocally new MRI-detected lesions, or increased disability on examination, over a 1-year period of using a DMT. (Level B)
    - Clinicians should evaluate the degree of disease activity, adherence, adverse event profiles, and mechanism of action of DMTs when switching DMTs in people with MS with breakthrough disease activity during DMT use. (Level B)
    - Clinicians should discuss a change to non-injectable or less frequently injected DMTs in people with MS who report intolerable discomfort with the injections or in those who report injection fatigue on injectable DMTs. (Level B)
    - Clinicians should inquire about medication adverse events with people with MS who are taking a DMT and attempt to manage these adverse events, as appropriate (Level B). Clinicians should discuss a medication switch with people with MS for whom these adverse events negatively influence adherence. (Level B)
    - Clinicians should monitor laboratory abnormalities found on requisite laboratory surveillance (as outlined in the medication's package insert) in people with MS who are using a DMT (Level B). Clinicians should discuss switching DMTs or reducing dosage or frequency (where there are data on different doses [eg, interferons, teriflunomide]) when there are persistent laboratory abnormalities. (Level B)
    - Clinicians should counsel people with MS considering natalizumab, fingolimod, ocrelizumab, and dimethyl fumarate about the PML risk associated with these agents (Level B). Clinicians should discuss switching to a DMT with a lower PML risk with people with MS taking natalizumab who are or who become JCV antibody–positive, especially with an index of above 0.9 while on therapy. (Level B)
    - Clinicians should counsel that new DMTs without long-term safety data have an undefined risk of malignancy and infection for people with MS starting or using new DMTs (Level B). If a patient with MS develops a malignancy while using a DMT, clinicians should promptly discuss switching to an alternate DMT, especially for people with MS

using fingolimod, teriflunomide, alemtuzumab, or dimethyl fumarate (Level B). People with MS with serious infections potentially linked to their DMTs should switch DMTs (does not pertain to PML management in people with MS using DMT). (Level B)
    - Clinicians should check for natalizumab antibodies in people with MS who have infusion reactions before subsequent infusions, or in people with MS who experience breakthrough disease activity with natalizumab use (Level B). Clinicians should switch DMTs in people with MS who have persistent natalizumab antibodies. (Level B)
    - Physicians must counsel people with MS considering natalizumab discontinuation that there is an increased risk of MS relapse or MRI-detected disease activity within 6 months of discontinuation (Level A). Physicians and people with MS choosing to switch from natalizumab to fingolimod should initiate treatment within 8 to 12 weeks after natalizumab discontinuation (for reasons other than pregnancy or pregnancy planning) to diminish the return of disease activity. (Level B)
    - Clinicians should counsel women to stop their DMT before conception for planned pregnancies unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy (Level B). Clinicians should discontinue DMTs during pregnancy if accidental exposure occurs, unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy (Level B). Clinicians should not initiate DMTs during pregnancy unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy. (Level B)
  - Stopping DMTs
    - In people with RRMS who are stable on DMT and want to discontinue therapy, clinicians should counsel people regarding the need for ongoing follow-up and periodic reevaluation of the decision to discontinue DMT (Level B). Clinicians should advocate that people with MS who are stable (that is, those with no relapses, no disability progression, and stable imaging) on DMT should continue their current DMT unless the patient and physician decide a trial off therapy is warranted. (Level B)
    - Clinicians should assess the likelihood of future relapse in individuals with SPMS by assessing patient age, disease duration, relapse history, and MRI-detected activity (eg, frequency, severity, time since most recent relapse or gadolinium-enhanced lesion) (Level B). Clinicians may advise discontinuation of DMT in people with SPMS who do not have ongoing relapses (or gadolinium enhanced lesions on MRI activity) and have not been ambulatory (EDSS 7 or greater) for at least 2 years. (Level C)
    - Clinicians should review the associated risks of continuing DMTs vs those of stopping DMTs in people with CIS using DMTs who have not been diagnosed with MS. (Level B)
- According to the 2013 Canadian recommendations for treatment of MS, treatment decisions should be based on the level of concern for the rate and severity of relapses, degree of functional impairment due to relapses and disability progression. First-line treatment recommendations for RRMS include IFNβ products and glatiramer acetate. Second-line therapies for RRMS include fingolimod and natalizumab *(Freedman et al 2013)*.
- With an increasing number of options for the treatment of RRMS, the place in therapy for an individual agent is not straightforward. Treatment decisions will likely be based on a consideration of the risks and benefits of each therapy, physician experience, patient comorbidities, and patient preferences. The 2015 AAN position statement supports access to all DMT for patients with MS. In addition, step therapy should be driven by evidence-based clinical and safety information and not just based on costs. Highly individualized treatment decisions are necessary for patients with MS according to the AAN *(Corboy et al 2015)*.
- The 2015 Association of British Neurologists state that all available DMTs are effective in reducing relapse rate and MRI lesion accumulation *(Scolding et al 2015)*. Evidence is less clear on the impact of DMT on long-term disability. Drugs are separated into 2 categories based on relative efficacy. Category 1 – moderate efficacy includes IFNs (including pegIFN), glatiramer acetate, teriflunomide, dimethyl fumarate, and fingolimod. Category 2 – high efficacy includes alemtuzumab and natalizumab – these drugs should be reserved for patients with very active MS.
- In September 2018, the MS Coalition published an update to its consensus paper on the principles and current evidence concerning the use of DMTs in MS. Major recommendations included the following:
  - Initiation of treatment with an FDA-approved DMT is recommended as soon as possible following a diagnosis of relapsing or primary progressive MS, regardless of the person's age; for individuals with a first clinical event and MRI features consistent with MS in whom other possible causes have been excluded; and for individuals with progressive MS who continue to demonstrate clinical relapses and/or demonstrate inflammatory activity.
  - Clinicians should consider prescribing a high efficacy medication such as alemtuzumab, fingolimod, ocrelizumab or natalizumab for newly-diagnosed individuals with highly active MS.

- Treatment with a given DMT should be continued indefinitely unless any of the following occur (in which case an alternative DMT should be considered):
  - Suboptimal treatment response as determined by the individual and his or her treating clinician
  - Intolerable side effects
  - Inadequate adherence to the treatment regimen
  - Availability of a more appropriate treatment option
  - The healthcare provider and patient determine that the benefits no longer outweigh the risks.
- Movement from one DMT to another should occur only for medically appropriate reasons as determined by the treating clinician and patient.
- When evidence of additional clinical or MRI activity while on treatment suggests a sub-optimal response, an alternative regimen (eg, different mechanism of action) should be considered to optimize therapeutic benefit.
- Due to significant variability in the MS population, people with MS and their treating clinicians require access to the full range of treatment options for several reasons:
  - Different mechanisms of action allow for treatment change in the event of a sub-optimal response.
  - Potential contraindications limit options for some individuals.
  - Risk tolerance varies among people with MS and their treating clinicians.
  - Route of delivery, frequency of dosing, and side effects may affect adherence and quality of life.
  - Individual differences related to tolerability and adherence may necessitate access to different medications within the same class.
  - Pregnancy and breastfeeding limit the available options.
- Individuals' access to treatment should not be limited by their frequency of relapses, level of disability, or personal characteristics such as age, sex, or ethnicity.
- Absence of relapses while on treatment is a characteristic of treatment effectiveness and should not be considered a justification for discontinuation of treatment.

SAFETY SUMMARY

- Warnings for IFNβ include decreased peripheral blood cell counts including leukopenia, higher rates of depression, suicide and psychotic disorders, injection site reactions, and risk of severe hepatic injury. IFNβ (Avonex, Rebif, Betaseron, Extavia, and Plegridy) is associated with influenza-like symptoms including injection site reactions, musculoskeletal pain, fatigue, and headache. All IFNβ products carry a warning for thrombotic microangiopathy including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Adverse events related to IFNβ therapy appear to be dose-related and transient.
- Glatiramer acetate is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol. Patients treated with glatiramer acetate may experience a transient, self-limited, post-injection reaction of flushing, chest pain, palpitations, tachycardia, anxiety, dyspnea, constriction of the throat, and urticaria immediately following injection. Injection site reactions including lipodystrophy and skin necrosis have been reported. Because glatiramer acetate can modify immune response, it may interfere with immune functions. In controlled studies of glatiramer acetate 20 mg/mL, the most common adverse reactions (≥ 10% and ≥ 1.5 times higher than placebo) were injection site reactions, vasodilatation, rash, dyspnea, and chest pain. In a controlled study of glatiramer acetate 40 mg/mL, the most common adverse reactions (≥ 10% and ≥ 1.5 times higher than placebo) were injection site reactions.
- Fingolimod was originally approved with a risk evaluation and mitigation strategies program (REMS) to inform healthcare providers about the serious risks including bradyarrhythmia, atrioventricular block, infections, macular edema, respiratory effects, hepatic effects, fetal risk, increased blood pressure, basal cell carcinoma, immune system effects following discontinuation, and hypersensitivity reactions; however, the FDA lifted the REMS requirements in November 2016. Posterior Reversible Encephalopathy Syndrome (PRES) has been reported with fingolimod. Patients with pre-existing cardiac disease may poorly tolerate fingolimod and may require additional monitoring. In clinical trials, the most common adverse reactions (incidence ≥ 10% and > placebo) were headache, liver transaminase elevation, diarrhea, cough, influenza, sinusitis, back pain, abdominal pain, and pain in extremity. If a serious infection develops, consider suspending fingolimod and reassess risks and benefits prior to re-initiation. Elimination may take up to 2 months thus, monitoring for infections should continue during this time. Do not start fingolimod in patients with active acute or chronic infection until the infection is resolved. Life-threatening and fatal infections have been reported in patients taking fingolimod. Establish immunity to varicella zoster virus prior to therapy initiation. Recent safety labeling changes warn of an increased risk of cutaneous malignancies, including melanoma, in patients treated with fingolimod. Cases of PML

have occurred in the postmarketing setting in patients who were treated with fingolimod for at least 2 years. A warning for PML has been added to the fingolimod labeling; at the first sign or symptom suggestive of PML, fingolimod should be withheld and an appropriate diagnostic evaluation performed. Monitoring for signs consistent with PML on MRI may be useful to allow for an early diagnosis. Additionally, severe increases in disability after discontinuation of fingolimod have been described in post marketing reports.

- Teriflunomide is contraindicated in patients with severe hepatic impairment; patients who are pregnant, of childbearing potential, or that are not using reliable contraception; and with concurrent use of leflunomide. Labeling includes boxed warnings regarding hepatotoxicity and teratogenicity/embryolethality that occurred in animal reproduction studies in multiple animal species at plasma teriflunomide exposures similar to or lower than in humans. Other warnings include risk of leukopenia, peripheral neuropathy, severe skin reactions, and elevated blood pressure. Teriflunomide has a half-life of 4 to 5 months; therefore, use of activated charcoal or cholestyramine in an 11-day regimen upon discontinuation of teriflunomide is recommended to reduce serum levels over 2 weeks. The most common adverse reactions (≥ 10% and ≥ 2% greater than placebo) are headache, diarrhea, nausea, alopecia, and an increase in alanine aminotransferase (ALT).
- Dimethyl fumarate has no contraindications, except in patients with hypersensitivity to dimethyl fumarate or any excipients. Warnings include anaphylaxis and angioedema, PML, lymphopenia, and clinically significant cases of liver injury reported in the post-marketing setting. Consider therapy interruption if severe lymphopenia for more than 6 months occurs. Cases of PML have been reported following dimethyl fumarate therapy. Monitoring for signs consistent with PML on MRI may be useful to allow for an early diagnosis. Common adverse events (incidence ≥ 10% and ≥ 2% more than placebo) were flushing, abdominal pain, diarrhea, and nausea. Administration of non-enteric aspirin up to 325 mg given 30 minutes prior to each dose or temporary dose reduction to 120 mg twice daily may reduce flushing.
- Natalizumab has a boxed warning regarding the risk of PML. PML is an opportunistic viral infection of the brain that usually leads to death or severe disability. Due to the risk of PML, natalizumab is only available through the TOUCH® Prescribing Program which is a restricted distribution program. Natalizumab is contraindicated in patients who have or have had PML and in patients who have had a hypersensitivity reaction. The most common adverse reactions (incidence ≥ 10%) were headache, fatigue, arthralgia, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort hypersensitivity reaction to natalizumab. Monitoring for signs consistent with PML on MRI may be useful to allow for an early diagnosis. Other warnings with natalizumab include hypersensitivity reactions, increased risk of Herpes encephalitis and meningitis, acute retinal necrosis, increased risk of infections (including opportunistic infections), and hepatotoxicity, diarrhea (not otherwise specified), and rash.
- Mitoxantrone has boxed warnings for the risk of cardiotoxicity, risk of bone marrow suppression, and secondary leukemia. Congestive heart failure (CHF), potentially fatal, may occur either during therapy with mitoxantrone or months to years after termination of therapy. The maximum cumulative lifetime dose of mitoxantrone for MS patients should not exceed 140 mg/kg/m^2. Monitoring of cardiac function is required prior to all mitoxantrone doses.
- Alemtuzumab is contraindicated in patients with human immunodeficiency virus (HIV). The boxed warning for alemtuzumab includes autoimmunity conditions (immune thrombocytopenia and anti-glomerular basement membrane disease), serious and life-threatening infusion reactions, serious and life-threatening stroke within 3 days of administration, and the possibility of an increased risk of malignancies. Alemtuzumab is only available through a restricted distribution and REMS program which requires the member, provider, pharmacy and infusion facility to be certified by the REMS program. Approximately one-third of patients who receive alemtuzumab develop thyroid disorders. The most commonly reported adverse events reported in at least 10% of alemtuzumab-treated patients and more frequently than with IFNβ-1a were rash, headache, pyrexia, nasopharyngitis, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract infection, herpes viral infection, urticaria, pruritus, thyroid disorders, fungal infection, arthralgia, pain in extremity, back pain, diarrhea, sinusitis, oropharyngeal pain, paresthesia, dizziness, abdominal pain, flushing, and vomiting. Nearly all patients (99.9%) in clinical trials had lymphopenia following a treatment course of alemtuzumab. Alemtuzumab may also increase the risk of acute acalculous cholecystitis; in controlled clinical studies, 0.2% of alemtuzumab-treated MS patients developed acute acalculous cholecystitis, compared to 0% of patients treated with IFNβ-1a. During postmarketing use, additional cases of acute acalculous cholecystitis have been reported in alemtuzumab-treated patients. Recent updates to the safety labeling include a warning that patients taking alemtuzumab are at risk for serious infections caused by *Listeria monocytogenes*. Patients that are prescribed alemtuzumab should be counseled about this risk, and to avoid or appropriately heat any foods that may be a source of *Listeria*, such as deli meats and unpasteurized cheeses. Patients should undergo tuberculosis screening according to local guidelines.

- The labeling of ocrelizumab does not contain any boxed warnings; however, ocrelizumab is contraindicated in patients with active hepatitis B virus (HBV) infection and in those with a history of life-threatening infusion reactions to ocrelizumab. Additional warnings for ocrelizumab concern infusion reactions, infections, and an increased risk of malignancies.
  - As of June 30, 2016, the overall incidence rate of first neoplasm among ocrelizumab-treated patients across all 3 pivotal studies and a Phase 2, dose-finding study *(Kappos et al [2011])* was 0.40 per 100 patient-years of exposure to ocrelizumab (6467 patient-years of exposure) vs 0.20 per 100 patient-years of exposure in the pooled comparator groups (2053 patient-years of exposure in groups receiving Rebif or placebo) *(Hauser et al 2017, Ocrevus Formulary Submission Dossier 2017)*.
    - Since breast cancer occurred in 6 out of 781 females treated with ocrelizumab (vs in none of 668 females treated with Rebif or placebo), the labeling of ocrelizumab additionally recommends that patients follow standard breast cancer screening guidelines.
    - In related postmarketing requirements, the FDA has asked the manufacturer to conduct a prospective, longitudinal, observational study in adult patients with RMS and PPMS exposed to ocrelizumab to determine the incidence and mortality rates of breast cancer and all malignancies. All patients enrolled in the study need to be followed for a minimum of 5 years or until death following their first exposure to ocrelizumab and the protocol must specify 2 appropriate populations to which the observed incidence and mortality rates will be compared *(FDA approval letter 2017)*.
  - No cases of PML have been reported to date in any studies of ocrelizumab (*Hauser et al 2017, McGinley et al 2017, Montalban et al 2017, Ocrevus Formulary Submission Dossier 2017*).
  - In patients with RMS, the most common adverse reactions with ocrelizumab (incidence ≥ 10% and greater than Rebif) were upper respiratory tract infections and infusion reactions. In patients with PPMS, the most common adverse reactions (incidence ≥ 10% and greater than placebo) were upper respiratory tract infections, infusion reactions, skin infections, and lower respiratory tract infections.
- Dalfampridine is contraindicated in patients with a history of seizure, moderate or severe renal impairment (CrCl ≤ 50 mL/min), and a history of hypersensitivity to dalfampridine or 4-aminopyridine. Dalfampridine can cause anaphylaxis; signs and symptoms of anaphylaxis have included respiratory compromise, urticaria, and angioedema of the throat and or tongue. Urinary tract infections (UTIs) were reported more frequently as adverse reactions in controlled studies in patients receiving dalfampridine 10 mg twice daily (12%) as compared to placebo (8%). The most common adverse events (incidence ≥ 2% and at a rate greater than the placebo rate) for dalfampridine were UTI, insomnia, dizziness, headache, nausea, asthenia, back pain, balance disorder, MS relapse, paresthesia, nasopharyngitis, constipation, dyspepsia, and pharyngolaryngeal pain.
- Siponimod is contraindicated in patients with a cytochrome P4502C9*3/*3 genotype, presence of Mobitz type II second-degree, third degree atrioventricular (AV) block or sinus syndrome. It is also contraindicated in patients that have experienced myocardial infarction, unstable angina, stroke, transient ischemic attack or decompensated heart failure requiring hospitalization in the past 6 months. Warnings and precautions of siponimod include macular edema, increased blood pressure, bradyarrhythmia and AV conduction delays, decline in pulmonary function, and liver injury. Women of childbearing potential should use effective contraception during and for 10 days after stopping siponimod due to fetal risk. The most adverse events are headache, hypertension, and transaminase increases.
- Cladribine is contraindicated in patients with current malignancy, HIV infection, active chronic infection such as hepatitis or tuberculosis, hypersensitivity to cladribine, and in pregnant women. There is a boxed warning for potential malignancy and risk of teratogenicity. The warnings and precautions are lymphopenia, active infection, hematologic toxicity, liver injury, and graft vs host disease with blood transfusion. The most common adverse events are upper respiratory tract infection, headache, and lymphopenia.

Table 3. Dosing and Administration*

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ampyra (dalfampridine)	Tablets	Oral	Twice daily	May be taken with or without food. Tablets should only be taken whole; do not divide, crush, chew, or dissolve. In patients with mild renal

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				impairment (CrCl 51 to 80 mL/min), dalfampridine may reach plasma levels associated with a greater risk of seizures, and the potential benefits of dalfampridine should be carefully considered against the risk of seizures in these patients. Dalfampridine is contraindicated in patients with moderate or severe renal impairment (CrCl ≤ 50 mL/min). Based on animal data, dalfampridine may cause fetal harm.
Aubagio (teriflunomide)	Tablets	Oral	Once daily	May be taken with or without food. No dosage adjustment is necessary for patients with mild and moderate hepatic impairment; contraindicated in patients with severe hepatic impairment. Teriflunomide is contraindicated for use in pregnant women and in women of reproductive potential who are not using effective contraception because of the potential for fetal harm. Exclude pregnancy before the start of treatment with teriflunomide in females of reproductive potential and advise females of reproductive potential to use effective contraception during teriflunomide treatment and during an accelerated drug elimination procedure after teriflunomide treatment. Teriflunomide should be stopped and an accelerated drug elimination procedure used if the patient becomes pregnant. Teriflunomide is detected in human semen; to minimize any possible risk, men not wishing to father a child and their female

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				partners should use effective contraception. Men wishing to father a child should discontinue use of teriflunomide and either undergo an accelerated elimination procedure or wait until verification that the plasma teriflunomide concentration is less than 0.02 mg/L.
Avonex (interferon β-1a)	Injection	IM	Once weekly Titration: To reduce the incidence and severity of flu-like symptoms that may occur during initiation, Avonex may be started at a dose of 7.5 mcg and the dose may be increased by 7.5 mcg each week for the next 3 weeks until the recommended dose of 30 mcg is achieved.	Following initial administration by a trained healthcare provider, Avonex may be self-administered. Rotate injection sites to minimize the likelihood of injection site reactions. Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with Avonex use. Use caution in patients with hepatic dysfunction.
Betaseron (interferon β-1b)	Injection	SC	Every other day Titration: Generally, start at 0.0625 mg (0.25 mL) every other day, and increase over a 6-week period to 0.25 mg (1 mL) every other day.	Following initial administration by a trained healthcare provider, IFNβ-1b may be self-administered. Rotate injection sites to minimize the likelihood of injection site reactions. Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with IFNβ-1b use.
Copaxone (glatiramer acetate) [and Glatopa]	Injection	SC	20 mg once daily **OR** 40 mg 3 times per week at least 48 hours apart Note: The 2 strengths are not interchangeable.	Following initial administration by a trained healthcare provider, Glatiramer acetate may be self-administered. Areas for SC self-injection include arms, abdomen, hips, and thighs.
Extavia (interferon β-1b)	Injection	SC	Every other day Titration:	Following initial administration by a trained healthcare provider, IFNβ-1b may be self-

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Generally, start at 0.0625 mg (0.25 mL) every other day, and increase over a 6-week period to 0.25 mg (1 mL) every other day.	administered. Rotate injection sites to minimize the likelihood of injection site reactions. Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with IFNβ-1b use.
Gilenya (fingolimod)	Capsules	Oral	Once daily Note: Patients who initiate fingolimod and those who re-initiate treatment after discontinuation for longer than 14 days require first dose monitoring (see right).	May be taken with or without food. Approved for adults and pediatric patients 10 years of age or older. For pediatric patients ≤40 kg, a lower dose is recommended. First dose monitoring: Observe all patients for bradycardia for at least 6 hours; monitor pulse and blood pressure hourly. Electrocardiograms (ECGs) prior to dosing and at end of the observation period are required. Monitor until resolution if heart rate < 45 bpm, atrioventricular (AV) block, or if lowest post-dose heart rate is at the end of the observation period. Monitor symptomatic bradycardia with ECG until resolved. Continue overnight if intervention is required; repeat first dose monitoring for second dose. Observe patients overnight if at higher risk of symptomatic bradycardia, heart block, prolonged QTc interval, or if taking drugs with known risk of torsades de pointes. Fingolimod exposure is doubled in patients with severe hepatic impairment; patients with severe hepatic impairment should be closely monitored. No dose adjustment is necessary in mild-to-moderate hepatic impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				The blood level of some fingolimod metabolites is increased (up to 13-fold) in patients with severe renal impairment; blood levels were not assessed in patients with mild or moderate renal impairment.
Lemtrada (alemtuzumab)†	Injection	IV	**2 treatment courses** First course: 12 mg/day on 5 consecutive days Second course: 12 mg/day on 3 consecutive days 12 months after the first treatment course Subsequent course: 12 mg/day for 3 consecutive days may be administered, as needed, at least 12 months after the last dose of any prior treatments courses. Important monitoring: Complete blood count with differential (prior to treatment initiation and at monthly intervals thereafter); serum creatinine levels (prior to treatment initiation and at monthly intervals thereafter); urinalysis with urine cell counts (prior to treatment initiation and at monthly intervals thereafter); and a test of thyroid function, such as thyroid stimulating hormone level (prior to treatment initiation and every 3 months thereafter). Conduct baseline and yearly skin exams to monitor for melanoma.	Infused over 4 hours for both treatment courses; patients should be observed for infusion reactions during and for at least 2 hours after each Lemtrada infusion. Vital signs should be monitored before the infusion and periodically during the infusion. Pre-medicate with corticosteroids prior to Lemtrada infusion for the first 3 days of each treatment course. Administer antiviral agents for herpetic prophylaxis starting on the first day of alemtuzumab dosing and continuing for a minimum of 2 months after completion of Lemtrada dosing or until CD4+ lymphocyte count is more than 200 cells/microliter, whichever occurs later. Patients should complete any necessary immunizations at least 6 weeks prior to treatment with alemtuzumab.
Mavenclad (cladribine)	Tablet	Oral	Cumulative dosage of 3.5 mg/kg divided into 2 yearly treatment courses of 1.75 mg/kg per treatment course. Each treatment course is divided into 2 treatment cycles:	The use of Mavenclad in patients weighing less than 40 kg has not been investigated. Mavenclad is contraindicated in pregnant women and in female/males of reproductive

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			• First course/first cycle: start anytime • First cycle/second cycle: administer 23 to 27 days after the last dose of first course/first cycle. • Second course/first cycle: administer at least 43 weeks after the last dose of first course/second cycle. • Second course/second cycle: administer 23 to 27 days after the last dose of second course/first cycle.	potential that do not plan to use effective contraception. The safety and effectiveness in pediatric patients have not been established.
Mayzent (siponimod)	Tablets: starter pack of tablets	Oral	Once daily	Mayzent can cause fetal harm when administered to pregnant women. Dosage should be titrated based on patient's CYP2C9 genotype. Patients with sinus bradycardia (HR < 55 bpm), first- or second-degree AV block or a history of myocardial infarction or heart failure should undergo first dose monitoring for bradycardia.
mitoxantrone	Injection	IV	Every 3 months Note: Left ventricular ejection fraction (LVEF) should be evaluated prior to administration of the initial dose of mitoxantrone injection (concentrate) and all subsequent doses. In addition, LVEF evaluations are recommended if signs or symptoms of congestive heart failure develop at any time during treatment with mitoxantrone. Complete blood counts, including platelets, should be monitored prior to each course of mitoxantrone and in the event that signs or symptoms of infection develop.	For MS-related indications: 12 mg/m^2 given as a short IV infusion over 5 to 15 minutes Mitoxantrone injection (concentrate) should not be administered to MS patients with an LVEF < 50%, with a clinically significant reduction in LVEF, or to those who have received a cumulative lifetime dose of > 140 mg/m^2. Mitoxantrone generally should not be administered to MS patients with neutrophil counts less than 1500 cells/mm^3. Mitoxantrone therapy in MS patients with abnormal liver function tests is not recommended because mitoxantrone clearance is reduced by hepatic impairment

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Liver function tests should be monitored prior to each course of therapy.	and no laboratory measurement can predict drug clearance and dose adjustments. Mitoxantrone may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant.
Ocrevus (ocrelizumab)	Injection	IV	Every 6 months (24 weeks) Titration: Initial dose: 300 mg IV, followed 2 weeks later by a second 300 mg IV infusion. Subsequent doses: 600 mg IV infusion every 6 months Hepatitis B virus screening is required before the first dose.	Observe patients for at least 1 hour after the completion of the infusion. Dose modifications in response to infusion reactions depend on the severity. See package insert for more details. Pre-medicate with methylprednisolone (or an equivalent corticosteroid) and an antihistamine (eg, diphenhydramine) prior to each infusion. An antipyretic (eg, acetaminophen) may also be considered. Administer all necessary immunizations according to immunization guidelines at least 6 weeks prior to initiation of ocrelizumab. Women of childbearing potential should use contraception while receiving ocrelizumab and for 6 months after the last infusion of ocrelizumab.
Plegridy (peginterferon β-1a)	Injection	SC	Every 14 days Titration: Start with 63 mcg on day 1, 94 mcg on day 15, and 125 mcg (full dose) on day 29	Following initial administration by a trained healthcare provider, Plegridy may be self-administered. Patients should be advised to rotate injection sites; the usual sites are the abdomen, back of the upper arm, and thigh. Analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Monitor for adverse reactions due to increased drug exposure in patients with severe renal impairment.
Rebif (interferon β-1a)	Injection	SC	Three times per week at least 48 hours apart Titration: Generally, the starting dose should be 20% of the prescribed dose 3 times per week, and increased over a 4-week period to the targeted recommended dose of either 22 mcg or 44 mcg injected SC 3 times per week	Following initial administration by a trained healthcare provider, Rebif may be self-administered. Patients should be advised to rotate the site of injection with each dose to minimize the likelihood of severe injection site reactions or necrosis. Decreased peripheral blood counts or elevated liver function tests may necessitate dose reduction or discontinuation of Rebif administration until toxicity is resolved. Concurrent use of analgesics and/or antipyretics may help ameliorate flu-like symptoms associated with Rebif use on treatment days.
Tecfidera (dimethyl fumarate)	Capsules	Oral	Twice daily Titration: 120 mg twice daily for 7 days (initiation), then 240 mg twice daily (maintenance) Temporary dose reductions to 120 mg twice a day may be considered for individuals who do not tolerate the maintenance dose.	May be taken with or without food; must be swallowed whole. Do not crush, chew, or sprinkle capsule contents on food. The incidence of flushing may be reduced by administration of dimethyl fumarate with food. Alternatively, administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to dimethyl fumarate dosing may reduce the incidence or severity of flushing. Obtain a complete blood cell count including lymphocyte count before initiation of therapy. Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to treatment with dimethyl fumarate.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Tysabri (natalizumab)†	Injection	IV	Once a month (every 4 weeks)	Both MS and Crohn's disease indications are dosed the same: 300 mg infused over 1 hour and given every 4 weeks. Tysabri should not be administered as an IV push or bolus injection. Patients should be observed during the infusion and for 1 hour after the infusion is complete.

*See the current prescribing information for full details
†Currently available through a restricted distribution program as part of a REMS requirement.

CONCLUSION

- DMTs for MS have shown benefits in patients with RRMS such as a decreased relapse rate and a slower accumulation of brain lesions on MRI. Therefore, it is recommended that all patients with a diagnosis of definite RRMS begin DMTs *(MS Coalition 2017)*.
- IFNβ products have been shown to decrease MRI lesion activity, prevent relapses, and delay disease progression. In general, patients treated with IFNβ or glatiramer acetate can expect a 30% reduction in ARR during a 2-year period *(MS Coalition 2017)*. Head-to-head clinical trials have found IFNβ and glatiramer acetate to be comparable in terms of efficacy on relapse rate. Several studies have demonstrated an improved tolerability at the cost of a decreased therapeutic response with the low dose IM IFNβ-1a compared to the higher dose SC IFNβ-1a *(Panitch et al 2002, Panitch et al 2005, Schwid et al 2005, Schwid et al 2007, Traboulsee et al 2008)*. Influenza-type symptoms, injection site reactions, headache, nausea, and musculoskeletal pain are the most frequently reported adverse events with IFNβ products including Plegridy. With IFNβ, use caution in patients with depression or other mood disorders. Peginterferon β-1a every 2 weeks has demonstrated efficacy in reducing the ARR in relapsing forms of MS compared to placebo. Potential advantages of Plegridy are less frequent administration every 2 weeks and possibly the reduced risk of NAb development. Adverse effect profile is similar among the IFNs.
- The most frequently reported adverse events with glatiramer acetate include a transient, self-limiting, post-injection systemic reaction immediately following drug administration consisting of flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, and urticaria. Glatiramer acetate does not have any known drug interactions and is not associated with an increased risk of hepatotoxicity or depression. Glatiramer acetate is generically available.
- Despite advancements in treatment, many patients fail initial DMTs with glatiramer acetate or IFNβ, primarily due to intolerable adverse effects or perceived inadequate efficacy *(Coyle 2008, Portaccio et al 2008)*. Clinical trials have shown that patients switching from IFNβ to glatiramer acetate therapy and vice versa, due to poor response, may achieve a significant reduction in relapse rates and a delay in disease and disability progression *(Coyle 2008, Caon et al 2006, Zwibel 2006)*. The guidelines suggest that all first-line MS DMTs should be made accessible, and the choice of initial treatment should be based on patient-specific factors *(Corboy et al 2015, MS Coalition 2017, Scolding et al 2015, Montalban et al 2018)*. Premature discontinuation rate is high among patients with MS; therefore, factors that will maximize adherence should be considered when initiating therapy. Failure with 1 agent does not necessarily predict failure to another. Therefore, patients experiencing an inadequate response or drug-induced adverse event should be switched to a different DMT *(Coyle 2008, Portaccio et al 2008)*.
- There are now 5 available oral agents: Gilenya (fingolimod), which was approved in 2010, Aubagio (teriflunomide), which was approved 2012, and Tecfidera (dimethyl fumarate), which was approved in 2013. The 2 new agents are Mavenclad (cladribine) and Mayzent (siponimod). Among other potential benefits, it is expected that the availability of oral agents may increase convenience and improve patient adherence to their drug regimen *(Sanvito et al 2011)*. The available oral drugs each have different mechanisms of action and tolerability profiles. The oral products have not been compared to one another in any head-to-head trials. Cases of PML have been reported in patients taking fingolimod and dimethyl fumarate.
  - Mayzent (siponimod) is a sphingosine 1-phosphate receptor modulator, similar to fingolimod, indicated for the treatment of relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive

disease. In a trial comparing Mayzent to placebo, Mayzent significantly reduced the risk of 3-month CDP, delayed the risk of 6-month CDP, and reduced the ARR (*Kappos et al 2018*). First dose cardiac monitoring is recommended for patients with a heart rate < 55 bpm or a history of cardiac disease. Siponimod shares many of the same warnings as fingolimod.

- Mavenclad (cladribine) is a purine antimetabolite indicated for the treatment of relapsing forms of MS, to include relapsing-remitting disease and active secondary progressive disease. In a trial comparing Mavenclad to placebo, both Mavenclad 3.5 mg/kg and 5.25 mg/kg treatment groups had reduced ARRs and disability progression vs placebo (*Giovannoni et al 2010*). Lymphopenia is the most common adverse effect.
- Gilenya (fingolimod) is a sphingosine 1-phosphate receptor modulator. In a trial comparing fingolimod to placebo, fingolimod-treated patients had a decreased ARR, improved MRI outcomes, and a lower likelihood of disability progression *(Kappos et al 2010)*. In a trial comparing fingolimod to IFNβ-1a IM (Avonex), fingolimod-treated patients had a decreased ARR and improved MRI outcomes, but disability progression was similar in the 2 groups *(Cohen et al, 2010)*. The adverse event profile for fingolimod includes cardiovascular risks including bradycardia. First dose administration of fingolimod requires at least 6 hours of observation with hourly monitoring of heart rate and blood pressure, and patients should have an ECG before dosing and at the end of the observation period.
  - Fingolimod is also FDA-approved for MS in the pediatric population. In a trial evaluating patients between 10 and 17 years of age, fingolimod significantly reduced ARR and the rate or new or newly enlarged lesions compared to IFNβ-1a (*Chitnis et al 2018*).
- Tecfidera (dimethyl fumarate) has efficacy similar to that of fingolimod; its benefit-risk profile makes it a reasonable initial or later stage DMT option for most patients with RRMS *(CADTH 2013, Wingerchuk et al 2014)*. Gastrointestinal intolerance and flushing are common side effects that may wane with time; slow titration to maintenance doses, taking the medication with food, and premedication with aspirin may reduce their severity.
- Aubagio (teriflunomide) inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme involved in de novo pyrimidine synthesis. Although its exact mechanism of action is unknown, it may involve a reduction in the number of activated lymphocytes in the CNS. Patients treated with teriflunomide in a clinical trial experienced a reduction in the ARR and improved MRI outcomes compared to placebo. Patients in the higher dose group (14 mg) also had a lower likelihood of disability progression, but this difference was not statistically significant in the lower dose group (7 mg) *(O'Connor et al, 2011)*. Teriflunomide has boxed warnings for the possibility of severe liver injury and teratogenicity. The most common adverse reactions include increases in ALT, alopecia, diarrhea, influenza, nausea, and paresthesia.

- Tysabri (natalizumab) has demonstrated very high efficacy vs placebo and although PML is a major safety concern, the overall incidence of PML has remained low (0.4%). Natalizumab can only be obtained through a restricted distribution program.
- Lemtrada (alemtuzumab) is a highly efficacious DMT that has demonstrated superiority in reducing relapses when compared to Rebif in both treatment-naïve and treatment-experienced patients. The dosing schedule of 2 annual treatment courses is counterbalanced by the need for regular monitoring of the increased risk for autoimmunity. Lemtrada is best reserved for patients who have failed at least 2 other DMTs and are not candidates for natalizumab (*Garnock-Jones 2014*).
- Ocrevus (ocrelizumab) is a recombinant monoclonal antibody designed to selectively target CD20-positive B cells. As a humanized form of Rituxan (rituximab), ocrelizumab is expected to be less immunogenic with repeated infusions and may have a more favorable benefit-to-risk profile than Rituxan *(Sorensen et al 2016)*.
  - The approval of Ocrevus provides another DMT option to the growing armamentarium of highly effective agents indicated for the treatment of RMS. Ocrelizumab is also indicated for the treatment of PPMS, making it the first DMT with substantial evidence supporting its use in this form of MS. Although the pivotal studies of ocrelizumab were of sufficient length to assess efficacy, more long-term safety data are needed to evaluate the effects of ocrelizumab on emergent neoplasms and the risk of PML.
- Mitoxantrone is a synthetic intercalating chemotherapeutic agent. While it is approved for the treatment of RRMS, SPMS, and PRMS, cumulative dose-related cardiac toxicity and the risk for secondary leukemia markedly limit its use. Mitoxantrone is, therefore, reserved for use in patients with aggressive disease.
- While DMTs do not sufficiently address QOL in RRMS, symptomatic agents such as Ampyra (dalfampridine) can be used to complement treatment with DMTs. Although a 25% improvement in T25FW may appear marginal, it has been established that improvements in T25FW speed of ≥ 20% are meaningful to people with MS. Dalfampridine can complement DMTs, which do not address the specific symptom of walking speed. Improved walking could potentially contain some of the direct and indirect costs (eg, reduced productivity, disability, unemployment, costs of assistive devices and caregivers) associated with MS.

- With an increasing number of DMTs currently on the market and no specific MS algorithm in place to guide treatment decisions, the selection of an agent is generally based on considerations of the risks and benefits of each therapy, physician experience, patient comorbidities, and patient preferences.

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Therapeutic Class Overview
Topical Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

INTRODUCTION

- Osteoarthritis (OA) is a key area where topical formulations of nonsteroidal anti-inflammatory drugs (NSAIDs) are used. OA, the most common form of arthritis, causes signs and symptoms such as pain, tenderness, reduced range of motion, bony swelling, joint deformity, and instability. Symptoms typically appear in one or a few joints in a middle-aged or older person, and are often progressive (*Doherty et al 2017*).
- The number of U.S. adults affected by OA has increased in the last several decades due to aging of the population and the increasing prevalence of obesity. Approximately 30 million U.S. adults are affected by OA, up from 21 million in 1995 (*Centers for Disease Control and Prevention 2017, Suri et al 2012*).
- Oral NSAIDs are effective for the treatment of moderate to severe pain, but are associated with an increased risk of several gastrointestinal (GI) and cardiovascular adverse events. The NSAID products as a class, including topical products, carry a Boxed Warning regarding the risk of cardiovascular and GI adverse events associated with their use. However, the use of topical NSAIDs applied directly to the affected area reduces overall systemic absorption and minimizes the risk of severe adverse events (*Galer 2011*). The adverse events associated with the topical NSAIDs are typically dermatologic in nature and are self-limiting in most cases.
- Solaraze (diclofenac sodium gel) is the only topical NSAID indicated for actinic keratoses. Actinic keratosis is a common cutaneous lesion, usually found on sun-exposed areas such as the head, neck, forearms, and hands in older, fair-skinned patients. Actinic keratosis is considered a potential premalignant lesion that may progress to squamous cell carcinoma. For patients with a single lesion, a few low-risk lesions, or thin lesions, treatment with cryotherapy, topical 5-fluorouracil, imiquimod, diclofenac, or ingenol mebutate may be considered (*de Berker et al 2017, Shoimer et al 2010*).
- Diclofenac is the only NSAID commercially available in topical formulations. There are currently 3 formulations available, and Food and Drug Administration (FDA)-approved indications vary among products.
- The following products are included within this review:
  - Flector (diclofenac epolamine patch, 1.3%) is indicated for the topical treatment of acute pain due to minor strains, sprains, and contusions. Flector is composed of an adhesive material containing 1.3% diclofenac epolamine applied to a polyester felt backing.
  - Licart (diclofenac epolamine topical system, 1.3%), which shares the same indication as Flector, is a topical system comprised of an adhesive material containing 1.3% diclofenac epolamine which is applied to a non-woven polyester felt backing and covered with a polypropylene film release liner. Licart differs from Flector in that it is applied once daily, while Flector is applied twice daily.
  - Pennsaid (diclofenac sodium topical solution, 1.5%) is indicated for the treatment of signs and symptoms of OA of the knee(s); and higher strength Pennsaid (diclofenac sodium topical solution, 2%) is indicated for the treatment of pain of OA of the knees. Pennsaid contains diclofenac sodium as well as the penetration enhancer dimethyl sulfoxide (DMSO) and other inactive ingredients.
  - Solaraze (diclofenac sodium topical gel, 3%) is indicated for the topical treatment of actinic keratoses. In addition to sun avoidance measures, diclofenac sodium topical gel (3%) is effective for lesions of the scalp, forehead, face, arm, forearm, and back of the hand. Solaraze provides diclofenac sodium in a gel base including benzyl alcohol, hyaluronate sodium, and other inactive ingredients.
  - Voltaren (diclofenac sodium topical gel, 1%) is indicated for the relief of pain of OA of joints amenable to topical treatment, such as the knees and those of the hands. Voltaren provides diclofenac sodium in a white gel base.
- A number of therapy packs, compounding products, and compounding kits (ie, EnovaRx, Rexaphenac, etc) are available; however, these products are excluded from this review.
- Medispan class: Anti-inflammatory Agents – Topical; Diclofenac sodium (actinic keratoses)

Table 1. Medications Included Within Class Review

Drug	Generic Availability
diclofenac sodium topical solution 1.5%*	✔
diclofenac sodium topical gel 3%†	✔

Drug	Generic Availability
Flector (diclofenac epolamine patch) 1.3%	✔
Licart (diclofenac epolamine topical system) 1.3%	-‡
Pennsaid (diclofenac sodium topical solution) 2%	-
Voltaren (diclofenac sodium topical gel) 1%	✔

*Pennsaid 1.5% solution is no longer marketed; however, branded generic (ie, Klofensaid II, etc) and generic formulations are available.
†Solaraze 3% topical gel is no longer marketed; however, generic formulations are available.
‡Launch plans are pending.

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Flector (diclofenac epolamine patch)	diclofenac sodium topical solution 1.5%	diclofenac sodium topical gel 3%	Licart (diclofenac epolamine) system 1.3%	Pennsaid (diclofenac sodium topical solution) 2%	Voltaren (diclofenac sodium topical gel) 1%
Treatment of acute pain due to minor strains, sprains and contusions	✔			✔		
Treatment of actinic keratoses*			✔			
Relief of the pain of OA of joints amenable to topical treatment, such as the knees and those of the hands						✔
Treatment of signs and symptoms of OA of the knee(s)		✔				
Treatment of the pain of OA of the knee(s)					✔	

*Sun avoidance is indicated during therapy.

(*Prescribing information: Flector 2018, diclofenac 1.5% 2016, Licart 2018, Pennsaid 2% 2016, Solaraze 2016, Voltaren 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

- Two studies evaluated the use of diclofenac patch vs placebo patch in patients with acute injuries.
  - Patients who had experienced a sports-related sprain, strain, or contusion experienced a statistically significantly improvement in scores for pain and functioning following application of the diclofenac epolamine patch over 14 days ($p = 0.036$ and $p = 0.048$, respectively) (*Galer et al 2000*).
  - Patients with a minor soft tissue injury experienced an 18.2% reduction in visual analog scale (VAS) pain scores following twice-daily application of the diclofenac epolamine patch over 14 days ($p = 0.002$) (*Kuehl et al 2011*).
- The efficacy and safety of diclofenac gel have been evaluated in patients with OA of the hands and knees in an 8-week study. Study results demonstrated greater pain relief, Australian/Canadian Osteoarthritis Hand Index (AUSCAN) score improvement, and global rating of disease with diclofenac sodium gel compared to placebo in patients with OA of the hand (*Altman et al 2009*). In patients with OA of the knee, treatment with diclofenac gel for 12 weeks led to greater

improvement in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score, WOMAC physical function score, and global rating of disease (*Barthel et al 2009*). Additionally, a 12-month, open-label study in patients with OA of the knee demonstrated sustained long-term improvement compared to baseline for WOMAC pain scores, stiffness, and physical function (*Peniston et al 2011*).

- In a study by Simon et al, patients with OA of the knee treated with topical diclofenac sodium 1.5% solution achieved statistically significant reductions in pain scores compared to patients treated with placebo (-6 vs -4.7; p = 0.015) and dimethyl sulfoxide alone (-6 vs -4.7; p = 0.009). There was no statistically significant difference in pain scores compared to patients receiving diclofenac tablets (-6 vs -7; p = 0.429) (*Simon et al 2009*).
- The safety and efficacy of diclofenac 2% solution were evaluated in a phase 2, randomized, double-blind, parallel-group, placebo-controlled, 4-week clinical trial in patients with osteoarthritis of the knee (N = 260). A reduction of 4.5 in the WOMAC pain score was noted in the diclofenac 2% group as compared to a 3.6 reduction in the placebo vehicle group (p = 0.04) (*Wadsworth et al 2016*).
- The safety and efficacy of diclofenac epolamine topical system 1.3% (Licart) was based on 2 placebo- and active-controlled studies in patients with minor sprains, strains, and/or contusions. Patients were randomized to receive Licart, placebo, or Flector (diclofenac epolamine patch 1.3%) once daily for 7 or 14 days. The primary efficacy endpoint was the mean change from baseline in pain on movement to day 3 of treatment. In both studies, Licart demonstrated a statistically significant difference vs placebo for the reduction in pain on movement at day 3. Conclusions regarding comparative efficacy of Licart vs Flector cannot be made because Flector was not administered according to its approved twice daily dosing regimen (*Licart prescribing information 2018*).
- The clinical effectiveness of the gel and solution formulations has not been compared in any head-to-head trials. However, a single-dose patient preference trial in 24 healthy volunteers demonstrated a preference for the solution formulation on several characteristics, including odor/smell, oiliness/greasiness, and stickiness/tackiness (*Galer et al 2011*).
- A systematic review of 19 trials summarized the benefits of diclofenac solution, gel, and patch based on clinical studies comparing the topical diclofenac products to placebo or oral NSAIDs. Key reported outcomes included:
  - Superiority of diclofenac patch and gel over placebo for the treatment of acute pain due to blunt impact injuries or ankle sprains
  - Superiority of diclofenac gel and solution over placebo for pain due to OA of the knee
  - Superiority of diclofenac gel over placebo for pain relief due to epicondylitis and periarthritis, and superiority of diclofenac patch over placebo for epicondylitis
  - Similar efficacy of diclofenac gel and/or diclofenac liquid with DMSO compared to oral NSAIDS for several outcomes including pain relief due to OA of the hand and knee and acute musculoskeletal injury (*Zacher et al 2008*)
- A recent meta-analysis of 9 randomized trials evaluated topical diclofenac therapy (patch, solution, or gel) compared to placebo or vehicle for the treatment of OA. The combined data demonstrated significantly improved pain scores with topical diclofenac compared to the control group (standard mean difference, 0.4; 95% confidence interval [CI], 0.19 to 0.62; p = 0.0003). The data also suggested an improvement in function scores, but further studies on this endpoint would be required to confirm the results (*Deng et al 2016*).
- In a Cochrane review, data from an analysis of 39 double-blind, randomized controlled trials comparing topical NSAIDs to placebo, oral NSAIDs, or other topical treatments demonstrated a small benefit of topical NSAIDs compared to a placebo vehicle in patients with chronic musculoskeletal conditions. Treatment success was achieved in 60% of patients treated with topical diclofenac vs 50% of patients treated with a placebo vehicle. The analysis also demonstrated similar efficacy with topical NSAIDs and oral NSAIDs, with treatment success in in 55% and 54% of patients, respectively (*Derry et al 2016*).
- Another Cochrane review focused on the use of topical NSAIDs for acute musculoskeletal pain, including sprains, strains, contusions, tendinitis, and acute low back pain. A total of 61 double-blind, randomized controlled trials comparing topical NSAIDs to topical placebo or an oral NSAID were included. Overall, topical NSAID formulations provided good levels of pain relief in acute conditions. The majority of the recent data is for topical diclofenac, and this recent data is of higher quality than earlier data. Based on 10 studies, 74% of patients treated with topical diclofenac experienced a successful treatment outcome, compared to 47% with placebo (relative risk [RR], 1.6; 95% CI, 1.5 to 1.7). Data was not sufficient to compare the efficacy of different topical NSAIDs or of oral vs topical formulations of the same NSAID.

- Topical NSAIDs were not associated with an increase in local or systemic adverse events compared to topical placebo. There were fewer systemic adverse events with topical vs oral treatment; however, this was based on limited data (*Derry et al 2015*).

- The clinical effectiveness of diclofenac sodium topical gel (3%) was evaluated in 427 patients, of whom 213 were treated with diclofenac sodium topical gel (3%) and had actinic keratosis lesions. In trials, significantly more patients treated with diclofenac sodium topical gel (3%) had complete clearing of lesions on the scalp (36% vs 13%; p = 0.09), forehead (39% vs 19%; p = 0.001), and face (47% vs 20%; p = 0.002) vs a vehicle alone. However, results were not significantly different for application to the arm/forearm (p = 0.20) or the back of hand (p = 0.36). Overall rates of clearing ranged from 18 to 47% in trials (*Solaraze prescribing information 2016*).
- One Cochrane review evaluated topical, oral, mechanical, and chemical interventions (totaling 24 different treatments) for actinic keratosis across 83 RCTs with 10,036 patients. A total of 60 trials evaluated 18 topical creams or gels. In those trials that evaluated topical diclofenac sodium 3% gel compared to a vehicle, diclofenac was associated with a significant improvement in complete clearance of lesions (32% vs 13%; RR, 2.46; 95% CI, 1.66 to 3.66) in 3 studies with 420 patients. There was also a significant increase in number of patients who withdrew from trials due to adverse events (RR, 3.59; 95% CI, 1.92 to 6.70) in 4 trials with 592 patients (*Gupta et al 2012*).

CLINICAL GUIDELINES

- According to the American College of Rheumatology (ACR) 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in OA of the hand, hip, and knee (updated guidelines are due to be published later in 2019):
  - For the initial management of OA pain of the hand, topical capsaicin, oral or topical NSAIDs, or tramadol may be used. In patients > 75 years of age, topical NSAIDs are preferred over oral formulations.
  - For the initial management of OA pain of the knee, acetaminophen, NSAIDs (oral or topical), tramadol, or intraarticular corticosteroid injections may be used. In patients > 75 years of age, topical NSAIDs are preferred over oral formulations.
  - No one topical NSAID product is recommended over another within the guidelines (*Hochberg et al 2012*).
- According to the American Academy of Orthopedic Surgeons (AAOS) 2013 Guidelines for the treatment of OA of the knee:
  - Acupuncture, lateral wedge insoles, and glucosamine and chondroitin are not recommended.
  - NSAIDs (oral or topical) or tramadol are recommended.
  - There is inconclusive evidence to recommend either for or against the use of acetaminophen, opioids, pain patches, or intraarticular corticosteroids.
  - No one topical NSAID product is recommended over another within the guidelines (*AAOS 2013*).
- According to the Osteoarthritis Research Society International (OARSI) 2014 guidelines for the non-surgical management of knee OA:
  - Appropriate treatments vary based on patient-specific comorbidities and whether patients have knee-only OA or multi-joint OA.
  - Topical NSAIDs are recommended as appropriate in patients with knee-only OA, but their use in patients with multi-joint OA is uncertain and will depend on an assessment of individual patients' risks and benefits.
  - No one topical NSAID product is recommended over another within the guidelines (*McAlindon et al 2014*).
- According to the Veterans Affairs (VA)/Department of Defense (DOD) clinical practice guideline for the non-surgical management of hip and knee OA:
  - In patients with no contraindications to pharmacologic therapy, clinicians should consider acetaminophen or oral NSAIDs as first-line treatment.
  - The recommendation to use topical NSAID therapy as an alternative to oral NSAIDs is supported by evidence from studies that have compared various topical and oral NSAIDs in patients with knee OA. The results have consistently shown that the topical and oral formulations of any given NSAID are similar in terms of improvement in pain and function in patients with knee OA.
  - For topical NSAIDs collectively, the reduction in the incidence of GI events has been shown to be 36% relative to the oral formulations. However, there is insufficient evidence to compare topical and oral NSAIDs in terms of serious GI adverse events (perforation, ulcers or bleeding).
  - The decision to use a topical NSAID (vs oral NSAID with or without proton pump inhibitor) should be based on consideration of patient preference, adverse event potential (including GI adverse events), and resource utilization.

- No studies have directly compared the solution and gel formulations in patients with OA (*VA/DOD 2014*).

- The British Association of Dermatologists (BAD) guidelines for the management of actinic keratoses recommend the following:
  - Treatment needs to address a wide range of variables including the nature of the actinic keratosis, the body site, patient preference, the premorbid state of the patient and previous treatments tried.
  - For mild actinic keratosis, treatment options include no treatment or emollient only.
  - Depending on severity, location, and other factors, topical and oral treatment options include 5-fluorouracil (strength of recommendation A), imiquimod (strength of recommendation A), diclofenac gel (strength of recommendation A), ingenol mebutate (strength of recommendation A), topical retinoids (strength of recommendation B), and systemic therapies (strength of recommendation C).
  - Overall, data with diclofenac gel indicate moderate efficacy with low morbidity in mild actinic keratoses. Treatment was well tolerated and reported adverse effects were mainly pruritus (41% estimated after 30 days' treatment) and rash (40% estimated after 60 days) (*de Berker et al 2017).*

SAFETY SUMMARY

- Diclofenac sodium topical solution, Flector, Licart, Pennsaid, Solaraze, and Voltaren carry a boxed warning for:
  - Cardiovascular thrombotic events
    - NSAIDs cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. These events were also observed in the first 10 to 14 days following coronary artery bypass graft (CABG) surgery via 2 large clinical trials. All agents are contraindicated in the setting of coronary artery bypass graft surgery. This risk may occur early in treatment and may increase with duration of use.
  - GI risk
    - NSAIDs cause an increased risk of serious GI adverse events, including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These reactions can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.
- Despite low systemic blood levels relative to oral NSAIDs, the topical NSAIDs carry a number of warnings and precautions related to potential systemic events, including:
  - Anaphylactic reactions
  - Exacerbation of asthma related to aspirin sensitivity
  - Heart failure and edema; avoid use in patients with severe heart failure
  - Hematologic toxicity
  - Hepatotoxicity
  - Hypertension
  - Premature closure of fetal ductus arteriosus; avoid use in pregnant women starting at 30 weeks gestation
  - Renal toxicity and hyperkalemia; avoid use in patients with advanced renal disease
  - Serious skin reactions
- The most common adverse reactions for the topical NSAIDs are application site reactions, such as dermatitis, pruritus, burning, dryness, and erythema.
- Warnings specific to the topical administration of NSAID products include the following:
  - The potential exists for a small child or pet to suffer serious adverse effects from chewing or ingesting a Flector patch or Licart topical system. Even a used Flector patch or Licart topical system contains a large amount of diclofenac. It is important for patients to store and dispose of the patch or topical system out of the reach of children and pets.
  - Avoid contact of diclofenac with eyes and mucosa.
  - Avoid exposure to natural or artificial sunlight on treated areas because studies in animals indicated topical diclofenac treatment resulted in earlier onset of ultraviolet light-induced skin tumors.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
diclofenac	1.5% solution	Topical	Four times daily	Apply to clean, dry skin; do not

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
sodium topical solution				apply heat or occlusive dressings
diclofenac sodium topical gel	3% gel	Topical	Twice daily	The recommended duration of therapy is from 60 to 90 days. Complete healing or optimal therapeutic effect may not be evident for up to 30 days following the cessation of therapy. Therapy may be interrupted for severe dermal reactions until the condition subsides.
Flector (diclofenac epolamine)	1.3% patch	Topical	Twice daily	Should not be applied to non-intact or damaged skin; should not be worn while bathing or showering
Licart (diclofenac epolamine)	1.3% topical system	Topical	Once daily	Do not apply Licart to nonintact or damaged skin resulting from any etiology (eg, exudative dermatitis, eczema, infected lesion, burns or wounds). Do not wear when bathing or showering.
Pennsaid (diclofenac sodium)	2% solution	Topical	Twice daily	Apply to clean, dry skin; do not apply heat or occlusive dressings
Voltaren (diclofenac sodium)	1% gel	Topical	Four times daily	Use enclosed dosing card to measure dose Apply to clean, dry, intact skin; do not apply heat or occlusive dressings

See the current prescribing information for full details.
Note: The lowest effective dosage of topical product should be used for the shortest duration consistent with individual patient treatment goals.

CONCLUSION

- NSAIDs are commonly used for the treatment of pain due to OA, actinic keratosis, or minor strains, sprains, and contusions. The topical application of NSAIDs may reduce the risk of severe adverse events associated with oral NSAID use. Diclofenac is currently the only NSAID available in topical formulations.
- Flector and Licart are available as 1.3% topical patch and topical system, respectively. These products are indicated for acute pain due to minor strains, sprains, and contusions. Pennsaid is available as a 1.5% topical solution and is indicated for the treatment of signs and symptoms of OA of the knee(s). A higher strength formulation of Pennsaid (2%) has also been made available; it is indicated for the treatment of pain of OA of the knees. Voltaren is available as a 1% topical gel and is indicated for the relief of pain of OA of joints amenable to topical treatment, such as the knees and those of the hands. A higher strength formulation of Solaraze (3%) has also been made available; it is indicated for the treatment of actinic keratoses. Of the topical NSAIDs, Solaraze 3%, Pennsaid 1.5% and Voltaren 1% are available generically. Branded Solaraze 3% and Pennsaid 1.5% solution are no longer marketed.
- The topical products carry many of the same warnings as their respective orally-administered products; however, systemic absorption is generally low, and the most frequent adverse events are administration site reactions.

- Treatment guidelines from BAD recommend topical diclofenac as a viable option for the treatment of actinic keratosis (*de Berker et al 2017*). Guidelines from ACR, AAOS, ORSI, and VA/DOD recommend the use of topical NSAIDs for the treatment of OA (for specific joints), however, they do not recommend one topical NSAID product over another *(Hochberg et al 2012)*.

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Therapeutic Class Overview
Anticonvulsants

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 2018*).
  - 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 2018*).

- 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*).
- 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.
- 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§)	✔ ‖
Hydantoins	
Ethotoin (Peganone)	-
Fosphenytoin (Cerebyx)	✔
Phenytoin (Dilantin§, Phenytek)	✔ ‖
Miscellaneous	
Brivaracetam (Briviact)	-
Cannabidiol (Epidiolex)	-
Carbamazepine (Carbatrol, Epitol**, Equetro, Tegretol§, Tegretol-XR)	✔
Divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)	✔
Eslicarbazepine (Aptiom)	-
Ethosuximide (Zarontin)	✔
Everolimus (Afinitor Disperz)	-
Felbamate (Felbatol)	✔
Gabapentin (Neurontin)	✔

Drug	Generic Availability
Lacosamide (Vimpat)	- #
Lamotrigine (Lamictal, Lamictal ODT, Lamictal XR)	✔
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
# Generic is FDA-approved for at least 1 strength or formulation, but not currently marketed
** 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	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	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
- **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 ≥ 4 years 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 2018*).
- 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 2018*). 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, 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).*

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 2015)

○ 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 (not available in the United States)
        - 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 2018*).
- Common AEs among AEDs include the following (*Schachter 2018*).
  - 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 2018*):
    - suicidal ideation and behavior (AEDs as a class, except everolimus)
    - neutropenia, leukopenia, pancytopenia, agranulocytosis, thrombocytopenia, and/or aplastic anemia (brivaracetam, carbamazepine, ethosuximide, felbamate, lacosamide, levetiracetam, oxcarbazepine, phenytoin, phenobarbital, primidone, stiripentol, valproate, zonisamide)
    - anaphylaxis or angioedema (brivaracetam, levetiracetam, 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 (gabapentin, lacosamide, lamotrigine, oxcarbazepine)
    - severe neuropsychiatric effects/hostility/aggression (perampanel)
    - hyponatremia (eslicarbazepine)
    - 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, and diazepam:
        - 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 is 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 (*Vigabatrin REMS 2017*). 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†, Solfotyn†)	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.
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.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Cannabidiol	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	
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,	tablets, chewable dispersible tablets, orally disintegrating 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

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Lamictal XR)	extended-release tablets			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.
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, delayed-release 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)	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.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
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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Therapeutic Class Overview
Ophthalmic Agents, Intraocular Pressure (IOP)-Modifying

INTRODUCTION

- Glaucoma is an optic neuropathy that causes gradual degeneration of the cells making up the optic nerve. Glaucoma is among the leading causes of blindness worldwide, and in 2020, an estimated 3.2 million people worldwide are anticipated to be blind due to glaucoma (*Flaxman et al 2017*). Open-angle glaucoma is the most common form; other forms include angle-closure, congenital, and secondary glaucoma *(Jacobs 2018[a])*. Patients with open-angle glaucoma initially experience peripheral visual field loss, followed by central field loss, which may progress to irreversible blindness if untreated *(Jacobs 2018[a])*. The exact etiology of open-angle glaucoma is unknown *(Jacobs 2018[a])*. Major risk factors for developing open-angle glaucoma include advanced age, African or Hispanic/Latino descent, elevated intraocular pressure (IOP), family history of glaucoma, low ocular perfusion pressure, type 2 diabetes mellitus, and myopia *(Ellis et al 2000, Girkin et al 2004, Lesk et al 2007, Prum et al 2016)*.
- Elevated IOP is the only major risk factor for glaucoma that is treatable. Available evidence suggests that lowering IOP inhibits or reduces the progression of optic nerve damage *(Jacobs 2018[a])*. Treatment may be initiated in patients with a raised IOP despite having no visual field loss or optic nerve damage *(Jacobs 2018[a])*. An IOP > 22 to 25 mmHg is generally considered to be elevated and would be treated by most clinicians; however, this number varies according to screening methods, risk factors, and disease progression *(Jacobs 2018[b])*. The target IOP should be individualized based on response to therapy and disease progression in order to maintain IOP within a range that is unlikely to adversely affect patients' health-related quality of life *(Jacobs 2018[b])*. The American Academy of Ophthalmology (AAO) recommends an initial target IOP reduction of 25% from pretreated baseline IOP. However, depending on the severity of disease, this target may vary since there is no consensus target IOP below which further visual loss and optic nerve damage will be prevented *(Prum et al 2016)*.
- The current treatment of glaucoma focuses on decreasing IOP by 1 of 3 methods: laser therapy, surgery, or medical intervention *(Prum et al 2016)*. Medical intervention is generally used as initial therapy prior to laser or surgical treatment *(Jacobs 2018[b])*. Medical intervention includes 6 classes of ophthalmic drugs used for the long-term management of glaucoma: alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, miotics or parasympathomimetics, prostaglandin analogues, and rho kinase (ROCK) inhibitors *(Jacobs 2018[b], Micromedex 2019)*. These treatments reduce IOP by either decreasing the amount of aqueous humor produced by the ciliary body or by increasing uveoscleral outflow *(Micromedex 2019, Prum et al 2016)*. Miotics, prostaglandin analogues, and ROCK inhibitors increase aqueous outflow, while beta-blockers and carbonic anhydrase inhibitors decrease aqueous humor production *(Micromedex 2019)*. Alpha-agonists decrease the amount of aqueous humor formed and increase its outflow *(Micromedex 2019, Prum et al 2016)*.
- Guidelines published in 2010 by the American Optometric Association (AOA) do not recommend preferential use of any drug class, although current guidelines by the AAO generally recommend ophthalmic prostaglandin analogues as first-line pharmacologic therapy in patients with elevated IOP *(AOA 2010, Prum et al 2016)*. Combination or monotherapy with agents from an alternative pharmacologic class is recommended for patients who experience intolerable adverse events or who do not achieve the optimal IOP reduction with first-line agents *(Jacobs 2018[b])*.
- Medispan Classes: Beta-Blockers – Ophthalmic; Miotics – Cholinesterase Inhibitors; Miotics – Direct Acting; Ophthalmic Carbonic Anhydrase Inhibitors; Ophthalmic Rho Kinase Inhibitors; Ophthalmic Selective Alpha Adrenergic Agonists; Prostaglandins – Ophthalmic; Alpha Adrenergic Agonist and Carbonic Anhydrase Inhibitor Combination; Beta-blockers – Ophthalmic Combinations
  - Note that bimatoprost is also available as Latisse (bimatoprost ophthalmic solution) 0.03% and indicated to treat hypotrichosis of the eyelashes by increasing their growth including length, thickness and darkness. Latisse is applied nightly directly to the skin of the upper eyelid margin at the base of the eyelashes using an applicator. Latisse is included here for informational purposes since it contains the same ingredient used for the reduction of elevated IOP.

Table 1. Medications Included Within Class Review

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

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

* Does not contain benzalkonium chloride; contains Purite 0.005% as a preservative.
† The Alphagan P 0.15% strength is available generically; however, the 0.1% strength is only available as a branded product.
‡ Branded Alphagan 0.2% is no longer marketed.
§ Apraclonidine 0.5% is available generically. Iopidine 1% strength is only available as a branded product only.
‖. Brand Betoptic is no longer available.
¶ Formulated as timolol hemihydrate.
# Brand Ocupress is no longer available.
** Brand OptiPranolol is no longer available.
†† Allergan discontinued brand Lumigan (bimatoprost) 0.03% in 2012; the discontinuation was not due to safety concerns. Generic bimatoprost 0.03% is available, but generic 0.01% is not.
‡‡ The original benzalkonium chloride-containing travoprost formulation (brand name: Travatan) was approved by the FDA on March 16, 2001; however, Travatan was discontinued by Alcon in June 2010. In March 2013, travoprost with benzalkonium chloride by Par Pharmaceuticals was approved by an abbreviated new drug application (ANDA); however, this generic product was discontinued on September 7, 2016 *(Clinical Pharmacology 2019)*. Only the brand product, Travatan Z, remains available.

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

INDICATIONS

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

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

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

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

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

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

Drug	Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension	Accommodative esotropia	Induction of miosis	Management of acute angle-closure glaucoma	Prevention of postoperative elevated IOP associated with laser surgery	Reduction of elevated IOP
Miotics						
Isopto Carpine (pilocarpine)	✔		✔	✔	✔	
Phospholine Iodide (echothiophate iodide)		✔				✔

(Prescribing information: Isopto Carpine 2010, Phospholine Iodide 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

Drug Class Comparisons

- In a large systematic review of medical therapy compared to various surgical treatments, evidence was insufficient to show that medical, laser, or surgical treatments of open-angle glaucoma prevented progressive visual field loss, optic nerve damage, any kind of patient reported outcomes, or visual impairment. Very little direct comparative evidence is available *(Boland et al 2012, Boland et al 2013)*.
- A network meta-analysis included 114 randomized controlled trials (n = 20,725) evaluating single active ophthalmic agents for the treatment of primary open-angle glaucoma *(Li et al 2016)*. All trials compared active first-line drugs to no treatment or placebo or another single topical agent for glaucoma. The mean reductions in IOP at 3 months (reported as mmHg) were as follows: bimatoprost 5.61 (95% confidence interval [CI], 4.94 to 6.29), latanoprost 4.85 (95% CI, 4.24 to 5.46), travoprost 4.83 (95% CI, 4.12 to 5.54), levobunolol 4.51 (95% CI, 3.85 to 5.24), tafluprost 4.37 (95% CI, 2.94 to 5.83), timolol 3.70 (95% CI, 3.16 to 4.24), brimonidine 3.59 (95% CI, 2.89 to 4.29), carteolol 3.44 (95 % CI, 2.42 to 4.46), levobetaxolol 2.56 (95% CI, 1.52 to 3.62) (currently not available in U.S.), apraclonidine 2.52 (95% CI, 0.94 to 4.11), dorzolamide 2.49 (95% CI, 1.85 to 3.13), brinzolamide 2.42 (95% CI, 1.62 to 3.23), betaxolol 2.24 (95% CI, 1.59 to 2.88), and unoprostone 1.91 (95% CI, 1.15 to 2.67) (currently not available in the U.S.). The authors concluded that the ophthalmic prostaglandin analogues have the greatest effect on IOP.
- A network meta-analysis evaluated 72 randomized controlled trials (n = 19,916) that reported efficacy and safety of medications for the treatment of primary open-angle glaucoma or ocular hypertension over at least 3 months (*Li et al 2018*). A total of 15 treatments were directly compared for change in IOP. Compared to prostaglandin analogues, beta-blockers showed relatively weaker ability to lower IOP, followed by alpha-agonists and carbonic anhydrase inhibitors. The most powerful combinations for dual therapy included prostaglandin analogues with another agent for lowering IOP; combinations with 2 non-prostaglandin analogues had lower efficacy in controlling IOP than monotherapy with a prostaglandin analogue. More severe hyperemia was associated with prostaglandin analogues compared to any other monotherapy, with beta-blockers having the lowest effect on the incidence of hyperemia. Most 2-drug combinations with prostaglandin analogues also led to serious hyperemia with the exception of the combination of prostaglandin analogues and alpha-agonists.
- A network meta-analysis evaluated data from 28 randomized controlled trials in patients with primary open-angle glaucoma or ocular hypertension for peak (n = 6841) and trough (n = 6953) effect of 8 drugs (*van der Valk et al 2009*). The studies assessed bimatoprost, travoprost, latanoprost, brimonidine, timolol, dorzolamide, betaxolol, and brinzolamide. All drugs differed from placebo in reducing IOP. At the peak, the largest reduction in mean IOP was observed with the prostaglandin analogues – bimatoprost, travoprost, and latanoprost. At the trough, the largest reduction in mean IOP was also with the prostaglandin analogues with bimatoprost followed by latanoprost and travoprost.
- The ophthalmic prostaglandin analogues have consistently demonstrated comparable or greater efficacy when compared to dorzolamide/timolol *(Coleman et al 2003, Fechtner et al 2004, Konstas et al 2008, Lesk et al 2008, Ozturk et al 2007, Sharpe et al 2008)*. Bimatoprost 0.03% significantly reduced the mean IOP compared to dorzolamide/timolol in a 6 week crossover trial (p = 0.03) (*Sharpe et al 2008*). In patients uncontrolled on beta-blocker monotherapy, bimatoprost also significantly reduced the mean IOP at 8 AM compared to dorzolamide/timolol in a 3 month study *(Coleman et al 2003)*. However, in a small study of 65 patients with primary open-angle glaucoma or ocular hypertension, the efficacy of lowering IOP was similar between bimatoprost and dorzolamide/timolol over a 6 month study period (p = 0.48) (*Ozturk et al 2007*). A meta-analysis of 14 randomized controlled trials found that latanoprost was associated with greater efficacy in lowering the diurnal mean IOP compared to the combination of dorzolamide/timolol in patients who were inadequately controlled with timolol monotherapy. Latanoprost was as effective as dorzolamide/timolol in patients without prior timolol treatment (*Cheng et al 2009*).
- A meta-analysis of 11 randomized controlled trials with 1256 patients with open angle glaucoma or ocular hypertension showed significant reductions in IOP with latanoprost compared to timolol. Latanoprost resulted in an average 1.6 mmHg further lowering in IOP compared to timolol (p < 0.001) (*Zhang et al 2001*).

Alpha-Agonists

- The comparative clinical trial data regarding the safety and efficacy of the ophthalmic alpha-agonists are limited. When the ophthalmic alpha-agonists are used for the management of postoperative elevations in IOP, both ophthalmic brimonidine and apraclonidine are effective treatment options with similar efficacy *(Barnes et al 1999, Chen et al 2001, Chen et al 2005, Sterk et al 1998)*.

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

Beta-Blockers

- Timolol has been a frequent comparator in numerous clinical trials with agents for the treatment of glaucoma and ocular hypertension. Head-to-head studies in the ophthalmic beta-blocker class involving patients with open-angle glaucoma or ocular hypertension have shown that all treatments are efficacious in decreasing IOP from baseline; however, conflicting results were seen when groups were compared to each other. Studies that reported adverse events categorized all events as mild to moderate; the most frequent adverse events reported included burning or stinging upon instillation and tearing (*Berry et al 1984, Berson et al 1985, Boozman et al 1988, Evans et al 1999, Geyer et al 1998, Halper et al 2002, Krieglstein et al 1987, Miki et al 2004, Mills et al 1986, Mundorf et al 2004, Schenker et al 2000, Shedden et al 2001, Sonty et al 2009, Stewart et al 1986, Stewart et al 2002, Vogel et al 1989, Walters et al 1998, Watson et al 2001*).
- Studies involving patients with open-angle glaucoma or ocular hypertension comparing betaxolol 0.5% to timolol maleate 0.5% have found conflicting results with regard to decrease in IOP from baseline *(Berry et al 1984, Evans et al 1999, Miki et al 2004, Stewart et al 1986, Vogel et al 1989)*.
  - Specifically, 1 study found that betaxolol 0.5% maintained the decrease in IOP that occurred from earlier treatment with timolol maleate 0.5% (*Miki et al 2004*).
  - In another study, betaxolol 0.5% was not found to significantly lower IOP after a washout period following treatment with timolol maleate 0.5% ($p = 0.09$) (*Evans et al 1999*).
  - In a separate study, betaxolol 0.5% was shown to produce a significant decrease in IOP from baseline at weeks 1 through 12 when both the mean IOP value averaged for both eyes and the worse eye were analyzed ($p \leq 0.001$). In this same study, timolol maleate 0.5% was not found to produce a significant decrease in IOP during weeks 1 through 8 when the mean IOP was averaged for both eyes ($p \leq 0.05$), as well as at week 12 when the worse eye was analyzed (p values not reported) *(Vogel et al 1989)*.
  - Additional studies have found that the difference from baseline in IOP was significant for both betaxolol and timolol groups, and there was no difference between groups in the reduction of IOP *(Berry et al 1984, Stewart et al 1986)*.
  - All studies reported mild adverse events including burning or stinging upon instillation and tearing. Although several studies have reported that betaxolol 0.5% was associated with more burning and/or stinging upon instillation than timolol 0.5%, only 1 study found this difference to be statistically significant *(Berry et al 1984, Vogel et al 1989)*.
- One study compared ophthalmic formulations of betaxolol 0.5% to carteolol hydrochloride 1% and timolol 0.25% and found that all 3 treatments significantly decreased IOP from baseline. However, carteolol 1% and timolol 0.25% achieved greater reductions in IOP than betaxolol 0.5% initially and maintained this difference through the follow up period (p values not reported). Eventually, betaxolol 0.5% achieved the same level of IOP after 12 months. In this study, the lowest number of adverse events was reported in the carteolol 1% group, followed by timolol 0.25%, and betaxolol 0.5% groups (p values not reported) *(Watson et al 2001)*.

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

Beta-Blockers compared to other drug classes

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

Carbonic Anhydrase Inhibitors

- Trials support the FDA-approved indications for ophthalmic formulations of brinzolamide and dorzolamide. The trials evaluated the effectiveness of these agents over 1 week to 18 months and demonstrated that carbonic anhydrase inhibitors are a viable treatment option for the management of elevated IOP (*Azopt prescribing information 2015* and *Trusopt prescribing information 2014).* However, the efficacy of ophthalmic carbonic anhydrase inhibitors in reducing vision loss due to glaucoma has not been established in clinical trials (*Jacobs 2018[b]*).

- Single agent ophthalmic carbonic anhydrase inhibitors, brinzolamide and dorzolamide, were evaluated in a multicenter, parallel group study. Reduction in IOP from baseline was statistically significant in each group ($p < 0.001$); however, the changes in IOP from baseline were comparable between the treatment groups (p value not reported) *(Silver 1998).* In a safety trial, significantly fewer patients reported ocular discomfort, specifically burning and stinging, with brinzolamide compared to dorzolamide ($p < 0.001$). Taste disturbance was reported in up to 12% of patients in the brinzolamide group, while only 8.5% of patients in the dorzolamide group experienced this adverse event *(Silver 2000).*
- Similar reductions in IOP were also observed when the agents were used in combination with timolol *(Michaud et al 2001).*

Carbonic Anhydrase Inhibitors compared to other classes

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

Miotics

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

Miotics compared to other drug classes

- For the treatment of glaucoma, ophthalmic pilocarpine has demonstrated comparable efficacy to reduce IOP to ophthalmic carbonic anhydrase inhibitors, beta-blockers, and prostaglandin analogues *(Bayer et al 2004, Diestelhorst et al 2000, Hartenbaum et al 1999).* A trial has evaluated pilocarpine plus a beta-blocker and found that pilocarpine is an effective agent at reducing IOP with comparable efficacy to prostaglandin analogues *(Diestelhorst et al 2000).*
- In a head-to-head trial comparing apraclonidine to pilocarpine administered 15 minutes before ophthalmic surgery, no significant differences were observed between the agents in their ability to reduce IOP after surgery *(Ren et al 1999).*

Prostaglandin Analogues

- Several meta-analyses with the prostaglandin analogues have been published. Ophthalmic bimatoprost appears to have the greatest efficacy in reducing IOP; however, trials have not consistently demonstrated a difference in IOP reduction between travoprost and latanoprost *(Aptel et al 2008, Cheng et al 2008, Honrubia et al 2009, Li et al 2006, Lin et al 2014, Sawada et al 2012)*.
  - A systematic review of 32 randomized controlled trials compared prostaglandin analogues for primary open-angle glaucoma, using timolol as a reference comparator. The analysis found that bimatoprost was most likely to achieve treatment success, defined as a 30% reduction in IOP (relative risk, 1.59; 95% CI, 1.28 to 1.98). The relative risk for treatment success with latanoprost was 1.32 (95% CI, 1.00 to 1.74), for travoprost was 1.33 (95% CI, 1.03 to 1.72), and for tafluprost was 1.1 (95% CI, 0.85 to 1.42). In terms of tolerability, bimatoprost was associated with the highest risk of developing hyperemia, while latanoprost had the lowest risk *(Lin et al 2014)*.
  - The results of a meta-analysis with 8 trials (N = 1610) demonstrated that reductions in IOP were significantly greater with bimatoprost 0.03% compared to travoprost at 8 AM ($p = 0.004$) and 12 noon ($p = 0.02$), but not at 4 PM ($p = 0.19$) or 9 PM ($p = 0.07$). Bimatoprost 0.03% also demonstrated greater reductions in IOP compared to latanoprost at

all time points. There were no statistically significant differences between latanoprost and travoprost at any time point *(Aptel et al 2008)*.
  - Results from a meta-analysis by Li et al did not demonstrate a significant difference in IOP reductions between bimatoprost 0.03% and travoprost (p = 0.8) or latanoprost and travoprost (p = 0.07) in 12 studies with 3048 patents with open-angle glaucoma or ocular hypertension *(Li et al 2006)*.
  - A meta-analysis of 13 trials evaluating adverse events associated with the ophthalmic prostaglandin analogues showed that latanoprost had a lower incidence of conjunctival hyperemia compared to both bimatoprost 0.03% and travoprost (p < 0.0001 for both) *(Honrubia et al 2009)*.
- Tafluprost was FDA approved in 2012, several years after other prostaglandin analogues; therefore, tafluprost data has not been included in many meta-analyses. Available trials suggest that tafluprost may have a similar IOP-lowering effect as latanoprost, but less than that of travoprost *(Konstas et al 2013, Schnober et al 2010, Traverso et al 2010, Uusitalo et al 2010[b])*.
  - One trial found no significant difference in IOP reduction from baseline between tafluprost and travoprost following 6 weeks of treatment (difference, 0.17 mmHg; 95% CI, -1.268 to 1.608; p = 0.811) *(Traverso et al 2010)*.
  - In a 6 week crossover trial, travoprost significantly reduced IOP from baseline compared to tafluprost (7.2 vs 6.6 mmHg; p = 0.01). Adverse events were similar between the treatment groups *(Schnober et al 2010)*.
  - In a randomized, double-blind trial (n = 533), tafluprost demonstrated non-inferiority to latanoprost after 24 months (p < 0.05). No difference in the incidence of adverse events was reported between treatments *(Uusitalo et al 2010[b])*.
  - Results from a similar trial demonstrated a significantly lower incidence of ocular irritation/burning, tearing, itching, dry eye sensation, and conjunctival hyperemia when switched from latanoprost to tafluprost due to ocular intolerance (p < 0.001 for all). Tafluprost also significantly reduced IOP compared to baseline treatment with latanoprost (16.4 vs 16.8 mmHg; p = 0.049) *(Uusitalo et al 2010[a])*.
  - Tafluprost 0.0015% (preservative-free) once daily was compared to timolol 0.5% (preservative-free) twice daily for monotherapy treatment of 643 patients with glaucoma or ocular hypertension in a double-blind, active control, randomized controlled trial. Tafluprost was non-inferior to timolol in IOP reduction at all visits and time points based upon a prespecified non-inferiority margin of 1.5 mmHg. Conjunctival hyperemia was more frequently reported with tafluprost (4.4%) than timolol (1.2%; p = 0.016) *(Chabi et al 2012)*.
- A pooled analysis of 2 similarly designed, Phase 3, double-masked, active control, multicenter, non-inferiority trials (APOLLO and LUNAR; N = 840 total) found that latanoprostene bunod 0.024% administered once daily led to greater reductions in mean IOP when compared to timolol maleate 0.5% administered twice daily at all evaluation time points (IOP was measured at 8 AM, 12 PM, and 4 PM at week 2, week 6, and months 3, 6, 9, and 12) (p < 0.001 for all) (*Medeiros et al 2016, Weinreb et al 2016*, *Weinreb et al 2018*). A greater proportion of patients treated with latanoprostene bunod vs timolol attained a mean IOP ≤ 18 mmHg and an IOP reduction ≥ 25% from baseline (p < 0.001). Patients who switched over from timolol to latanoprostene bunod also experienced additional IOP lowering (p ≤ 0.009). Efficacy was maintained through 12 months of therapy.
- Latanoprostene bunod was also evaluated in a 28 day, Phase 2, randomized, investigator-masked, active control, multicenter, dose-ranging study (n = 413). The objective of the study was to assess the efficacy and safety of latanoprostene bunod vs latanoprost 0.005%, and to determine the optimum drug concentrations of latanoprostene bunod in reducing IOP. Patients were randomized into 1 of 5 treatment groups, including 4 different concentrations of latanoprostene bunod (0.006%, 0.012%, 0.024%, and 0.040%) and latanoprost 0.005% *(Weinreb et al 2015)*.
  - Efficacy for latanoprostene bunod was dose-dependent and reached a plateau at 0.024% to 0.040%. Latanoprostene bunod 0.024% led to significantly greater reductions in mean diurnal IOP compared with latanoprost 0.005% at day 28 (-9 mmHg vs -7.77 mmHg, respectively; p = 0.005).
  - A significantly greater proportion of patients had mean diurnal IOP ≤ 18 mmHg in the latanoprostene bunod 0.024% group at all measurement time points (p ≤ 0.046) compared to the latanoprost group.

ROCK Inhibitor

- The safety and efficacy of netarsudil were evaluated in 3 Phase 3, randomized, double-masked, active control, parallel group, multicenter trials. Patients were randomized to ophthalmic netarsudil or timolol maleate 0.5%. In these trials, the primary efficacy endpoint was the mean IOP, measured at multiple time points (8 AM, 12 PM, and 4 PM at week 2, week 6, and at 3 months). Netarsudil was considered to be non-inferior to timolol if the upper limit of the 2-sided 95% CIs around the difference (netarsudil – timolol) was within 1.5 mmHg at all time points and was within 1.0 mmHg at a majority of the time points *(Rhopressa FDA Medical Review, Rhopressa Prescribing Information 2017, Serle et al 2018).*

- Overall, netarsudil 0.02% dosed once a day demonstrated statistically significant reductions of up to 5 mmHg in IOP from baseline in the clinical trials.
- In ROCKET-1, netarsudil failed in its primary endpoint; netarsudil was not non-inferior to timolol in patients with baseline IOP < 27 mmHg. However, netarsudil was non-inferior to timolol in patients with a baseline IOP < 25 mmHg in a post-hoc analysis. Netarsudil did have an IOP-lowering effect at baseline IOPs ≥ 25 mmHg, but was not statistically non-inferior to timolol when including these patients (*Rhopressa FDA Medical Review, Serle et al 2018)*.
- In ROCKET-2, netarsudil achieved success in its primary endpoint, demonstrating non-inferiority to timolol in patients with a baseline IOP < 25 mmHg (*Rhopressa FDA Medical Review, Serle et al 2018)*.
- In ROCKET-4, netarsudil achieved success in its primary endpoint, demonstrating non-inferiority to timolol in patients with a baseline IOP < 30 mmHg in the per-protocol (PP) population, but this result was not replicated in the intent-to-treat (ITT) population. In a secondary endpoint analysis, non-inferiority of netarsudil to timolol was demonstrated in patients with baseline IOP < 25 mmHg in both PP and ITT populations (*Rhopressa FDA Medical Review).*

- Netarsudil was also evaluated in a 28 day, Phase 2, dose-response, double-masked, active control, parallel group, multicenter trial evaluating netarsudil compared with latanoprost solution, in patients with open-angle glaucoma or ocular hypertension. The study found that netarsudil 0.02% was less effective than latanoprost by approximately 1 mmHg in patients with unmedicated IOPs of 22 to 35 mmHg (differences from latanoprost in the change from baseline mean diurnal IOP for netarsudil 0.02% were 0.9 mmHg at day 14 and 1.2 mmHg at day 28) (*Bacharach et al 2015*).

Fixed Dose Combinations

- Combigan (brimonidine/timolol)
  - The combination of brimonidine/timolol has been shown to be safe and effective in reducing mean IOP from baseline *(Craven et al 2005, Goñi et al 2005, Sherwood et al 2006)*. In clinical trials comparing the fixed combination to the individual components, the reduction of IOP with brimonidine/timolol dosed twice a day was slightly less than that seen with the concomitant administration of timolol maleate ophthalmic solution 0.5% dosed twice a day and brimonidine tartrate ophthalmic solution 0.2% dosed 3 times per day.
  - The combination of brimonidine/timolol was compared to latanoprost 0.005% in 148 patients with glaucoma or ocular hypertension in a randomized, investigator-masked study *(Katz et al 2012)*. The primary outcome, mean diurnal IOP at 12 weeks, did not demonstrate a significant difference between treatment groups at any time point or mean change from baseline at any time point at week 12. The reported mean diurnal IOP at week 12 was 17.8 mmHg for brimonidine/timolol and 17.9 mmHg for latanoprost (p = 0.794). The between-group mean difference in diurnal IOP at week 12 was -0.14 mmHg (95% CI, -1.27 to 0.98), demonstrating non-inferiority of fixed brimonidine/timolol to latanoprost based on predefined criteria. Nine patients in the combination group discontinued the study compared to 2 patients treated with latanoprost, mostly due to adverse effects. Treatment-related adverse events were reported in 16.4% of patients treated with brimonidine/timolol compared to 10.7% treated with latanoprost.
- Simbrinza (brinzolamide/brimonidine)
  - The efficacy and safety of the combination of brinzolamide/brimonidine were established in 2 double-blind, multicenter, randomized controlled trials. The brinzolamide/brimonidine 1%/0.2% combination was shown to significantly lower the mean IOP compared to either monotherapy (eg, brinzolamide and brimonidine) at all time points of the day in 2 identical, 3 month studies. Adverse events were mostly ocular in nature, and the combination group had a higher percentage of patients reporting adverse events compared to each monotherapy group *(Katz et al 2013, Nguyen et al 2013, Realini et al 2013)*.
    - An additional trial comparing the combination to each monotherapy evaluated secondary efficacy endpoints and safety over 6 months. The combination of brinzolamide/brimonidine had higher rates of adverse events and discontinuation rates. The mean IOP reductions after 6 months were similar to those observed after 3 months *(Whitson et al 2013)*. Another trial evaluating twice daily dosing was conducted after the US approval of the thrice daily dosing. Results were similar to those previously observed *(Aung et al 2014)*.
    - In another trial, compared with dorzolamide/timolol, brinzolamide/brimonidine provided significantly greater morning IOP reductions at 12 weeks *(Kozobolis et al 2017)*.

- Cosopt / Cosopt PF (dorzolamide/timolol)
  - In a study comparing dorzolamide/timolol to the individual components, the combination product was more effective at reducing IOP from baseline at all time periods over 3 months of treatment *(Clineschmidt et al 1998)*.

- One open-label study evaluated the safety and efficacy of dorzolamide/timolol preservative-free formulation *(Renieri et al 2010).* Patients receiving the preservative-free product experienced a statistically significant reduction in IOP from baseline (p value not reported). Local tolerability improved in 79.3% of patients who switched to this formulation from other anti-glaucoma therapies. Of note, 84% of patients switching from Cosopt experienced an improvement in tolerability with the preservative-free dorzolamide/timolol formulation.

- Cosopt (dorzolamide/timolol) vs Combigan (brimonidine/timolol)
  - Combined dorzolamide/timolol was compared to brimonidine/timolol, and both demonstrated significant reductions in IOP from baseline. The differences between groups were not found to be significant in any of the 3 studies (p value not reported) *(Gulkilik et al 2011, Martinez et al 2010, Siesky et al 2012)*. However, 2 other studies had conflicting findings. In a crossover study of 20 patients, brimonidine/timolol had significantly lower mean diurnal IOP than dorzolamide/timolol after 6 weeks (16.28 vs 17.23 mmHg, respectively; p = 0.03) *(Garcia-Feijoo et al 2010)*. In a crossover study of 77 patients, dorzolamide/timolol was associated with a greater reduction in the mean 24-hour IOP level from baseline, compared to brimonidine/timolol (mean difference, 0.7 mmHg; p < 0.001). Likewise, the peak and minimum 24-hour IOP levels were significantly lower with dorzolamide/timolol compared to brimonidine/timolol (p = 0.03 and p = 0.012, respectively) *(Konstas et al 2012)*. It is not clear how population size and duration of the crossover studies affected these results.

CLINICAL GUIDELINES

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

- The 2010 AOA guideline (currently under review) provides a summary of the efficacy and adverse effects for the various classes of pharmacologic therapy for open angle glaucoma, but does not specifically recommend 1 class over another. Combination therapy can be considered in patients who have not achieved optimal IOP reduction with a prostaglandin analogue.

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

- Medical therapy is presently the most common initial intervention to lower IOP. There are many drugs available for initial therapy, and medication choice may be influenced by potential cost, side effects, dosing schedules, and the degree of IOP lowering needed.
- Prostaglandin analogues are the most frequently used initial eye drops for lowering IOP. They are the most efficacious drugs for lowering IOP, and they are relatively safe. They are, therefore, often considered as initial medical therapy unless other considerations such as contraindications, cost, side effects, intolerance, or patient refusal preclude their use.
  - Other agents include beta-blockers, alpha-agonists, ROCK inhibitors, topical and oral carbonic anhydrase inhibitors, and parasympathomimetics.
  - The AAO guidelines do not recommend 1 ophthalmic prostaglandin analogue over another.
- If a single medication is effective in lowering IOP but the target IOP is not reached, combination therapy or switching to an alternative therapy may be appropriate. Similarly, if a drug fails to reduce IOP sufficiently despite good adherence to therapy, it can be replaced with an alternative agent until effective medical treatment, whether alone or in combination, is established.

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

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

SAFETY SUMMARY

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

- ROCK inhibitor
  - Bacterial keratitis: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

- Adverse reactions
  - Alpha-Agonists
    - The most common adverse events (5 to 20% of patients) with brimonidine included allergic conjunctivitis, burning sensation, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, hypertension, ocular allergic reaction, oral dryness, and visual disturbance.
    - Common adverse events (5 to 15% of patients) with apraclonidine included ocular discomfort, ocular hyperemia, ocular pruritus, and dry mouth.
    - The alpha-agonists can potentially cause systemic adverse effects including somnolence and dizziness.
  - Beta-blockers
    - Local ocular adverse events reported with ophthalmic beta-blockers include blurred vision and instillation reactions (itching, burning, tearing).
  - Carbonic Anhydrase Inhibitors
    - Adverse events are primarily limited to local ocular effects including blurred vision, conjunctival hyperemia, foreign body sensation, ocular burning/stinging, ocular discharge, ocular pruritus, and pain.
    - Ophthalmic carbonic anhydrase inhibitors also are associated with alterations of taste which have been reported in up to 30% of patients.
  - Miotics
    - Most adverse events reported with the miotics are associated with the eye. Visual blurring, burning, eye irritation, and eye pain have been reported.
  - Prostaglandin Analogues
    - The most frequently reported adverse events associated with these agents are ocular in nature and include burning/stinging, hyperemia, pruritus, iris pigmentation changes, and growth and darkening of eyelashes.
  - ROCK inhibitor
    - The most common adverse event with Rhopressa was conjunctival hyperemia (53%). Other common (approximately 20%) ocular adverse reactions reported were corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5 to 10% of patients.
      - Corneal verticillata occurred in approximately 20% of the patients in controlled clinical studies. The corneal verticillata seen in Rhopressa-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes in patients. Most corneal verticillata resolved upon discontinuation of treatment.

- Drug interactions
  - Alpha-agonists may reduce pulse and blood pressure when administered with antihypertensives. When used with central nervous system depressants, alpha-agonists may have an additive or potentiating effect. Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine; it is not known whether the concurrent use of these agents with ophthalmic alpha-agonists can interfere with their IOP-lowering effect. Concomitant therapy of brimonidine and monoamine oxidase inhibitors may result in hypotension.
  - Drug interactions with ophthalmic beta-blockers include the potentiation of the effects of calcium channel blockers, beta-blockers, clonidine, and quinidine on the cardiovascular system.

DOSING AND ADMINISTRATION

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

Table 3. Dosing and Administration

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

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

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Twice daily; may be used once daily or once every other day Accommodative esotropia: Daily or every other day	Pregnancy: Unclassified†
Isopto Carpine (pilocarpine)	Ophthalmic solution	Ophthalmic	Up to 4 times daily (varies by indication) Induction of miosis prior to procedure and prevention of postoperative elevated IOP: 15 to 60 minutes prior to surgery Management of acute angle-closure glaucoma: Initial: 1 drop up to 3 times over a 30 minute period; Maintenance: 4 times daily Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension: 4 times daily Dosing in children < 2 years of age: 3 times daily; children ≥ 2 years of age should follow adult dosing	Safety and effectiveness in pediatric patients have been established. Pregnancy Category C‡
Prostaglandin Analogues				
latanoprost	Ophthalmic solution Latanoprost 0.005% solution contains benzalkonium chloride 0.02%	Ophthalmic	Daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy Category C‡
Latisse (bimatoprost)	Ophthalmic solution	Ophthalmic	Daily	May be used in patients aged ≥ 5 years for hypotrichosis of the eyelashes. Bimatoprost has been studied in patients aged 5 to 17 years who were post-chemotherapy or had alopecia and ages 15 to 17 years with

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				hypotrichosis not associated with a medical condition. Pregnancy: Unclassified†
Lumigan (bimatoprost) 0.01%; generic bimatoprost 0.03%	Ophthalmic solution	Ophthalmic	Daily	Use in pediatric patients < 16 years of age is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy: Unclassified†
Travatan Z (travoprost)	Ophthalmic solution	Ophthalmic	Daily	Use in pediatric patients < 16 years of age is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy Category C‡
Vyzulta (latanoprostene bunod)	Ophthalmic solution	Ophthalmic	Daily	Use in pediatric patients < 16 years of age is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy: Unclassified†
Xelpros (latanoprost)	Ophthalmic emulsion Xelpros is preservative-free swollen micelle microemulsion.	Ophthalmic	Daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy Category C‡
Zioptan (tafluprost)	Ophthalmic solution	Ophthalmic	Daily	Use in pediatric patients is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy Category C‡
ROCK Inhibitor				
Rhopressa (netarsudil)	Ophthalmic solution	Ophthalmic	Daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
Combinations				
Combigan (brimonidine/timolol)	Ophthalmic solution	Ophthalmic	Twice daily	Safety and effectiveness of Combigan have been established in children ages 2 to 16 years of age; contraindicated in pediatric

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

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

CONCLUSION

- Treatment of glaucoma currently focuses on decreasing IOP by 1 of 3 methods: laser therapy, surgery, or medical intervention *(Prum et al 2016)*. There are no standard guidelines for a target IOP (*Jacobs 2018[b]*). Medical intervention includes 6 classes of ophthalmic agents used for the long-term management of glaucoma: alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, miotics, prostaglandin analogues, and ROCK inhibitors. Guidelines published in 2010 by the AOA (currently under review per the AOA website) do not recommend preferential use of any drug class,

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

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INTRODUCTION

- Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder among children, with an estimated prevalence of up to 10% of school-age children in the United States (U.S.). It is more common in boys than girls and frequently persists into adulthood (*Feldman et al 2014*). Epidemiologic studies of adult ADHD have estimated the current prevalence to be 4.4% in the U.S. (*Bukstein 2018*).
  - In children, this chronic disorder is characterized by symptoms of hyperactivity, impulsivity, and/or inattention. These symptoms affect cognitive, academic, behavioral, emotional, and social functioning (*Krull 2019a*). Common comorbid psychiatric disorders include oppositional defiant disorder, conduct disorder, depression, anxiety disorder, and learning disabilities (*Krull 2019b*). Approximately 20% of children with ADHD develop chronic tic disorders and approximately 50% of children with chronic tics or Tourette syndrome have comorbid ADHD (*Krull 2018*).
  - ADHD in adults is characterized by symptoms of inattention, impulsivity, and restlessness. Impairment in executive function and emotional dysregulation frequently occur. Common comorbid psychiatric disorders include mood and anxiety disorders, substance use disorder, and intermittent explosive disorder (*Bukstein 2018*).
- For children < 17 years of age, the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) diagnosis of ADHD requires ≥ 6 symptoms of hyperactivity and impulsivity or ≥ 6 symptoms of inattention. For adolescents ≥ 17 years of age and adults, ≥ 5 symptoms of hyperactivity and impulsivity or ≥ 5 symptoms of inattention are required.
  - The symptoms of hyperactivity/impulsivity or inattention must occur often; be present in more than 1 setting; persist for at least 6 months; be present before the age of 12 years; impair function in academic, social, or occupational activities; and be excessive for the developmental level of the child.
  - Other physical, situational, or mental health conditions that could account for the symptoms must be excluded.
- Treatment of ADHD may involve behavioral/psychologic interventions, medication, and/or educational interventions, alone or in combination (*Krull 2019c*).
  - For preschool children (age 4 through 5 years), behavioral therapy is considered the first-line treatment; when medication is necessary, methylphenidate is generally recommended.
  - For children and adolescents with moderate to severe ADHD, medication and behavioral therapy are recommended. In general, stimulants are the first-line agents; however, non-stimulant medications may be more appropriate for certain children.
    - About 30% of patients do not respond to or may not tolerate the initial stimulant treatment. At least one-half of children who do not respond to one type of stimulant will respond to the other. If there is still no improvement, consideration should be given to switching to or adding a non-stimulant ADHD medication (*Pharmacist's Letter 2015, Krull 2019d*).
- Multiple agents are currently approved by the Food and Drug Administration (FDA) for the treatment of ADHD. They include central nervous system (CNS) stimulants (amphetamine- and methylphenidate-based formulations), as well as non-stimulants: a selective norepinephrine reuptake inhibitor (SNRI), atomoxetine, and 2 alpha$_2$-adrenergic agonists, clonidine extended-release (ER) and guanfacine ER.
  - Due to the potential for abuse, the stimulant agents are classified as Schedule II controlled substances.
  - Several stimulants are also approved for the treatment of narcolepsy and exogenous obesity; the use of stimulants for the treatment of obesity will not be covered in this review. Lisdexamfetamine dimesylate is the only FDA-approved drug for the treatment of binge eating disorder (BED).
- In August of 2018, an extended-release methylphenidate capsule (Jornay PM) was approved by the FDA. In addition, an orally disintegrating amphetamine sulfate tablet (Evekeo ODT) was also approved in late January 2019. Launch dates have not yet been announced for either product.
- Medispan Classes: ADHD Agents – Amphetamines, Dexmethylphenidate, Methylphenidate, Selective Alpha Adrenergic Agonists, Selective Norepinephrine Reuptake Inhibitor

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Stimulants	
Evekeo (amphetamine sulfate)	✔
Evekeo ODT (amphetamine sulfate)†	-
Adderall (mixed amphetamine salts)	✔
Focalin (dexmethylphenidate hydrochloride [HCl])	✔
ProCentra (dextroamphetamine sulfate)	✔
Zenzedi (dextroamphetamine sulfate)	✔
Desoxyn (methamphetamine HCl)	✔
methylphenidate HCl chewable tablets	✔
Methylin Oral Solution (methylphenidate HCl)	✔
Ritalin (methylphenidate HCl)	✔
Dexedrine Spansule (dextroamphetamine sulfate sustained-release)	✔
Adzenys ER (amphetamine ER)	-
Adzenys XR-ODT (amphetamine ER)	-
Dyanavel XR (amphetamine ER)	-
Adderall XR (mixed amphetamine salts ER)	✔
Mydayis (mixed amphetamine salts ER)	-
Focalin XR (dexmethylphenidate HCl ER)	✔
Vyvanse (lisdexamfetamine dimesylate)	-
Aptensio XR (methylphenidate HCl ER)	-
Concerta (methylphenidate HCl ER)	✔
Cotempla XR-ODT (methylphenidate ER)	-
Jornay PM (methylphenidate HCl ER)†	-
methylphenidate HCl ER (CD)	✔
methylphenidate HCl ER	✔
QuilliChew ER (methylphenidate HCl ER)	-
Quillivant XR (methylphenidate HCl ER)	-
Ritalin LA (methylphenidate HCl ER)	✔
Daytrana (methylphenidate transdermal system)	-
Non-stimulants	
Strattera (atomoxetine HCl)	✔
Kapvay (clonidine HCl ER)	✔
Intuniv (guanfacine HCl ER)	✔

†An extended-release methylphenidate capsule (Jornay PM) and an orally disintegrating amphetamine sulfate tablet (Evekeo ODT) have both been recently approved by the FDA; however, launch dates have not yet been announced for either product.

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Evekeo (amphetamine sulfate)	Evekeo ODT (amphetamine sulfate)	Adzenys ER, Adzenys XR-ODT, Dyanavel XR (amphetamine ER)	Adderall (mixed amphetamine salts)	Adderall XR, Mydayis (mixed amphetamine salts ER)	Strattera (atomoxetine HCl)	Kapvay (clonidine HCl ER)	Focalin (dexmethylphenidate IR); Focalin XR (dexmethylphenidate ER)	ProCentra, Zenzedi (dextroamphetamine sulfate IR); Dexedrine Spansule (dextroamphetamine sulfate SR)	Intuniv (guanfacine HCl ER)	Vyvanse (lisdexamfetamine dimesylate)	Desoxyn (methamphetamine HCl)	Methylin Oral Solution, Ritalin methylphenidate HCl IR); methylphenidate HCl chewable tablets; Metadate ER (methylphenidate ER)	Aptensio XR, Concerta , Cotempla XR-ODT, Daytrana, methylphenidate ER (CD), Jornay PM, QuilliChew ER, Quillivant XR, Ritalin LA (methylphenidate ER)
ADHD*		✓	✓	✓	✓	✓		✓			✓			✓
ADHD, as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, and social) for a stabilizing effect in pediatric patients with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal electroencephalogram (EEG) may or may not be present, and a diagnosis of CNS dysfunction may or may not be warranted.*	✓								✓			✓	✓	
Treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications							✓			✓				
Narcolepsy**	✓			✓					✓				✓	
Exogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction for patients refractory to alternative therapy	✓											✓		

(eg, repeated diets, group programs, and other drugs).†														
Moderate to severe BED in adults											✓			

(*Prescribing Information*: *Adderall 2017*, *Adderall XR 2018*, *Adzenys ER 2017*, *Adzenys XR-ODT 2018*, *Aptensio XR 2017*, *Concerta 2017*, *Cotempla 2017*, *Daytrana 2017, Desoxyn 2017, Dexedrine Spansule 2019*, *Dyanavel XR 2019*, *Evekeo 2016*, *Evekeo ODT 2019*, *Focalin 2019*, *Focalin XR 2019*, *Intuniv 2018, Jornay PM 2018, Kapvay 2018, Mydayis 2017, Methylin Oral Solution 2017, methylphenidate chewable tablets 2018, methylphenidate ER 2017, methylphenidate ER (CD) 2018, ProCentra 2017*, *QuilliChew ER 2018*, *Quillivant XR 2018*, *Ritalin 2019*, *Ritalin LA 2019*, *Strattera 2017*, *Vyvanse 2018, Zenzedi 2017*)

* Adderall, Evekeo, ProCentra, and Zenzedi are approved for use in children 3 years of age and older. Daytrana, Desoxyn, Dexedrine Spansule, Dyanavel XR, Intuniv, and Kapvay are approved for use in children 6 years of age and older. Adderall XR, Adzenys ER, Adzenys XR-ODT, Aptensio XR, Focalin, Focalin XR, Jornay PM, methylphenidate ER (CD), Methylphenidate ER, Methylin Oral Solution, methylphenidate chewable tablets, QuilliChew ER, Quillivant XR, Ritalin, Ritalin LA, Strattera, and Vyvanse are approved for use in patients 6 years of age and older. Cotempla XR-ODT and Evekeo ODT are approved for use in pediatric patients 6 to 17 years of age. Concerta is approved for use in children 6 years of age and older, adolescents, and adults up to 65 years of age. Mydayis is approved for use in patients 13 years of age and older.
**These drugs are approved for use in patients 6 years of age and older.
†These drugs are not recommended for use in children under 12 years of age for treatment of exogenous obesity. The limited usefulness of these products should be weighed against possible risks inherent in use of the drugs.

- Limitation of use:
  - Lisdexamfetamine: Lisdexamfetamine is not indicated or recommended for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular (CV) adverse events (AEs). The safety and effectiveness of this drug for the treatment of obesity have not been established.
  - Mydayis: Pediatric patients 12 years and younger experienced higher plasma exposure than patients 13 years and older at the same dose and experienced higher rates of AEs, mainly insomnia and decreased appetite.

- 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

- Randomized trials, systematic reviews, and meta-analyses have found stimulants, atomoxetine, and alpha$_2$-adrenergic agonists to be more efficacious than placebo in reducing the core symptoms of ADHD in children and adolescents.
  - Adzenys ER, an amphetamine ER oral suspension, was approved under the 505(b)(2) regulatory pathway and was found to be bioequivalent to Adderall XR. No clinical efficacy studies were conducted.
  - Evekeo ODT, an orally disintegrating amphetamine tablet, was approved under the 505(b)(2) regulatory pathway. The safety and effectiveness of Evekeo ODT for the treatment of ADHD was established based on an adequate and well-controlled study of Evekeo (amphetamine sulfate).
  - Cotempla XR-ODT, a new methylphenidate ER orally disintegrating tablet formulation, was approved based on a randomized, double-blind (DB), multi-center (MC), placebo-controlled (PC) laboratory classroom study (*Childress et al 2017*) (N = 87) which found that the average Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP)-Combined score was significantly better for Cotempla XR-ODT than for placebo (least squares [LS] mean 14.3 [95% CI, 12.2 to 16.4] vs 25.3 [9% CI, 23.0 to 27.6], respectively, $p < 0.0001$).
  - Jornay PM, an ER methylphenidate capsule formulation, was approved based on the results of 2 clinical studies conducted in patients 6 to 12 years of age with ADHD:
    - The first study was a 6-week open-label (OL) dose-optimization study, followed by a 1-week DB, PC withdrawal phase where patients were randomized to continue treatment with Jornay PM or switch to placebo (*Jornay PM Prescribing Information 2018*). The study, which was conducted in an analog classroom setting and included 117 children aged 6 to 12 years, found that Jornay PM was associated with a significant reduction in the SKAMP symptom score over a 12-hour period (difference in least squares [LS] mean -5.9; 95% CI, -9.1 to -2.7).

- A randomized, DB, MC, PC, parallel group, forced-dose titration trial conducted over 3 weeks in 161 children 6 to 12 years of age with ADHD (*Pliszka et al 2017*). The study found that 40 to 80 mg/day of Jornay PM achieved significant improvements vs placebo in ADHD symptoms (LS mean ADHD rating scale-IV 24.1 vs 31.2; p = 0.002) at 3 weeks. Significant improvements were also seen vs placebo in key secondary outcomes including at-home early morning and late afternoon/evening functional impairment at 3 weeks. The most commonly reported treatment-emergent AEs were insomnia and decreased appetite.

- Mydayis, a new mixed amphetamine salts product, was approved for the treatment of ADHD based on the results of 5 MC, DB, PC, randomized controlled trials (RCTs): 3 in adults and 2 in pediatric patients 13 to 17 years of age. The studies found that Mydayis demonstrated a statistically significant treatment effect compared with placebo on various ADHD outcomes measures (eg, ADHD-Rating Scale [ADHD-RS] score, Permanent Product Measure of Performance [PERMP] score) (*Mydayis Prescribing Information 2017, Weisler et al 2017*) (see results below in Table 3 below).

Table 3. Summary of Primary Efficacy Results for Mydayis

Study Number (Age range)	Primary Endpoint	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline	Placebo-subtracted Difference (95% CI)
Adult Studies					
Study 1 (18 to 55 years)	ADHD-RS	Mydayis 12.5 mg/day§ Mydayis 37.5 mg/day§ Placebo	39.8 (6.38) 39.9 (7.07) 40.5 (6.52)	-18.5 -23.8 -10.4	-8.1 (-11.7 to -4.4) -13.4 (-17.1 to -9.7)
Study 2 (18 to 55 years)	Average PERMP	Mydayis 50 mg/day§ Placebo	239.2 (75.6)† 249.6 (76.7)†	293.23* 274.85*	18.38 (11.28 to 25.47)
Study 3 (18 to 55 years)	Average PERMP	Mydayis 25 mg/day§ Placebo	217.5 (59.6)† 226.9 (61.7)†	267.96* 248.67*	19.29 (10.95 to 27.63)
Pediatric Studies					
Study 4 (13 to 17 years)‡	ADHD-RS-IV	Mydayis 12.5 to 25 mg/day§ Placebo	36.7 (6.15) 38.3 (6.67)	-20.3 -11.6	-8.7 (-12.6 to -4.8)
Study 5 (13 to 17 years)	Average PERMP	Mydayis 25 mg/day§ Placebo	214.5 (87.8)† 228.7 (101)†	272.67* 231.41*	41.26 (32.24 to 50.29)

SD= standard deviation; LS = least squares; CI = confidence interval
†Pre-dose PERMP total score
*LS mean for PERMP is post-dose average score over all sessions of the treatment day, rather than change from baseline
‡Results are for a subgroup of study 4 and not the total population
§Doses statistically significant for placebo

- A systematic (Cochrane) review of 185 RCTs (*Storebø et al 2015*) (N = 12,245) in children and adolescents with ADHD found that methylphenidate may improve teacher-rated ADHD symptoms, teacher-reported general behavior, and parent-reported quality of life (QOL) vs placebo. However, the evidence was of low quality.
- An RCT called the Preschool ADHD Treatment Study (PATS) (*Greenhill et al 2006*) evaluated the efficacy of methylphenidate immediate-release (IR) in 303 preschool children with ADHD and found that it demonstrated significant reductions on ADHD symptom scales; however, the effect sizes (0.4 to 0.8) were smaller than those generally reported for school-age children.
- A systematic (Cochrane) review of 23 PC, RCTs (*Punja et al 2016*) (N = 2675) found that amphetamines were effective at improving the core symptoms of ADHD, but they were also associated with a higher risk of AEs compared to placebo. There was no evidence that one kind of amphetamine was better than another and there was no difference between short-acting and long-acting formulations.
- A meta-analysis of 25 DB, PC, RCTs (*Schwartz et al 2014*) (N = 3928) in children and adolescents with ADHD found atomoxetine to be superior to placebo for overall ADHD symptoms, with a medium effect size (-0.64).

- A meta-analysis of 12 RCTs (*Hirota et al 2014*) (N = 2276) in pediatric patients with ADHD found that alpha$_2$-adrenergic agonists were significantly superior to placebo for overall ADHD symptoms both as monotherapy and, to a lesser extent, as augmentation therapy to stimulants.
  - Meta-analytic results failed to demonstrate a significant difference in efficacy between alpha$_2$-adrenergic agonists. In sub-analyses of individual formulations, the ER formulations separated robustly from placebo whereas the IR formulations did not separate from placebo.
- A systematic review of 16 RCTs and 1 meta-analysis (*Chan et al 2016*) (N = 2668) found evidence supporting the use of methylphenidate ER and amphetamine ER formulations, atomoxetine, and guanfacine ER for the treatment of ADHD in adolescents. For the primary outcome measure of mean change in ADHD-RS total symptom score, both stimulant and non-stimulant medications led to clinically significant reductions of 14.93 to 24.60 points.

- For the treatment of ADHD in children and adolescents, stimulants typically have a slightly larger treatment effect size (standardized mean difference [SMD]) than non-stimulants (approximately 1.0 vs approximately 0.7 for both atomoxetine and alpha$_2$-adrenergic agonists). However, there is insufficient evidence to definitively conclude that one stimulant is more efficacious than another (*Krull 2019d*, *AAP 2011).*
  - An Agency for Healthcare Research and Quality (AHRQ) review of 78 studies (*Jadad et al 1999*) evaluating the efficacy of various interventions for the treatment of ADHD in children and adults found few, if any, differences between methylphenidate and dextroamphetamine.
  - A meta-analysis of 23 DB, PC trials (*Faraone 2010a*) comparing the efficacy of methylphenidate and amphetamine formulations found that amphetamine products may be moderately more efficacious than methylphenidate products.
  - A DB, PC, RCT (*Newcorn et al 2008*) (N = 516) comparing the efficacy of atomoxetine vs methylphenidate ER (osmotic-release formulation) in patients 6 to 16 years of age with ADHD found that both drugs were superior to placebo in terms of response rate, and that methylphenidate ER was superior to atomoxetine.
  - A meta-analysis of 29 DB, PC trials (*Faraone et al 2006*) evaluated the efficacy of various medications (methylphenidate and amphetamine compounds, atomoxetine, pemoline [no longer available in the U.S.], bupropion, and modafinil) for the treatment of ADHD. The effect sizes for non-stimulant medications were significantly less than those for IR stimulants or long-acting stimulants. The 2 classes of stimulant medications did not differ significantly from one another.
  - A meta-analysis of 28 DB, PC, RCTs (*Stuhec et al 2015*) (N = 4699) compared the efficacy of various medications for the treatment of ADHD in children and adolescents. Efficacy in reducing ADHD symptoms compared to placebo was small for bupropion (SMD = -0.32; 95% confidence interval [CI], -0.69 to 0.05), modest for atomoxetine (SMD = -0.68; 95% CI, -0.76 to -0.59) and methylphenidate (SMD = -0.75; 95% CI, -0.98 to -0.52), and highest for lisdexamfetamine (SMD = -1.28; 95% CI, -1.84 to -0.71).
  - A network meta-analysis and mixed treatment comparison of 36 RCTs (*Joseph et al 2017*) evaluating the comparative efficacy and safety of ADHD pharmacotherapies in children and adolescents found that lisdexamfetamine had greater efficacy than guanfacine ER, atomoxetine, and methylphenidate ER. Guanfacine ER had a high posterior probability of being more efficacious than atomoxetine, but their credible intervals overlapped.
  - A network meta-analysis of 48 DB, RCTs (*Padilha et al 2018*) compared the safety and efficacy of various ADHD medications in children and adolescents. Of the 12 trials that were evaluated for efficacy, analysis was performed using the Clinical Global Impression Improvement (CGI-I) scale for 3 drugs, which showed that methylphenidate was more effective than atomoxetine (MD, 3.15; 95% CI, 0.75 to 13.71) and guanfacine (MD, 1.92; 95% CI, 0.64 to 5.94). Thirty-three trials were evaluated for safety. Ranking of AEs showed that lisdexamfetamine was more likely to cause sleep disorders, loss of appetite, and behavior problems compared to other treatments.
- Alpha$_2$-adrenergic agonists have been associated with improvements in ADHD symptoms and comorbid tics.
  - A meta-analysis of 9 DB, PC, RCTs (*Bloch et al 2009*) (N = 477) was conducted to determine the relative efficacy of different medications in treating ADHD and tic symptoms in children with both Tourette syndrome and ADHD.
  - Methylphenidate seemed to offer the greatest improvement of ADHD symptoms and did not seem to worsen tic symptoms.
  - Alpha$_2$-adrenergic agonists offered the best combined improvement in both tic and ADHD symptoms.
  - Atomoxetine significantly improved both tic and ADHD severity compared to placebo.
  - One small study found that tic severity was significantly increased with higher doses of dextroamphetamine treatment.
  - A Cochrane review of 8 RCTs (*Osland et al 2018*) including 510 children with both ADHD and a chronic tic disorder found low-quality evidence for improvement of ADHD symptoms with methylphenidate, atomoxetine, and clonidine, and very low-quality evidence for desipramine, dextroamphetamine, guanfacine, and deprenyl. Tic symptoms improved with guanfacine, desipramine, methylphenidate, clonidine, and a combination of methylphenidate and

clonidine. The authors noted that in 1 study with a short duration (3 weeks), high doses of dextroamphetamine worsened tics.

- There are limited efficacy data regarding the treatment of ADHD in the adult population. Comparison of effect sizes in clinical trials suggests that stimulant medications are more efficacious in adult ADHD than non-stimulants.
  - In a meta-analysis of 12 clinical trials (*Cunill et al 2009*) (N = 3375) comparing atomoxetine with placebo in adult ADHD, atomoxetine led to a modestly greater reduction in ADHD symptom severity, but was associated with higher all-cause discontinuation.
  - A meta-analysis (*Faraone 2010b*) of 19 randomized trials of 13 medications for adult ADHD found a greater average effect size for reduction in ADHD symptoms in patients receiving short- and long-acting stimulant medications (vs placebo; 0.86 and 0.73, respectively) compared with patients receiving non-stimulant medication (vs placebo; 0.39). No difference in effect size was found between short- and long-acting stimulants.
  - A meta-analysis of 20 randomized trials (*Stuhec et al 2018*) compared the efficacy, acceptability, and tolerability of lisdexamfetamine, mixed amphetamine salts, methylphenidate, and modafinil in the treatment of ADHD in adults. The highest effect size in reducing ADHD symptoms was found with lisdexamfetamine (SMD -0.89; 95% CI, -1.09 to -0.70), while moderate reductions in symptoms were seen with mixed amphetamine salts (SMD -0.64; 95% CI, -0.83 to -0.45) and methylphenidate (SMD -0.50; 95% CI, -0.58 to -0.41). No efficacy was reported with modafinil.
  - A Cochrane review of 19 studies (*Castells et al 2018*, N = 2521) comparing dextroamphetamine, lisdexamfetamine, and mixed amphetamine salts for the treatment of ADHD in adults found that overall, amphetamines reduced the patient- and clinician-rated severity of ADHD symptoms compared to placebo; however, they did not improve retention in treatment. Amphetamines were associated with an increased proportion of patients who withdrew because of AEs. When comparing different types of amphetamines, lisdexamfetamine and mixed amphetamine salts reduced the severity of ADHD symptoms as rated by clinicians, but dextroamphetamine did not. No differences in any outcome were found when comparing immediate- and sustained-release formulations.
  - Another meta-analysis (*Cortese et al 2018*) of 133 RCTs comparing the use of amphetamines, atomoxetine, bupropion, clonidine, guanfacine, methylphenidate, and modafinil for the treatment of ADHD found that all drugs were superior to placebo for ADHD core symptoms as rated by clinicians in children and adolescents, and all drugs except for modafinil were more efficacious than placebo in adults.
    - When comparing the various drugs based on teachers' ratings in children and adolescents, only methylphenidate and modafinil were found to be more efficacious than placebo.
    - In head-to-head comparisons, differences in efficacy based on clinicians' ratings were found, favoring amphetamines over modafinil (SMD -0.39; 95% CI -0.67 to -0.12), atomoxetine (SMD -0.46; 95% CI, -0.65 to -0.27), and methylphenidate (SMD-0.24; 95% CI, -0.44 to -0.05) in children and adolescents. Efficacy results based on clinicians' ratings were similar for adults, and favored amphetamines over modafinil (SMD -0.94; 95% CI -1.43 to -0.46), atomoxetine (SMD -0.34; 95% CI, -0.58 to -0.10), and methylphenidate (SMD-0.29; 95% CI, -0.54 to -0.05).
- Lisdexamfetamine dimesylate has demonstrated efficacy in the treatment of BED. Direct comparison trials between lisdexamfetamine and other drugs used off-label to treat BED are lacking.
  - In 2 Phase 3, 12-week, randomized, DB, PC trials (*McElroy et al 2016*) (N = 773) in patients with moderate to severe BED, lisdexamfetamine-treated patients had a statistically significantly greater reduction from baseline in mean number of binge days per week at week 12 vs placebo (treatment difference in study 1: -1.35 [-1.70 to -1.01]; study 2: -1.66 [-2.04 to -1.28]; both $p < 0.001$).
    - A 12-month, OL extension study (*Gasior et al 2017*) (N = 599) in adults with BED found that the long-term safety and tolerability of lisdexamfetamine were generally consistent with the safety profile observed in 3 previous short-term trials in BED as well as its established profile for ADHD. Common treatment-emergent AEs included dry mouth, headache, insomnia, and upper respiratory tract infection. Weight loss and increases in blood pressure and pulse rate were also observed.
  - In a phase 3, DB, randomized, PC, withdrawal study (*Hudson et al 2017*) (N = 418) in adults with moderate to severe BED, responders to lisdexamfetamine during a 12-week OL phase were randomized to placebo or continued lisdexamfetamine during a 26-week, DB phase. The percentage of patients meeting relapse criteria was 3.7% with lisdexamfetamine vs 32.1% with placebo; time to relapse statistically favored lisdexamfetamine ($p < 0.001$). The hazard ratio (HR) was 0.09 (95% CI, 0.04 to 0.23).
  - A systematic review and meta-analysis of 9 waitlist-controlled psychological trials and 25 PC trials evaluating pharmacologic (n = 19) or combination (n = 6) treatment for BED (*Brownley et al 2016*) found that therapist-led CBT, lisdexamfetamine, and second-generation antidepressants (SGAs) increased binge-eating abstinence (relative risk

[RR], 4.95 [95% CI, 3.06 to 8.00], 2.61 [CI, 2.04 to 3.33], and 1.67 [CI, 1.24 to 2.26], respectively), while lisdexamfetamine and SGAs decreased binge-eating frequency (mean difference in days/week, -1.35 [CI, -1.77 to -0.93] and -0.67 [CI, -1.26 to -0.09], respectively). Topiramate and other forms of CBT also increased abstinence and reduced binge-eating frequency.

- A 2018 systematic review and meta-analysis of 45 RCTs (*Ghaderi et al 2018*) compared various psychological, pharmacological, and combined treatments for BED, and found moderate support for the efficacy of cognitive behavioral therapy (CBT) and CBT-guided self-help (moderate quality of evidence), and low quality evidence to support interpersonal psychotherapy, selective serotonin reuptake inhibitors, and lisdexamfetamine for the cessation of or reduction in the frequency of binge eating. Only lisdexamfetamine showed a modest effect on weight loss (SMD for body mass index -5.23; 95% CI, -6.52 to -3.94).

CLINICAL GUIDELINES

ADHD

- Several clinical guidelines have provided recommendations on the treatment of ADHD in children and adolescents.
  - According to the American Academy of Pediatrics (AAP) guidelines (2011), the evidence is particularly strong for stimulant medications, and sufficient but less strong for atomoxetine, guanfacine ER, and clonidine ER (in that order). Guanfacine ER and clonidine ER have evidence to support their use as adjunctive therapy with stimulant medications. Methylphenidate is recommended for preschool-aged children who have had an inadequate response to behavioral interventions.
  - The American Academy of Child and Adolescent Psychiatry (AACAP) guidelines (*Pliszka et al 2007*) state that both methylphenidate and amphetamines are equally efficacious in the treatment of ADHD. The long-acting formulations are equally efficacious as the IR formulations and may be used as initial therapy. Short-acting stimulants are often used as initial treatment in small children (< 16 kg in weight), for whom there are no long-acting preparations in a sufficiently low dose. Some patients may respond similarly to different stimulant classes, whereas other patients may respond preferentially to only 1 of the classes of stimulants. Although stimulants have demonstrated greater efficacy compared to atomoxetine in published studies, atomoxetine may be used first-line in patients with an active substance abuse problem, comorbid anxiety or tics, and in those who experience severe AEs with stimulants.
  - The Medical Letter (2015) recommends that treatment of ADHD in school-age children or adults should begin with an oral stimulant, either a methylphenidate- or amphetamine-based formulation. Mixing short- and long-acting stimulants can be helpful to achieve an immediate effect for early-morning school classes or for reducing rebound irritability or overactivity, especially in the evening. An ER alpha$_2$-adrenergic agonist may be helpful as adjunctive therapy with a stimulant in patients who cannot tolerate usual doses of the stimulant, particularly those with tics. Atomoxetine is an alternative for patients who cannot tolerate stimulants or for whom treatment with a controlled substance is undesirable.
  - The AACAP practice parameter for the treatment of children and adolescents with tic disorders (2013) states that alpha$_2$-adrenergic agonists have demonstrated an effect size of 0.5 for the amelioration of tics and may be preferred by some prescribers over antipsychotics due to their relatively favorable AE profile.

Narcolepsy

- The American Academy of Sleep Medicine (AASM) practice parameters (*Morgenthaler et al 2007*) recommend various drugs for the treatment of daytime sleepiness due to narcolepsy including modafinil (high degree of clinical certainty); amphetamine, methamphetamine, dextroamphetamine, and methylphenidate (moderate degree of clinical certainty); sodium oxybate (high degree of clinical certainty); and selegiline (uncertain clinical certainty).

BED

- According the American Psychiatric Association (APA) practice guidelines on eating disorders (*Yager et al 2006*, *Yager et al 2012* [guideline watch update]), treatment of BED may include the following:
  - Nutritional rehabilitation and counseling
  - Psychosocial treatment
    - CBT, behavior therapy, dialectical behavior therapy (DBT), and interpersonal therapy (IPT) have all been associated with binge frequency reduction rates of 67% or more and significant abstinence rates during active treatment.
    - Self-help programs using self-guided, professionally designed manuals have been effective in reducing the symptoms of BED in the short-run for some patients and may have long-term benefit.
  - Medications

- Antidepressant treatment is associated with short-term reductions in binge-eating but generally does not result in substantial weight loss. Selective serotonin reuptake inhibitors (SSRIs) have the fewest difficulties with AEs and the most evidence for efficacy when used at the high end of the recommended dose range.
- Topiramate can reduce bingeing and decrease weight, but its use may be limited by AEs.

o Combination psychotherapy and pharmacotherapy
- For most patients, adding antidepressant therapy to a behavioral weight control and/or CBT regimen does not have a significant effect on binge suppression.
- Although limited evidence is available, combined treatment is frequently used in clinical practice.

- The American Association of Clinical Endocrinologists and the American College of Endocrinology (AACE/ACE) guidelines for medical care of patients with obesity (*Garvey et al 2016*) recommend the following for patients with overweight or obesity who have BED:
  - o Patients should be treated with a structured behavioral/lifestyle program, combined with CBT or other psychological interventions
  - o Treatment with orlistat or approved medications containing topiramate or bupropion may be considered in conjunction with structured lifestyle therapy, CBT, and/or psychological interventions
- The Task Force on Eating Disorders of the World Federation of Societies of Biological Psychiatry (*Aigner et al 2011*) concluded that for the treatment of BED, grade A evidence supports the use of imipramine (moderate risk-benefit ratio), sertraline (good risk-benefit ratio), citalopram/escitalopram (good risk-benefit ratio), orlistat (low to moderate risk-benefit ratio), and topiramate (moderate risk-benefit ratio). Atomoxetine has grade B evidence supporting its use.

SAFETY SUMMARY

- Due to the potential for abuse, the stimulants are classified as Schedule II controlled substances. Atomoxetine, clonidine ER, and guanfacine ER are not classified as controlled substances.
- Various stimulants are contraindicated for use in patients with advanced arteriosclerosis, symptomatic CV disease, moderate to severe hypertension, hyperthyroidism, hypersensitivity to sympathomimetic amines, glaucoma, agitated states, history of drug abuse, tics, and in those using monoamine oxidase inhibitors (MAOIs). The stimulants carry a boxed warning for potential drug abuse and dependence. They also have warnings for increased risks of serious CV reactions, psychiatric AEs, suppression of growth, peripheral vasculopathy, and priapism. Amphetamines have a warning for risk of serotonin syndrome when used in combination with other drugs affecting the serotonergic neurotransmitter systems.
  - ○ Common AEs of stimulants include anorexia, decreased weight, tachycardia, anxiety, irritability, and insomnia.
  - ○ Refer to the prescribing information for details on warnings, precautions, and AEs for individual products. For example:
    - QuilliChew ER can be harmful to patients with phenylketonuria (PKU) since it contains phenylalanine.
    - Because the Concerta tablet is nondeformable and does not appreciably change in shape in the gastrointestinal tract, it should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing.
    - The use of Daytrana may result in chemical leukoderma and contact sensitization; in addition, exposure of the application site to external heat sources should be avoided due to increased absorption of the drug.
- Atomoxetine is contraindicated for use in patients with narrow angle glaucoma, pheochromocytoma, severe CV disorders, hypersensitivity to any component of the product, and in those taking MAOIs. It carries a boxed warning for rare increased risk of suicidal ideation in children and adolescents. It also has warnings for serious CV events, effects on blood pressure and heart rate, effects on growth, psychiatric AEs, rare cases of severe liver injury, and priapism.
  - ○ Common AEs associated with atomoxetine include somnolence, nausea, and vomiting.
- The alpha$_2$-adrenergic agonists are contraindicated in patients known to be hypersensitive to any constituent of the product. They carry warnings for increased risk of hypotension, bradycardia, and syncope; sedation and somnolence; rebound hypertension; and cardiac conduction abnormalities.
  - ○ Common AEs associated with clonidine ER include somnolence, fatigue, and irritability while common AEs with guanfacine ER include somnolence, fatigue, and hypotension.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Stimulants					
Evekeo (amphetamine)	4 to 6 h	Tablets	Oral	*ADHD, narcolepsy*: Daily up to divided doses daily *Exogenous obesity*: Divided doses daily	*ADHD and narcolepsy* The first dose should be given upon awakening; additional doses at intervals of 4 to 6 hours.
Evekeo ODT (amphetamine)	4 to 6 h	Orally disintegrating tablets	Oral	Once or twice daily in the morning	As soon as the blister pack is opened, the tablet should be placed on the patient's tongue and allowed to disintegrate without chewing or crushing. The tablet will disintegrate in saliva so that it can be swallowed.
Adzenys ER (amphetamine ER)	10 to 12 h	Suspension	Oral	Daily in the morning	
Adzenys XR-ODT (amphetamine ER)	10 to 12 h	Orally disintegrating tablets	Oral	Daily in the morning	As soon as the blister pack is opened, the tablet should be placed on the patient's tongue and allowed to disintegrate without chewing or crushing. The tablet will disintegrate in saliva so that it can be swallowed.
Dyanavel XR (amphetamine ER)	Up to 13 h	Suspension	Oral	Daily in the morning	The bottle should be shaken before administration.
Adderall (mixed amphetamine salts)	4 to 6 h	Tablets	Oral	*ADHD, narcolepsy*: Daily up to divided doses daily	The first dose should be given on awakening, then additional doses at intervals of 4 to 6 hours.
Adderall XR (mixed amphetamine salts ER)	10 to 12 h	Capsules	Oral	Daily in the morning	Capsules may be taken whole, or the capsule may be opened and the entire contents

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
					sprinkled on applesauce and consumed immediately. The dose of a single capsule should not be divided.
Mydayis (mixed amphetamine salts ER)	16 h	Capsules	Oral	Daily in the morning	Dosage adjustment is needed for severe renal impairment. Use in end stage renal disease (ESRD) is not recommended. Capsules may be taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce and consumed immediately in its entirety without chewing. The dose of a single capsule should not be divided.
Focalin (dexmethylphenidate)	5 to 6 h	Tablets	Oral	Twice daily	
Focalin XR (dexmethylphenidate ER)	10 to 12 h	Capsules	Oral	Daily in the morning	ER capsules may be taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce.
ProCentra, Zenzedi (dextroamphetamine)	4 to 6 h	Solution (ProCentra) Tablets (Zenzedi)	Oral	*ADHD, narcolepsy*: Daily up to divided doses daily	The first dose should be given upon awakening; additional doses at intervals of 4 to 6 hours
Dexedrine Spansule (dextroamphetamine SR)	6 to 8 h	Capsules	Oral	*ADHD* Daily or twice daily Narcolepsy Daily	

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Vyvanse (lisdexamfetamine)	10 to 12 h	Capsules, chewable tablets	Oral	*ADHD, BED*: Daily in the morning	Dosage adjustment is needed for renal impairment/ESRD. The capsules may be swallowed whole or can be opened, emptied, and mixed with yogurt, water, or orange juice and consumed immediately. A single capsule should not be divided. The chewable tablets must be chewed thoroughly before swallowing. A single dose should not be divided.
Desoxyn (methamphetamine)	3 to 5 h	Tablets	Oral	*ADHD*: Daily to twice daily *Obesity*: 30 min before each meal	
Methylin, Ritalin (methylphenidate)	3 to 5 h	Chewable tablets, tablets (Ritalin), solution (Methylin)	Oral	Twice daily to 3 times daily	The chewable tablets should be taken with at least 8 ounces (a full glass) of water or other fluid. The liquid should be given 30 to 45 minutes before meals. The ER tablets may be used in place of the IR tablets when the 8-hour dosage of the ER product corresponds to the titrated 8-hour dosage of the IR products.
Methylphenidate ER	3 to 8 h	Tablets			

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
					The ER tablets must be swallowed whole and never crushed or chewed.
Aptensio XR (methylphenidate ER)	12 h	Capsules	Oral	Daily in the morning	The capsules may be taken whole or they can be opened and sprinkled onto applesauce; the applesauce should be consumed immediately and it should not be chewed. The dose of a single capsule should not be divided.
Concerta (methylphenidate ER)	10 to 12 h	Tablets	Oral	Daily in the morning	The tablets should not be chewed or crushed. Note: An FDA analysis of methylphenidate ER products manufactured by UCB/Kremers (formerly Kudco) and Mallinckrodt indicated that in some individuals, they may deliver the drug in the body at a

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Methylphenidate ER					slower rate during the 7- to 12-hour range. As a result, the FDA changed the therapeutic equivalence of these products from AB to BX. Because these manufacturers have subsequently failed to demonstrate that their products are bioequivalent to the brand-name reference drug, the FDA proposes to withdraw their approval (*FDA 2016*).
Cotempla XR-ODT (methylphenidate ER)	12 h	Orally disintegrating tablets	Oral	Daily in the morning	As soon as the blister pack is opened, the tablet should be placed on the patient's tongue and allowed to disintegrate without chewing or crushing. The tablet will disintegrate in saliva so that it can be swallowed.
Jornay PM (methylphenidate ER)	Peak concentration occurs 14 hours after dose with gradual decline thereafter.	Capsules	Oral	Daily in the evening	The capsules may be swallowed whole or it may be opened and the contents sprinkled onto applesauce and given immediately. The capsule contents must not be crushed or chewed, the dose of a single capsule should not be divided, and the contents of the entire capsule should be taken at the same time.

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Methylphenidate ER (CD)	8 to 12 h	Capsules	Oral	Daily in the morning	The capsule may be swallowed whole or it may be opened and the contents sprinkled onto a small amount (tablespoon) of applesauce and given immediately. The capsule contents must not be crushed or chewed.
QuilliChew ER (methylphenidate ER)	12 h	Chewable tablets	Oral	Daily in the morning	A 10 mg or 15 mg dose can be achieved by breaking in half the functionally scored 20 mg and 30 mg tablets, respectively.
Quillivant XR (methylphenidate ER)	12 h	Suspension	Oral	Daily in the morning	The bottle of Quillivant XR should be shaken vigorously for 10 seconds prior to administration. The suspension is stable for up to 4 months once reconstituted.
Ritalin LA (methylphenidate ER)	8 to 12 h	Capsules	Oral	Daily in the morning	The capsule may be swallowed whole or may be administered by sprinkling the capsule contents on a small amount of applesauce; the contents should not be crushed, chewed, or divided. The mixture should be consumed immediately.
Daytrana (methylphenidate transdermal system)	10 to 12 h	Transdermal system	Transdermal	The patch should be applied 2 hours before an effect is needed and removed within 9	

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
				hours. It may be removed earlier than 9 hours if a shorter duration of effect is desired or late day side effects appear.	
Non-stimulants					
Strattera (atomoxetine)	24 h	Capsules	Oral	Daily in the morning or divided dose in the morning and late/afternoon early evening	Dosage adjustment is recommended for patients with moderate or severe hepatic insufficiency. The capsules are not intended to be opened and should be taken whole.
Kapvay (clonidine ER)	12 h	Tablets	Oral	Daily at bedtime or twice daily divided doses.	With twice daily dosing, either an equal or higher split dosage should be given at bedtime. The tablets should not be crushed, chewed, or broken prior to swallowing. The initial dosage should be based on the degree of renal impairment.
Intuniv (guanfacine ER)	8 to 24 h	Tablets	Oral	Daily in the morning or evening	The tablets should not be crushed, chewed, or broken prior to swallowing; they should not be administered with high fat meals, due to increased exposure It may be necessary to reduce the dosage in patients with significant renal and hepatic impairment.

See the current prescribing information for full details
*References: Prescribing information for individual products, *Medical Letter 2015, Pharmacist's Letter 2016, Krull 2019d*

CONCLUSION

- Both CNS stimulants and non-stimulants may be used for the treatment of ADHD. In general, stimulants are first-line treatment due to their superior efficacy. Clinical evidence suggests that methylphenidate and amphetamines are equally efficacious, but some patients may respond to one stimulant and not the other. Various short-, intermediate- and long-acting formulations (eg, tablets/capsules, chewable/orally disintegrating tablets, solution/suspension, transdermal patch) are available to provide a range of dosing options. Although non-stimulants such as atomoxetine and alpha$_2$-adrenergic agonists have smaller effect sizes, they may be used in patients who have failed or are intolerant to stimulants or when there is concern about possible abuse or diversion. The alpha$_2$-adrenergic agonists are approved both as monotherapy and as adjunctive therapy to stimulants, and they have been shown to improve both tic and ADHD symptoms in patients with comorbid tic disorder.
  - Current consensus clinical guidelines for the treatment of children and adolescents with ADHD recommend that stimulants are highly effective for reducing core symptoms of ADHD in children (*AACAP 2007*; *AAP 2011*).
- Ultimately, the choice of the initial agent for treatment of ADHD depends upon various factors such as: duration of desired coverage; ability of the child to swallow pills; coexisting tic disorder (use of alpha$_2$-adrenergic agonists may be warranted); potential AEs, history of substance abuse in the patient or household member (eg, avoid stimulants or use stimulants with less potential for abuse [eg, lisdexamfetamine, osmotic-release preparation, methylphenidate patch]); and preference of the patient and parent/guardian (*Krull 2019d*).
- Various stimulants are indicated for treatment of narcolepsy and are generally considered to be second-line agents after modafinil/armodafinil due to their sympathomimetic AEs (*Scammell 2019*).
- Lisdexamfetamine is the only FDA-approved drug indicated for the treatment of moderate to severe BED, with demonstrated efficacy in reduction of mean binge days per week vs placebo. Direct comparison trials between lisdexamfetamine and other drugs used off-label to treat BED are lacking.

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INTRODUCTION

- The respiratory anticholinergics class includes short- and long-acting agents. Short-acting agents include Atrovent HFA (ipratropium bromide) inhalation aerosol, and ipratropium bromide solution for nebulization (available generically). Long-acting agents, also called long-acting muscarinic antagonists (LAMAs), include Spiriva Handihaler (tiotropium bromide) inhalation powder, Spiriva Respimat (tiotropium bromide) inhalation spray, Incruse Ellipta (umeclidinium) inhalation powder, and Yupelri (revefenacin) solution for nebulizer, which are all administered once daily; Lonhala Magnair (glycopyrrolate) solution for nebulization is administered twice daily. Other relatively long-acting agents are Tudorza Pressair (aclidinium bromide) inhalation powder and Seebri Neohaler (glycopyrrolate) inhalation powder, which are administered twice daily. The predominant use of respiratory anticholinergics is for the treatment of chronic obstructive pulmonary disease (COPD); Spiriva Respimat is also indicated for selected patients with asthma.
- COPD is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities. The abnormalities are usually caused by exposure to noxious particles or gases. Airflow limitation is caused by a combination of small airway disease (eg, obstructive bronchiolitis) and parenchymal destruction (emphysema); the relative contributions of each component vary between patients. The most common symptoms of COPD include dyspnea, cough, and sputum production (*Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2019*).
- COPD affects 6.4% of the United States population and is the major contributor to mortality from chronic lower respiratory diseases, the third leading cause of death in the United States (*Centers for Disease Control and Prevention 2018*). Globally, COPD is the fourth leading cause of death and is expected to be the third leading cause of death by 2020; the burden of COPD continues to increase due to continued exposure to risk factors and aging of the population (*GOLD 2019*).
- Cigarette smoking is the main risk factor for COPD; other risk factors include biomass fuel exposure (such as from cooking and heating in poorly ventilated dwellings) and air pollution. Host factors such as genetic abnormalities, abnormal lung development, and accelerated aging can predispose individuals to COPD development (*GOLD 2019*).
- Patients with COPD may experience exacerbations, which are periods of acute worsening of respiratory symptoms (*GOLD 2019*).
- Pharmacologic therapy for COPD can reduce symptoms, reduce the risk and severity of exacerbations, and improve patients' health status and exercise tolerance. There is no conclusive evidence that COPD medications modify the long-term decline in lung function characteristic of COPD (*GOLD 2019*).
- Pharmacologic options for COPD treatment comprise several classes, including beta-agonists, anticholinergics, methylxanthines, various combination products (including bronchodilators with inhaled corticosteroids [ICSs]), and the phosphodiesterase (PDE)-4 inhibitor, roflumilast. Pharmacologic treatments should be individualized based on symptom severity, risk of exacerbations, side effects, comorbidities, drug availability, and cost, as well as the patient's response, preference, and ability to use various drug delivery devices (*GOLD 2019*).
- In 2015, tiotropium inhalation spray became the first LAMA to be Food and Drug Administration (FDA)-approved for the treatment of asthma (See Table 2). Asthma is a chronic lung disease that inflames and narrows the airways, making it difficult to breathe. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing. Asthma affects people of all ages, but most often starts during childhood. In the United States, more than 25 million people are known to have asthma, including about 7 million children (*National Heart, Lung, and Blood Institute [NHLBI] 2014*).
- The most effective, commonly recommended long-term control medications for the treatment of asthma are ICSs. Alternative long-term control monotherapy medications, such as leukotriene modifiers, mast-cell stabilizers, and methylxanthines, are considered less effective as monotherapy compared to ICSs. Long-acting beta$_2$-agonists (LABAs) should not be used as monotherapy for asthma due to increased risk for serious adverse events including death; however, they are considered the most effective adjunctive therapy in patients not adequately controlled with an ICS

alone. Tiotropium is an option for add-on therapy in certain patients requiring an additional controller medication. An interleukin-5 (IL-5) antagonist or the immunoglobulin E (IgE) antagonist, omalizumab, may be added if patients require a higher level of care. Omalizumab is used in patients with moderate to severe allergic asthma while IL-5 antagonists are used for severe eosinophilic asthma. Short-acting beta$_2$-agonists (SABAs) are the medication of choice for the relief of bronchospasm during acute asthma exacerbations (*Global Initiative for Asthma [GINA] 2018, NHLBI, 2007*).

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

Table 1. Medications Included Within Class Review

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

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

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

*Once-daily maintenance treatment

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

COPD

- Efficacy of the LAMAs for the management of COPD is well established through placebo-controlled trials and a number of systematic reviews and meta-analyses. The primary endpoint in most trials has focused on lung function, including measures of the forced expiratory volume in 1 second (FEV_1). Several studies have also evaluated the impact of LAMAs on measures of quality of life and health status, and frequency of COPD exacerbations.
  - All of the LAMAs have demonstrated improved FEV_1 compared to placebo (*Karner et al 2014, Kerwin et al 2016, Kerwin et al 2017, LaForce et al 2016, Ni et al 2014, Ni et al 2017, Pleasants et al 2016, Aziz et al 2018*).
  - All of the LAMAs have demonstrated improvement in health status and/or COPD symptoms (*Karner et al 2014, Kerwin et al 2016, Kerwin et al 2017, LaForce et al 2016, Ni et al 2014, Ni et al 2017, Pleasants et al 2016, Aziz et al, 2018, Han et al 2018, Sliwka et al 2018*).
  - Tiotropium and umeclidinium have demonstrated a significant reduction in moderate COPD exacerbations (*Karner et al 2014, Ni et al 2017, Pleasants et al 2016, Sliwka et al 2018*).

Placebo-controlled trials

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

- A systematic review summarized the data on exacerbation risk reduction with tiotropium compared to placebo (as well as compared to other COPD maintenance treatments). A total of 29 articles were included, of which 20 compared tiotropium to placebo (16 with the Handihaler and 4 with the Respimat device). Although a formal meta-analysis was not conducted as part of this review, overall, the data demonstrated that tiotropium was associated with a longer time to first exacerbation and fewer exacerbations, including severe exacerbations, compared to placebo. Exacerbations were generally comparable with the Handihaler and Respimat formulations (*Halpin et al 2016*).
- A systematic review and meta-analysis of 22 trials and 23,309 participants evaluated the efficacy of tiotropium (delivered via the Respimat or Handihaler device) vs placebo. The analysis showed that tiotropium led to statistically and clinically significant improvements in quality of life vs placebo, as measured by SGRQ. Compared to placebo, tiotropium significantly reduced the number of exacerbations and led to fewer hospitalizations due to exacerbations, but no significant difference was found for all-cause hospitalization or mortality. Pooled analysis showed an improvement in trough FEV_1 with tiotropium vs placebo (mean difference, 119 mL; 95% CI, 113 to 125) (*Karner et al 2014*).
- Aclidinium has also been evaluated in a number of placebo-controlled trials.
  - In a large, randomized double-blind study (N = 828), patients were randomized to receive aclidinium 200 or 400 mcg twice daily or placebo over 24 weeks. The mean change from baseline in trough FEV_1, the primary endpoint, was significantly larger in patients treated with aclidinium 200 or 400 mcg compared to patients treated with placebo. In addition, a significantly higher proportion of patients treated with aclidinium 200 or 400 mcg experienced a clinically significant improvement in SGRQ score and TDI score when compared to patients treated with placebo (*Jones et al 2012*).
  - In the 12-week double-blind ACCORD COPD I study (N = 561), patients randomized to receive aclidinium 200 or 400 mcg twice daily experienced a statistically significant increase from baseline in trough FEV_1 compared to patients in the placebo group. Statistically significant improvements on SGRQ were demonstrated for both dose groups, but on average were less than those considered clinically meaningful. A higher proportion of patients receiving aclidinium achieved a clinically meaningful improvement in TDI scores compared to those in the placebo group (*Kerwin et al 2012*).
  - In the 12-week double-blind ACCORD COPD II study (N = 544), patients randomized to receive aclidinium 200 or 400 mcg twice daily experienced a statistically significant increase from baseline in trough FEV_1 compared to patients in the placebo group. SGRQ scores improved in all groups, but differences between aclidinium and placebo were not significant. A higher proportion of patients receiving aclidinium achieved a clinically meaningful improvement in TDI scores compared to those in the placebo group (*Rennard et al 2013*).
- A systematic review and meta-analysis of 12 multicenter randomized trials (total N = 9547) evaluated aclidinium vs placebo in patients with stable COPD. The analysis found that aclidinium resulted in a significant improvement in pre-dose FEV_1 compared to placebo (MD, 90 mL; 95% CI, 80 to 100 mL), a reduction in the number of patients with exacerbations requiring hospitalization (OR, 0.64; 95% CI, 0.46 to 0.88), and a reduced SGRQ score (MD, -2.34; 95% CI, -3.18 to -1.51]). However, no difference was demonstrated in all-cause mortality or in the number of patients with exacerbations requiring oral steroids and/or antibiotics (*Ni et al 2014*). A similar meta-analysis included 7 trials (total N = 7001) evaluating aclidinium vs placebo for a duration of ≥ 12 weeks. This analysis found that compared to placebo, aclidinium did not significantly reduce the incidence of exacerbations (OR, 0.90; 95% CI, 0.75 to 1.07; P = 0.22) or all-cause mortality (OR, 0.92; 95% CI, 0.43 to 1.94; P = 0.82). However, a significant difference was demonstrated for the rate of hospitalization due to exacerbation (OR, 0.64; 95% CI, 0.47 to 0.89; P = 0.008) and improvement in SGRQ (MD, -2.34; 95% CI, -3.18 to -1.51). Secondary endpoints, including FEV_1, forced vital capacity (FVC), and TDI, supported the efficacy of aclidinium on lung function and dyspnea symptoms (*Zou et al 2016*).
- Umeclidinium has been evaluated for the treatment of COPD in several Phase 3, multicenter, randomized, placebo-controlled trials.
  - One trial (N = 206) compared 2 doses of umeclidinium, 62.5 mcg and 125 mcg daily, to placebo over a period of 12 weeks. Patients receiving an ICS at baseline continued treatment at a stable dose. No other long-acting bronchodilators were permitted. Improvements in the primary endpoint, the least squares mean (LSM) change from baseline in FEV_1, were observed for umeclidinium 62.5 mcg daily vs placebo (127 mL; 95% CI, 52 to 202; $p < 0.001$) and for umeclidinium 125 mcg daily vs placebo (152 mL; 95% CI, 76 to 229; $p < 0.001$). Improvements were also noted for dyspnea, rescue medication use (62.5 mcg strength only), and SGRQ (*Trivedi et al 2014*).
  - A second trial (N = 1,536) compared umeclidinium 62.5 mcg daily, vilanterol 25 mcg daily, umeclidinium/vilanterol 62.5 mcg/25 mcg daily, and placebo over a period of 24 weeks. Concomitant use of ICSs at a stable dose was permitted. Improvements in the primary endpoint, the LSM change from baseline in FEV_1, were observed for all active

treatments. For umeclidinium 62.5 mcg daily, the improvement vs placebo was 115 mL (95% CI, 76 to 155). Improvements were also noted for dyspnea and time to first COPD exacerbation (*Donohue et al 2013*).
  - Two additional randomized, double-blind trials (published together, N = 862 and N = 872) evaluated the addition of umeclidinium to fluticasone propionate/salmeterol in patients with COPD. Patients received once-daily umeclidinium 62.5 mcg, umeclidinium 125 mcg, or placebo added to twice-daily fluticasone propionate/salmeterol 250/50 mcg for 12 weeks. In both studies, improvement in the primary endpoint, the trough FEV_1 on day 85, was significantly better in both umeclidinium groups vs placebo, with differences of 147 mL (95% CI, 107 to 187) and 127 mL (95% CI, 89 to 164) for the 62.5 mcg strength and 138 (95% CI, 97 to 178) and 148 (95% CI, 111 to 185) for the 125 mcg strength. Significant improvements were also demonstrated for the weighted mean FEV_1 over 0 to 6 hours post-dose and rescue albuterol use, while results on SGRQ and the COPD Assessment Test were mixed (*Siler et al 2016*).
- A review and meta-analysis evaluated the use of umeclidinium compared to placebo (as well as compared to active controls). The meta-analysis included randomized trials with a duration of ≥ 12 weeks. A total of 10 trials were included. Key results from this meta-analysis were as follows (*Pleasants et al 2016*):
  - The weighted mean difference in FEV_1 change from baseline (primary endpoint) for umeclidinium 62.5 mcg vs placebo was 120 mL (95% CI, 100 to 130) (based on data from 7 studies).
  - The weighted mean difference in TDI change from baseline for umeclidinium 62.5 mcg vs placebo was 0.61 (95% CI, -0.17 to 1.39) (based on data from 2 studies).
  - The weighted mean difference in SGRQ change from baseline for umeclidinium 62.5 mcg vs placebo was -2.34 (95% CI, -4.59 to 0.08) (based on data from 5 studies).
  - Umeclidinium 62.5 mcg significantly improved the time to first COPD exacerbation, with an HR of 0.61 (95% CI, 0.41 to 0.90) (based on data from 1 study).
- A systematic review and meta-analysis of 4 randomized controlled trials with a duration ≥ 12 weeks evaluated umeclidinium compared to placebo in patients with moderate to severe COPD (n = 37,98). Key results from this meta-analysis were as follows (*Ni et al 2017*):
  - Odds of moderate exacerbations requiring steroids and/or antibiotics were reduced with umeclidinium vs placebo (OR, 0.61; 95% CI, 0.46 to 0.80), but there was no difference in odds of severe exacerbations requiring hospitalization between groups (based on data from 4 studies).
  - Umeclidinium reduced SGRQ total score compared to placebo (MD, -4.79 units; 95% CI, -8.84 to -0.75) and the odds of having an improvement ≥ 4 units in SGRQ total score was higher with umeclidinium vs placebo (OR, 1.45; 95% CI, 1.16 to 1.82) (based on data from 3 studies).
  - TDI focal score was improved with umeclidinium vs placebo (MD, 0.76 units; 95% CI, 0.43 to 1.09 units) (based on data from 3 studies).
  - Change from baseline in trough FEV_1 was higher with umeclidinium vs placebo (MD, 0.14 L; 95% CI, 0.12 to 0.17 L) (based on data from 4 studies).
- Glycopyrrolate has been evaluated for the treatment of COPD in Phase 3, randomized, multicenter, double-blind, placebo-controlled trials.
  - Two 12-week trials (N = 441 and 428) evaluated the efficacy of glycopyrrolate inhalation powder 15.6 mcg twice daily vs placebo. Both trials met their primary endpoint, demonstrating differences from placebo in the mean change from baseline in FEV_1 area under the curve (AUC) from 0 to 12 hours (FEV_1 AUC_{0-12}) of 139 mL (95% CI, 95 to 184; $p < 0.001$) and 123 mL (95% CI, 81 to 165; $p < 0.001$), respectively. Improvement in several secondary endpoints was also demonstrated, including trough FEV_1, and SGRQ score. The difference in the TDI score was significant in one of the 2 studies (*Clinicaltrials.gov 2015, Kerwin et al 2016, LaForce et al 2016*).
  - The efficacy of nebulized glycopyrrolate was evaluated in 2 replicate 12-week randomized controlled trials (GOLDEN 3 and 4; N = 653 and N = 641, respectively) in patients with moderate to very severe COPD. Compared with placebo, patients in the intention to treat analysis who were randomized to nebulized glycopyrrolate 25 mcg or 50 mcg twice daily experienced significant increases in the primary endpoint, FEV_1 from baseline (mean placebo-adjusted differences, 0.096 and 0.104, respectively, in GOLDEN 3; 0.081 and 0.074, respectively, in GOLDEN 4; all $p < 0.0001$). Improvements from baseline were also observed with both doses of nebulized glycopyrrolate vs placebo in FVC and SGRQ scores (*Kerwin et al 2017*).

<u>Comparisons between different anticholinergics and formulations</u>

- A small number of clinical trials have compared tiotropium to ipratropium.

- A randomized, double-blind, double-dummy study (N = 288) compared tiotropium 18 mcg daily to ipratropium 40 mcg 4 times daily over 15 weeks. This study demonstrated that the FEV_1 response was significantly greater for tiotropium compared to ipratropium at all time points ($p < 0.05$). Differences in trough FEV_1 values were most pronounced, whereas differences in peak FEV_1 did not reach statistical significance. Improvements were also greater for tiotropium for morning and evening PEF rate and use of rescue albuterol (*van Noord et al 2000*).
- A second double-blind, double-dummy study (N = 535) also compared tiotropium 18 mcg daily to ipratropium 40 mcg 4 times daily. At the end of 1 year, trough FEV_1 was significantly better in the tiotropium group (difference, 150 mL; $p < 0.001$). FVC results paralleled those for FEV_1. Tiotropium also led to improved PEF rates and reduced use of rescue albuterol (*Vincken et al 2002*).
- Two identical double-blind, double-dummy 12-week trials (total N = 719) compared tiotropium Respimat in both 5 mcg and 10 mcg daily doses to placebo and to ipratropium bromide. Results for the 5 mcg dose demonstrated that trough FEV_1 was improved significantly more with tiotropium vs placebo (difference, 118 mL; $p < 0.0001$) and compared to ipratropium (difference, 64 mL; $p < 0.01$) (*Voshaar et al 2008*).

- A meta-analysis demonstrated that compared to patients receiving ipratropium, patients receiving tiotropium were more likely to experience improvement in SGRQ scores and TDI scores. Patients receiving tiotropium also experienced a reduced rate of exacerbations compared to patients receiving ipratropium (*Yohannes et al 2011*).
- A systematic review and meta-analysis (N = 2 studies; 1073 patients) evaluated the safety and efficacy of tiotropium compared to ipratropium (*Cheyne et al 2015*). In one study, patients used tiotropium by Handihaler for 12 months, and in the other, patients used tiotropium by Respimat for 12 weeks. Primary endpoints included the trough FEV_1 at 3 months and serious adverse events.
  - Trough FEV_1 at 3 months was significantly increased with tiotropium compared to ipratropium (MD, 109 mL; 95% CI, 81 to 137; $I^2 = 62\%$).
  - Fewer patients experienced ≥ 1 non-fatal serious adverse events with tiotropium compared to ipratropium (OR, 0.5; 95% CI, 0.34 to 0.73). Patients taking tiotropium were also less likely to experience a COPD-related serious adverse event (OR, 0.59; 95% CI, 0.41 to 0.85).
  - Benefits were also demonstrated for tiotropium compared to ipratropium for secondary endpoints including exacerbations, hospital admissions, and quality of life. There was no significant difference in mortality between the 2 treatments.
- The large, randomized, double-blind TIOSPIR trial (N = 17,135) compared tiotropium Respimat at a dose of 2.5 mcg or 5 mcg daily to tiotropium Handihaler (18 mcg daily). During a mean follow-up of 2.3 years, tiotropium via Respimat and Handihaler were shown to have similar safety and efficacy profiles (*Wise et al 2013*).
  - Risk of death for tiotropium Respimat 5 mcg daily vs Handihaler: HR, 0.96; 95% CI, 0.84 to 1.09.
  - Risk of first exacerbation for tiotropium Respimat 5 mcg daily vs Handihaler: HR, 0.98; 95% CI, 0.93 to 1.03.
- A systematic review evaluated tiotropium Respimat 5 mcg daily vs tiotropium Handihaler 18 mcg daily on pharmacokinetic, efficacy, and safety data. Data were included from a total of 22 comparative studies (10 published studies, 1 submitted manuscript, and 11 Congress abstracts). Key results from this review were as follows (*Dahl et al 2016*):
  - Several clinical trials demonstrated similar pharmacokinetic profiles between the 2 formulations. Although it had previously been suggested that systemic exposure may be greater with tiotropium Respimat, a recent study showed that exposure may actually be slightly lower with the Respimat formulation.
  - Results of several randomized trials demonstrated that the efficacy and safety profiles are comparable between the 2 formulations, and results from post-hoc and pooled analyses provide further support for similarity on lung function, exacerbations, and safety outcomes in various patient subtypes.
  - Similar results for health-related quality of life were demonstrated with each formulation based on the SGRQ total score.
- A double-blind, double-dummy, randomized Phase 3b trial (N = 414) compared tiotropium 18 mcg daily to aclidinium 400 mcg twice daily. This trial demonstrated no significant differences between active treatments at week 6 in the change from baseline in FEV_1 AUC over 24 hours (AUC_{0-24}). FEV_1 AUC_{0-12} was numerically greater with tiotropium vs aclidinium, and AUC_{12-24} was numerically greater with aclidinium vs tiotropium; however, differences between active treatments were not statistically significant. The 2 groups also had comparable results for most COPD symptom measures (*Beier et al 2013*).
- A 48-week, open-label trial (GOLDEN 5; N = 1086) compared glycopyrrolate nebulizer solution 50 mcg twice daily to tiotropium 18 mcg daily in 1086 patients with moderate to very severe COPD. The trial demonstrated that the rates of

treatment-emergent adverse events were generally similar between groups, while rates of respiratory events were somewhat higher with glycopyrrolate vs tiotropium (35.2% vs 28.8%, respectively); the authors attributed this in part to incorrect nebulizer technique early in treatment. There were no significant differences between groups in the change from baseline in FEV_1 or SGRQ. There was a similar and numerically lower incidence of exacerbations with glycopyrrolate nebulizer solution vs tiotropium (18.5% and 22.5%, respectively) (*Ferguson et al 2017*).

- Results were reported in abstract form of an open-label randomized control trial comparing tiotropium 18 mcg daily with aclidinium 400 mcg twice daily in addition to background therapy in adults with moderate to severe COPD. After 8 weeks of treatment, the primary endpoint, FEV_1 AUC_{0-3} was not significantly different between groups. Secondary outcomes evaluating other measures of lung function were not significantly different; however, SGRQ and Modified Medical Research Council scores were significantly improved with aclidinium (*Nakamura et al 2017*).
- A network meta-analysis (N = 21 studies; 22,542 patients) demonstrated no significant differences between tiotropium 18 mcg daily and aclidinium 400 mcg twice daily in FEV_1, SGRQ, or TDI score (*Karabis et al 2013*).
- A 12-week, blinded, double-dummy, randomized trial (N = 1107) compared umeclidinium 62.5 mcg daily delivered via the Ellipta device and tiotropium 18 mcg daily delivered via the Handihaler device (*Feldman et al 2016*). The primary endpoint, LSM change from baseline in trough FEV_1 at day 85 in the per-protocol population (N = 976), was greater with umeclidinium vs tiotropium (difference, 59 mL; 95% CI, 29 to 88; $p < 0.001$). Similar results were seen in the intention-to-treat population (difference, 53 mL; 95% CI, 25 to 81; $p < 0.001$). Improvements in the weighted mean FEV_1 over 0 to 24 hours post-dose were similar between treatments, but greater with umeclidinium vs tiotropium over 12 to 24 hours post-dose (difference, 70 mL; 95% CI, 14 to 127; $p = 0.015$). No differences were observed between umeclidinium and tiotropium in patient-reported outcomes (TDI and SGRQ), and the safety profiles were similar with both treatments. More patients preferred the Ellipta device compared to the Handihaler, including an overall device preference and scores for ease of use.
  - There were several limitations to this trial, including a short duration and incomplete blinding (markings differed among active tiotropium capsules and placebo, and stickers were used to obscure inhaler markings).
- A network meta-analysis (N = 24 studies; 21,311 participants) compared tiotropium 18 mcg daily to aclidinium 400 mcg twice daily, glycopyrronium 50 mcg daily (not the FDA-approved dosing), and umeclidinium 62.5 mcg daily in patients with COPD. All active treatments demonstrated favorable outcomes vs placebo for 12-week trough FEV_1, 24-week trough FEV_1, 24-week SGRQ, 24-week TDI, and 24-week rescue inhaler use (*Ismaila et al 2015*).
  - Based on 17 studies (11,935 participants) for the primary endpoint, the mean change from baseline in trough FEV_1 vs placebo at 12 weeks ranged from 101.4 to 136.7 mL, and was greatest for umeclidinium, followed by glycopyrronium, tiotropium, and aclidinium. However, the 95% credible interval (CrI) crossed zero in all between-treatment comparisons, so superiority was not demonstrated for any single LAMA over another.
- A network meta-analysis (N = 27 studies; 48,140 participants) compared tiotropium, aclidinium, and glycopyrronium for preventing COPD exacerbations (*Oba et al 2015*). All of the studied LAMAs reduced moderate-to-severe exacerbations compared to placebo; however, there were no significant differences demonstrated among the active treatments.
  - The analysis also evaluated the rate of severe exacerbations. Tiotropium dry powder inhaler was the only LAMA demonstrated to reduce severe exacerbations vs placebo (HR, 0.73; 95% CI, 0.6 to 0.86). However, the 95% CrI crossed zero in all between-treatment comparisons. The authors concluded that there were no statistically significant differences among LABAs in preventing COPD exacerbations.
- Revefenacin was compared to placebo in a randomized-controlled trial of 355 COPD patients; ICSs and SABAs were also allowed for the duration of the trial period. Revefenacin at a dose of 88 mcg, 175 mcg and 350 mcg daily yielded significant improvements in trough FEV_1 at day 28 vs placebo (187.4, 166.6 and 170.6 mL, respectively; $p < 0.001$ for all comparisons). Doses ≥ 88 mcg also led to the following improvements over placebo: > 80% of patients achieved a ≥ 100 mL increase from baseline FEV_1 at 4 hours post dose; sustained bronchodilation for 24 hours post dose; and reduction in daily albuterol puffs by > 1 puff per day. Lastly, the 350 mcg dose did not demonstrate additional efficacy compared to the 175 mcg dose (*Pudi et al 2018).*

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

- In a meta-analysis of 4 trials, there was no statistically significant differences in short-term FEV_1 changes (up to 90 minutes post dose) between individuals receiving ipratropium compared to a $beta_2$-adrenergic agonist (albuterol, metaproterenol, or fenoterol) (*McCrory et al 2002*).
- Tiotropium has been compared to the LABAs salmeterol and indacaterol in several large comparative trials.

- Two placebo-controlled trials of tiotropium 18 mcg daily also included an active control arm in which patients received salmeterol 50 mcg twice daily. In the first trial (N = 623), the improvement in trough FEV_1 at 24 weeks was greater with tiotropium compared to salmeterol (difference, 52 mL; $p < 0.01$). Differences also favored tiotropium for FVC (difference, 112 mL; $p < 0.01$) and PEF rate (difference, 5.9 L/minute; $p < 0.01$). Tiotropium was also better than salmeterol in improving TDI focal score (difference, 0.78 units; $p < 0.05$). The difference between active treatments in SGRQ was not statistically significant (*Donohue et al 2002*). In the second trial (N = 1207), improvements in FEV_1, FEV_1 area under the curve over 3 hours (AUC_{0-3}), and FVC were greater for tiotropium vs salmeterol; however, there were no significant differences among active treatment groups for time to first COPD exacerbation, hospital admissions, or TDI focal scores (*Brusasco et al 2003*).
- A large double-blind randomized trial (N = 7348) (POET-COPD) demonstrated that tiotropium 18 mcg daily increased the time to first COPD exacerbation, the risk of moderate exacerbations, and the risk of severe exacerbations compared to treatment with salmeterol (*Vogelmeier et al 2011*). Prolongation of time to the first exacerbation was also demonstrated in prespecified subgroups of patients with GOLD stage II COPD and patients who were maintenance-therapy-naïve (*Vogelmeier et al 2013*).
- A randomized trial (N = 1683) compared 2 doses of the once-daily LABA indacaterol (150 mcg and 300 mcg) to tiotropium 18 mcg daily and to placebo. In this trial, patients receiving placebo or indacaterol were blinded, but tiotropium was open-label because blinded tiotropium was not available. The primary endpoint, trough FEV_1 at 12 weeks, was greater for indacaterol (both doses) than for tiotropium (difference, 40 mL; $p \leq 0.01$). Greater improvements were also demonstrated for indacaterol vs tiotropium for the proportions of patients achieving a clinically important improvement in TDI total score ($p \leq 0.01$), use of rescue albuterol ($p \leq 0.001$), and change from baseline in morning and evening PEF ($p < 0.05$). Rates of exacerbations did not differ among active treatment groups (*Donohue et al 2010*).
- A randomized, double-blind, double-dummy trial compared tiotropium 18 mcg daily to indacaterol 150 mcg daily. In this trial, trough FEV_1 with tiotropium was determined to be non-inferior to indacaterol, but not superior (treatment difference, 0 mL; 95% CI, -20 to 20). However, FEV_1 and FVC were demonstrated to be greater with indacaterol on day 1 when evaluated 5 minutes, 30 minutes, and 1 hour after dosing. More patients receiving indacaterol compared to those taking tiotropium experienced a clinically significant improvement in TDI scores (OR, 1.49; $p < 0.001$) and SGRQ scores (OR, 1.43; $p < 0.001$). In addition, use of rescue medication was lower in the indacaterol group (*Buhl et al 2011*).

- Tiotropium has also been compared to combination ICS/LABAs.
  - Tiotropium 18 mcg daily has been compared to fluticasone/salmeterol 250 mcg/50 mcg in a randomized, double-blind, double-dummy, 2-year trial (N = 1323). The primary endpoint in this trial, the rate of exacerbations over 2 years, was comparable in the tiotropium (1.32/year) and fluticasone/salmeterol (1.28/year) groups ($p = 0.656$). Patients randomized to tiotropium were significantly more likely to withdraw from the study than those randomized to fluticasone/salmeterol (HR, 1.29; 95% CI, 1.08 to 1.54; $p = 0.005$). In addition, mortality was significantly lower in the fluticasone/salmeterol group (3%) than in the tiotropium group (6%) (HR, 0.48; 95% CI, 0.27 to 0.85; $p = 0.012$) (*Wedzicha et al 2008*).

  - Tiotropium 18 mcg daily has also been compared to fluticasone furoate/vilanterol 100/25 mcg daily in a randomized, double-blind, double-dummy, 12-week trial (N = 623) in patients with COPD and cardiovascular disease (CVD) or CVD risk (≥ 1 risk factor of hypertension, hypercholesterolemia, or treated diabetes). The primary endpoint, change from baseline in weighted mean FEV_1 over 24 hours at 12 weeks, was similar in the 2 treatment arms (LSM change, 95 mL and 117 mL in the tiotropium and fluticasone furoate/vilanterol groups, respectively, with a difference of 22 mL [95% CI, -12 to 55; $p = 0.201$]). Trough FEV_1 after 12 weeks was improved to a similar extent in both groups. Some secondary endpoints seemed to favor tiotropium (change from baseline in FVC and inspiratory capacity), while other endpoints seemed to favor fluticasone furoate/vilanterol (onset of bronchodilation, rescue medication use, dyspnea, SGRQ, and COPD Assessment Test scores). Safety was generally similar, although pneumonia was reported more frequently in the fluticasone furoate/vilanterol group. Cardiovascular monitoring did not demonstrate an increased cardiovascular risk. The cardiovascular safety profile was similar between groups; however, there were 2 deaths from cardiovascular events in the tiotropium group (both patients had hypertension and 1 smoked and had a family history of CVD). Fewer patients experienced a COPD exacerbation in the fluticasone furoate/vilanterol group (2%) than the tiotropium group (4%) (*Covelli et al 2016*).
  - In a Cochrane review which included the *Covelli et al 2016* trial and one additional 12 week trial comparing tiotropium to fluticasone furoate/vilanterol (N = 880 across both trials), there were no differences between treatments when

considering the following outcomes: mortality, COPD exacerbation, pneumonia, SGRQ score, hospital admissions, or use of rescue medication (*Sliwka et al 2018*).

- Meta-analyses comparing tiotropium to LABAs do not consistently demonstrate superiority on key endpoints for either treatment. One meta-analysis (N = 7 trials; 12,223 participants) demonstrated a reduction in the proportion of patients experiencing ≥ 1 exacerbations with tiotropium compared to a LABA; however, 1 trial contributed the most weight to this analysis (*Chong et al 2012*).
- A systematic review and network meta-analysis (N = 71 trials; 73,062 participants) evaluated the efficacy of various treatment options for patients with COPD that could not be controlled by short-acting therapies alone. This analysis ranked ICS/LABA combinations first for results on SGRQ and trough FEV_1. LAMAs and LABAs were ranked second and third for each measure, and these 2 categories of medications had similar effects overall (*Kew et al 2014*).
- A systematic review and network meta-analysis (N = 74 trials; 74,832 participants) evaluated the efficacy of SAMAs, LABAs, LAMA/LABAs and LABA/ICSs for maintenance treatment of COPD. At 12 and 24 weeks, LAMA, LAMA/LABAs, and LABA/ICSs led to a significantly greater improvement in trough FEV_1 compared with placebo and SAMA monotherapy. With the exception of aclidinium/formoterol, all other LAMA/LABA therapies were superior to LAMA monotherapy and LABA/ICS therapy in improving trough FEV_1. Furthermore, LAMA/LABA therapy had the highest probability of being the best treatment for in FEV_1 improvement; similar trends were observed for the transition dyspnea index and SGRQ scores. Authors concluded that there were no significant differences among the LAMAs and LAMA/LABAs within their respective classes (*Aziz et al 2018*).
- A systematic review and network meta-analysis (N = 10 trials; 10,894 participants) compared the effects of LABA/tiotropium combination therapy vs either therapy alone (*Farne et al 2015*).
  - Compared to tiotropium alone, combination treatment resulted in a slightly larger improvement in SGRQ (MD, -1.34; 95% CI, -1.87 to -0.8; 6709 participants; 5 studies). There were no significant differences in hospital admissions (4 studies; 4,856 participants) or all-cause mortality (10 studies; 9633 participants). The improvement in pre-bronchodilator FEV_1 at the end of the study showed a statistically significant increase in the combination group compared to the tiotropium group (MD, 60 mL; 95% CI, 50 to 70; 10 studies; 9573 participants). Results for exacerbations were not pooled due to clinical heterogeneity.
  - Compared to LABA alone, combination treatment resulted in a small but statistically significant improvement in SGRQ (MD, -1.25; 95% CI, -2.14 to -0.37; 3378 participants; 4 studies). There were no significant differences in all-cause hospitalizations, hospitalizations for exacerbations, or all-cause mortality (3 studies; 3514 participants for all endpoints). The improvement in pre-bronchodilator FEV_1 at the end of the study showed a statistically significant increase in the combination group compared to the LABA group (MD, 70 mL; 95% CI, 60 to 90; 4 studies; 3513 participants). There was a significantly lower risk of exacerbation with combination treatment vs LABA monotherapy (OR, 0.8; 95% CI, 0.69 to 0.93; 3 studies; 3514 participants).
- A large, randomized-controlled trial (N = 7880) of patients with COPD and a history of exacerbations did not find a difference in the rate of exacerbations between LAMA/LABA therapy with tiotropium/olodaterol vs LAMA therapy with tiotropium (relative risk [RR], 0.93; 99% CI, 0.85 to 1.02; p = 0.0498) (*Calverley et al 2018*).
- A systematic review and meta-analysis (N = 8 trials) compared tiotropium 5 or 18 mcg with LAMA/LABA therapy in patients with moderate-to-severe COPD; ICS therapy was also allowed and use ranged from 33.7% to 54.4% among patients in the included trials. Therapy with LABA/LAMA was superior to tiotropium monotherapy for all of the following outcomes at 12 and 24 weeks: FEV1 peak and trough, SGRQ responder rate, mean SGRQ score, and use of rescue medication. At 12 weeks, LABA/LAMA improved FEV_1 trough by 63 ml compared to tiotropium alone (95% CI, 39.2 to 86.8; $p < 0.01$). During the same time period, LABA/LAMA improved the mean SGRQ responder rate by 19% (RR, 1.19; 95% CI, 1.09 to 1.28; $p < 0.01$) and reduced SGRQ total score by 1.87 points (95% CI, -2.72 to -1.02; $p < 0.01$) compared to tiotropium (*Han et al 2018).*
- There is little data on the use of aclidinium compared to $beta_2$-agonists. A small study (N = 79) compared various doses of aclidinium to the LABA formoterol in a crossover study in which each treatment was given for 7 days. The primary endpoint, difference in FEV_1 AUC_{0-12} on day 7, was not significantly different in the aclidinium 400 mcg twice daily and formoterol 12 mcg twice daily groups (208 mL and 210 mL, respectively). There also was no difference between treatment with aclidinium 400 mcg and formoterol with regard to changes in FEV_1 AUC_{0-24}; however, patients treated with aclidinium 400 mcg experienced a statistically significant improvement in FEV_1 AUC_{12-24} compared to treatment with formoterol (56 mL; $p < 0.01$) *(Singh et al 2012*).

ASTHMA

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

Placebo-controlled and trials

- Clinical trials have compared tiotropium Respimat to placebo in patients with asthma not well controlled on baseline therapy that included at least an ICS.
- A 12-week, Phase 3, multicenter, randomized trial (N = 465) compared tiotropium Respimat 2.5 mcg daily, 5 mcg daily, and placebo in adults with asthma who were symptomatic despite treatment with a low- to medium-dose ICS (200 to 400 mcg budesonide or equivalent), which was continued during the trial. The primary endpoint, change from baseline in peak FEV_1 within 3 hours of dosing (FEV_1 [0 to 3 hr]), was greater for both tiotropium doses compared to placebo, with adjusted MDs of 159 mL and 128 mL for the 2.5 mcg and 5 mcg doses, respectively ($p < 0.001$ for both comparisons vs placebo). Both doses of tiotropium were also superior to placebo with regard to the secondary endpoints of adjusted mean trough FEV_1 and FEV_1 $AUC_{0 \text{ to } 3}$ responses, and the other endpoints of morning and evening PEF. Adverse events were comparable across the treatment groups (*Paggiaro et al 2016*).
- Two 24-week, Phase 3, multicenter, randomized trials (total N = 2103) compared tiotropium Respimat 2.5 mcg daily, 5 mcg daily, salmeterol 50 mcg twice daily, or placebo in adults with asthma who were symptomatic despite treatment with a medium-dose ICS (400 to 800 mcg budesonide or equivalent) alone or in combination with a $beta_2$-agonist. During the study, patients continued their ICS, but pre-study LABAs were discontinued. Co-primary endpoints were the peak FEV_1 (0 to 3 hr), trough FEV_1, and responder rate according to the 7-question Asthma Control Questionnaire (ACQ-7). Pooled data demonstrated the following (*Kerstjens et al 2015*):
  - The differences vs placebo in peak FEV_1 were 223 mL (95% CI, 185 to 262) in the tiotropium 2.5 mcg group, 185 mL (95% CI, 146 to 223) in the tiotropium 5 mcg group, and 196 mL (95% CI, 158 to 234) in the salmeterol group (all $p <$ 0.0001 vs placebo).
  - The differences in trough FEV_1 were 180 mL (95% CI, 138 to 221) in the tiotropium 2.5 mcg group, 146 mL (95% CI, 105 to 188) in the tiotropium 5 mcg group, and 114 mL (95% CI, 73 to 155) in the salmeterol group (all $p < 0.0001$ vs placebo).
  - There were more ACQ-7 responders (improvement of ≥ 0.5) in the tiotropium 2.5 mcg group (OR, 1.33; 95% CI, 1.03 to 1.72; $p = 0.031$), tiotropium 5 mcg group (OR, 1.32; 95% CI, 1.02 to 1.71; $p = 0.035$), and salmeterol group (OR, 1.46; 95% CI, 1.13 to 1.89; $p = 0.0039$), than in the placebo group.
  - Severe asthma exacerbations were recorded in 4%, 6%, 6%, and 8% of patients in the tiotropium 2.5 mcg, 5 mcg, salmeterol, and placebo groups, respectively. At least 1 episode of asthma worsening was recorded in 22%, 28%, 25%, and 32% of patients, respectively. The investigators noted a statistically significant reduction in risk of first severe exacerbation with tiotropium 2.5 mcg ($p = 0.0084$) and of first asthma worsening with tiotropium 2.5 mcg and salmeterol ($p = 0.0007$ and 0.013, respectively) vs placebo.
  - The numbers of adverse events and serious adverse events were comparable among groups.
- Additional support for the safety and efficacy of tiotropium for asthma treatment was provided by the results of two 48-week, Phase 3, multicenter, randomized trials (total N = 912) comparing tiotropium Respimat 5 mcg daily to placebo in adults with asthma not adequately controlled on an ICS (≥ 800 mcg budesonide or equivalent) and a LABA. Tiotropium was superior to placebo for endpoints including mean change in peak FEV_1, trough FEV_1, and the time to first severe

exacerbation. Adverse events were similar in the 2 groups. However, it should be noted that this study only evaluated a dose that is higher than the FDA-approved dose for asthma (*Kerstjens et al 2012*).

- Two randomized Phase 3 trials evaluated the use of tiotropium Respimat in adolescents 12 to 17 years of age.
  - A 12-week trial (N = 392) compared tiotropium Respimat 2.5 mcg daily, 5 mcg daily, and placebo in patients with severe asthma who were on background treatment of an ICS plus ≥ 1 controller medications, such as a LABA. The difference vs placebo for the primary endpoint, peak FEV_1 (0 to 3 hr), was 111 mL (95% CI, 2 to 220) for the 2.5 mcg dose and 90 mL (95% CI, -19 to 198) for the 5 mcg dose (*Hamelmann et al 2017*).
  - A 48 week trial (N = 398) compared tiotropium Respimat 2.5 mcg daily, 5 mcg daily, and placebo in patients with moderate asthma who were on background treatment of at least an ICS. The difference vs placebo in the primary endpoint, peak FEV_1 (0 to 3 hr) was 134 mL (95% CI, 34 to 234) for the 2.5 mcg dose and 174 mL (95% CI, 76 to 272) for the 5 mcg dose (*Clinicaltrials.gov 2014, Spiriva Respimat prescribing information 2018*).
- According to the prescribing information, efficacy of tiotropium in pediatric patients 6 to 11 years of age was based on extrapolation of efficacy in adults, and on 2 randomized, double-blind, placebo-controlled trials of 12 and 48 weeks duration. A total of 801 patients aged 6 to 11 years were enrolled in the 2 trials (271 receiving tiotropium 2.5 mcg daily 265 receiving tiotropium 5 mcg daily, and 265 receiving placebo). The primary endpoint in both trials was the change from baseline in the peak FEV_1 (0 to 3 hr), with the evaluation defined at week 12 in the 12-week trial and at week 24 in the 48-week trial (*Spiriva Respimat prescribing information 2018*).
  - The 12-week trial enrolled patients with severe asthma who were on background treatment of ICS plus ≥ 1 controller medication (eg, LABA). The mean difference vs placebo in the primary endpoint was 40 mL (95% CI, -30 mL to 100 mL; not significant).
  - The 48-week trial enrolled patients with moderate asthma on background treatment of at least an ICS. The mean difference vs placebo in the primary endpoint was 170 mL (95% CI, 110 to 230).
- An additional trial in children aged 6 to 11 years with severe symptomatic asthma randomized patients to double-blind tiotropium 5 mcg, 2.5 mcg, or placebo administered via a Respimat device in addition to background therapy with medium-dose ICS. After 12 weeks, tiotropium 5 mcg, but not 2.5 mcg, improved the primary end point, peak FEV_1 within 3 hours after dosing compared with placebo (MD, 139 mL; 95% CI, 75 to 203 and 35 mL; 95% CI, -28 to 99 for 5 and 2.5 mcg doses, respectively). Results were similar for the key secondary endpoint, trough FEV_1 *(Szefler et al 2017*).

Systematic reviews and network meta-analyses

- A systematic review and meta-analysis (N = 13 studies; 4966 patients) evaluated the efficacy and safety of tiotropium in patients with asthma. Tiotropium was given via the Respimat device in most studies, and the duration of the included studies ranged from 4 to 52 weeks (*Rodrigo et al 2015a*).
  - In 10 studies evaluating the addition of tiotropium to an ICS vs ICS alone in patients with mild or moderate asthma, the analysis demonstrated significant improvements in morning and evening PEF (MD, 22 to 24 L/min; $p < 0.00001$) and peak and trough FEV_1 (MD, 150 mL; 95% CI, 110 to 180 and 140 mL; 95% CI, 110 to 160, respectively) with the addition of tiotropium. Tiotropium also significantly improved ACQ-7 and Asthma Quality of Life Questionnaire (AQLQ) scores from baseline (MD, -0.14 units; 95% CI, -0.19 to -0.09 and 0.07 units; 95% CI, 0.01 to 0.13, respectively). Tiotropium was also associated with a decrease in the number of patients with ≥ 1 asthma exacerbation (10.5% vs 13.3%; RR, 0.74; 95% CI, 0.57 to 0.95).
  - In 4 studies comparing the addition of either tiotropium or LABA to an ICS in patients with moderate asthma, tiotropium improved morning PEF more than LABA, but the magnitude of the difference was small (6.6 L/min). There were no significant differences in evening PEF or peak or trough FEV_1. The addition of tiotropium was inferior to the addition of LABA for AQLQ (MD, -0.12 units; 95% CI, -0.06 to -0.18). There were no significant differences in ACQ-7 total score or the number of patients with ≥ 1 exacerbation.
  - In 3 studies comparing triple therapy (tiotropium with ICS/LABA) vs LABA with a high-dose ICS in patients with severe asthma, the analysis demonstrated significant improvements with triple therapy in morning and evening PEF (MD, 16 L/min; $p < 0.0004$ and 20 L/min; $p < 0.00001$, respectively). Peak and trough FEV_1 was also significantly greater with triple therapy (MD, 120 mL; 95% CI, 90 to 160 and 80 mL; 95% CI, 40 to 110, respectively). Triple therapy was associated with significant improvements in ACQ-7 and AQLQ (MD, -0.2 units; 95% CI, -0.25 to -0.09 and 0.12 units; 95% CI, 0.05 to 0.18, respectively). Patients treated with triple therapy also had a lower likelihood of experiencing ≥ 1 exacerbation (18.2% vs 24%; RR, 0.7; 95% CI, 0.53 to 0.94).

- A systematic review and meta-analysis (N = 3 studies; 895 patients) evaluated the use of tiotropium Respimat in adolescents aged 12 to 18 years with moderate to severe asthma. Patients were also receiving an ICS or ICS/LABA and the duration of the studies ranged from 4 to 48 weeks. Primary outcomes were peak and trough FEV_1 (*Rodrigo et al 2015b*).
  - Tiotropium was associated with significant improvements in peak and trough FEV_1 with mean changes from baseline of 120 mL and 100 mL vs placebo, respectively ($p < 0.001$ for both comparisons).
  - Benefits were also shown with tiotropium for the secondary endpoint of exacerbation risk. There were no significant differences in the rate of ACQ-7 response, rescue medication use, withdrawals, adverse events, or serious adverse events.
- A systematic review and meta-analysis (N = 3 studies; approximately 900 patients) evaluated the use of tiotropium Respimat in children aged 6 to 11 years with moderate to severe symptomatic asthma. Patients were also receiving maintenance therapy with ICS or ICS plus ≥ 1 controller medication and the duration of the studies ranged from 4 to 48 weeks. Primary outcomes were peak and trough FEV_1 (*Rodrigo et al 2017*).
  - Tiotropium demonstrated significant improvements in peak FEV_1 of 102 mL and trough FEV_1 of 82 mL vs placebo ($p < 0.0001$ for both comparisons).
  - Tiotropium significantly increased the rate of ACQ-7 responders ($p = 0.04$) and decreased the number of patients ≥ 1 exacerbations ($p = 0.002$) vs placebo.
  - There were no significant differences in rescue medication use, study withdrawals, adverse events, or withdrawals due to adverse events.
- A systematic review and meta-analysis (N = 5 studies; 2563 patients) evaluated the safety and efficacy of an ICS plus LAMA vs ICS alone in patients with asthma. The LAMA used was tiotropium Respimat in all studies, and the duration of treatment ranged from 12 to 52 weeks. All studies used a double-blind, double-dummy design. The primary outcomes included exacerbations requiring oral corticosteroids, quality of life, and all-cause serious adverse events (*Anderson et al 2015*).
  - Based on 4 studies in 2277 patients, the rate of exacerbations requiring oral corticosteroids was lower in patients taking a LAMA add-on than in those receiving the same dose of ICS alone (OR, 0.65; 95% CI, 0.46 to 0.93; $I^2 = 0\%$).
  - Based on 3 studies in 1713 patients, scores on the AQLQ were slightly higher for those taking a LAMA add-on compared to ICS alone (MD, 0.05; 95% CI, -0.03 to 0.12; $I^2 = 0\%$), but the difference was not statistically significant and was less than the established minimal clinically important difference of 0.5.
  - Based on 5 studies in 2,562 participants, patients taking a LAMA reported fewer serious adverse events, but the effect was too inconsistent and imprecise to suggest a definite benefit over an ICS alone (OR, 0.6; 95% CI, 0.23 to 1.57; $I^2 = 59\%$).
  - Benefits were also demonstrated with add-on LAMA therapy compared to ICS alone for the secondary endpoints including FEV_1 and PEF. Differences were not statistically significant for ACQ results or the number of exacerbations requiring hospitalization.
- A systematic review and meta-analysis compared the use of a LAMA vs a LABA when added to an ICS in patients with asthma. A total of 7 trials were included in the narrative review, and 4 of these trials (N = 2049) were included in the meta-analysis. All of the studies included in the meta-analysis used tiotropium as the LAMA and salmeterol as the LABA, and the duration of the trials ranged from 14 to 24 weeks. The primary outcomes included exacerbations requiring oral corticosteroids, quality of life, and serious adverse events (*Kew et al 2015*).
  - Based on 3 studies in 1753 patients, there was no significant difference in the rate of exacerbations requiring oral corticosteroids between the LAMA and LABA groups (OR, 1.05; 95% CI, 0.50 to 2.18).
  - Based on 4 studies in 1,745 patients, those treated with a LAMA scored slightly worse than those treated with a LABA for quality of life measured on the AQLQ (MD, -0.12; 95% CI, -0.18 to -0.05). The difference was statistically significant, but both results fell below the established minimal clinically important difference of 0.5.
  - There was no difference detected in the rate of serious adverse events (OR, 0.84; 95% CI, 0.41 to 1.73); however, the rate of serious adverse events was too low for this result to be considered reliable.
  - Secondary endpoints showed little or no difference between the LAMA and LABA groups; these included FEV_1, PEF, FVC, exacerbations requiring hospitalization, and ACQ results.
- A systematic review and meta-analysis evaluated the addition of a LAMA to adults with asthma not well controlled by an ICS/LABA. Three double-blind trials (total N = 1197) comparing LAMA to placebo were included, and all trials evaluated tiotropium (mostly 5 mcg once daily via Respimat) (*Kew et al 2016*).

- Based on 2 studies enrolling 907 patients, it was found that patients taking tiotropium plus an ICS/LABA had numerically fewer exacerbations requiring oral corticosteroids than those taking an ICS/LABA alone, but the confidence intervals did not rule out lack of a difference (OR, 0.75; 95% CI, 0.57 to 1.07). No benefit on quality of life was seen with the addition of tiotropium, based on results from the AQLQ (MD, 0.09; 95% CI, -0.03 to 0.20).
- Secondary endpoints demonstrated a benefit on lung function, but no significant improvement in exacerbations requiring hospital admission or scores on asthma control measured by the ACQ.

- A meta-analysis of 4 randomized controlled trials evaluated tiotropium when added to low- to medium-dose ICS in adults with moderate uncontrolled asthma, and found significant improvement with tiotropium in FEV percent predicted (3.46%; 95% CI, 2.20 to 4.63), peak FEV_1 (146.85 mL; (114.89 to 178.82), trough FEV_1 (122.03 mL; 95% CI, 92.92 to 151.13). These results were consistent among subgroups treated with different doses of tiotropium (*Wang et al 2018*).

CLINICAL GUIDELINES

COPD

- The 2019 GOLD guidelines state that the management strategy for stable COPD should be predominantly based on an assessment of the patient's symptoms and risk of exacerbations; the risk of exacerbations is based on a patient's exacerbation history. Key recommendations from the GOLD guidelines are as follows (*GOLD 2019*):
  - Inhaled bronchodilators are central to symptom management in COPD and commonly given on a regular basis to prevent or reduce symptoms.
    - Inhaled bronchodilators are recommended over oral bronchodilators.
  - LAMAs and LABAs significantly improve lung function, dyspnea, and health status, and reduce exacerbation rates.
    - LAMAs and LABAs are preferred over short-acting agents except for patients with only occasional dyspnea.
    - LAMAs have a greater effect on exacerbation reduction compared to LABAs and decrease hospitalizations.
  - Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on 1 bronchodilator, treatment should be escalated to 2 bronchodilators.
  - Combination treatment with a LABA and LAMA:
    - Reduces exacerbations compared to monotherapy or ICS/LABA.
    - Increases FEV_1 and reduces symptoms compared to monotherapy.
  - Long-term monotherapy with ICSs is not recommended. Long-term treatment with ICSs may be considered in association with LABAs for patients with a history of exacerbations despite treatment with long-acting bronchodilators.
  - Triple inhaled therapy of LAMA/LABA/ICS improves lung function, symptoms, and health status and reduces exacerbations compared to ICS/LABA or LAMA monotherapy.
  - Treatment recommendations are given for patients with COPD based on their GOLD patient group (see Table 3).
    - Group A: Patients should be offered bronchodilator treatment (short- or long-acting), based on its effect on breathlessness. This should be continued if symptomatic benefit is documented.
    - Group B: Initial therapy should consist of a long-acting bronchodilator (LAMA or LABA). For patients with persistent breathlessness on monotherapy, use of 2 bronchodilators is recommended (LAMA + LABA). For patients with severe breathlessness, initial therapy with 2 bronchodilators may be considered. If the addition of a second bronchodilator does not improve symptoms, it is suggested that treatment could be stepped down to a single bronchodilator; switching to another device or molecules can also be considered.
    - Group C: Initial therapy should be a LAMA. Patients with persistent exacerbations may benefit from adding a second long-acting bronchodilator (LAMA + LABA, preferred) or using an ICS + LABA. For patients who have a history and/or findings suggestive of asthma-COPD overlap or blood eosinophil count ≥ 300 cells/µL, ICS + LABA is preferred.
    - Group D: In general, it is recommended to start therapy with a LAMA. For patients with more severe symptoms, especially dyspnea and/or exercise limitation, LAMA/LABA may be considered for initial treatment. In some patients, initial therapy with an ICS + LABA may be the first choice; these patients may have a history and/or findings suggestive of asthma-COPD overlap or blood eosinophil count ≥ 300 cells/µL. In patients who develop further exacerbations on LAMA + LABA therapy, alternative pathways include escalation to a LAMA + LABA + ICS (preferred) or a switch to an ICS + LABA. If patients treated with a LAMA + LABA + ICS still have exacerbations, options for selected patients may include addition of roflumilast, addition of a macrolide, or stopping the ICS.

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

Exacerbation history	Symptoms

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

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

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

Asthma

- The National Asthma Education and Prevention Program (NAEPP) guideline from the NHLBI states that the initial treatment of asthma should correspond to the appropriate asthma severity category, and it provides a stepwise approach to asthma management. Long-term control medications such as ICSs, long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline, and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. ICSs are the most potent and consistently effective long-term asthma control medication. Quick-relief medications such as SABAs and anticholinergics are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness, and wheezing. Systemic corticosteroids are important in the treatment of moderate or severe exacerbations because these medications prevent progression of the exacerbation, speed recovery, and prevent relapses (*NHLBI 2007*).
  - Ipratropium provides additive benefit to a SABA in moderate-to-severe asthma exacerbations, and may be used as an alternative bronchodilator for patients who do not tolerate a SABA.
  - The guideline states that ipratropium and tiotropium have not demonstrated effectiveness in the long-term management of asthma; however, it should be noted that this guideline has not been updated since 2007.
- The GINA guideline also provides a stepwise approach to asthma management. It recommends an ICS as a preferred initial controller medication choice, with an increased ICS dose and/or addition of a LABA for increasing symptom severity (higher steps). At the highest step, it is recommended that the patient be referred for add-on treatment (eg, tiotropium, anti-IgE, or anti-IL5 agent) (*GINA 2018*).
  - Tiotropium by mist inhaler is recommended as an add-on controller option in patients at higher steps (4 and 5). At step 4, it is recommended under “other controller options” (not preferred), and at step 5, it is recommended as one of several preferred add-on treatment options. In this setting, tiotropium is recommended as an add-on treatment for patients with a history of exacerbations; however, the guideline states that tiotropium is not for use in children less than 12 years of age.
  - Add-on tiotropium by mist inhaler improves lung function and increases the time to severe exacerbation.
- A guideline on the definition, evaluation, and treatment of severe asthma is available from the European Respiratory Society (ERS) and the American Thoracic Society (ATS) (*Chung et al 2014*).
  - The guideline notes that ipratropium is commonly used in severe asthma patients in an attempt to reduce the daily use of beta$_2$-agonists, as well as in the treatment of asthma exacerbations. Although considered to be less effective, ipratropium is well tolerated and may be used alternately with beta$_2$-agonists for as-needed use throughout the day.
  - Tiotropium has been shown to improve lung function and symptoms in moderate-to-severe asthma patients not controlled on a moderate- to high-dose ICS with or without a LABA. In patients taking high doses of an ICS and a LABA, the addition of tiotropium has provided improvements in FEV$_1$, reduced as-needed SABA use, and modestly reduced the risk of a severe exacerbation. However, there have been no studies of tiotropium in children with asthma.

SAFETY SUMMARY

- Ipratropium solution and Atrovent HFA are contraindicated in patients with hypersensitivity to ipratropium, atropine and its derivatives, or components of the product. Incruse Ellipta and Tudorza Pressair are contraindicated in patients with severe hypersensitivity to milk proteins or hypersensitivity to any ingredient. Seebri Neohaler and Lonhala Magnair are contraindicated in patients with known hypersensitivity to glycopyrrolate or any of the product ingredients. Spiriva Handihaler and Spiriva Respimat are contraindicated in patients with hypersensitivity to tiotropium, ipratropium, or

components of the product. Yupelri (revefenacin) is contraindicated in patients with hypersensitivity to revefenacin or components of the product.

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

DOSING AND ADMINISTRATION

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

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Atrovent HFA (ipratropium bromide)	Inhalation aerosol	Inhalation	Four times a day	• May use additional inhalations as required; maximum 12 inhalations per 24 hours • Canister-style inhaler; requires inserting the canister and priming before use • Hand/breath coordination is required
Incruse Ellipta (umeclidinium)	Inhalation powder	Inhalation	Once daily	• Disc-shaped inhaler with self-contained foil blister strips; opening the inhaler prepares a dose • Breath-activated; hand/breath coordination not required
ipratropium bromide solution	Inhalation solution	Inhalation (with nebulizer)	Three to 4 times per day	• May be mixed in nebulizer with albuterol or metaproterenol if used within 1 hour
Lonhala Magnair (glycopyrrolate)	Inhalation solution	Inhalation (with nebulizer)	Twice daily	• Lonhala should only be administered with the Magnair device. • Supplied in vials with complete Magnair nebulizer system (starter kit) or refill handset (refill kit)

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				• 2 to 3 minutes to administer, plus cleaning/prep time
Seebri Neohaler (glycopyrrolate)	Inhalation powder	Inhalation	Twice daily	• Capsules should not be swallowed • Dry powder inhaler; requires insertion of a capsule into the inhaler and piercing before each dose • Breath-activated; hand/breath coordination not required
Spiriva Handihaler (tiotropium bromide)	Inhalation powder	Inhalation	Once daily	• Capsules should not be swallowed • Dry powder inhaler; requires insertion of a capsule into the inhaler and piercing before each dose • Breath-activated; hand/breath coordination not required
Spiriva Respimat (tiotropium bromide)	Inhalation spray	Inhalation	Once daily	• Inhaler should be primed before first use and if not used for > 3 days; if not used for > 21 days, inhaler should be actuated until an aerosol cloud is visible, and then the process should be repeated 3 more times to prepare the inhaler for use. • Maximum benefits in asthma treatment may take up to 4 to 8 weeks • Canister-style inhaler; requires inserting the canister and priming before use • Twisting the canister prepares a dose for inhalation • Hand/breath coordination is required
Tudorza Pressair (aclidinium bromide)	Inhalation powder	Inhalation	Twice daily	• Dry powder inhaler; pressing a button prepares a dose • Breath-activated; hand/breath coordination not required
Yupelri (revefenacin)	Inhalation solution	Inhalation (with nebulizer)	Once daily	• The safety and efficacy of revefenacin delivered from non-compressor based nebulizer systems have not been established. • Unit-dose vial should only be removed from the foil pouch and opened immediately before use. • Revefenacin should not be mixed with any other medications. • Treatment requires 8 minutes for administration, plus cleaning/prep time.

See the current prescribing information for full details.

CONCLUSION

- The respiratory anticholinergics are used predominantly for the management of COPD, with an additional asthma indication specific to Spiriva Respimat (tiotropium).
  - Short-acting respiratory anticholinergics include Atrovent HFA (ipratropium bromide) inhalation aerosol and ipratropium bromide solution for nebulization.
  - The LAMAs include 5 molecular entities in 6 formulations: Incruse Ellipta (umeclidinium) inhalation powder, Lonhala Magnair (glycopyrrolate) inhalation solution and Seebri Neohaler (glycopyrrolate) inhalation powder, Spiriva

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

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

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Therapeutic Class Overview
Respiratory Beta-Agonist Combination Agents

INTRODUCTION

- Respiratory beta$_2$-agonist combination agents include a beta$_2$-agonist combined with an inhaled corticosteroid (ICS), inhaled anticholinergic, or both. Beta$_2$-agonists can be short-acting beta$_2$-agonists (SABA) or long-acting beta$_2$-agonists (LABA); most combinations contain a LABA. Similarly, inhaled anticholinergics, also known as muscarinic antagonists, can be short-acting muscarinic antagonists (SAMA) or long-acting muscarinic antagonists (LAMA); most combinations contain a LAMA.
- Individual beta$_2$-agonist combinations are Food and Drug Administration (FDA) approved for the treatment of asthma, chronic obstructive pulmonary disease (COPD), or both.
  - All combinations of a beta2-agonist and an ICS are indicated for the treatment of asthma, and some are additionally indicated for the treatment of COPD.
  - Combinations of a beta$_2$-agonist and an anticholinergic medication are indicated for COPD, as is the one available LAMA/LABA/ICS triple combination agent.
  - Refer to Tables 2A, 2B, and 2C for specific indications for each product.
- Asthma is a chronic lung disease that inflames and narrows the airways. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing. Asthma affects people of all ages, but most often starts during childhood. In the United States (U.S.), more than 25 million people are known to have asthma, including about 7 million children (*National Heart, Lung, and Blood Institute [NHLBI] 2017*).
- COPD is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities. The abnormalities are usually caused by exposure to noxious particles or gases, and cigarette smoking is a key risk factor. Airflow limitation is caused by a combination of small airway disease (eg, obstructive bronchiolitis) and parenchymal destruction (emphysema). The most common symptoms of COPD include dyspnea, cough, and sputum production (*Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2019*). COPD affects 6.4% of the U.S. population and is a major contributor to mortality from chronic lower respiratory diseases, the third leading cause of death in the U.S. (*Centers for Disease Control and Prevention 2018*).
- Medispan class/subclass: Sympathomimetics/Adrenergic Combinations

Table 1. Medications Included Within Class Review

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

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

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

INDICATIONS

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

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

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

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

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

(*Prescribing information: Anoro Ellipta 2017, Bevespi Aerosphere 2017, Combivent Respimat 2016, ipratropium/albuterol solution 2015, Stiolto Respimat 2018, Utibron Neohaler 2017*)

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

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

(*Trelegy Ellipta prescribing information 2018*)

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

CLINICAL EFFICACY SUMMARY

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

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

- Numerous trials have compared the combination ICS/LABA products to their respective individual components as monotherapy, and in general, results have demonstrated that administration of the combination product is more effective than monotherapy for improving lung function and/or achieving control of symptoms in asthma and COPD (*Bateman et al 2001, Bateman et al 2004, Bateman et al 2006, Bateman et al 2014, Bateman et al 2018, Berger et al 2010, Bernstein et al 2015, Bleecker et al 2014, Calverley et al 2003, Corren et al 2007, Eid et al 2010, FDA AirDuo RespiClick Medical Review 2017, Gappa et al 2009, Hanania et al 2003, Jenkins et al 2006, Kerwin et al 2009, Kerwin et al 2013, Kuna et al 2006, Lalloo et al 2003, Lundback et al 2006, Martinez et al 2013, Meltzer et al 2012, Morice et al 2007, Murphy et al 2008, Nelson et al 2003a, Nathan et al 2006, Noonan et al 2006, O'Byrne et al 2014, Pearlman et al 2004, Pearlman et al 2017, Pohl et al 2006, Raphael et al 2018, Rennard et al 2009, Rodrigo et al 2016, Rodrigo et al 2017, Sharafkaneh et al 2012, Sher et al 2017, Tal et al 2002, Tashkin et al 2008, Vaessen-Verberne et al 2010, Vestbo et al 2005, Weinstein et al 2010*). Results for reducing COPD exacerbations have been inconsistent (*Dransfield et al 2013, Ohar et al 2014*).
- Although a synergistic effect of combination inhalers has been suggested by some data, overall there are similar efficacy between the administration of the combination ICS/LABA products and their individual components used in combination (*Chapman et al 1999, Jenkins et al 2006, Marceau et al 2006, Nelson et al 2003b, Noonan et al 2006, Perrin et al 2010, Rosenhall et al 2002*). Improved adherence with combination inhalers has also been suggested but not been shown conclusively (*Marceau et al 2006, Perrin et al 2010*).
- A large, double-blind, randomized trial (N = 6112) compared fluticasone propionate/salmeterol 500/50 mcg twice daily to its individual components and to placebo over a 3-year period in patients with COPD (*Calverley et al 2007*). The primary endpoint, time to death from any cause, for the combination vs placebo failed to reach statistical significance (12.6% vs 15.2%; p = 0.052). However, the difference in mortality between the combination therapy and fluticasone monotherapy did reach statistical significance (12.6% vs 16%; p = 0.007). Treatment with the combination regimen resulted in significantly fewer exacerbations, improved health status, and improved lung function compared with placebo.
- A large, double-blind, randomized trial (SUMMIT; N = 16,590) evaluated the use of fluticasone furoate/vilanterol vs fluticasone furoate alone, vilanterol alone, or placebo in a population of patients with moderate COPD and heightened cardiovascular risk (age ≥ 60 years and receiving medication for >2 of the following: hypercholesterolemia, hypertension, diabetes mellitus, or peripheral arterial disease) (*Vestbo et al 2016a*). Compared with placebo, there was no significant benefit or worsening in all-cause mortality with combination therapy (hazard ratio [HR], 0.88 [95% confidence interval (CI), 0.74 to 1.04; p = 0.137]) or with the components (fluticasone furoate HR, 0.91 [95% CI, 0.77 to 1.08; p = 0.284]; vilanterol HR, 0.96 [95% CI, 0.81 to 1.14; p = 0.655]). Composite cardiovascular events were also similar in the 4 groups (3.9% to 4.4%). All treatments reduced the risk of moderate to severe COPD exacerbations compared to placebo, with percent reductions of 29% (95% CI, 22 to 35), 12% (95% CI, 4 to 19), and 10% (95% CI, 2 to 18) in the fluticasone furoate/vilanterol, fluticasone furoate, and vilanterol groups, respectively.
- A 12-month, randomized, open-label trial (Salford Lung Study; N = 2799) compared the use of fluticasone furoate/vilanterol 100/25 mcg daily to continuation of usual care in a real-world patient population in the United Kingdom (*Vestbo et al 2016b*). Enrolled patients had COPD, had had ≥ 1 exacerbations in the previous 3 years, and were taking regular maintenance inhaler therapy (≥ 1 long-acting bronchodilators; ICS alone or in combination with a long-acting bronchodilator; or a combination of ICS, LABA, and LAMA). The primary endpoint, the rate of moderate or severe exacerbations among patients who had had an exacerbation within 1 year before the trial, was 1.74 per year in the fluticasone furoate/vilanterol group and 1.90 per year in the usual-care group, for a difference of 8.4% (95% CI, 1.1 to 15.2; p = 0.02). Serious adverse events, including pneumonia, were similar between the 2 groups.
- A meta-analysis of 19 trials evaluated the use of ICS/LABA combinations compared to placebo in patients with COPD, and demonstrated a significant reduction in exacerbation rate between fluticasone propionate/salmeterol and placebo and between budesonide/formoterol and placebo (*Nannini et al 2013a*). For the number of patients who experienced ≥ 1 exacerbations, the differences between fluticasone propionate/salmeterol vs placebo and mometasone furoate/formoterol 200/10 mcg strength vs placebo were not statistically significant; however, the mometasone

furoate/formoterol 400/10 mcg strength was associated with a lower proportion of patients experiencing ≥ 1 exacerbation. This meta-analysis also demonstrated that when results for all combined inhalers vs placebo were pooled, there was an overall reduction in mortality (odds ratio [OR], 0.82; 95% CI, 0.68 to 0.99).

- A meta-analysis of 14 trials evaluated the use of ICS/LABA combinations compared to use of the same LABA as monotherapy in patients with COPD (*Nannini et al 2012*). This analysis demonstrated that exacerbation rates were reduced with ICS/LABA combination therapy compared to LABA monotherapy (rate ratio, 0.76; 95% CI, 0.68 to 0.84). However, there was a significant increase in the incidence of pneumonia with combination therapy compared to LABA monotherapy (OR, 1.55; 95% CI, 1.2 to 2.01).
- A meta-analysis of 15 trials evaluated the use of ICS/LABA combinations compared to use of ICS monotherapy in patients with COPD (*Nannini et al 2013b*). This analysis demonstrated that exacerbation rates were significantly reduced with ICS/LABA combination therapy vs ICS monotherapy (rate ratio, 0.87; 95% CI, 0.80 to 0.94). Adverse events were similar between treatments; pneumonia rates as diagnosed by chest x-ray were lower than those reported in earlier trials.
- A meta-analysis of 14 trials (total N = 6641) compared fluticasone furoate/vilanterol to placebo, fluticasone furoate monotherapy, fluticasone propionate monotherapy, vilanterol monotherapy, or fluticasone propionate/salmeterol in patients with asthma (*Dwan et al 2016*). Primary endpoints included health-related quality of life (HRQoL) and severe asthma exacerbations (defined by hospital admission or treatment with oral corticosteroids). Fewer than half of the studies reported on these primary endpoints, and there were few opportunities to combine results from the included studies. One of the 14 studies evaluated HRQoL (as measured by the Asthma Quality of Life Questionnaire [AQLQ]) for fluticasone furoate/vilanterol 100/25 mcg vs placebo; it identified a significant advantage of fluticasone furoate/vilanterol (mean difference, 0.30; 95% CI, 0.14 to 0.46). Two studies compared fluticasone furoate/vilanterol 100/25 mcg vs placebo with respect to exacerbations; both studies reported no exacerbations in either treatment arm. No comparisons relevant to the primary outcomes were found for fluticasone furoate/vilanterol at a higher dose (200/25 mcg) vs placebo. There was insufficient evidence to assess whether once-daily fluticasone furoate/vilanterol had better or worse safety or efficacy compared to twice-daily fluticasone propionate/salmeterol. The authors stated that firm conclusions could not be drawn due to the limited number of studies, variety of endpoints, and short duration of most trials.
- Several large studies focused primarily on safety endpoints, with efficacy endpoints as secondary (*Peters et al 2016, Stempel et al 2016a, Stempel et al 2016b*). The studies compared the use of ICS/LABA combinations to ICS monotherapy in patients with asthma. These studies each demonstrated non-inferiority of the ICS/LABA combination to ICS monotherapy for the risk of serious asthma-related events, offering reassurance for the safety of these agents.
  - A randomized, double-blind study (AUSTRI; N = 11,679) enrolled adults and adolescents (age ≥ 12 years) with persistent asthma and a history of exacerbation within the previous year (*Stempel et al 2016a*). Patients were randomized to receive fluticasone propionate/salmeterol or fluticasone propionate monotherapy for 26 weeks. Patients were stratified by their baseline asthma control questionnaire (ACQ)-6 score and current asthma medication to determine the fluticasone propionate dose (100, 250, or 500 mcg twice daily) and were randomized to receive this dose with or without concomitant salmeterol.
    - The primary safety endpoint was the first serious asthma-related event, a composite endpoint that included death, endotracheal intubation, and hospitalization. There were 36 events in 34 patients in the fluticasone propionate/salmeterol group and 38 events in 33 patients in the fluticasone propionate group (HR, 1.03; 95% CI, 0.64 to 1.66). Fluticasone propionate/salmeterol was shown to be non-inferior to fluticasone propionate for this endpoint. There were no asthma-related deaths.
    - The main efficacy endpoint was the first severe asthma exacerbation, defined as asthma deterioration leading to the use of systemic glucocorticoids for ≥ 3 days or an asthma-related hospitalization or emergency department visit leading to the use of systemic glucocorticoids. At least 1 severe asthma exacerbation was reported in 480 patients (8%) in the fluticasone propionate/salmeterol group and in 597 patients (10%) in the fluticasone propionate group (HR, 0.79; 95% CI, 0.70 to 0.89; p < 0.001).
  - A similarly designed trial (VESTRI; N = 6208) enrolled pediatric patients 4 to 11 years of age (*Stempel et al 2016b*). Enrolled patients had a history of exacerbation within the previous year and consistent use of asthma medication during the 4 weeks before enrollment. Patients were randomized, on the basis of pretrial medication, Childhood Asthma Control Test (C-ACT) score, and exacerbation history, to receive fluticasone propionate/salmeterol 100/50 mcg or 250/50 mcg or fluticasone propionate alone 100 mcg or 250 mcg twice daily for 26 weeks.
    - The primary safety endpoint, the first serious asthma-related event (death, intubation, or hospitalization), occurred in 27 patients in the fluticasone propionate/salmeterol group and 21 patients in the fluticasone propionate group

(HR, 1.28; 95% CI, 0.73 to 2.27); this demonstrated non-inferiority for fluticasone propionate/salmeterol compared to fluticasone propionate (p = 0.006). All of the events were asthma-related hospitalizations; there were no deaths or asthma-related intubations in either group.
    - The primary efficacy endpoint was the first severe asthma exacerbation, defined as asthma deterioration leading to the use of systemic glucocorticoids for ≥ 3 days or a depot injection of glucocorticoids. One or more severe asthma exacerbations occurred in 8.5% of patients in the fluticasone propionate/salmeterol group and 10.0% of patients in the fluticasone propionate group (HR, 0.86; 95% CI, 0.73 to 1.01).
  - An additional randomized, double-blind trial (N = 11,693) compared the safety of formoterol/budesonide to budesonide alone in patients ≥ 12 years of age (*Peters et al 2016*). Enrolled patients were receiving daily asthma medication and had had ≥ 1 exacerbation in the previous year. Patients were stratified to a dose level of budesonide on the basis of asthma control and prior treatment. Patients were then randomized to receive budesonide/formoterol (2 actuations of 80/4.5 mcg or 160/4.5 mcg) or budesonide alone (2 actuations of 80 mcg or 160 mcg) twice daily for 26 weeks.
    - The primary safety endpoint, the first serious adverse event (death, intubation, or hospitalization), occurred in 43 of 5,846 patients receiving budesonide/formoterol and 40 of 5,847 patients receiving formoterol alone (HR, 1.07; 95% CI, 0.70 to 1.65); this demonstrated non-inferiority for budesonide/formoterol vs budesonide alone. Two of the events (both in the budesonide/formoterol group) were asthma-related deaths; the remaining events were asthma-related hospitalizations.
    - The primary efficacy endpoint, the first asthma exacerbation (defined as a deterioration of asthma requiring systemic glucocorticoids for ≥ 3 days, inpatient hospitalization for asthma, or an emergency department visit for asthma that resulted in receipt of systemic glucocorticoids) occurred in 9.2% of patients in the budesonide/formoterol group and 10.8% of patients in the budesonide group (HR, 0.84; 95% CI, 0.74 to 0.94).
  - A trial of 4215 patients ≥ 12 years of age with mild asthma found that budesonide/formoterol as needed was noninferior to budesonide twice daily for the reduction of severe asthma exacerbation. The annualized rate of severe exacerbations was 0.11 (95% CI, 0.10 to 0.13) and 0.12 (95% CI, 0.10 to 0.14), respectively (rate ratio, 0.97; upper one-sided 95% confidence limit, 1.16) However, budesonide/formoterol was inferior to budesonide for symptom control as the change in ACQ-5 score showed a difference of 0.11 units (95% CI, 0.07 to 0.15) in favor of budesonide maintenance therapy (*Bateman et al 2018*).

Comparisons between different ICS/LABA combinations

- There are some data available comparing different combination ICS/LABA products for the treatment of COPD.
  - One crossover study comparing budesonide/formoterol to fluticasone propionate/salmeterol demonstrated no significant difference between products for the primary endpoint, the increase from baseline in peak expiratory flow 5 minutes after the morning dose (*Partridge et al 2009*). However, the mean morning forced expiratory volume in 1 second (FEV_1) improved more with budesonide/formoterol at 5 minutes and 15 minutes post-dose compared to fluticasone propionate/salmeterol.
  - Several published trials compared fluticasone furoate/vilanterol to fluticasone propionate/salmeterol in patients with COPD. Three of the trials were published together; pooled results demonstrated a greater improvement with fluticasone furoate/vilanterol 100/25 mcg once daily compared to fluticasone propionate/salmeterol 250/50 mcg twice daily on the primary endpoint, the weighted mean (wm) FEV_1 (0 to 24 hr) (*Dransfield et al 2014*). However, 2 of these 3 trials did not demonstrate a significant difference on this endpoint. An additional trial compared fluticasone furoate/vilanterol 100/25 mcg daily to fluticasone propionate/salmeterol 500/50 mcg twice daily, and found no significant difference between groups on the wm FEV_1 (0 to 24 hr) (*Agusti et al 2014*).
- There have been several trials comparing combination ICS/LABA products to one another for the treatment of asthma.
  - Several head-to-head trials have compared budesonide/formoterol to fluticasone propionate/salmeterol. The trials varied in their design and the doses of medications. In general, these head-to-head trials have failed to demonstrate that one product is consistently superior to the other. Some trials showed benefits for fluticasone propionate/salmeterol on some endpoints (*Dahl et al 2006, Fitzgerald et al 2005, Price et al 2007*); some showed benefits for budesonide/formoterol (*Aalbers et al 2004, Palmqvist et al 2001*), and another showed no significant differences between the 2 products (*Busse et al 2008*).
  - A meta-analysis of 5 trials comparing fluticasone propionate/salmeterol 250/50 mcg twice daily vs varied doses of budesonide/formoterol twice daily failed to demonstrate significant differences in exacerbations, asthma-related serious adverse events, FEV_1, rescue medication use, symptom scores, or peak expiratory flow (*Lasserson et al 2011*).

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

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

- A double-blind, double-dummy, 2-year trial (N = 1323) compared the use of fluticasone propionate/salmeterol 250/50 mcg twice daily to tiotropium 18 mcg daily in patients with COPD (*Wedzicha et al 2008*). This trial demonstrated no significant difference between groups in the rate of exacerbations or post-dose FEV_1. The study demonstrated higher mortality in the tiotropium group (6%) compared to the fluticasone propionate/salmeterol group (3%). This study was limited by the high number of withdrawals, which were unevenly distributed between the study arms.
- A double-blind, double-dummy, 12-week trial (N = 494) compared the use of umeclidinium/vilanterol 62.5/25 mcg daily to tiotropium 18 mcg daily in patients with COPD who had been treated with tiotropium monotherapy at the time of enrollment (*Kerwin et al 2017a*). The primary endpoint, trough FEV_1, showed improved efficacy in the group that stepped up to combination therapy, with a between-group difference of 88 mL (95% CI, 45 to 131; $p < 0.001$). Improvements with umeclidinium/vilanterol were also observed in some secondary endpoints, including the use of rescue medication use and transition dyspnea index (TDI) score.
- A double-blind, double-dummy, 12-week trial (N = 623) evaluated the use of fluticasone furoate/vilanterol 100/25 mcg daily and tiotropium 18 mcg daily in patients with moderate-to-severe COPD and an increased cardiovascular risk (*Covelli et al 2016*). There was no significant difference in the primary endpoint, the change from baseline in wm FEV_1 (0 to 24 hr). Minor differences were noted in some secondary efficacy endpoints and in the safety profiles. Pneumonia occurred more frequently in the fluticasone furoate/vilanterol group, and 2 patients in the tiotropium group died following cardiovascular events. The duration of this trial was not long enough to allow any firm conclusions about the relative efficacy and safety of fluticasone furoate/vilanterol vs tiotropium.
- In a Cochrane review that included the *Covelli et al 2016* trial and 1 additional 12 week trial comparing tiotropium to fluticasone furoate/vilanterol (N = 880 across both trials), there were no differences between treatments when considering the following outcomes: mortality, COPD exacerbation, pneumonia, St. George's respiratory questionnaire (SGRQ) score, hospital admissions, or use of rescue medication (*Sliwka et al 2018*).
- Several trials have evaluated the potential benefits of adding a combination ICS/LABA to tiotropium vs the use of tiotropium alone in patients with COPD. These trials generally demonstrated an improvement in FEV_1 and some other lung function, symptom score, and quality-of-life endpoints (*Hanania et al 2012, Lee et al 2016, Rojas-Reyes et al 2016, Welte et al 2009*). Some trials (*Lee et al 2016, Welte et al 2009*) also demonstrated a reduction in the risk of COPD exacerbations or severe exacerbations; however, other trials and a meta-analysis have not confirmed a significant benefit for exacerbations (*Aaron et al 2007, Hanania et al 2012, Karner et al 2011, Rojas-Reyes et al 2016*).

Beta$_2$-agonist/anticholinergic combinations for COPD

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

- Numerous trials have compared the combination beta$_2$-agonist/anticholinergic products to their respective individual components as monotherapy, and in general, results have demonstrated that administration of the combination product is more effective than monotherapy for improving lung function and/or achieving control of symptoms in COPD (*Beeh et al 2015, Bone et al 1994, Buhl et al 2015, Decramer et al 2014, Donohue et al 2013, Dorinsky et al 1999, Friedman et al 1999, Hanania et al 2017, Mahler et al 2015, Martinez et al 2017*).
- A large, randomized-controlled trial (N = 7880) of patients with COPD and a history of exacerbations did not find a difference in the rate of exacerbations between LAMA/LABA therapy with tiotropium/olodaterol vs LAMA therapy with tiotropium (relative risk [RR], 0.93; 99% CI, 0.85 to 1.02; $p = 0.0498$) (*Calverley et al 2018*).

- A systematic review of 23 studies of beta$_2$-agonist/anticholinergic combinations compared to their monocomponents and to other single-agent treatments in patients with COPD was conducted (*Price et al 2016*). The analysis demonstrated that beta$_2$-agonist/anticholinergic combinations significantly improved lung function compared to their individual components. These combinations generally improved other outcomes compared to monotherapies as well, including symptoms and health status, but there were some discrepancies between lung function results and these patient-reported outcomes.
- A systematic review and network meta-analysis (N = 74 trials; 74,832 participants) evaluated the efficacy of SAMAs, LABAs, LAMA/LABAs and LABA/ICSs for maintenance treatment of COPD. At 12 and 24 weeks, LAMA, LAMA/LABAs, and LABA/ICSs led to a significantly greater improvement in trough FEV$_1$ compared with placebo and SAMA monotherapy. With the exception of aclidinium/formoterol, all other LAMA/LABA therapies were superior to LAMA monotherapy and LABA/ICS therapy in improving trough FEV$_1$. Furthermore, LAMA/LABA therapy had the highest probability of being the best treatment for in FEV$_1$ improvement; similar trends were observed for the transition dyspnea index and SGRQ scores. Authors concluded that there were no significant differences among the LAMAs and LAMA/LABAs within their respective classes (*Aziz et al 2018*).
- A systematic review and meta-analysis (N = 8 trials) compared tiotropium 5 or 18 mcg with LAMA/LABA therapy in patients with moderate-to-severe COPD; ICS therapy was also allowed and use ranged from 33.7% to 54.4% among included trials. Therapy with LABA/LAMA was superior to tiotropium monotherapy for all of the following outcomes at 12 and 24 weeks: FEV$_1$ peak and trough, SGRQ responder rate, mean SGRQ score, and use of rescue medication. At 12 weeks, LABA/LAMA improved FEV$_1$ trough by 63 ml compared to tiotropium alone (95% CI, 39.2 to 86.8; $p < 0.01$). During the same time period, LABA/LAMA improved mean SGRQ responder rate by 19% (RR, 1.19; 95% CI, 1.09 to 1.28; $p < 0.01$) and reduced SGRQ total score by 1.87 points (95% CI, -2.72 to -1.02; $p < 0.01$) compared to tiotropium (*Han et al 2018).*

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

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

- The analysis by *Sion et al* noted that both Utibron Neohaler (glycopyrrolate/indacaterol) and Anoro Ellipta (umeclidinium/vilanterol) appeared to improve lung function to a greater extent than Stiolto Respimat (tiotropium/olodaterol) at 12 weeks, with differences in trough FEV_1 of 52 mL (95% credible interval [CrI], 18 to 86) and 38 mL (95% CrI, 13 to 63), respectively.
- The *Schlueter et al* meta-analysis included 27 trials (N = 30,361) including 4 LAMA/LABA fixed-dose combination agents (aclidinium/formoterol 400/12 mcg [not FDA approved for use in the U.S.], glycopyrrolate/indacaterol 110/50 mcg, tiotropium/olodaterol 5/5 mcg, and umeclidinium/vilanterol 62.5/25 mcg), and showed non-significant differences in efficacy, exacerbations, and discontinuation rates (*Schlueter et al 2016*). Safety profiles were also similar among the products.

ICS/LABA compared to LAMA/LABA combinations for COPD

- A randomized, double-blind, 12-week trial (N = 717) compared umeclidinium/vilanterol 62.5/25 mcg once daily to fluticasone propionate/salmeterol 500/50 mcg twice daily in patients with moderate to severe COPD and no exacerbations in the previous year (*Singh et al 2015*). It should be noted that the dose of fluticasone propionate was higher than what is recommended in the U.S. for treatment of COPD. Treatment with umeclidinium/vilanterol resulted in greater improvement in lung function than fluticasone propionate/salmeterol, with a difference of 80 mL (95% CI, 46 to 113) in the wm FEV_1 (0 to 24 hr) and a difference of 90 mL (95% CI, 55 to 125) in trough FEV_1. Effects on rescue bronchodilator use, mean TDI focal score, and SGRQ total scores, and the incidence of adverse events, were similar between groups.
- Two randomized, double-blind, 12-week trials (N = 707 and N = 700; reported together) compared umeclidinium/vilanterol 62.5/25 mcg daily to fluticasone propionate/salmeterol 250/50 mcg twice daily in patients with moderate to severe COPD without exacerbations in the previous year (*Donohue et al 2015*). These trials also demonstrated a greater improvement in lung function endpoints for umeclidinium/vilanterol compared to fluticasone propionate/salmeterol, with differences in wm FEV_1 (0 to 24 hr) and trough FEV_1 ranging from 74 to 101 mL ($p < 0.001$ for all comparisons). Adverse event rates and effects on TDI score and SGRQ were similar between groups.
- A randomized, double-blind, 26-week trial (ILLUMINATE; N = 523) compared indacaterol/glycopyrrolate 110/50 mcg daily to fluticasone propionate/salmeterol 500/50 mcg twice daily in patients with COPD and a history of ≥ 1 exacerbation during the previous year (*Vogelmeier et al 2013*). The dosing regimens for indacaterol/glycopyrrolate and fluticasone propionate/salmeterol evaluated in this study are different from those available and/or recommended for COPD in the U.S. The primary endpoint, FEV_1 AUC (0 to 12 hr), was significantly higher with indacaterol/glycopyrrolate than fluticasone propionate/salmeterol, with a treatment difference of 138 mL (95% CI, 100 to 176; $p < 0.0001$). Benefits were also seen for indacaterol/glycopyrrolate for some secondary endpoints, including additional lung function measures, change from baseline in rescue medication use, and TDI focal score; the difference in SGRQ was not statistically significant.
- A large, randomized, double-blind, 52-week trial (FLAME; N = 3362) compared indacaterol/glycopyrrolate 110/50 mcg daily to fluticasone propionate/salmeterol 500/50 mcg twice daily in patients with COPD and a history of ≥ 1 exacerbation during the previous year (*Wedzicha et al 2016*). Again, these dosing regimens varied from U.S. recommendations. The primary endpoint, the annual rate of all COPD exacerbations, was 11% lower in the indacaterol/glycopyrrolate group than in the fluticasone propionate/salmeterol group (3.59 vs 4.03; rate ratio, 0.89; 95% CI, 0.83 to 0.96; $p = 0.003$). Lung function was also improved to a greater extent with indacaterol/glycopyrrolate, with a difference in trough FEV_1 of 62 mL between groups ($p < 0.001$).
- A randomized, double-blind, crossover trial (N = 229) evaluated the use of tiotropium/olodaterol 2.5/5 mcg and 5/5 mcg once daily and fluticasone propionate/salmeterol 250/50 mcg and 500/50 mcg twice daily in patients with moderate to severe COPD; each patient received each of the 4 treatments for 6 weeks separated by 3-week washout periods (*Beeh et al 2016*). The lower dose of each combination is the dose available/recommended for COPD in the U.S. The primary endpoint, FEV_1 AUC (0 to 12 hr), was greater for the tiotropium/olodaterol regimens (range, 295 to 317 mL) than for the fluticasone propionate/salmeterol regimens (range, 188 to 192 mL) ($p < 0.0001$). FEV_1 AUC (12 to 24 hr) and FEV_1 AUC (0 to 24 hr) also favored tiotropium/olodaterol. Rates of adverse events were similar among the treatments.

Triple combination for COPD

- Fluticasone furoate/umeclidinium/vilanterol is the first FDA-approved “closed triple” inhaler – an inhaler containing 3 active ingredients: an ICS, a LAMA, and a LABA. FDA approval was based primarily on the coadministration of umeclidinium plus the fluticasone furoate/vilanterol combination.

- Two 12-week randomized studies (N = 619 and N = 620; published together) evaluated the efficacy and safety of double-blind treatment with umeclidinium 62.5 mcg, umeclidinium 125 mcg, or placebo when added to open-label fluticasone furoate/vilanterol 100/25 mcg (*Siler et al 2015*). In both studies, the primary endpoint, trough FEV_1, was significantly improved with the addition of umeclidinium, with improvements ranging from 111 to 128 mL ($p < 0.001$ for all comparisons vs placebo). Improvement was also demonstrated on the secondary endpoint of wm FEV_1 (0 to 6 hr), with improvements ranging from 125 to 153 mL ($p < 0.001$ for all comparisons vs placebo). SGRQ results were inconsistent. No substantial benefit was observed with umeclidinium 125 mcg over 62.5 mcg, which is consistent with findings in the umeclidinium monotherapy studies.
- Once-daily triple therapy with fluticasone furoate/umeclidinium/vilanterol has also been compared to twice-daily budesonide/formoterol 400/12 mcg in a 24-week, double-blind, double-dummy randomized trial (FULFIL; N = 1810) (Lipson et al 2017). The formulation/dosing regimen of budesonide/formoterol in this trial is different from the formulation available in the U.S. The trial demonstrated improvements in the change from baseline in trough FEV_1 (difference, 171 mL; 95% CI, 148 to 194; $p < 0.001$), SGRQ (difference, -2.2; 95% CI, -3.5 to -1.0; $p < 0.001$), and the rate of moderate/severe exacerbations (rate ratio, 0.65; 95% CI, 0.49 to 0.86; $p = 0.002$). Although the comparator regimen is not available in the U.S., this trial further supports the efficacy of triple inhaler therapy with fluticasone furoate/umeclidinium/vilanterol.
- Once-daily triple therapy with fluticasone furoate/umeclidinium/vilanterol was compared to fluticasone furoate/vilanterol and umeclidinium/vilanterol in a 52-week, double-blind, randomized trial among patients with COPD (IMPACT; *Lipson et al 2018*). The primary endpoint of moderate or severe exacerbations was significantly lower with triple therapy in comparisons both with fluticasone furoate/vilanterol (rate ratio, 0.85; 95% CI, 0.80 to 0.90) and with umeclidinium/vilanterol (rate ratio, 0.75; 95% CI, 0.70 to 0.81). The annual rate of severe exacerbation resulting in hospitalization was also significantly lower with triple therapy vs umeclidinium/vilanterol (rate ratio, 0.66; 95% CI, 0.56 to 0.78), but not vs fluticasone furoate/vilanterol. The mean change from baseline in trough FEV_1 was significantly increased with triple therapy by 97 and 54 mL vs fluticasone furoate/vilanterol and umeclidinium/vilanterol, respectively. The risk of pneumonia was significantly higher with triple therapy vs umeclidinium/vilanterol (HR, 1.53; 95% CI, 1.22 to 1.92), but not vs fluticasone furoate/vilanterol. Significant improvements in SGRQ total scores also occurred with triple therapy vs fluticasone furoate/vilanterol (mean difference, -1.8; 95% CI, -2.4 to -1.1) and vs umeclidinium/vilanterol (mean difference, -1.8; 95% CI, -2.6 to -1.0).

CLINICAL GUIDELINES

Asthma

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

with controller therapy with the same dose of ICS and LABA (RR, 0.68; 95% CI, 0.58 to 0.80) (*Sobieraj et al 2018*). Of the 16 trials, 15 studied budesonide/formoterol in a dry powder inhaler. Results were similar in comparisons with doses of ICS and LABA controller therapy that were higher than the combined LABA/ICS, and in comparison with ICS controller therapy only.

COPD

- The 2019 GOLD guidelines state that the management strategy for stable COPD should be predominantly based on an assessment of the patient's symptoms and risk of exacerbations; the risk of exacerbations is based on a patient's exacerbation history. Key recommendations from the GOLD guidelines are as follows (*GOLD 2019*):
  - Inhaled bronchodilators are central to symptom management in COPD and commonly given on a regular basis to prevent or reduce symptoms.
    Inhaled bronchodilators are recommended over oral bronchodilators.
- LAMAs and LABAs significantly improve lung function, dyspnea, and health status, and reduce exacerbation rates.
  LAMAs and LABAs are preferred over short-acting agents except for patients with only occasional dyspnea.
  LAMAs have a greater effect on exacerbation reduction compared to LABAs and decrease hospitalizations.
- Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on 1 bronchodilator, treatment should be escalated to 2 bronchodilators.
  - Combination treatment with a LABA and LAMA:
    Reduces exacerbations compared to monotherapy or ICS/LABA.
    Increases FEV_1 and reduces symptoms compared to monotherapy.
- Long-term monotherapy with ICSs is not recommended. Long-term treatment with ICSs may be considered in association with LABAs for patients with a history of exacerbations despite treatment with long-acting bronchodilators.
  - Triple inhaled therapy of LAMA/LABA/ICS improves lung function, symptoms, and health status and reduces exacerbations compared to ICS/LABA or LAMA monotherapy.
  - Treatment recommendations are given for patients with COPD based on their GOLD patient group (see Table 3 below).
    - Group A: Patients should be offered bronchodilator treatment (short- or long-acting), based on its effect on breathlessness. This should be continued if symptomatic benefit is documented.
    - Group B: Initial therapy should consist of a long-acting bronchodilator (LAMA or LABA). For patients with persistent breathlessness on monotherapy, use of 2 bronchodilators is recommended (LAMA + LABA). For patients with severe breathlessness, initial therapy with 2 bronchodilators may be considered. If the addition of a second bronchodilator does not improve symptoms, it is suggested that treatment could be stepped down to a single bronchodilator; switching to another device or molecules can also be considered.
    - Group C: Initial therapy should be a LAMA. Patients with persistent exacerbations may benefit from adding a second long-acting bronchodilator (LAMA + LABA, preferred) or using an ICS + LABA. For patients who have a history and/or findings suggestive of asthma-COPD overlap or blood eosinophil count ≥ 300 cells/μL, ICS + LABA is preferred.
    - Group D: In general, it is recommended to start therapy with a LAMA. For patients with more severe symptoms, especially dyspnea and/or exercise limitation, LAMA/LABA may be considered for initial treatment. In some patients, initial therapy with an ICS + LABA may be the first choice; these patients may have a history and/or findings suggestive of asthma-COPD overlap or blood eosinophil count ≥ 300 cells/μL. In patients who develop further exacerbations on LAMA + LABA therapy, alternative pathways include escalation to a LAMA + LABA + ICS (preferred) or a switch to an ICS + LABA. If patients treated with a LAMA + LABA + ICS still have exacerbations, options for selected patients may include addition of roflumilast, addition of a macrolide, or stopping the ICS.

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

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

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

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

SAFETY SUMMARY

Beta$_2$-agonist/corticosteroid combinations

- Beta$_2$-agonist/ICS combinations are generally contraindicated for the primary treatment of status asthmaticus or other acute episodes of asthma/COPD where intensive measures are required.
- Advair Diskus, AirDuo RespiClick, and Breo Ellipta are contraindicated in patients with a severe hypersensitivity to milk proteins.
- Previously, ICS/LABA combinations had a boxed warning about an increased risk of asthma-related death, which had been observed with the LABA salmeterol. However, the boxed warning was removed from the prescribing information for ICS/LABA combinations in December 2017 based on an FDA review of 4 large clinical safety trials, which demonstrated that these combinations do not result in a significantly increased risk of asthma-related death, hospitalizations, or the need for intubation compared to ICS alone. There is still a warning/precaution in the prescribing information of ICS/LABA combinations related to the increased risk of asthma-related death with LABA monotherapy. A description of the clinical safety trials with ICS/LABA combinations has been added to the prescribing information for these products (*FDA 2017*).
- Other key warnings and precautions include:
  - Significant cardiovascular effects and fatalities with excessive use of beta$_2$-agonists
  - Cardiovascular and/or central nervous system effects from beta-adrenergic stimulation (seizures, angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia)
  - Paradoxical bronchospasm
  - Hypercorticism and adrenal suppression due to systemic absorption of the corticosteroid
  - The need for caution when transferring patients from systemic corticosteroid therapy (deaths due to adrenal insufficiency have occurred)
  - Lower respiratory tract infections/pneumonia
  - Local infections of the mouth and pharynx with *Candida albicans*
  - Reduced growth velocity in pediatric patients
  - The potential for drug interactions with strong CYP3A4 inhibitors; concomitant use is not recommended due to the potential for increased systemic effects
  - The potential for developing glaucoma, increased intraocular pressure, blurred vision, central serous chorioretinopathy, or cataracts
  - Immunosuppression
  - Hypersensitivity
  - Reduction in bone mineral density
- It is also important to note that ICS/LABA combinations should not be initiated in the setting of disease deterioration or potentially life-threatening episodes.
- Commonly reported adverse events (≥ 5% for at least 1 medication in the class) include oral candidiasis, hoarseness/dysphonia, nasopharyngitis/pharyngitis, pharyngolaryngeal/oropharyngeal pain, sinusitis, upper respiratory tract infection, upper respiratory tract inflammation, bronchitis, cough, headache, gastrointestinal discomfort, and nausea/vomiting.

Beta$_2$-agonist/anticholinergic combinations

- Both albuterol/ipratropium combination products are contraindicated in patients with hypersensitivity to atropine or its derivatives. Anoro Ellipta is contraindicated in patients with hypersensitivity to any component of the product, as well as in patients with severe hypersensitivity to milk proteins. Bevespi Aerosphere, Stiolto Respimat, and Utibron Neohaler are all contraindicated in patients with asthma without use of a long-term asthma control medication (and are not indicated for the treatment of asthma).

- There are no boxed warnings for the albuterol/ipratropium combination products. Anoro Ellipta, Bevespi Aerosphere, Stiolto Respimat and Utibron Neohaler have boxed warnings stating that LABA increase the risk of asthma-related death. Data from a large placebo-controlled U.S. trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including formoterol (an active ingredient in Bevespi Aerosphere), indacaterol (an active ingredient in Utibron Neohaler), vilanterol (an active ingredient in Anoro Ellipta), and olodaterol (an active ingredient in Stiolto Respimat). The safety and efficacy of Anoro Ellipta, Bevespi Aerosphere, Stiolto Respimat, and Utibron Neohaler in patients with asthma have not been established, and these products are not indicated for the treatment of asthma.
- Warnings and precautions are very similar among products, and include the following:
  - Paradoxical bronchospasm: May produce paradoxical bronchospasm, which can be life-threatening. If it occurs, the product should be discontinued and alternative therapy instituted.
  - Cardiovascular effect: Beta$_2$-agonists can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, and/or symptoms. If these symptoms occur, the product may need to be discontinued. In addition, electrocardiogram (ECG) changes may occur. These products should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
  - Ocular effects: Ipratropium and other anticholinergic agents may increase intraocular pressure, which may precipitate or worsen narrow-angle glaucoma. They should be used with caution in patients with narrow-angle glaucoma. In addition, patients should avoid spraying product into eyes, as this can cause eye pain and visual symptoms.
  - Urinary retention: Ipratropium and other anticholinergic agents may cause urinary retention. Caution is advised when administering to patients with prostatic hyperplasia or bladder-neck obstruction.
  - The recommended dose should not be exceeded: Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma.
  - Hypersensitivity reactions: Urticaria, angioedema, rash, pruritus, bronchospasm, laryngospasm, oropharyngeal edema, and anaphylaxis may occur. If such a reaction occurs, therapy should be discontinued and alternative treatment considered.
  - Coexisting conditions: Due to the beta$_2$-agonist component, caution is advised in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines.
  - Hypokalemia: β-agonists may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.
  - Drug interactions with strong CYP3A4 inhibitors; increased cardiovascular effects may occur (Anoro Ellipta only).
  - Reports of anaphylactic reactions in patients with severe milk protein allergy (Anoro Ellipta only).
  - Deterioration of disease and acute episodes; drug has not been studied in this setting and is not to relieve acute symptoms (Anoro Ellipta and Stiolto Respimat only).
- Adverse reactions are similar among products and include back pain, bronchitis, upper respiratory infection, lung disease, headache, dyspnea, nasopharyngitis/pharyngitis, and cough.
- In a 12-week trial comparing Combivent Respimat to Combivent inhalation aerosol, rates of adverse reactions were very similar between groups. In a 48-week safety trial, most adverse reactions were similar in type and rate between treatment groups; however, cough occurred more frequently in patients enrolled in the Combivent Respimat group (7%) than the Combivent inhalation aerosol group (2.6%).
- The choice of a specific LAMA/LABA fixed-dose combination product is not based on any difference in the safety profile (*Matera et al 2016*).

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

- Trelegy Ellipta is contraindicated in patients with severe hypersensitivity to milk proteins or any ingredients in the formulation.
- Similar to other combination agents for COPD (and/or asthma), Trelegy Ellipta has a number of additional warnings and precautions; these include:
  - Increased risk of asthma-related death
  - Not indicated for treatment of asthma
  - Not initiating in patients with rapidly deteriorating COPD
  - Avoiding excessing use
  - Local effects of ICS

- Risk of pneumonia
- Immunosuppression
- Using caution when transferring patients from systemic corticosteroid therapy
- Hypercorticism and adrenal suppression
- Drug interactions with strong CYP3A4 inhibitors
- Paradoxical bronchospasm
- Hypersensitivity reactions
- Cardiovascular effects
- Reduction in bone mineral density
- Glaucoma and cataracts
- Urinary retention
- Using caution in patients with certain coexisting conditions such as convulsive disorders or thyrotoxicosis
- Hypokalemia and hyperglycemia

- The most common adverse reactions with Trelegy Ellipta include headache, back pain, dysgeusia, diarrhea, cough, oropharyngeal pain, and gastroenteritis.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

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

See the current prescribing information for full details.

CONCLUSION

- Respiratory medications, including bronchodilators and corticosteroids, are a mainstay of treatment for asthma and COPD, and a large amount of clinical evidence supports the safety and efficacy of combination beta$_2$-agonist agents for these indications.
  - Clinical trials have demonstrated that the combination products superior efficacy compared with the individual separate components when given as monotherapy for the treatment of both asthma and COPD. The combination products are generally well tolerated.
- Several single-ingredient inhalers containing beta$_2$-agonists, ICS, or anticholinergics are also available. Beta$_2$-agonist combinations offer improved convenience over the use of multiple separate inhalers.
  - Trelegy Ellipta is the first fixed-dose combination inhaler combining a LAMA, a LABA, and an ICS, and provides an alternative to the use of multiple inhalers for patients with COPD in whom triple therapy is indicated.

- GINA guidelines support the use of combination ICS/LABA products for long-term control and prevention of symptoms in patients with asthma who do not achieve sufficient symptom control with ICS monotherapy.
  - Single-agent LABA therapy should not be used for asthma management due to the increased risk of asthma-related death, as well as asthma-related hospitalization in pediatric and adolescent patients. However, recent drug safety information from the FDA states that no significantly increased risk of serious asthma outcomes has been seen with the use of ICS/LABA combinations, and boxed warnings about this potential risk have been removed from the prescribing information for the ICS/LABA combinations.
  - An advantage of the ICS/LABA combinations is that their use ensures that patients are not using a LABA without a concomitant ICS.
- GOLD guidelines recommend the use of combination ICS/LABA products as an option for some patients at higher risk of exacerbations, a history and/or findings suggestive of asthma-COPD overlap, or blood eosinophil count ≥ 300 cells/µL; however, the use of 1 or more bronchodilator without an ICS is recommended as first-line treatment for most COPD patients.
  - A LAMA is recommended as first-line treatment in most patients with COPD, with the exception of low-risk patients with milder symptoms, or patients with more severe symptoms.
- None of the current asthma or COPD treatment guidelines recommend the use of one specific combination product over another.
  - Administration instructions and inhalation devices vary among products and should be considered in product selection.

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INTRODUCTION

- Inhaled corticosteroids (ICSs) are approved by the Food & Drug Administration (FDA) for the treatment of asthma. These agents are effective in the treatment of asthma due to their wide range of inhibitory activities against multiple cell types (e.g., mast cells and eosinophils) and mediators (e.g., histamine and cytokines) involved in the asthmatic response.
- Asthma is a chronic lung disease that inflames and narrows the airways, making it difficult to breathe. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing. Asthma affects people of all ages, but most often starts during childhood. In the United States, more than 25 million people are known to have asthma, including about 7 million children (*National Heart, Lung, and Blood Institute [NHLBI] 2014*).
- The exact cause(s) of asthma are unknown. A combination of factors such as genetics, certain respiratory infections during childhood, and contact with airborne allergens can contribute to its development. Most patients with asthma have allergies (*NHLBI 2014*).
- Current pharmacologic options for asthma management are categorized as: (1) long-term control medications to achieve and maintain control of persistent asthma, and (2) quick-relief medications used to treat acute symptoms and exacerbations (*NHLBI 2007*).
- Long-term control medications include (*NHLBI 2007*):
  - Corticosteroids (ICSs for long-term control; short courses of oral corticosteroids to gain prompt control of disease, long-term oral corticosteroids for severe persistent asthma)
  - Cromolyn sodium and nedocromil
  - Immunomodulators (i.e., omalizumab)
  - Leukotriene modulators
  - Long-acting β-agonists (LABAs)
  - Methylxanthines (i.e., theophylline)
- Quick-relief medications include (*NHLBI 2007*):
  - Short-acting β-agonists (SABAs) as the therapy of choice for relief of acute symptoms and prevention of exercise-induced bronchospasm
  - Anticholinergics (i.e. ipratropium bromide) as an alternative bronchodilator for those not tolerating a SABA
  - Systemic corticosteroids, although not short-acting, are used for moderate and severe exacerbations as part of initial treatment.
- In recent years, additional medications have been made available for select subsets of patients with asthma, including the interleukin-5 (IL-5) antagonists benralizumab, mepolizumab, and reslizumab, and the interleukin-4 (IL-4) antagonist dupilumab, for the management of severe asthma with an eosinophilic phenotype (*Prescribing information: Cinqair 2018, Dupixent 2018, Fasenra 2017, Nucala 2017*). Additionally, tiotropium, long used for COPD, has been FDA-approved for the treatment of asthma (*Spiriva Respimat prescribing information 2018*).
- ICSs are the most effective and most commonly recommended long-term control medications used for the treatment of asthma. The LABAs should not be used as monotherapy for the management of asthma due to increased risk for serious adverse events including death. However, they are effective adjunctive therapy in patients who are not adequately controlled with an ICS alone. Theophylline and mast-cell stabilizers have weak to low efficacy in asthma. Theophylline has an unfavorable side-effect profile and may be life-threatening at high doses. Mast-cell stabilizers have a more favorable safety profile. Tiotropium is an option for add-on therapy in patients with a history of exacerbations. An IL-5 antagonist or the immunoglobulin E (IgE) antagonist, omalizumab, may be added if patients require a higher level of care. Omalizumab is used in patients with moderate to severe allergic asthma while IL-5 antagonists are used for severe eosinophilic asthma. SABAs are the medication of choice for the relief of bronchospasm during acute exacerbations of asthma (*Fasenra prescribing information 2017, NHLBI 2007, Global Initiative for Asthma [GINA] 2018*).
- This review includes single-agent ICSs (ie, respiratory corticosteroids). While respiratory corticosteroids are commonly available in combination with other bronchodilators such as LABAs, combination agents are not included within this

review. Although inflammation is also a component of COPD pathogenesis, no single-entity ICS has been FDA-approved for use in COPD (*Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2019*).

- Of note, QVAR RediHaler, a new breath-actuated inhalation formulation of beclomethasone dipropionate manufactured by Teva, was approved by the FDA in August 2017 and was launched in February 2018, replacing the previous QVAR product (*Teva 2018*). Additionally, in January 2018, Mylan informed the FDA of the discontinuation of Aerospan (flunisolide) due to business reasons (*FDA Drug Shortages 2018*).
- Medispan class: Steroid Inhalants

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Alvesco (ciclesonide) inhalation aerosol	-
ArmonAir RespiClick (fluticasone propionate) dry powder inhaler	-
Arnuity Ellipta (fluticasone furoate) dry powder inhaler	-
Asmanex HFA (mometasone furoate) inhalation aerosol	-
Asmanex Twisthaler (mometasone furoate) dry powder inhaler	-
Flovent Diskus (fluticasone propionate) dry powder inhaler	-
Flovent HFA (fluticasone propionate) inhalation aerosol	-
Pulmicort Flexhaler (budesonide) dry powder inhaler	-
Pulmicort Respules (budesonide) solution for nebulization	✔
QVAR RediHaler (beclomethasone dipropionate) inhalation aerosol	-

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

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

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

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

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

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

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

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

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

CLINICAL GUIDELINES

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

SAFETY SUMMARY

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

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

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Alvesco (ciclesonide)	Inhalation aerosol (HFA): 80 or 160 mcg per actuation	Inhalation	Patients treated previously with only bronchodilators: initial, 80 mcg twice daily; maximum, 160 mcg twice daily Patients treated previously with an ICS: initial, 80 mcg twice daily; maximum, 320 mcg twice daily Patients treated previously with oral corticosteroids: initial, 320 mcg twice daily; maximum, 320 mcg twice daily	Not indicated for children < 12 years of age.
ArmonAir RespiClick (fluticasone propionate)	Dry powder inhaler: 55, 113, or 232 mcg per inhalation	Inhalation	Patients ≥ 12 years of age: initial, 55, 113, or 232 mcg twice daily (dependent on asthma severity); maximum, 232 mcg twice daily	Not indicated for children < 12 years of age.
Arnuity Ellipta (fluticasone furoate)	Dry powder inhaler: 50, 100 or 200 mcg per actuation	Inhalation	Patients not previously on an ICS: initial, 100 mcg once daily; maximum, 200 mcg once daily Patients treated previously with an ICS: Starting dose should be based on previous asthma drug therapy and disease severity, 100 mcg or 200 mcg once daily	Age 5 to 11 years: 50 mcg once daily
Asmanex HFA (mometasone furoate)	Inhalation aerosol (HFA): 100 or 200 mcg per actuation	Inhalation	Patients previously receiving a medium-dose ICS: 100 mcg, 2 inhalations twice daily Patients previously receiving a high-dose ICS: 200 mcg, 2 inhalations twice daily Patients currently receiving oral corticosteroids: 200 mcg, 2 inhalations twice daily	Not indicated for children < 12 years of age.
Asmanex Twisthaler (mometasone furoate)	Dry powder inhaler: 110 or 220 mcg per actuation	Inhalation	Patients treated previously with bronchodilators alone or an ICS: initial, 220 mcg once daily in the evening; maximum, 440 mcg administered as once daily in the evening or as 220 mcg twice daily	Children 4 to 11 years of age: initial, 110 mcg once daily in the evening; maximum, 110 mcg per day.

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

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

See the current prescribing information for full details.

CONCLUSION

- ICS agents are considered the cornerstone of drug therapy for long-term asthma control. Consensus guidelines emphasize the important role of ICS agents as long-term controller medications. The NHLBI and GINA asthma guidelines agree that ICSs are the preferred treatment for initiating therapy in children and adults with persistent asthma. It is important to note that the current consensus guidelines do not give preference to one ICS over another (*GINA 2018, NHLBI 2007*).
- Although individual head-to-head clinical trials have demonstrated some differences among ICS agents on certain endpoints, results have not conclusively demonstrated one agent to be significantly more effective than another in the management of asthma. Contraindications, warnings/precautions, and adverse effects are also similar among products.
- There are differences among products with respect to their available formulations, dosing schedule, and use in the pediatric population. Notably, some products are available as dry powder formulations, while others are available as inhalation aerosols. Most ICSs are dosed twice daily; however, Arnuity Ellipta is administered once daily. Asmanex Twisthaler and Pulmicort Respules may be administered either once or twice daily.
  - The appropriate choice of an ICS agent for an individual patient may depend on ease of use of the ICS device, dosing schedule, and contraindications such as hypersensitivity to milk proteins.
  - The inhaler device is an important component of treatment, and the patient's response, preference, and ability to use the inhaler device should be considered in product selection.

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Established Drug Classes

Therapeutic Class Overview
Pulmonary Arterial Hypertension Agents

INTRODUCTION

- Pulmonary arterial hypertension (PAH), a subtype of pulmonary hypertension (PH), is a chronic, life-threatening disease that is characterized by increased resistance in the pulmonary circulation caused by progressive pulmonary artery remodeling and constriction of the pulmonary vasculature (*Buckley et al 2013, Wu et al 2013*).
  - PH is defined as a mean pulmonary arterial pressure (mPAP) of ≥ 25 mmHg at rest. Normal pulmonary arterial systolic pressure ranges from 15 to 30 mmHg, diastolic pressure from 4 to 12 mmHg, and normal mPAP is ≤ 20 mmHg (*Rubin et al 2018*).
  - PAH often manifests with clinical symptoms such as shortness of breath and decreased functional capacity, and eventually leads to right heart failure and death (*Gomberg-Maitland et al 2011*).
- Early recognition of PAH is essential and the gold standard for the clinical diagnosis of PAH is right heart catheterization (*Buckley et al 2013*).
- The World Health Organization (WHO) classifies PH into 5 groups:
  - Group 1 – PAH
  - Group 2 – PH secondary to heart disease
  - Group 3 – PH secondary to lung diseases and/or hypoxia
  - Group 4 – Chronic thromboembolic PH (CTEPH)
  - Group 5 – PH with unclear or multifactorial etiologies
- WHO Group I encompasses PAH, including idiopathic PAH, heritable PAH, drug- and toxin-induced PAH, and PAH associated with other disorders such as connective tissue disease, portal hypertension, human immunodeficiency virus infection, congenital heart disease, and schistosomiasis (*Simonneau et al 2013*).
- In addition to the diagnostic classification, patients may be stratified according to their WHO functional capacity, which was adapted from the New York Heart Association (NYHA) classification of left heart failure. A brief description of these functional classes (FC) is as follows (*Stringham et al 2010*):
  - Class I: No limitation of physical activity
  - Class II: Slight limitation of physical activity
  - Class III: Marked limitation of physical activity
  - Class IV: Inability to carry out any physical activity without symptoms
- The prevalence of WHO Group 1 PAH has been estimated at 7 to 26 cases per million adults (*Pogue et al 2016*). The disease has a poor prognosis and an approximate mortality rate of 15% within 1 year on therapy (*McLaughlin et al 2009*). The median survival in the 1980s was 2.8 years; this had improved to 7 years in the late 2000s (*Pogue et al 2016*).
- CTEPH (WHO Group 4) is a leading cause of severe PH that results from thrombus formation leading to fibrous stenosis or complete obliteration of pulmonary arteries.
  - The incidence of CTEPH is uncertain, but it occurs in up to 4% of patients after an acute pulmonary embolism (*Simonneau et al 2009*).
- Specific agents to treat PAH primarily target 3 pathways critical to its pathobiology: the prostacyclin, endothelin, and nitric oxide pathways (*Wu et al 2013*). There are currently 10 molecular entities within 5 therapeutic classes that are Food and Drug Administration (FDA)-approved for the treatment of PAH (*Lexicomp 2018*).
  - Drugs active within the prostacyclin pathway are the prostacyclin analogues (PCAs) or prostanoids (intravenous [IV] epoprostenol; inhaled iloprost; and IV, subcutaneous [SC], inhaled, and oral treprostinil) and a prostacyclin receptor agonist (oral selexipag).
  - Drugs active within the endothelin pathway are the endothelin receptor antagonists (ERAs) (oral ambrisentan, oral bosentan, and oral macitentan).
  - Drugs active within the nitric oxide pathway are the phosphodiesterase-type-5 (PDE-5) inhibitors (IV and oral sildenafil and oral tadalafil) and a soluble guanylate cyclase (sGC) stimulator (oral riociguat).
- The goals of treatment include improvement in the patient's symptoms, quality of life (QOL), and survival. The optimal therapy for a patient should be individualized, taking into account many factors including severity of illness, route of administration, side effects, comorbid illness, treatment goals, and clinician preference (*McLaughlin et al 2009*).

- Initial management of PAH includes the use of warfarin, diuretics, and/or oxygen depending on the patient's diagnosis and symptoms. Prior to the initiation of advanced therapy, patients with PAH should undergo a vasoreactivity test. Oral calcium channel blockers (CCBs) are indicated only for patients who have a positive acute vasodilator response to testing (*Galiè et al 2015[b], McLaughlin et al 2009, Taichman et al 2014*).
- For patients who do not have a positive acute vasodilator response to testing and are considered low to moderate risk based on clinical assessment, oral mono- or combination therapy with certain agents are recommended. These include ERAs, PDE-5 inhibitors, an sGC stimulator, and a prostacyclin receptor (IP) agonist. In patients with high risk disease, continuous treatment with an IV PCA therapy (epoprostenol or treprostinil) would be recommended. Combination therapy may be considered if patients are not responding adequately to monotherapy or are not candidates for monotherapy (*Barst, 2009, Galiè et al 2015[b], McLaughlin et al 2009, Taichman et al 2014*).
- The PAH agents are FDA-approved for the treatment of patients with WHO Group I PAH; however, there are differences in the study populations for which their FDA-approvals were based (*McLaughlin et al 2009*).
- Adempas (riociguat) is a first-in-class sGC stimulator with a dual mode of action involving endogenous nitric oxide that leads to increased generation of cyclic guanosine monophosphate (cGMP) with subsequent vasodilation. This agent has the additional FDA approval for treating adults with persistent/recurrent CTEPH (WHO Group 4) after surgical treatment or inoperable CTEPH. Adempas is the first and only drug to be FDA-approved in the treatment of CTEPH. Pulmonary endarterectomy is curative for CTEPH, but it is technically demanding which may limit access to its use as a treatment (*Archer 2013*).
- In PAH, prostacyclin synthase is reduced resulting in inadequate production of prostacyclin I_2, a potent vasodilator with antiproliferative effects and an inhibitor of platelet aggregation (*McLaughlin et al 2009*). The PCAs, iloprost and treprostinil, were developed as chemically stable alternatives to epoprostenol, which requires continuous IV infusion due to its lack of stability (*Asaki et al 2015*). Orenitram (treprostinil) is the first FDA-approved oral PCA. It may represent a more convenient dosage form to the other treprostinil formulations (Remodulin and Tyvaso). However, patients with more severe PAH are likely to receive infused PCA rather than oral therapy (*McLaughlin et al 2009*). Among these agents, epoprostenol IV is the only agent that has demonstrated improved patient survival in high risk PAH patients (*Galiè et al 2015[b]*). Uptravi (selexipag) works at the same pathway as the PCAs, but activates the IP receptor, also known as the prostacyclin receptor. Orenitram and Uptravi are the only orally administered agents that work within the prostacyclin pathway (*Asaki et al 2015*).
- Endothelial dysfunction in PAH causes increased production of endothelin-1 resulting in vasoconstriction, which is mediated by the endothelin receptors, ET_A and ET_B. Stimulation of ET_A causes vasoconstriction and cell proliferation, while stimulation of ET_B results in vasodilatation, antiproliferation and endothelin-1 clearance. The ERAs (Letairis [ambrisentan], Opsumit [macitentan], and Tracleer [bosentan]) competitively bind to both receptors with different affinities. Letairis and Opsumit are highly selective for the ET_A receptor, while Tracleer is slightly selective for the ET_A receptor over the ET_B receptor. In addition, Opsumit has a pharmacologically active metabolite and is considered "tissue-targeting" because it displays high affinity and sustained occupancy at the ET receptors in human pulmonary arterial smooth muscles. However, the clinical significance of receptor affinities of the ERAs has not been established (*McLaughlin et al 2009*).
- In patients with PAH, there is also an impaired release of nitric oxide by the vascular endothelium, thereby reducing cGMP concentrations. The PDE-5 enzyme is the predominant phosphodiesterase in the pulmonary vasculature and is responsible for the degradation of cGMP. The PDE-5 inhibitors, Revatio (sildenafil) and Adcirca (tadalafil), increase the concentrations of cGMP resulting in relaxation of the pulmonary vascular bed.
- Medispan class: Cardiovascular Agents, Miscellaneous – Prostaglandin Vasodilators; Pulmonary Hypertension: Endothelin Receptor Antagonists, Phosphodiesterase Inhibitors, Prostacyclin Receptor Agonist, and Soluble Guanylate Cyclase Stimulator.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
ERAs	
Letairis (ambrisentan)	-
Opsumit (macitentan)	-
Tracleer (bosentan)	-
PDE-5 inhibitors	
Adcirca (tadalafil)	✔
Revatio (sildenafil)	✔ *
Prostacyclin receptor agonist	
Uptravi (selexipag)	-
PCAs	
Flolan (epoprostenol)	✔
Veletri (epoprostenol)	-
Orenitram (treprostinil)	-
Remodulin (treprostinil)	-**
Tyvaso (treprostinil)	-
Ventavis (iloprost)	-
sGC stimulator	
Adempas (riociguat)	-

*Revatio tablet and IV formulations are currently available generically; however, the oral suspension is brand-only.
**A generic was approved by the FDA but has not yet been launched by its manufacturer (Sandoz); settlement agreements may apply.

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

INDICATIONS

Table 2. FDA-approved Indications

Indication	Adcirca (tadalafil)	Adempas (riociguat)	Flolan (epoprostenol)	Letairis (ambrisentan)	Opsumit (macitentan)	Orenitram (treprostinil)	Remodulin (treprostinil)	Revatio (sildenafil)	Tracleer (bosentan)	Tyvaso (treprostinil)	Uptravi (selexipag)	Veletri (epoprostenol)	Ventavis (iloprost)
Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening				✔ *				✔ §	✔ †				
Treatment of PAH (WHO Group I) to improve exercise ability/diminish symptoms associated with exercise	✔ ¶		✔ ≠			✔ ¶¶	✔ ₴			✔ Ω		✔ ₳	
Treatment of PAH (WHO Group I) to delay/reduce risks of disease progression and reduce risk of hospitalization					✔ **						✔ ‡		

Treatment of PAH (WHO Group I) to improve exercise capacity, to improve WHO FC, and to delay clinical worsening		✔											
Treatment of PAH (WHO Group I) to improve a composite endpoint of exercise tolerance, symptoms, and lack of deterioration													✔ ¥
For patients who require transition from epoprostenol, to reduce the rate of clinical deterioration; risks and benefits of each drug should be carefully considered prior to transition							✔						
Treatment of persistent/recurrent CTEPH (WHO Group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO FC		✔											
Treatment of PAH (WHO Group I), in combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability				✔ *									
Treatment of PAH (WHO Group I) in pediatric patients aged ≥ 3 years with idiopathic or congenital PAH to improve pulmonary vascular resistance, which is expected to improve exercise ability									✔				

Abbreviations: CTEPH=chronic thromboembolic pulmonary hypertension; FC=functional class; NYHA=New York Heart Association, PAH=pulmonary arterial hypertension, WHO=World Health Organization.

*Studies establishing effectiveness included predominantly patients with WHO FC II to III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%).

§The delay in clinical worsening was demonstrated when Revatio was added to background epoprostenol therapy. Studies establishing effectiveness were short-term (12 to 16 weeks) and included predominately patients with NYHA FC II to III symptoms and idiopathic etiology (71%) or associated with connective tissue disease (25%).

†Studies establishing effectiveness included predominately patients with WHO FC II to IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%).

¶Studies establishing effectiveness included predominately patients with NYHA FC II to III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

≠Studies included predominately patients with NYHA FC III to IV symptoms and etiologies of idiopathic or heritable PAH (49%) or PAH associated with connective tissue diseases (51%).
¶¶The study that established effectiveness included predominantly patients with WHO FC II to III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%). As the sole vasodilator, the effect on exercise is small. Orenitram has not been shown to add to other vasodilator therapy.
ƧStudies establishing effectiveness included predominately patients with NYHA FC II to IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), and PAH associated with connective tissue diseases (19%).
ΩStudies establishing effectiveness included predominately patients with NYHA FC III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).
₳Studies establishing effectiveness included predominately patients with NYHA FC III to IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.
**Effectiveness was established in a long-term study in PAH patients with predominantly WHO FC II to III symptoms treated for an average of 2 years. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).
‖Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominately patients with WHO FC II to III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%).
¥Studies establishing effectiveness included predominately patients with NYHA FC III to IV symptoms and etiologies of idiopathic or heritable PAH (65%) or PAH associated with connective tissue diseases (23%).
‡Effectiveness was established in a long-term study in PAH patients with WHO FC II to III symptoms. Patients had idiopathic PAH (58%), PAH associated with connective tissue diseases (29%), and PAH associated with congenital systemic-to-pulmonary shunts (10%).

(*Prescribing information: Adcirca 2017, Adempas 2018, Flolan 2018, Letairis, 2015, Opsumit 2018, Orenitram 2017, Remodulin 2018, Revatio 2018, Tracleer 2018, Tyvaso 2017, Uptravi 2017, Veletri 2018, Ventavis 2017*)

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

CLINICAL EFFICACY SUMMARY

Adcirca (tadalafil)

- Adcirca was evaluated in the PHIRST study, a 16-week, randomized, double-blind, placebo-controlled trial consisting of 405 patients with predominantly WHO FC II or III symptoms. Treatment with Adcirca significantly improved exercise capacity, as measured by the 6MWD and reduced clinical worsening compared to placebo (*Galiè et al 2009*). In a 52-week extension trial, PHIRST-2, the improvements in 6MWD observed at the end of PHIRST appeared to be maintained through week 52 of PHIRST-2 (68 weeks total). In addition, 34% of patients enrolled in PHIRST-2 experienced an improvement in WHO FC compared to baseline of the PHIRST trial (*Oudiz et al 2012*).

Adempas (riociguat)

- The efficacy and safety of Adempas were evaluated in CHEST-1, a multinational, multicenter, double-blind,16-week trial in 261 adult patients with CTEPH. The majority of patients were WHO FC II (31%) or class III (64%). The primary endpoint of CHEST-1 was change from baseline in 6MWD after 16 weeks. Secondary endpoints included changes from baseline in pulmonary vascular resistance (PVR), N-terminal pro-brain natriuretic peptide (NT-proBNP) level, WHO FC, time to clinical worsening, Borg dyspnea score, QOL variables, and safety. Improvements in walking distance occurred beginning at week 2. At week 16, the placebo adjusted mean increase in 6MWD within the Adempas group was 46 m (95% confidence interval [CI], 25 m to 67 m; $p < 0.001$) (*Ghofrani et al 2013[a]*).
  - An open-label, non-comparative, extension study (CHEST-2) included 237 patients who completed CHEST-1. CHEST-2 consisted of an 8-week, double-blind dose-adjustment phase, followed by an open-label study phase that continued until Adempas received official approval and became commercially available. At the March 2013 cut-off date, 211 patients (89%) were receiving ongoing treatment, and 179 (76%) had received over 1 year of treatment. The safety profile of Adempas in CHEST-2 was similar to CHEST-1, with no new safety signals. Improvements in 6MWD and WHO FC observed in CHEST-1 persisted for up to 1 year in CHEST-2. In the observed population at 1 year, mean±standard deviation (SD) 6MWD had changed by 51±62 m (n = 172) versus CHEST-1 baseline (n = 237), and WHO FC had improved, stabilized, or worsened in 47, 50, or 3% of patients (n = 176) versus CHEST-1 baseline (n = 236). Of patients treated for 1 year in CHEST-2, 145 (92%) out of 157 were continuing to receive monotherapy, and 12 (8%) patients were receiving additional PH-specific medication (8 [5%] were receiving ERAs and 4 [3%] were receiving prostanoids). No patient required additional treatment with both an ERA and prostanoid at 1 year (Simmoneau et al 2015). An exploratory analysis noted a significant association with overall survival for

6MWD and NT-proBNP concentration at baseline (p = 0.0199, and 0.0183, respectively), and at follow-up (p = 0.0385, and 0.0068, respectively). Additionally, short-term improvements were associated with long-term survival and worsening-free survival. At 2 years, the overall survival rate was 93% (95% CI, 89 to 96%) and the rate of clinical worsening-free survival was 82% (95% CI, 77 to 87%) (*Simonneau et al 2016*). Due to lack of a control group and because certain outcomes were considered exploratory, data from this study must be interpreted cautiously.

- The efficacy and safety of Adempas were also evaluated in PATENT-1, a multinational, multicenter, double-blind, 12-week trial in 443 adult patients with PAH as defined by PVR > 300 dyn*sec*cm^{-5} and a PAP_{mean} > 25 mmHg. In this study, 50% of the patients were treatment-naïve with respect to PAH therapy, 44% were pre-treated with an ERA, and 6% were pretreated with a PCA (inhaled, oral, or SC). Patients were randomized to 1 of 3 treatment groups: placebo (n = 126), an exploratory capped titration arm of Adempas 1.5 mg 3 times daily (n = 63), or a capped maximum dose of Adempas 2.5 mg 3 times daily (n = 254). The primary endpoint of PATENT-1 was change from baseline in 6MWD after 12 weeks in the Adempas 2.5 mg group compared to placebo. Secondary endpoints included changes from baseline in PVR, NT-proBNP level, WHO FC, time to clinical worsening, Borg dyspnea score, QOL variables, and safety. At week 12, the placebo-adjusted mean increase in 6MWD within the Adempas 2.5 mg treatment group was 36 m (95% CI, 20 m to 52 m, p < 0.001). The group receiving the capped dose at 1.5 mg was excluded from the efficacy analysis (*Ghofrani et al 2013[b]*).
  - An open-label, non-comparative, extension study (PATENT-2) included 396 patients who completed PATENT-1. PATENT-2 consisted of an 8-week, double-blind dose-adjustment phase, followed by an open-label study phase that continues until all patients have transitioned to the commercially available drug. A total of 197 patients received Adempas monotherapy and 199 received Adempas in combination with an ERA or prostanoid, or both. The primary objective of the study was to assess the safety and tolerability of long-term Adempas treatment. Assessments took place at entry to PATENT-2, at weeks 2, 4, 6, 8, and 12, and every 3 months thereafter. At the March 2013 data cut-off, 324 patients (82%) were receiving ongoing treatment and 84% had received 1 year or more of treatment. Mean treatment duration was 95 weeks (median 91 weeks), and cumulative treatment exposure was 718 patient-years (Rubin et al 2015). An exploratory analysis concluded that there was a significant association between overall survival and 6MWD, NT-proBNP concentration, and WHO FC at baseline (p = 0.0006, 0.0225, and 0.0191, respectively), and at follow-up (p = 0.021, 0.0056, and 0.0048, respectively). Additionally, short-term improvements were associated with long-term survival and worsening-free survival. The estimated survival rate was 97% (95% CI, 95 to 98%) and rate of clinical worsening-free survival was 88% (95% CI, 85 to 91%) at 1 year and 79% (95% CI, 74 to 82%) at 2 years (*Ghofrani et al 2016*). Certain outcomes were considered exploratory, so data from this study must be interpreted cautiously.

Flolan (epoprostenol)

- The safety and efficacy of chronically-infused Flolan were evaluated in 2 similar, open-label, randomized trials of 8 to12 weeks' duration comparing Flolan plus conventional therapy (eg, anticoagulants, oral vasodilators, diuretics, digoxin, oxygen) with conventional therapy alone in idiopathic or heritable PAH (NYHA Class II to IV) patients (n = 106). The average Flolan dose was 9.2 ng/kg/min at the trials' end. A statistically significant improvement was observed in the 6MWD in patients receiving Flolan plus conventional therapy for 8 to 12 weeks compared with those receiving conventional therapy alone. Improvements were noted as early as week 1. Increases in exercise capacity were accompanied by statistically significant improvement in dyspnea and fatigue, as measured by the Chronic Heart Failure Questionnaire and the Dyspnea Fatigue Index, respectively.
- The efficacy of chronically-infused Flolan in PAH and scleroderma spectrum of diseases (NYHA Class II to IV) was evaluated in an open-label, randomized, 12-week trial (n = 111) comparing Flolan plus conventional therapy with conventional therapy alone. The mean Flolan dose was 11.2 ng/kg/min at the end of week 12. Statistically significant improvement was observed in the 6MWD in patients receiving continuous Flolan plus conventional therapy for 12 weeks compared to those receiving conventional therapy alone. Increases in exercise capacity were accompanied by statistically significant improvement in dyspnea and fatigue, as measured by Borg Dyspnea Index and Dyspnea Fatigue Index. At week 12, the NYHA FC improved in 41% of patients treated with Flolan plus conventional therapy compared to none of the patients treated with conventional therapy alone. However, the majority of patients in both treatment groups showed no change in FC, with 4% of the Flolan plus conventional therapy group and 27% of conventional therapy group alone worsening.

Letairis (ambrisentan)

- The safety and efficacy of Letairis in the treatment of PAH were established in the ARIES trials. ARIES-1 and ARIES-2 were 12-week, randomized, double-blind, placebo-controlled trials that compared Letairis to placebo in 394 patients. Compared to placebo, treatment with Letairis resulted in a significant increase in exercise capacity as measured by 6MWD (*Galiè et al 2008[a]*). ARIES-E was the open-label extension study for ARIES-1 and ARIES-2. After 1 year of treatment, there was an improvement in 6MWD in the 2.5, 5 and 10 mg Letairis groups (25, 28 and 37 m, respectively). After 2 years of treatment, the improvement was sustained in the 5 and 10 mg groups (23 and 28 m), but not the 2.5 mg group (7 m) (*Oudiz et al 2009*).
- ARIES-3 was a long-term, open-label, single-arm, safety, and efficacy study of Letairis in patients with PH receiving Letairis 5 mg once daily for 24 weeks. The primary endpoint was change from baseline in 6MWD at week 24. Secondary efficacy endpoints included change in plasma NT-proBNP, Borg Dyspnea Index, WHO FC, time to clinical worsening of PAH, survival and adverse events (AEs). A total of 224 patients with PH due to idiopathic and familial PAH (31%), connective tissue disease (18%), chronic hypoxemia (22%), chronic thromboembolic disease (13%), or other etiologies (16%) were enrolled, and 53% of patients received stable background PAH therapies. After 24 weeks of therapy, there was an increase in 6MWD of 21 m (95% CI, 12 to 29), and a decrease in NT-proBNP of -26% (95% CI, -34 to -16%) observed in the overall population compared to baseline. However, increases in 6MWD were not observed in several non-Group 1 PH subpopulations. Peripheral edema, headache, and dyspnea were the most common AEs (*Badesch et al 2012*).
- The AMBITION trial (n = 610) was a double-blind, randomized, Phase 3/4 trial, which compared combination treatment with Letairis plus Adcirca to monotherapy with each in patients with WHO FC II or III symptoms. The study protocol was amended during the trial resulting in 17% of the initial protocol patients being excluded from the analysis, and treatment was administered significantly longer in the combination group vs. monotherapy groups (p = 0.03). Results demonstrated that patients receiving combination therapy had significantly fewer clinical failure events (defined as death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response) compared to patients receiving individual monotherapy (combination vs. pooled-monotherapy group, hazard ratio [HR] 0.5; 95% CI, 0.35 to 0.72; p < 0.001). Primary event outcomes were primarily driven by hospitalization. No significant differences were observed in terms of change in FC or all-cause death. The most common AEs that occurred more often with combination treatment included peripheral edema, headache, nasal congestion, anemia, and bronchitis (*Galiè et al 2015[a]*). Based on results from the AMBITION trial, the FDA-approved Letairis in combination with Adcirca to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability.

Opsumit (macitentan)

- The efficacy and safety of Opsumit on progression of PAH were demonstrated in a multicenter, Phase 3, event-driven, placebo-controlled trial (SERAPHIN) in 742 patients with symptomatic PAH (WHO FC II, III, or IV) with or without concomitant use of oral PDE-5 inhibitors, oral or inhaled PCAs, CCBs, or L-arginine for the 3 month period prior to randomization. Patients were randomized to placebo (n = 250), Opsumit 3 mg once daily (n = 250), or Opsumit 10 mg once daily (n = 242). The mean treatment durations were 85.3, 99.5, and 103.9 weeks in the placebo, Opsumit 3 mg, and Opsumit 10 mg groups, respectively. The primary study endpoint was time to the first occurrence of death, a significant morbidity event (defined as atrial septostomy, lung transplantation, initiation of IV or SC PCAs), or other worsening of PAH (defined as a sustained ≥ 15% decrease from baseline in 6MWD, worsening of PAH symptoms as determined by worsening of WHO FC, and need for additional treatment of PAH) during the double-blind treatment plus 7 days. Pre-specified secondary endpoints included change from baseline to month 6 in the 6MWD and percentage of patients with improvement in WHO FC. Other critical pre-specified secondary endpoints were time to PAH death or PAH hospitalization. The primary endpoint occurred in 46.4%, 38%, and 31.4% of the patients in the placebo, Opsumit 3 mg, and Opsumit 10 mg groups, respectively. Opsumit 10 mg once daily therapy resulted in a 45% reduction compared to placebo (HR, 0.55; 97.5% CI, 0.39 to 0.76; p < 0.001) in the occurrence of the primary endpoint to the end of the double-blind treatment. The beneficial effect of Opsumit 10 mg was primarily due to its reduction in clinical worsening (*Pulido et al 2013*).
  - In a sub-group analysis of the effect of Opsumit on hospitalizations, there were 117 (46.8%), 104 (41.6%), and 90 (37.2%) patients in the placebo, Opsumit 3 mg and 10 mg groups, respectively, who were hospitalized for any cause at least once during double-blind treatment, and they experienced a total of 171, 159, and 135 all-cause hospitalizations, respectively. Compared with that of placebo, the risk of all-cause hospitalization with Opsumit 3 mg was reduced by 18.9% (HR, 0.811; 95% CI, 0.623 to 1.057; p = 0.1208) and with Opsumit 10 mg by 32.3% (HR,

0.677; 95% CI, 0.514 to 0.891; p = 0.0051). Compared with placebo, the rate of PAH-related hospitalization was reduced by 44.5% in the Opsumit 3 mg group (p = 0.0004) and by 49.8% in the Opsumit 10 mg group (p < 0.0001). The mean number of annual hospital days for PAH-related hospitalizations was reduced by 53.3% in the Opsumit 3 mg arm (p = 0.0001) and by 52.3% in the Opsumit 10 mg arm (p = 0.0003). Due to the exploratory nature of this endpoint and small population, data from this study must be interpreted cautiously (*Channick et al 2015*).

Remodulin (treprostinil)

- The safety and efficacy of Remodulin were evaluated in 2 identical 12-week, multi-center, randomized, placebo-controlled, double-blind trials in a total of 470 patients with NYHA Class II, III, and IV PAH. Remodulin was administered SC at an average dose of 9.3 ng/kg/min. The effect on the 6MWD was small and did not achieve statistical significance at 12 weeks. For the combined populations, the median change from baseline for patients on Remodulin was 10 m and the median change from baseline on placebo was 0 m from a baseline of approximately 345 m. Remodulin significantly improved the Borg dyspnea score during the 6-minute walk test. Remodulin also consistently improved indices of dyspnea, fatigue, and signs and symptoms of PH. However, these results were difficult to interpret in the context of incomplete blinding to treatment assignment resulting from infusion site symptoms.

Orenitram (treprostinil)

- The efficacy and safety of Orenitram were evaluated in 3 multi-center, randomized, placebo-controlled, double-blind trials in 349 patients (FREEDOM-M), 350 patients (FREEDOM-C), and 310 patients (FREEDOM-C2).
  - FREEDOM-M compared twice daily administration of Orenitram with placebo in patients newly diagnosed with PAH and not receiving any background PAH treatment. The dose titration was based on patient's clinical response and tolerability. The primary endpoint was change in 6MWD over 12 weeks. The Orenitram group showed a significant improvement in 6MWD of 23 m (p = 0.0125). More than 50% of patients had an improvement of ≥ 20 m, and over 30% of patients had an improvement of > 50 m (*Jing et al 2013*). Orenitram demonstrated AEs typical of prostacyclin treatments (*Waxman 2013*).
  - FREEDOM-C and FREEDOM-C2 failed to meet the primary endpoint of improved 6MWD (*Tapson et al 2012, Tapson et al 2013*).

Revatio (sildenafil)

- The safety and efficacy of Revatio were evaluated in the SUPER-1 study, a 12-week, randomized, double-blind, placebo-controlled trial consisting of 278 patients with predominantly WHO FC II or III symptoms. Compared to placebo, Revatio significantly improved exercise capacity, as measured by the 6MWD, WHO FC symptoms and hemodynamics (*Galiè et al 2005*). In a 3-year extension study (SUPER-2), 46% of patients increased 6MWD relative to SUPER-1 baseline, 18% decreased 6MWD from baseline, 19% had died and 17% discontinued treatment or were lost to follow-up (*Rubin et al 2011*). The addition of Revatio to epoprostenol was evaluated in PACES, a 16-week, randomized, double-blind, placebo-controlled trial consisting of 267 patients receiving epoprostenol with predominantly WHO FC II or III symptoms. Revatio added to epoprostenol improved exercise capacity, hemodynamic measurements and time to clinical worsening more than epoprostenol plus placebo (*Simonneau et al 2008*).

Tracleer (bosentan)

- Tracleer was originally FDA-approved in PAH patients with WHO FC III and IV symptoms based on the results from 2 randomized, double-blind, placebo-controlled trials in 32 (Study 351) and 213 (BREATHE-1) patients treated for 16 and 12 weeks, respectively. In both studies, significant increases in the 6MWD were observed in all Tracleer groups compared to placebo. Tracleer was also associated with a significant reduction in dyspnea during walk tests and a significant improvement in WHO FC symptoms (*Channick et al 2001, Rubin et al 2002*). The FDA-approved indication was subsequently expanded to include patients with WHO FC II symptoms based on the results of the EARLY study consisting of 168 patients. In this 26-week study, treatment with Tracleer resulted in an increase in the 6MWD of 11.2 m compared to a decrease of 7.9 m in the placebo group; however, the difference was not statistically significant. The study did show a significant delay in clinical worsening and a lower incidence of worsening FC symptoms in the Tracleer group compared to placebo (*Galiè et al 2008[b], McLaughlin et al 2006*).
  - The results of an open-label extension phase of the EARLY trial suggested that the majority of patients exposed to long-term Tracleer therapy maintained or improved their FC. Approximately 20% of patients discontinued treatment because of AEs, which were most commonly PAH worsening (defined as death or initiation of IV or SC PCAs) and

elevated liver enzymes. Due to lack of a control group, data from this study must be interpreted cautiously (*Simmoneau et al 2014*).

- The COMPASS-2 trial (n = 334) was a prospective, double-blind, randomized controlled trial consisting of symptomatic PAH patients ranging from WHO FC II to IV who were taking stable Revatio doses (mean dose, 60 mg) for ≥ 3 months. Patients were randomized to Tracleer 125 mg twice daily plus Revatio or placebo plus Revatio for 16 weeks. There was no difference in the primary endpoint, time to the first morbidity/mortality event (defined as time to all-cause death, hospitalization for worsening PAH, initiation of IV prostanoid, atrial septostomy, lung transplant, or worsening PAH). There were also no significant differences in the individual measures of the primary endpoint; however, observed benefits were seen in terms of the mean 6MWD test. A high drop-out rate was observed during the trial; therefore, study power was reduced (*McLaughlin et al 2015*).

Tyvaso (treprostinil)

- The safety and efficacy of Tyvaso were evaluated in TRIUMPH I, a 12-week, multi-center, randomized, placebo-controlled, double-blind trial in WHO Group I PAH (98% NYHA Class III) patients who were receiving either Tracleer or Revatio (n = 235) for at least 3 months prior to study initiation. Patients received either placebo or Tyvaso in 4 daily treatments with a target dose of 9 breaths (54 mcg) per session. The primary endpoint, 6MWD, was measured at peak exposure (10 to 60 minutes post dose) and 3 to 5 hours after Tracleer or 30 to 120 minutes after Revatio. Patients receiving Tyvaso had a placebo-corrected median change from baseline in peak 6MWD of 20 meters (m) at week 12 ($p < 0.001$). The 6MWD measured at trough exposure (measured 4 hours after dosing) improved by 14 m.
- In a long-term follow-up of patients who were treated with Tyvaso in the pivotal study and the open-label extension (n = 206), Kaplan-Meier estimates of survival at 1, 2, and 3 years were 97%, 91%, and 82%, respectively. Of note, these observations were uncontrolled and therefore cannot be compared to the control group to determine the long-term effect of Tyvaso on mortality.

Uptravi (selexipag)

- The safety and efficacy of Uptravi were evaluated in the GRIPHON study (n = 1,156), a randomized, double-blind, placebo-controlled trial consisting of patients with predominantly idiopathic PAH, and WHO FC II or III symptoms. The median duration of treatment varied from 1.2 to 1.4 years for placebo and Uptravi, respectively, and treatment end was defined as 7 days after the last day of treatment intake. Compared to placebo, Uptravi significantly reduced the composite endpoint signifying the time to progression of PAH, defined as all-cause death or a PAH complication (27% vs. 41.6%; HR, 0.6; 99% CI, 0.46 to 0.78; $p < 0.001$); however, there were no differences in mortality between groups. The reduction in PAH complications was primarily driven by a reduction in disease progression (17.2% vs. 6.6%) and PAH-related hospitalization (18.7% vs. 13.6%). The safety of Uptravi compared to other agents in class is not clear. The GRIPHON pre-specified sub-group analysis did not stratify AEs by background treatment, but the study allowed stable doses of PDE-5 inhibitors and/or an ERA which accounted for ~80% of patients within the placebo baseline group. Those AEs that occurred significantly more often with Uptravi treatment included headache, diarrhea, jaw pain, nausea, myalgia, vomiting, extremity pain, flushing ($p < 0.001$ for all AEs), anemia ($p = 0.05$), and hyperthyroidism ($p = 0.004$) (*Sitbon et al 2015*).
- Frost and colleagues demonstrated that transitioning patients from inhaled treprostinil to Uptravi was effective and safe (*Frost et al 2018*). Of 34 enrolled patients, 32 (94.1%) stopped inhaled treprostinil and were receiving Uptravi, with 28 patients (82.4%) meeting all criteria for sustained treatment transition. In general, patients remained clinically stable throughout therapy and reported improved outcomes.

Veletri (epoprostenol)

- Please refer to the clinical efficacy summary for Flolan above.

Ventavis (iloprost)

- The efficacy of Ventavis was evaluated in a 12-week, randomized, multicenter, double-blind, placebo-controlled trial consisting of 203 patients with NYHA Class III PAH (majority), Class IV PAH, or CTEPH. Patients received 2.5 or 5 mcg of Ventavis 6 to 9 times daily during waking hours. The difference in the primary composite endpoint (10% increase in 6MWD 30 minutes after dose, improvement by at least one NYHA class compared to baseline, and no death or deterioration of PH) was statistically significant (19% vs. 4% placebo, $p = 0.0033$). The results for the CTEPH patients were not included in the aforementioned results, since there was inadequate evidence of benefit in this

patient population. The placebo-corrected difference in the 6MWD in Ventavis patients at 12 weeks was 40 m ($p < 0.01$).

- The safety of Ventavis was evaluated in a prospective, 2 year, open-label study with 63 PAH patients. Patients received Ventavis 2 to 4 mcg 6 to 9 times daily. Thirty-six patients completed at least 630 days of therapy, 19 patients dropped out prematurely, and 8 patients died. AEs were mild to moderate, the most common of which were cough and flushing. Two-year survival was found to be 87% [95% CI, 76% to 98%] (*Olschewski et al 2010*).

Meta-analyses and systematic reviews

- The results of a meta-analysis of 18 randomized controlled trials (n = 4,363) suggested that all oral PAH therapies confer a therapeutic benefit. More specifically, the findings showed:
  - PDE-5 inhibitors were associated with a statically significant reduction in mortality (relative risk [RR], 0.22; 95% CI, 0.07 to 0.71; p = 0.011), while other drugs only showed a trend toward reducing mortality.
  - Compared with placebo, ERAs, PDE-5 inhibitors, and riociguat significantly reduced clinical worsening, ameliorated WHO function class, and increased 6MWD. Oral prostanoids only showed a mild effect on 6MWD (19.88 m; 95% CI, 10.12 to 29.64, p = 0), and did not have any effect on reducing mortality and clinical worsening. Additionally, oral prostanoids significantly increased the incidence of treatment discontinuation due to AEs (RR, 3.41; 95% CI, 2.06 to 5.63; p = 0) (*Zheng et al 2014[a]*).
- A meta-analysis of 14 randomized controlled trials (n = 2,244) that evaluated the improvement in overall survival with use of oral, SC, IV, and inhaled PCAs, suggested the following:
  - Only IV PCAs showed a survival benefit (RR, 0.36; 95% CI, 0.16 to 0.79; p = 0.011), while oral (RR, 0.73; 95% CI, 0.32 to 1.66; p = 0.446), inhaled (RR, 0.28; 95% CI, 0.05 to 1.67; p = 0.162), and SC administration (RR, 0.91; 95% CI, 0.38 to 2.20; p = 0.837) did not show a benefit.
  - Overall mortality in the 14 studies was 3.30% (74 of 2,244 patients) with 2.52% (30 of 1,189 patients) mortality in the PCA-treated group and 4.17% (44 of 1,055 patients) mortality in the placebo group. The cumulative RR estimate of death showed a significant reduction of 44% (RR, 0.56; 95% CI, 0.35 to 0.88; p = 0.01), and no heterogeneity ($I^2 = 0.0\%$; p = 0.84) was detected among studies (*Zheng et al 2014[b]*).
- The results of a meta-analysis of 21 randomized controlled trials (n = 5,105) suggested that there was a reduction in the number of combined clinical worsening events (defined as all-cause mortality, lung or heart-lung transplant, hospitalization for PAH, and escalation of treatment) in patients with PAH with oral treatments, but showed less favorable effects on life expectancy in the short-term follow-up. Results demonstrated:
  - All classes reduced clinical worsening compared to placebo, including oral prostanoids (odds ratio [OR], 0.616; 95% CI, 0.419 to 0.906; p = 0.014), ERAs (OR, 0.504; 95% CI, 0.409 to 0.621; p < 0.001), PDE-5 inhibitors (OR, 0.468; 95% CI, 0.329 to 0.664; p < 0.001), and Adempas (OR, 0.277; 95% CI, 0.098 to 0.782; p = 0.015).
  - There were no significant reductions in mortality with any class versus placebo (*Zhang et al 2015*).
- A meta-analysis of 5 randomized controlled trials (n = 962) of < 16 weeks duration in adults and children treated with an sGC stimulator determined the following (all comparisons are vs. placebo):
  - sGC stimulators improve PAP in patients with PAH (who are treatment naïve or receiving a prostanoid or ERA) or those with recurrent or inoperable CTEPH.
  - Pooled analysis showed a mean difference in 6MWD of 30.13 m (95% CI, 5.29 to 54.96; $I^2 = 64\%$). On subgroup analysis, for PAH, there was no effect on 6MWD (11.91 m; 95% CI, -44.92 to 68.75; $I^2 = 77\%$), and for CTEPH, sGC stimulators improved 6MWD by a mean difference of 45 m (95% CI, 23.87 to 66.13; $I^2 = 0\%$).
  - The secondary outcome of mortality showed no change on pooled analysis.
  - Although pooled results demonstrated an increase (improvement) in WHO FC (OR, 1.53; 95% CI, 0.87 to 2.72; $I^2 = 49\%$), the results did not reach statistical significance. Also, there was no effect on clinical worsening (OR, 0.45; 95% CI, 0.17 to 1.14; $I^2 = 54\%$) or a reduction in MAP (−2.77 mmHg; 95% CI, −4.96 to −0.58; $I^2 = 49\%$). The pooled analysis did not show any significant difference in serious AEs (OR, 1.12; 95% CI, 0.66 to 1.90; $I^2 = 39\%$).
  - sGC stimulators should not be taken by people also receiving PDE-5 inhibitors or nitrates due to the risks of hypotension, and there is currently no evidence supporting their use in pulmonary hypertension associated with left heart disease (*Wardle et al 2016*).
- Several additional meta-analyses have been conducted evaluating ERAs, PDE-5 inhibitors, and PCAs. Notable observations in meta-analyses include the following:
  - Survival benefit was seen more with IV PCAs, especially in patients with more severe disease, compared with other routes such as oral and inhalation (*Ryerson et al 2010*).

- ERAs (Letairis and Tracleer) may have a somewhat lower effect on exercise tolerance in patients with connective tissue diseases, whereas PDE-5 inhibitors (Revatio and Adcirca) and the PCA epoprostenol showed consistent effects regardless of the presence or absence of connective tissue diseases (*Kuwana et al 2013*).
- Combination therapy appears to improve exercise capacity and reduce the risk of clinical worsening in PAH patients compared with monotherapy (*Zhu et al 2012*).
- Favorable effects on clinical events were not predicted by changes in the 6MWD (*Savarese et al 2012*). In addition, pulmonary hemodynamics correlated with exercise capacity, but not with clinical events (*Savarese et al 2013*).
- According to an Agency for Healthcare Research and Quality meta-analysis, prostacyclin analogues showed a statistically significant improvement in mortality. In addition, all drug classes improved 6MWD, but comparisons between agents were inconclusive. Combination therapy also improved 6MWD compared with monotherapy, but comparisons between specific regimens were inconclusive. Patients taking ERAs and PDE-5 inhibitors had a lower risk of hospitalization than those taking placebo, while the reduction in patients taking PCAs compared with placebo was similar, but not statistically significant (*McCrory et al 2013*).
- A meta-analysis including 15 RCTs comparing combination and monotherapy for the treatment of PAH found that the absolute risk reduction of clinical worsening was relatively constant beyond a 6 to 12-month treatment duration, and cast doubt on the need for trials of longer duration for measuring treatment efficacy in this population (*Lajoie et al 2017*).

CLINICAL GUIDELINES

- Several published clinical guidelines on PAH are available.
  - The Chest Guideline and Expert Panel Report on pharmacologic therapy for PAH provides several options for initial and subsequent therapy (*Taichman et al 2014*).
    - Initial therapy: For patients in WHO FC II or III, monotherapy with an ERA, PDE-5 inhibitor, or sGC stimulator is recommended. In WHO FC III patients with evidence of rapid progression or markers of poor prognosis, a parenteral prostanoid should be considered. For patients in WHO FC IV, a parenteral PCA is recommended; however, if patients are unable or unwilling to manage a parenteral product, an alternative is an inhaled PCA combined with an ERA.
    - Subsequent therapy: For patients in WHO FC III who have evidence of progression or markers of poor prognosis, addition of an inhaled or parenteral prostanoid should be considered. In patients in WHO FC III or IV, if clinical status is unacceptable, a second (and if needed, a third) class of PAH therapy can be added.
  - The European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines for the diagnosis and treatment of PH (*Galiè et al 2015[b]*) provide several options for both monotherapy and combination therapy of PAH.
    - Monotherapy: For patients in WHO FC II, recommendations include an ERA, a PDE-5 inhibitor, an sGC stimulator, or a prostacyclin receptor agonist. For patients in WHO FC III, the same medications may be used, and another option is a PCA. PCAs (eg, epoprostenol) are generally preferred for patients in WHO FC IV.
    - Initial drug combination therapy: Only the combination of Adcirca and Letairis has a category I recommendation for patients in WHO FC II and III; this combination also has a category IIb recommendation for patients in WHO FC IV. Other double- and triple-therapy combinations are also options, including other ERA and PDE-5 inhibitor combinations (WHO FC II, III, and IV) and some combinations of oral therapies with parenteral PCAs (WHO FC III and IV).
    - Sequential drug combination therapy: Several options are provided for sequential combination therapy. Oral combinations are commonly recommended for patients in WHO FC II and III, including Opsumit added to Revatio, Adempas added to Tracleer, and Uptravi added to an ERA and/or a PDE-5 inhibitor. Other oral combinations and combinations of oral therapies with inhaled or parenteral agents may also be used in patients in WHO FC II, III, and/or IV, but in most cases these recommendations are not as strong.
  - A 2018 scientific statement on the evaluation and management of right-sided heart failure from the American Heart Association (AHA) summarizes data for the use of prostacyclin analogs, PDE-5 inhibitors, and endothelin receptor agonists in patients with PAH (*Konstam et al 2018*). However, specific recommendations concerning the use of these agents in the PAH population are not provided in this document.
  - Reputable society groups agree that evidence supporting pediatric treatment is lacking. The AHA and American Thoracic Society (ATS) recently published a guideline on pediatric PH. This guideline states that in pediatric patients with lower-risk PAH, oral therapy with either a PDE-5 inhibitor or an ERA is recommended, and in pediatric

patients with higher-risk PAH, IV or SC PCAs should be initiated without delay (*Abman et al 2015*). A recent expert consensus statement from the European Pediatric Pulmonary Vascular Disease Network, the International Society of Heart and Lung Transplantation, and the German Society of Pediatric Cardiology reaffirm the AHA/ATS guideline. Additionally, early combination therapy with oral PAH drugs in treatment-naïve children who are FC II or III may be considered (*Hansmann et al 2016*).

SAFETY SUMMARY

- sGC Stimulator
  - Adempas has a boxed warning due to embryo-fetal toxicity. It is contraindicated in pregnancy because it may cause fetal harm when administered to pregnant women.
  - Females can only receive Adempas through the Adempas REMS Program, a restricted distribution program that requires enrollment and certification of prescribers, patients, and pharmacies. The program also requires females of reproductive potential to comply with pregnancy testing and contraception requirements.
  - Adempas is contraindicated in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias.
  - Additional contraindications for Adempas include co-administration with nitrates or nitric oxide donors and PDE-inhibitors (specific and non-specific).
  - Warnings and precautions for Adempas include symptomatic hypotension, bleeding, and pulmonary edema in patients with veno-occlusive disease (if confirmed, treatment should be discontinued).
  - The most common AEs associated with Adempas include headache, dyspepsia and gastritis, dizziness, nausea, diarrhea, hypotension, vomiting, anemia, gastroesophageal reflux disease, and constipation.
- ERAs
  - The ERAs (Letairis, Opsumit, and Tracleer) have boxed warnings for embryo-fetal toxicity and/or risks of teratogenicity due to the potential for fetal harm when administered to women who are or may become pregnant.
  - The Letairis and Opsumit REMS programs, respectively, are designed in the same manner as the Adempas REMS program described above.
  - The Tracleer Access Program (T.A.P.) program has been re-listed as the Tracleer REMS program. As a requirement of the REMS, healthcare professionals who prescribe or dispense Tracleer must enroll and comply with the requirements. Requirements include monthly reviews of pregnancy tests in women of reproductive potential, and liver enzymes and bilirubin in all patients. All patients must understand the risks and complete an enrollment form.
  - Letairis has an additional contraindication for idiopathic pulmonary fibrosis (IPF).
  - Tracleer has an additional boxed warning for risks of hepatotoxicity and birth defects. Throughout treatment and for 1 month after stopping Tracleer, females of reproductive potential must use 2 reliable methods of contraception unless the patient has had a tubal sterilization or had an intrauterine device (IUD) inserted.
  - Drug Reaction with Eosinophilia and Systematic Symptoms (DRESS), anaphylaxis, rash, and angioedema have been reported with Tracleer.
  - Warnings and precautions for Adcirca and Revatio include prolonged erection (for more than 4 hours), hearing loss, and vision loss (in 1 or both eyes), all of which require immediate medical attention.
  - Pulmonary edema/fluid retention has been reported during postmarketing surveillance of Letairis and Tracleer. Fluid retention may occur within weeks after starting Letairis and is more common when Letairis is used in combination with Adcirca than with Letairis or Adcirca alone.
  - Use of Opsumit and Tracleer should be avoided in patients taking potent inhibitors or inducers of CYP3A.
  - Decreases in sperm count, decreased hemoglobin and hematocrit levels, and pulmonary edema (associated with pulmonary veno-occlusive disease (PVOD) have been observed in patients taking ERAs.
- PDE-5 Inhibitors
  - All PDE-5 inhibitor products have a contraindication for use in patients on nitrates as well as a warning with concomitant alpha blocker use due to resulting hypotension. The patient should allow 48 hours to elapse between the last dose of Adcirca and taking nitrates. Additionally, Revatio and Adcirca are contraindicated for concomitant use with the sGC stimulator, Adempas.
  - In August 2012, the prescribing information for Revatio was updated with a warning stating that the use of Revatio in pediatric patients is not recommended due to increased mortality associated with higher doses and noted that lower doses are not effective in improving exercise capacity. The FDA clarified the warning related to pediatric use

of Revatio in March 2014, stating it was not intended to suggest that Revatio never be used in children. The FDA acknowledged there may be situations in which the benefit-to-risk profile may be acceptable in individual children, for example, when other treatment options are limited, in which case Revatio can be used with close monitoring (FDA Drug Safety Communication, 2014).
  - Co-administration of Revatio or Adcirca with potent CYP3A inhibitors is not recommended. Co-administration of Adcirca with potent CYP3A inducers is not recommended.
  - Blood pressure lowering effects are increased when Adcirca is taken with alcohol.
  - Revatio and Adcirca are generally well tolerated with headaches, myalgia, flushing, and dyspepsia being the most common AEs reported for both products.
  - Stevens-Johnson syndrome and exfoliative dermatitis have been reported with Adcirca, and anaphylactic reaction, anaphylactic shock and anaphylactoid reaction have been reported with Revatio.
  - Vision loss, including permanent vision loss because of non-arteritic anterior ischemic optic neuropathy has been reported with the use of PDE-5 inhibitors.
- Prostacyclin Receptor Agonist
  - Uptravi has a warning/precaution to consider PVOD if acute pulmonary edema develops.
  - Uptravi is not recommended in patients with severe hepatic impairment (Child-Pugh Class C) and has not been studied in dialysis patients (or with eGFR < 15 mL/min/1.73m^2).
  - Concomitant administration of Uptravi is contraindicated with strong inhibitors of CYP2C8 (eg, gemfibrozil).
  - The most common AEs reported with Uptravi are headache, diarrhea, jaw pain, nausea, myalgia, vomiting, pain in extremity, and flushing. These AEs are more frequent during the dose titration phase.
- PCAs
  - Orenitram is contraindicated for use in patients with severe hepatic impairment (Child-Pugh Class C).
  - Flolan and Veletri are contraindicated in patients with heart failure due to severe left ventricular dysfunction. Additionally, Veletri is contraindicated in patients with pulmonary edema, stating that the development of pulmonary edema during dose initiation may be associated with pulmonary veno-occlusive disease.
  - Orenitram and Tyvaso both carry a warning/precaution related to an increased risk of bleeding, particularly in patients receiving anticoagulants. Additional warnings and precautions for Tyvaso include symptomatic hypotension, possible Tyvaso dose changes when inhibitors or inducers of CYP2C8 are added or withdrawn, and a possible increase in exposure or a decrease in tolerability with hepatic or renal impairment. Orenitram should be avoided in patients with blind-end pouches (diverticulosis).
  - The safety of Tyvaso and Ventavis has not been established in patients with significant underlying lung disease (eg, asthma, chronic obstructive pulmonary disease, acute pulmonary infections). Patients with acute pulmonary infections who are taking Tyvaso should be carefully monitored to detect any worsening of lung disease and loss of drug effect. Ventavis can induce bronchospasm.
  - Hypotension leading to syncope has been observed with Ventavis. It should not be administered in patients with a systolic blood pressure below 85 mmHg.
  - Flolan and Ventavis carry additional warnings and precautions regarding pulmonary edema. If signs of pulmonary edema occur, treatment should be stopped because this could be a sign of pulmonary venous hypertension or pulmonary veno-occlusive disease.
  - With Flolan, Orenitram, Remodulin, and Veletri, abrupt withdrawal (including interruptions in drug delivery) or sudden large reductions in the dose can worsen PAH symptoms (or cause rebound PH in patients taking Flolan).
  - Flolan carries additional warnings and precautions that include vasodilation reactions and an increased risk of bleeding.
  - Flolan, Remodulin, and Veletri are administered via an indwelling central venous catheter. This route of administration is associated with blood stream infections (BSI) and sepsis, which may be fatal. During long-term follow-up, sepsis was reported at a rate of 0.3 infections per patient per year in patients treated with Flolan. In an open-label study of IV Remodulin using an external infusion pump (n = 47), there were 7 catheter-related line infections during approximately 35 patient years, or about one BSI event per 5 years of use. A Centers for Disease Control and Prevention survey of 7 sites that used IV Remodulin for the treatment of PAH found approximately one BSI event per 3 years of use. In an open-label study of an implantable pump (n = 60), there were 2 BSIs related to the implant procedure during approximately 265 patient-years. Continuous SC infusion (undiluted) is the preferred mode of administration of Remodulin. VELTERI was associated with chills/fever/sepsis/flu-like symptoms in 25% of patients in controlled trials for idiopathic or heritable PAH.

- Remodulin and Tyvaso exposure may increase or decrease when administered with strong inhibitors or inducers of CYP2C8.
- AEs reported with Tyvaso include cough, headache, throat irritation/pharyngolaryngeal pain, nausea, flushing, and syncope. AEs with Remodulin include infusion site pain, infusion site reaction, headache, diarrhea, nausea, rash, jaw pain, vasodilation, dizziness, edema, pruritus, and hypotension. The most common AEs reported with Orenitram include headache, diarrhea, nausea, and flushing.
- AEs associated with Ventavis include vasodilation (flushing), increased cough, headache, trismus, insomnia, nausea, hypotension, vomiting, increased alkaline phosphatase, flu syndrome, back pain, tongue pain, palpitations, syncope, increased gamma-glutamyl transpeptidase, muscle cramps, hemoptysis, and pneumonia.
- The most common AEs reported with Flolan and Veletri include dizziness, jaw pain, nausea, vomiting, headache, hypotension, flushing, and musculoskeletal pain.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Adcirca (tadalafil)	Tablet: 20 mg	Oral	Daily	Dividing the dose over the course of the day is not recommended.
Adempas (riociguat)	Tablet: 0.5, 1, 1.5, 2, and 2.5 mg	Oral	Three times daily	Patients who smoke may tolerate higher doses. If they stop smoking, dose decreases may be required. Lower starting doses should be considered in patients unable to tolerate the hypotensive effects and patients receiving strong CYP and P-gp/BCRP inhibitors. Adempas may be crushed and mixed with water or soft foods immediately before administration. Discontinue at least 24 hours prior to administering a PDE-5 inhibitor. Pregnancy test required prior to treatment initiation and monthly during treatment.
Flolan (epoprostenol)	Powder for injection: 0.5 and 1.5 mg	IV	Continuous infusion; Initiate infusion through a central venous catheter at 2 ng/kg/min; increase in increments of 1 to 2 ng/kg/min at intervals of at least 15 minutes based on clinical response	Abrupt withdrawal or sudden large reductions in infusion rates should be avoided. Continuous chronic infusion is administered through a central venous catheter. Temporary peripheral IV infusion may be used until central access is established.
Letairis (ambrisentan)	Tablet: 5 and 10 mg	Oral	Once daily (with or without tadalafil daily); titrate at 4-week intervals	Doses > 10 mg once daily have not been studied. Tablets should not be split, crushed, or chewed.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Pregnancy test required prior to treatment initiation and monthly during treatment.
Opsumit (macitentan)	Tablet: 10 mg	Oral	Once daily	Doses > 10 mg once daily are not recommended.
Orenitram (treprostinil)	Extended-release tablet: 0.125, 0.25, 1, 2.5 mg, and 5 mg	Oral	Twice or 3 times daily; maximum dose is determined by tolerability; titrate not more than every 3 to 4 days as tolerated	Should be taken with food. Tablets should be swallowed whole. Coadministration with CYP2C8 inhibitors (eg, gemfibrozil) and the presence of mild hepatic impairment require a lower starting dose.
Remodulin (treprostinil)	Multi-dose vials for injection: 1, 2.5, 5, 10 mg/mL	SC, IV	Continuous infusion; initial dose for patients new to therapy: 1.25 ng/kg/min; increase in increments of 1.25 to 2.5 ng/kg/min at weekly intervals, depending on clinical response	SC is preferred, although administration via a central IV line can be performed if SC administration is not tolerated. An implantable IV infusion pump has recently been approved for use with Remodulin (Implantable System for Remodulin or ISR). Refer to the pump manufacturer's manual for specific instructions for use.
Revatio (sildenafil)	Tablet: 20 mg Powder for oral suspension: 10 mg/mL Solution for injection: 10 mg/12.5 mL	Oral, IV	Oral: 3 times daily approximately 4 to 6 hours apart Injection: IV bolus 3 times daily	Doses above 20 mg 3 times daily are not recommended. Revatio 10 mg injection dose is predicted to be the equivalent of a 20 mg oral dose. Revatio injection is for continued treatment of patients who are temporarily unable to take oral treatment. Oral suspension expires within 60 days of reconstitution.
Tracleer (bosentan)	Tablet: 62.5 and 125 mg Tablet for oral suspension: 32 mg	Oral	Twice daily (age and weigh based dosing) Concurrent ritonavir: Once daily or every other day in patients who have been receiving ritonavir for ≥ 10 days; discontinue Tracleer at least 36 hours prior to initiation of ritonavir; resume	Tablets for oral suspension should be dispersed in a minimal amount of water immediately before administration. Pregnancy test required prior to treatment initiation, monthly during treatment, and one month after stopping. Initiation should be avoided in patients with aminotransferases > 3x ULN. Doses > 125 mg twice daily do not

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Tracleer 10 days following ritonavir initiation	have additional benefit sufficient to offset the increased risk of hepatotoxicity.
Tyvaso (treprostinil)	Inhalation solution (solution, refill, and starter solution): 0.6 mg/mL (1.74 mg per 2.9 mL)	Inhale	3 breaths per treatment session, 4 times a day (4 hours apart); titrate by an additional 3 breaths per session in 1 to 2 week intervals; maximum: 9 breaths per treatment session, 4 times daily	Inhalation system consists of an ultrasonic, pulsed delivery device and its accessories.
Uptravi (selexipag)	Tablet: 200, 400, 600, 800, 1000, 1200, 1400, and 1600 mcg Therapy pack: 200/800 mcg	Oral	Twice daily; titrate dose weekly	Swallow tablets whole. Food may improve tolerability.
Veletri (epoprostenol)	Powder for injection: 0.5 and 1.5 mg	IV	Continuous infusion; Initiate infusion at 2 ng/kg/min; increase in increments of 2 ng/kg/min at intervals of at least 15 minutes based on clinical response If symptoms persist or recur after improving, increase in increments of 1 to 2 ng/kg/min at intervals of at least 15 minutes	Abrupt withdrawal or sudden large reductions in infusion rates should be avoided. Continuous chronic infusion is administered through a central venous catheter. Temporary peripheral IV infusion may be used until central access is established.
Ventavis (Iloprost)	Inhalation solution: 10 and 20 mcg	Inhale	Administered 6 to 9 times per day (no more than once every 2 hours); maximum: 9 times daily	Ventavis is intended to be inhaled using the I-neb Adaptive Aerosol Delivery (AAD) System. The 20 mcg/mL concentration is for patients who are maintained at the 5 mcg dose and who have repeatedly experienced extended treatment times, which could result in incomplete dosing. Vital signs should be monitored while initiating Ventavis.

Abbreviations: CYP = cytochrome P450; IV = intravenous; P-gp/BCRP = P-glycoprotein/breast cancer resistance protein; SC = subcutaneous

CONCLUSION

- Pulmonary arterial hypertension (PAH) is a life-threatening disorder that is associated with a poor prognosis.
- There are 5 classes of drugs that are used in the management of PAH, including endothelin receptor antagonists (ERAs), phosphodiesterase (PDE)-5 inhibitors, a prostacyclin analog (PCA), a prostacyclin receptor agonist, and a soluble guanylate cyclase (sGC) stimulator.
- All of the PAH agents have shown improved pulmonary hemodynamics and exercise capacity in PAH patients as compared to placebo. Their effects on mortality have not been adequately demonstrated.
- Most trials for PAH have been relatively short-term trials (12 to 18 weeks) that evaluated changes in exercise capacity using the 6-minute walk distance (6MWD) as a primary endpoint. However, recently there has been a preference toward longer, event-driven trials that evaluate composite clinical worsening events (*LeVarge et al 2015*). Published event-driven trials include SERAPHIN, GRIPHON, AMBITION, and COMPASS-2 (*Galiè et al 2015[a], McLaughlin et al 2015, Pulido et al 2013, Sitbon et al 2015*).
- Clinical trials have demonstrated the safety and efficacy of the individual PAH agents; however, there is limited data comparing the agents within classes or between classes. Data are conflicting regarding the benefits of combination vs. monotherapy (*Barst, 2009, McLaughlin et al 2009, Galiè et al 2015[b], Taichman et al 2014*). Two recent trials evaluating this include the AMBITION and COMPASS-2 trials. The AMBITION trial has demonstrated that combination treatment with Letairis and Adcirca resulted in reduced disease progression and hospitalization in mainly FC II and III PAH patients compared to monotherapy (*Galiè et al 2015[a]*). However, the COMPASS-2 trial demonstrated no difference between Tracleer plus Revatio versus Revatio monotherapy for most endpoints with the exception of the mean 6MWD test (*McLaughlin et al 2015*).
- Adempas is the first and only drug to be FDA-approved in the treatment of CTEPH. Pulmonary endarterectomy can be curative for CTEPH, but it is technically demanding which may limit access to its use as a treatment. Adempas is dosed 3 times daily, which is more frequent than several other oral treatments for PAH.
- The ERAs (Letairis, Opsumit, and Tracleer) competitively bind to both receptors with different affinities. Letairis and Opsumit are highly selective for the ET_A receptor, while Tracleer is slightly selective for the ET_A receptor over the ET_B receptor. In addition, Opsumit has a pharmacologically active metabolite and is considered “tissue-targeting” because it displays high affinity and sustained occupancy at the ET receptors in human pulmonary arterial smooth muscles. However, the clinical significance of receptor affinities of the ERAs has not been established.
- The PDE-5 inhibitors (Adcirca and Revatio) are generally well tolerated; the most common side effects include headache, myalgia, flushing, dizziness, and gastrointestinal upset. Both products are contraindicated for use in patients on nitrates and have warnings about their use in patients on alpha-adrenergic inhibitors. Use of Adcirca with potent CYP3A inhibitors or inducers may significantly alter serum levels of Adcirca and is not recommended. Use of Adcirca in patients who are using an sGC stimulator may potentiate the hypotensive effects of sGC stimulators and is not recommended. Use of Revatio with potent CYP3A inhibitors is not recommended as they may significantly alter serum levels of Revatio.
- In addition to the oral formulation, Revatio is available in an oral suspension formulation and an intravenous formulation. Currently, Revatio tablets and intravenous formulation are available generically.
- Adcirca is taken just once a day compared to 3 times a day with Revatio.
- Orenitram is the first oral PCA approved by the FDA. The PCAs are frequently reserved for more severe forms of PAH. As the first oral option in this subclass for treatment of PAH, Orenitram may offer a more convenient alternative dosage form leading to earlier PCA initiation in treatment. Orenitram is dosed twice daily and requires dosage titration every 3 to 4 days. Orenitram did not demonstrate added benefit when added to other vasodilator therapy.
- Uptravi is a first-in-class prostacyclin receptor agonist, which works within the same pathway as Orenitram. Based on results from the GRIPHON trial, Uptravi has reduced disease progression and hospitalization. This is in contrast to Orenitram, which has only improved exercise tolerability. Unlike Orenitram, Uptravi has also demonstrated efficacy when combined with a PDE-5 inhibitor and/or an ERA. The safety of Uptravi compared to other oral agents in the class is not clear. The GRIPHON pre-specified sub-group analysis did not stratify AEs by background treatment, but the study allowed stable doses of PDE-5 inhibitors and/or an ERA throughout the trial. Background treatment was used by ~80% of patients within the placebo baseline group. Those AEs reported significantly more often with Uptravi treatment include headache, diarrhea, jaw pain, nausea, myalgia, vomiting, extremity pain, flushing, anemia, and hyperthyroidism (*Sitbon et al 2015*). Based on indirect trial evidence, the proportion of patients discontinuing Uptravi vs. placebo (14% vs. 7%) due to AEs in the GRIPHON trial was higher than those within the Orenitram labeling vs.

placebo (4% vs. 3%) (*Orenitram prescribing information 2014, Sitbon et al 2015*). Overall, it is not clear how the Uptravi safety profile compares to other agents in class due to different study populations. Head-to-head trials are needed to confirm safety risks and differences.

- The 2014 CHEST Guideline and Expert Panel Report update identifies PDE-5 inhibitors, ERAs, the oral PCA, and the sGC stimulator as viable alternatives in treating PAH adults with varying severity levels (FC II to IV) based primarily on consensus opinions (*Taichman et al 2014*).
- The 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines stratifies PAH treatment by low or intermediate risk or high risk patients. In adult patients with low or intermediate risk (FC II to III), initial monotherapy or initial oral combination therapy is recommended. Based on the AMBITION trial, guidelines state that initial combination treatment with ambrisentan plus tadalafil has proven to be superior to initial monotherapy with ambrisentan or tadalafil in delaying clinical failure. In adult patients with high risk (FC IV), initial combination therapy including IV PCAs are recommended with epoprostenol IV considered first-line due to the mortality benefits in trials (*Galiè et al 2015[b]*).
- Reputable society group guidelines agree that there is a lack of randomized trials in pediatric patients, making it difficult to deliver strong guidelines (*Abman et al 2015, Galiè et al 2015[b], Hansmann et al 2016*). The 2015 American Heart Association and American Thoracic Society guidelines recommend oral therapy with either a PDE-5 inhibitor or an ERA in lower risk PAH pediatric patients. In pediatric patients with higher-risk PAH, IV and SC PCAs should be initiated immediately with a goal to transition patients to oral or inhaled therapy after the patient is asymptomatic and stable (*Abman et al 2015*). The 2015 ESC/ERS guidelines recommend that pediatric treatment follows adult guidelines taking in account risks (*Galiè et al 2015[b]*). The European Pediatric Pulmonary Vascular Disease Network, the International Society of Heart and Lung Transplantation, and the German Society of Pediatric Cardiology reaffirm much of the aforementioned guidance, but also stipulate that early combination therapy with two oral PAH drugs in treatment-naïve children who are FC II or III may be considered (*Hansmann et al 2016*).
- A 2018 scientific statement on the evaluation and management of right-sided heart failure from the American Heart Association (AHA) summarizes data for the use of prostacyclin analogs, PDE-5 inhibitors, and endothelin receptor agonists in patients with PAH (*Konstam et al 2018*). However, specific recommendations concerning the use of these agents in the PAH population are not provided in this document.

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INTRODUCTION

- Atopic dermatitis, also referred to as atopic eczema, is a chronic, highly pruritic, and relapsing inflammatory skin condition. The prevalence of atopic dermatitis is estimated to be between 15% to 30% in children and 2% to 10% in adults; approximately 18 million children and adults have atopic dermatitis in the United States *(Berke et al 2012, Eichenfield et al 2014a, Food and Drug Administration [FDA] presentation 2015)*. Atopic dermatitis is one of the most common skin disorders in children with more than 90% of cases starting before the age of 5 years *(Eichenfield et al 2014a)*.
- The pathogenesis of atopic dermatitis can be explained by impaired epidermal barrier function due to structural and functional abnormalities in the skin as well as a cutaneous inflammatory response to environmental factors *(Weston & Howe 2018)*. Pruritus is one of the most common symptoms of atopic dermatitis, and it is an essential feature which provokes a vicious "itch-scratch" cycle that compromises the epidermal barrier which results in water loss, xerosis, microbial colonization, and secondary infection *(Castro 2008)*. The clinical manifestations of atopic dermatitis vary according to age and disease activity; however, almost all patients with atopic dermatitis report dry skin. The infantile and childhood stages are characterized by pruritic, red, crusted lesions and generally involve the face, neck, and extensor skin surfaces *(Eichenfield et al 2014a)*. The adult stage of atopic dermatitis is more lichenified and localized to the flexural folds of the extremities *(Eichenfield et al 2014a)*.
- Diagnosis of atopic dermatitis is based on a constellation of clinical symptoms. There is no optimal long-term maintenance treatment for atopic dermatitis, and there is no known cure. The general approach for the treatment of atopic dermatitis involves elimination of exacerbating factors, restoring the skin's abnormal barrier function, hydrating the skin, and controlling active disease with topical anti-inflammatory agents *(Eichenfield et al 2014b, Schneider et al 2013, Tollefson et al 2014)*.
- Patients with atopic dermatitis should avoid exacerbating factors including excessive bathing, low humidity environments, emotional stress, xerosis, and exposure to detergents. Thick creams with low water content or ointments which have zero water content protect against xerosis and should be utilized. Antihistamines are utilized as an adjunct in patients with atopic dermatitis to control pruritus and eye irritation. Sedating antihistamines (eg, diphenhydramine, hydroxyzine) appear to be more effective than non-sedating ones (eg, fexofenadine, loratadine) *(Eichenfield et al 2014b)*. However, evidence supporting their use is weak due to lack of controlled trials.
- Topical corticosteroids are considered to be the standard of care for the treatment of atopic dermatitis *(Eichenfield et al 2014b, Schneider et al 2013, Tollefson et al 2014)*. Low- to high-potency topical corticosteroids are utilized 1 or more times daily for the treatment of acute flares, as well as intermittently to prevent relapses. One large trial showed that twice-daily application of topical corticosteroids was no more effective than once-daily application *(Krakowski et al 2008)*. There are tolerability and safety concerns regarding the use of topical corticosteroids including skin atrophy, striae, and telangiectasia, which may limit long-term use of these agents. These adverse reactions occur more frequently when topical corticosteroids are used on sensitive areas of thin skin including skin folds and the face or neck *(Eichenfield et al 2014b, Krakowski et al 2008, Schneider et al 2013)*.
- Immunosuppressive agents for atopic dermatitis include Elidel (pimecrolimus) and Protopic (tacrolimus). The exact mechanism of action in atopic dermatitis is not known. Elidel and Protopic inhibit calcineurin, a calcium-dependent phosphatase, by binding with high affinity to immunophilin-12 (FKBP-12), which is theorized to be the primary mode of inflammation reduction in atopic dermatitis *(Clinical Pharmacology 2019)*. Protopic and Elidel provide immunosuppression via inhibition of T-cell activation.
- There are some concerns regarding the long-term safety of these agents. On January 19, 2006, the FDA approved updated labeling for the agents *(FDA press release 2006)*. This updated labeling was a result of cancer-related adverse events (AEs) with the use of these medications. The labeling includes a boxed warning about a possible risk of cancer and a medication guide for patients to ensure that they are aware of this concern. The labeling clarifies that these medications are recommended for use as second-line treatments and are not recommended in children under 2 years of

age. A definitive causal link between the topical immunosuppressants and the incidence of malignancy has not been established.

- Eucrisa (crisaborole) is a non-steroidal, topical treatment for atopic dermatitis that works by way of phosphodiesterase (PDE)-4 inhibition. Inflammation is associated with elevated PDE-4 enzyme activity and overactive PDE-4 has been shown to contribute to the signs and symptoms of atopic dermatitis *(Zane et al 2016)*. Eucrisa enhances cellular control of inflammation by inhibiting PDE-4 and its ability to degrade intracellular cyclic adenosine monophosphate (cAMP), thereby suppressing the release of cytokines *(Paller et al 2016)*. The novel boron chemistry of Eucrisa additionally enables synthesis of a low molecular weight compound that facilitates effective penetration through human skin *(Paller et al 2016)*.
- Medispan Class: Immunosuppressive Agents – Topical; Phosphodiesterase 4 (PDE4) Inhibitors – Topical; Macrolide Immunosuppressants - Topical

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Elidel (pimecrolimus)	✔
Protopic (tacrolimus)	✔
Eucrisa (crisaborole)	-

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Elidel (pimecrolimus)	Protopic (tacrolimus)	Eucrisa (crisaborole)
Second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adults and children 2 years of age and older, who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable.	✔		
Second-line therapy for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.		✔ *	
Topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older			✔

*Both 0.03% and 0.1% ointment for adults and only 0.03% ointment for children 2 to 15 years of age.

(*Prescribing information: Elidel 2017, Eucrisa 2017, Protopic 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

Elidel and Protopic

- The FDA approval of Elidel cream was based on 3 randomized, double-blind, vehicle-controlled, Phase III studies in patients 3 months to 17 years of age with mild to moderate atopic dermatitis (N = 589). Two of these 3 trials support the use of Elidel cream in patients 2 years of age and older with mild to moderate atopic dermatitis. Two other identical, 6-

week, vehicle-controlled, Phase III trials were conducted in pediatric patients 2 to 17 years of age (N = 403). These studies showed significant clinical response based on physician's global evaluation for Elidel-treated patients compared to patients in the vehicle group. These studies are outlined in the manufacturer product labeling.

- The FDA approval of Protopic ointment was based on 3 randomized, double-blind, vehicle-controlled, Phase III studies in patients with moderate to severe atopic dermatitis. One of the studies was conducted in pediatric patients (N = 351) ages 2 to 15 years, and the other 2 studies were conducted in adult patients (N = 632). The primary efficacy endpoint was met by all 3 studies with a significantly greater percentage of patients achieving at least 90% improvement based on the physician's global evaluation of clinical response in the Protopic group compared to the vehicle group ($p < 0.001$). There was some evidence that Protopic 0.1% ointment may provide more efficacy than the 0.03% ointment in adult patients who had severe disease at baseline. There was no difference in efficacy between the Protopic strengths in the pediatric study. These studies are outlined in the manufacturer product labeling.
- Elidel and Protopic have been directly compared in clinical trials. One trial compared Elidel 1% to Protopic 0.03% in patients 2 to 17 years of age (N = 141) and found no difference in the incidence of application site reactions between the topical immunomodulators in the 6-week study *(Kempers et al 2004)*. However, itching was reported at a significantly higher rate in the Protopic group. In 2 other clinical trials, Protopic 0.1% was compared to Elidel in adult patients over 6 weeks. Patients treated with Protopic had a significantly greater improvement in the Eczema Area Severity Index (EASI) score compared to those treated with Elidel (*Abramovits et al 2008, Fleischer et al 2007*). The success in therapy based on the Investigator Global Atopic Dermatitis Assessment, improvement in percent body surface area (BSA) affected, and improvement in signs and symptoms of atopic dermatitis in face and neck were all statistically significant for the Protopic group in both studies *(Abramovits et al 2008, Fleischer et al 2007)*. There were no differences in AEs between the groups.
- A meta-analysis of 3 randomized clinical trials showed that both adults and children in the Protopic-treated group had a significantly greater improvement in EASI score at week 6 as compared to the Elidel group *(Paller et al 2005)*. The most common AEs in all studies were local application site reactions including burning and stinging *(Paller et al 2005)*.
- A meta-analysis of 25 randomized controlled trials (N = 6897) showed that Protopic 0.1% was equally efficacious as potent topical corticosteroids and more efficacious than mild topical corticosteroids for the treatment of atopic dermatitis *(Ashcroft et al 2005)*. Additionally, Elidel was found to be less effective than potent topical corticosteroids *(Ashcroft et al 2005)*. Individual clinical trials have reported conflicting results *(Bieber et al 2007, Doss et al 2009, Doss et al 2010)*.
- A meta-analysis and systematic review assessed the effectiveness of topical immunomodulators compared to topical corticosteroids and/or placebo (N = 7378) *(El-Batawy et al 2009)*. In terms of overall comparison, Elidel was found to be more effective than vehicle at 3 and 6 weeks. However, a long-term study that was included in this review did not find any difference between these 2 groups at 6 and 12 months. Also, betamethasone valerate, a potent topical corticosteroid, was found to be significantly more effective in adults (3 weeks) than Elidel in the treatment of moderate to severe atopic dermatitis. Although this meta-analysis showed that Elidel seems to be less effective than topical corticosteroids, Elidel would be efficacious in areas where topical corticosteroids may not be recommended such as the face and sensitive areas including skin folds. Pooled analysis of Protopic trials demonstrated that Protopic was more effective than vehicle *(El-Batawy et al 2009)*. When compared to mild potency topical corticosteroids like hydrocortisone acetate, Protopic was more efficacious. However, when compared to moderate potency topical corticosteroids, Protopic 0.03% was significantly less effective than topical corticosteroids, and Protopic 0.1% was equal in effectiveness to the topical corticosteroids. Overall, Protopic was found to be more effective than mild topical corticosteroids and equally effective as moderately potent topical corticosteroids *(El-Batawy et al 2009)*.
- A systematic review of 20 randomized controlled trials (N = 6288) showed that Protopic was more efficacious than placebo or mild topical corticosteroids for the treatment of atopic dermatitis *(Chen et al 2010)*. Additionally, Elidel was more efficacious than placebo and equally efficacious as mild topical corticosteroids for the treatment of atopic dermatitis. In this review, 3 trials comparing Elidel to Protopic were identified. While 2 of the trials did find Protopic to be significantly more efficacious, no significant difference was found in the third trial.
- A retrospective cohort evaluated initial cancer diagnosis in patients with a diagnosis of atopic dermatitis or eczema and found that while exposure to Elidel or Protopic was not associated with an increase in overall cancer rates, exposure to these agents was associated with an increased risk of T-cell lymphoma ($p < 0.001$ and $p = 0.01$, respectively). However, after the exclusion of 4 cases due to physician suspected T-cell lymphoma prior to exposure, the risks were only significant for patients exposed to Protopic and not Elidel ($p < 0.001$, $p = 0.086$, respectively) *(Hui et al 2009)*.

Eucrisa

- The safety and efficacy of Eucrisa were demonstrated in 2 identically designed, randomized, Phase III, double-blind, vehicle-controlled trials in a total of 1522 patients with mild to moderate atopic dermatitis and ≥ 5% treatable BSA *(Eucrisa formulary submission dossier 2016, Paller et al 2016)*. The primary endpoint of success was defined as the proportion of subjects at Day 29 who were clear or almost clear with a ≥ 2-grade improvement from baseline by the Investigator's Static Global Assessment (ISGA) scale. More patients receiving Eucrisa vs vehicle achieved the primary endpoint of ISGA success (Study AD-301: 32.8% vs 25.4%, p = 0.038; Study AD-302: 31.4% vs 18.0%, p < 0.001), with a greater percentage achieving clear/almost clear overall (51.7% vs 40.6%, p = 0.005; 48.5% vs 29.7%, p < 0.001). In addition, Eucrisa-treated patients achieved greater ISGA score improvements and improvement in pruritus earlier (both p < 0.001).
  - An open-label extension trial of AD-301 and AD-302 evaluated the safety of Eucrisa in 517 patients with mild to moderate atopic dermatitis for 48 weeks. Patients underwent an average of 6 treatment periods and used an average of 133 grams of ointment/month. Most treatment-emergent AEs were mild (51.2%) or moderate (44.6%) and were considered unrelated to treatment with Eucrisa (93.1%). The most commonly observed AEs (≥ 1% of patients) included atopic dermatitis flares (3.1%), application site pain (2.3%), and application site infection (1.2%). Most patients (77.8%) did not require rescue medications. Children and adolescents made up 48% of those patients that initiated rescue therapies (*Eichenfield et al 2017*).

CLINICAL GUIDELINES

- Treatment guidelines generally agree that a stepwise approach to treatment is needed. Nonpharmacological therapies (ie, lukewarm baths, skin moisturizers, etc.) are followed by topical corticosteroids and/or topical calcineurin inhibitors. Low to high potency topical corticosteroids are the standard of care, and strength is selected based on severity, duration of treatment, location of exacerbation, and age of the patient. Elidel and Protopic are topical calcineurin inhibitors that are recommended as second-line therapy in patients who fail or cannot tolerate corticosteroids. Eucrisa has not yet been added to the guidelines *(Eichenfield et al 2014a, Eichenfield et al 2014b, Schneider et al 2013, Sidbury et al 2014, Tollefson et al 2014)*.

SAFETY SUMMARY

Elidel and Protopic

- Boxed warning: Although a causal relationship has not been established, rare cases of malignancy (eg, skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors.
  - Avoid continuous long-term use, in any age group, and limit application to areas of involvement with atopic dermatitis.
  - Both agents are not indicated for use in children less than 2 years of age. Only Protopic 0.03% ointment is indicated for use in children 2 to 15 years of age; Elidel is indicated for children 2 years and older and adults.
- Key Warnings/Precautions:
  - Do not use on malignant or pre-malignant skin conditions.
  - Resolve bacterial or viral infections at the treatment site.
  - While using avoid exposure to sunlight.
  - Do not use in immunocompromised patients.
- AEs: Application site irritation and reactions such as skin burning, itching, redness, and rash. Hypersensitivity reactions can also occur.
- A 5-year, open-label, multicenter study evaluated the use of Elidel in 2418 infants compared to topical corticosteroids *(Sigurgeirsson et al 2015)*. The primary endpoint was safety; the secondary endpoint was long-term efficacy defined as a score of 0 to 5 on the Investigator's Global Assessment (IGA). Topical corticosteroids included low potency such as hydrocortisone 1% or medium potency such as hydrocortisone butyrate 0.1%. For safety, no differences between the groups were observed for growth rate or bacterial or viral infections. More Elidel patients reported bronchitis (p = 0.02), infected eczema (p < 0.001), impetigo (p = 0.045), and nasopharyngitis (p = 0.04). Serious infections and infestations were similar between the groups. Two malignancies occurred in the corticosteroid-treated group, and one benign tumor was reported in the Elidel-treated group. Over the 5-year period, 88.7% and 92.3% of the Elidel- and corticosteroid-treatment groups, respectively, reported overall IGA treatment success. Significant attrition occurred with only 69.4% and 72.1% of Elidel- and corticosteroid-treated patients completing the study.

Eucrisa

- Contraindications: Known hypersensitivity to Eucrisa or any component of the formulation

- Warnings/precautions:
  - Hypersensitivity reactions, including contact urticaria, have occurred in patients treated with Eucrisa. Hypersensitivity should be suspected in the event of severe pruritus, swelling, and erythema at the application site or at a distant site. If signs and symptoms of hypersensitivity occur, Eucrisa should be discontinued immediately and appropriate therapy initiated.
- AEs:
  - In pivotal studies AD-301 and AD-302, 1012 patients (2 to 79 years of age) with mild to moderate atopic dermatitis were treated with Eucrisa twice daily for 4 weeks. The AE reported by ≥ 1% of Eucrisa-treated patients (45/1012 [4%] vs. 6/499 [1%] of vehicle-treated patients) was application site pain, referring to skin sensations such as burning or stinging. Less common (< 1%) AEs in patients treated with Eucrisa included contact urticaria.
  - No safety signals were identified from vital signs or laboratory assessments in the pivotal studies or in the 48-week, long-term safety extension study *(Eucrisa formulary submission dossier 2016, Paller et al 2016)*.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Elidel (pimecrolimus)	Cream (1%)	Topical	Two times daily (applied as a thin layer)	Do not use in children less than 2 years of age. Do not use with occlusive dressings since occlusion may promote systemic exposure. Safety has not been evaluated. If signs and symptoms persist beyond 6 weeks, patients should be re-examined by their health care provider to confirm the diagnosis. Continuous long-term use should be avoided, and application should be limited to areas of involvement.
Protopic (tacrolimus)	Ointment (0.03% and 0.1%)	Topical	Two times daily (applied as a thin layer)	Do not use in children less than 2 years of age. Do not use with occlusive dressings since occlusion may promote systemic exposure. Safety has not been evaluated. If signs and symptoms persist beyond 6 weeks, patients should be re-examined by their health care provider to confirm the diagnosis. Continuous long-term use should be avoided, and application should be limited to areas of involvement.
Eucrisa (crisaborole)	Ointment (2%)	Topical	Two times daily (applied as a thin layer)	Safety and effectiveness in pediatric patients below the age of 2 years have not been established.

See the current prescribing information for full details

CONCLUSION

- The topical calcineurin inhibitors, Elidel (pimecrolimus 1% cream) and Protopic (tacrolimus 0.03% and 0.1% ointment), are indicated as second-line therapies for the short-term and non-continuous chronic treatment of atopic dermatitis (Elidel: mild to moderate atopic dermatitis; Protopic: moderate to severe atopic dermatitis) in non-immunocompromised adults and children (Elidel: ≥ 2 years of age; Protopic: 0.03% and 0.1% in adults, 0.03% in patients 2 to 15 years of age) who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable. The FDA added another agent to the atopic dermatitis armamentarium with the approval of Eucrisa (crisaborole) ointment for the topical treatment of mild to moderate atopic dermatitis in patients ≥ 2 years of age.
- The topical anti-inflammatory agents work by way of several mechanisms of action; however, the exact mechanism of action in atopic dermatitis is not known. Elidel and Protopic inhibit calcineurin, a calcium-dependent phosphatase, by binding with high affinity to immunophilin-12 (FKBP-12). Protopic and Elidel provide immunosuppression via inhibition of T-cell activation, which is theorized to be the primary mode of inflammation reduction in atopic dermatitis. Eucrisa is a non-steroidal treatment option with a novel mechanism of action. In patients with atopic dermatitis, PDE-4 activity increases circulating inflammatory cells resulting in increased cytokine production. It is believed that Eucrisa enhances cellular control of inflammation by inhibiting PDE-4 and its ability to degrade intracellular cAMP, thereby suppressing the release of cytokines *(Clinical Pharmacology 2019, Paller et al 2016)*.
- Several head-to-head studies comparing the efficacy of the calcineurin inhibitors have been conducted. A meta-analysis of 3 studies directly comparing Elidel and Protopic evaluated the change from baseline in EASI score at week 6 of treatment *(Paller et al 2005)*. Results favored treatment with Protopic, and AEs between the groups were similar. Another meta-analysis evaluating Elidel, Protopic, topical corticosteroids, and vehicle preparations demonstrated a significantly greater change in EASI score in patients using Protopic compared to patients using Elidel in addition to better Investigator Global Atopic Dermatitis Assessment in patients with moderate to severe disease *(Ashcroft et al 2005)*. Protopic was found to be more effective than mild topical corticosteroids and equally effective as moderately potent topical corticosteroids *(El-Batawy et al 2009)*.
- Concerns regarding the long-term safety of the topical calcineurin inhibitors have been addressed in the guidelines and position papers outlined in this review. In 2005, the FDA released a Public Health Advisory to communicate the potential risk of cancer of these products to healthcare providers and patients. The FDA has advised that Elidel and Protopic be used only as labeled and asked providers and patients to consider these agents only as second-line therapies; new labeling was approved in early 2006 *(FDA press release 2006)*. Topical calcineurin inhibitors may be associated with immunosuppression or malignancy.
- Eucrisa demonstrated short-term efficacy over vehicle ointment in 2 identically designed, 28-day, Phase III, randomized, double-blind trials; more patients receiving Eucrisa vs vehicle achieved the primary endpoint of ISGA success, with a greater percentage of Eucrisa-treated patients achieving clear/almost clear overall. Over 28 days, application site pain was the most commonly reported AE. Unpublished data gleaned from the 48-week, long-term study revealed no significant safety signals.
- Current guidelines for the treatment of atopic dermatitis recommend the use of topical corticosteroids as first-line treatment and recommend the use of topical Elidel or Protopic in those patients intolerant or unresponsive to corticosteroids or in whom corticosteroids are contraindicated or when corticosteroid-sparing measures may be desired. Eucrisa has not yet been added to the guidelines *(Eichenfield et al 2014a, Eichenfield et al 2014b, Schneider et al 2013, Sidbury et al 2014, Tollefson et al 2014)*.

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INTRODUCTION

- 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 four clinical classes: 1) Type 1 diabetes (T1DM) which results from beta-cell (β-cell) destruction, usually leading to absolute insulin deficiency; 2) Type 2 diabetes (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, e.g., 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 HIV/AIDS or after organ transplantation; and 4) Gestational diabetes mellitus (diabetes diagnosed during pregnancy that is not clearly overt diabetes) *(ADA 2019).*
- In 2015, an estimated 30.3 million people, or 9.4%, of the United States (US) population had diabetes mellitus, with 7.2 million estimated to be undiagnosed *(Centers for Disease Control and Prevention [CDC] 2017).*
- The insulin products are approved for use in the management of both T1DM and T2DM. Other pharmacologic options for T2DM include sulfonylureas, biguanides, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, amylinomimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and combination products.
- Insulin is used as replacement therapy in patients with diabetes, replacing deficient endogenous insulin and temporarily restoring the ability of the body to properly utilize carbohydrates, fats, and proteins. Insulin is secreted by the β-cells in the pancreas and lowers blood glucose by facilitating peripheral glucose uptake into cells and by inhibiting gluconeogenesis in the liver. In addition to its glycemic effects, insulin has anabolic properties, enhancing protein synthesis, inhibiting lipolysis in adipocytes, and stimulating lipogenesis *(Powers 2018)*.
- The first insulin products were derived from animal sources, primarily pork and beef; however, they are no longer available in the US. These older products have been replaced with human insulin and insulin analogs. Human insulin is biosynthesized utilizing recombinant deoxyribonucleic acid (DNA) with strains of *Escherichia coli* or *Saccharomyces cerevisiae* (baker's yeast) and is structurally identical to endogenous insulin. Insulin analogs are also derived from recombinant DNA technology. They are structurally different from human insulin but have comparable glucose-lowering effects. The insulin analogs differ in the addition, deletion, or substitution of amino acids on the B chain *(Powers 2018)*. Insulin analogs available today include insulin aspart, insulin degludec, insulin detemir, insulin glargine, insulin glulisine, and insulin lispro. The primary differences between commercially available insulin products revolve around pharmacodynamic and pharmacokinetic properties, particularly onset and duration of action. Individual insulin products are often classified into categories based on their onset and duration of action.
  - Bolus insulin products, also known as rapid- or short-acting insulin, include insulin aspart, insulin glulisine, insulin lispro, and certain human insulins. Unique formulations within this category include a rapid-acting, human insulin inhalation powder, and a higher strength of rapid-acting insulin lispro that provides 200 units (U) per milliliter (U-200). In September 2017, Fiasp (insulin aspart) was approved *(Novo Nordisk news release 2017).* Fiasp is a new formulation of Novolog that contains niacinamide. Niacinamide helps to increase the speed of initial insulin absorption, resulting in an onset of appearance in the blood in an estimated 2.5 minutes. Additionally, in December 2017, Admelog (insulin lispro) was the first short-acting insulin approved as a "follow-on" product through the Food and Drug Administration's (FDA) abbreviated 505(b)(2) pathway *(FDA news release 2017).*
  - Basal insulin products, also known as intermediate- or long-acting insulin, include neutral protamine Hagedorn (NPH) isophane, insulin degludec, insulin detemir, and insulin glargine. Unique products within this category include a formulation of insulin glargine that provides 300 U of insulin glargine per mL and enables patients to utilize a higher dose in one injection. Additionally, Basaglar (insulin glargine) was approved under the FDA 505(b)(2) pathway. *(Fierce Biotech FDA press release 2015, Drugs@FDA 2019).*
- Insulin therapy is usually administered by subcutaneous (SC) injection, which allows for prolonged absorption and less pain compared to intramuscular (IM) injection. Currently there are no generic insulin products available. Of note, insulin products are available by prescription, as well as over-the-counter (OTC) (short- and intermediate-acting products only).
- This review will focus on the insulin preparations and combination insulin/GLP-1 agonist products outlined in Table 1 for their respective FDA-approved indications. FDA-approved products that do not have upcoming launch plans, such as

Ryzodeg 70/30 (insulin degludec/insulin aspart), have been excluded from this review *(Novo Nordisk press release 2015*).

- Medispan Class: Antidiabetics, Insulin

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Rapid-Acting Insulins	
Admelog, Admelog Solostar (insulin lispro)	-
Afrezza (insulin human) inhalation powder	-
Apidra, Apidra SoloStar (insulin glulisine)	-
Fiasp, Fiasp FlexTouch (insulin aspart)	-
Humalog, Humalog Kwikpen, Humalog Junior Kwikpen (insulin lispro)	-
Novolog, Novolog PenFill, Novolog FlexPen (insulin aspart)	-
Short-Acting Insulins	
Humulin R (insulin, regular, human recombinant)	-
Humulin R U-500, Humulin R U-500 Kwikpen (insulin, regular, human recombinant)	-
Novolin R, Novolin R ReliOn (insulin, regular, human recombinant)	-
Intermediate-Acting Insulins	
Humulin N, Humulin N Kwikpen (insulin, NPH human recombinant isophane)	-
Novolin N, Novolin N ReliOn (insulin, NPH human recombinant isophane)	-
Long-Acting Insulins	
Basaglar (insulin glargine)	-
Lantus, Lantus SoloStar (insulin glargine)	-
Levemir, Levemir FlexTouch (insulin detemir)	-
Toujeo SoloStar, Toujeo Max SoloStar (insulin glargine U-300)	-
Tresiba FlexTouch (insulin degludec)	-
Combination Insulins, Rapid-Acting and Intermediate-Acting	
Humalog Mix 50/50, Humalog Mix 50/50 KwikPen (50% insulin lispro protamine/50% insulin lispro)	-
Humalog Mix 75/25, Humalog Mix 75/25 Kwikpen (75% insulin lispro protamine/25% insulin lispro)	-
Novolog Mix 70/30, Novolog Mix 70/30 FlexPen (70% insulin aspart protamine/30% insulin aspart)	-
Combination Insulins, Short-Acting and Intermediate-Acting	
Humulin 70/30, Humulin 70/30 KwikPen (70% NPH, human insulin isophane/30% regular human insulin)	-
Novolin 70/30, Novolin 70/30 ReliOn, Novolin 70/30 FlexPen (70% NPH, human insulin isophane/30% regular human insulin)	-
Combination, Long-Acting Insulin and GLP-1 Receptor Agonist	
Soliqua 100/33 (insulin glargine/lixisenatide)	-
Xultophy 100/3.6 (insulin degludec/liraglutide)	-

(Drugs@FDA 2019)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications – Insulins

Product	Control of hyperglycemia in patients with diabetes mellitus	Improve glycemic control in adults with diabetes mellitus	Improve glycemic control in adults and children with diabetes mellitus
Rapid-Acting Insulins			
Admelog			✔
Afrezza		✔ §	
Apidra			✔
Fiasp		✔	
Humalog			✔
Novolog			✔
Short-Acting Insulins			
Humulin R			✔ *
Novolin R			✔
Intermediate-Acting Insulins			
Humulin N			✔
Novolin N			✔
Long-Acting Insulins†			
Basaglar			✔ ‡
Lantus			✔ ‡
Levemir			✔
Toujeo		✔	
Tresiba			✔ ‖
Combination Insulins, Rapid-Acting and Intermediate-Acting			
Humalog Mix 50/50 Humalog Mix 75/25	✔		
Novolog Mix 70/30		✔	
Combination Insulins, Short-Acting and Intermediate-Acting			
Humulin 70/30		✔	
Novolin 70/30			✔

* Humulin R U-500 is useful for the treatment of insulin-resistant patients with diabetes requiring daily doses of more than 200 units.
† Limitations of use: Not recommended for treating diabetic ketoacidosis. Use intravenous, rapid-acting or short-acting insulin instead.
‡ Not indicated for children with T2DM.
§ Limitations of use: Must use with a long-acting insulin in patients with T1DM. Not recommended for treating diabetic ketoacidosis. Not recommended in patients who smoke.
‖ Indicated for patients 1 year of age and older with diabetes mellitus; the U-100 vial is recommended for pediatric patients requiring < 5 units daily.

(Prescribing information: Admelog 2018, Afrezza 2018, Apidra 2018, Basaglar 2018, Fiasp 2018, Humalog 2018, Humalog Mix 50/50 2018, Humalog Mix 75/25 2018, Humulin 70/30 2018, Humulin N 2018, Humulin R U-100 2018, Humulin R U-500 2018, Lantus 2018, Levemir 2019, Novolin 70/30 2018, Novolin N 2018, Novolin R 2018, Novolog 2018, Novolog Mix 70/30 2018, Toujeo 2018, Tresiba 2018)

Table 3. Food and Drug Administration Approved Indications – Insulins and GLP-1 Receptor Agonists

Indication	**Soliqua** (insulin glargine/ lixisenatide)	**Xultophy** (insulin degludec/ liraglutide)
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM	✔	✔
Limitations of Use		
Not recommended as first-line therapy for patients inadequately controlled on diet and exercise.	--	✔
Has not been studied in patients with a history of unexplained pancreatitis. Other antidiabetic therapies should be considered in patients with a history of pancreatitis.	✔	--
Not recommended for use in combination with any other product containing another GLP-1 receptor agonist.	✔	✔
Not for treatment of T1DM or diabetic ketoacidosis.	✔	✔
Not recommended for use in patients with gastroparesis.	✔	--
Has not been studied in combination with prandial insulin.	✔	✔

(*Prescribing information: Soliqua 2019, Xultophy 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

Rapid- and Short-Acting Insulins

- Clinical trials conducted with the newer insulin analogs have shown that they are at least as effective as the older insulin formulations. A large meta-analysis revealed that both insulin aspart and insulin lispro produced comparable lowering of glycosylated hemoglobin (HbA1c) in patients with T2DM compared to regular insulin *(Plank et al 2005).* In patients with T1DM, insulin lispro and insulin aspart produced small, but significant differences in lowering HbA1c compared to regular insulin. Clinical trials comparing insulin glulisine to regular insulin demonstrated similar results, with at least comparable decreases in HbA1c and a few trials reporting a significantly greater decrease in HbA1c when compared to regular insulin in patients with T1DM and T2DM *(Dailey et al 2004, Fullerton et al 2016, Garg et al 2005, Rayman et al 2007).*
- The rapid-acting analogs have demonstrated a more favorable post-prandial glycemic profile compared to regular insulin in patients with T1DM or T2DM *(Anderson et al 1997a, Chen et al 2006, Dailey et al 2004, Melo et al 2019, Raskin et al 2000, Vignati et al 1997).* Most trials reported comparable rates of hypoglycemia between rapid-acting insulin analogs and regular insulin *(Anderson et al 1997b, Bretzel et al 2004, Chen et al 2006, Colquitt et al 2003, Dailey et al 2004, Fairchild et al 2000, Garg et al 2005, Home et al 2006, McSorley et al 2002, Mortensen et al 2006, Plank et al 2005, Raskin et al 2000, Vignati et al 1997).* One large trial of patients with T1DM reported a 12% lower incidence of hypoglycemia with insulin lispro compared to regular insulin ($p < 0.001$) *(Anderson et al 1997a).* In another trial, a significantly lower frequency of nocturnal hypoglycemia was reported in patients with T2DM patients with insulin glulisine compared to regular insulin (9.1% vs 14.5%; $p = 0.029$) *(Rayman et al 2007).* A meta-analysis comparing rapid-acting agents with regular insulin in patients with T1DM found that rapid-acting agents are associated with less total hypoglycemic episodes (risk ratio [RR], 0.93; 95% confidence interval [CI], 0.87 to 0.99), nocturnal hypoglycemia (RR, 0.55; 95% CI, 0.40 to 0.76), severe hypoglycemia (RR, 0.68; 95% CI, 0.60 to 0.77), post-prandial glucose (mean difference [MD], -19.44 mg/dL; 95% CI, -21.49 to -17.39), and lower HbA1c (MD, -0.13%; 95% CI, -0.16 to -0.10) (*Melo et al 2019).* In contrast, in a Cochrane review comparing rapid-acting insulins with regular insulin in adult, non-pregnant patients with T2DM, no clear significant differences were found between the groups for all-cause mortality or hypoglycemia events (*Fullerton et al 2018*).

- Afrezza was evaluated in both T1DM and T2DM patients; in a 24-week open-label (OL), active-controlled (AC), non-inferiority trial, patients with T1DM on basal insulin were randomized to receive prandial Afrezza or insulin aspart. Afrezza met the prespecified non-inferiority margin of 0.4% reduction of HbA1c from baseline, but reductions were significantly less with Afrezza compared to insulin aspart and fewer Afrezza patients achieved a HbA1c target of < 7% *(Bode et al 2015).* T2DM patients inadequately controlled on oral antidiabetic agents (OADs) were randomized to receive Afrezza or placebo in a double-blind (DB) trial. At week 24, treatment with Afrezza provided a statistically significantly greater mean reduction in HbA1c than placebo *(Rosenstock et al 2015[a]).*
- Fiasp was evaluated in the Onset clinical trial program. Onset 1 *(Russell-Jones et al 2017)* was a 26-week, Phase 3, AC, RCT that compared Fiasp (mealtime and postmeal) to Novolog in patients with T1DM. Both mealtime and postmeal Fiasp were demonstrated to be noninferior to Novolog in change in HbA1c (Estimated treatment difference [ETD], -0.15; p < 0.0001; ETD 0.04%; p < 0.0001, respectively). Onset 2 *(Bowering et al 2017)* was a 26-week, Phase 3, DB, AC, RCT in T2DM patients on insulin and OADs. Patients were randomized to receive mealtime Fiasp (n = 345) or Novolog (n = 344). Fiasp demonstrated noninferiority to Novolog in HbA1c lowering (ETD -0.02%; p < 0.0001). Onset 3 *(Rodbard et al 2017)* was an 18-week, Phase 3, OL, RCT in T2DM patients inadequately controlled on basal insulin and OADs. Patients were randomized to receive mealtime Fiasp + basal insulin (n = 116), or basal insulin alone (n = 120). The addition of Fiasp to basal insulin demonstrated superior HbA1c lowering from baseline (ETD -0.94%; p < 0.0001 for superiority) and significantly more patients achieved an HbA1c < 7.0% (60.3% vs 18.3%; OR, 9.31; p < 0.0001); however, with the addition of Fiasp, there was an increase in the frequency of severe or blood glucose (BG)-confirmed hypoglycemic episodes (RR, 8.24; p < 0.0001) and modest weight gain.
- The safety and efficacy of Admelog, the first “follow-on” rapid-acting insulin, were evaluated in two 26-wk, Phase 3, OL, PG, RCTs in both T1DM (N = 506) (SORELLA 1; *Garg et al 2017)* and T2DM (N = 505) patients (SORELLA 2; *Derwahl et al 2018).* Patients were randomized to receive Admelog or its reference product, Humalog. Change in HbA1c in Admelog-treated patients was found to be noninferior in both trials (SORELLA 1: least squares mean difference [LSMD], 0.06%; 95% CI, -0.084 to 0.197; SORELLA 2: LSMD, -0.07%; 95% CI, -0.215 to 0.067). Rates of hypoglycemia were similar between the treatment arms in both trials.
- Head-to-head trials of rapid-acting analogs suggest comparable effectiveness in terms of decreasing HbA1c, achieving similar self-monitored glucose profiles, rates of hypoglycemia, and achieving glycemic goals in patients with T1DM *(Dreyer et al 2005, Philotheou et al 2011, Van Ban et al 2011).*

Long-Acting Insulins

- While not consistently demonstrated, data suggest that long-acting insulin analogs are superior to isophane (NPH) insulin in decreasing HbA1c, as well as the incidence of hypoglycemia in patients with T1DM and T2DM as demonstrated by the results of several active-comparator trials and meta-analyses *(Bartley et al 2008, Bazzano et al 2008, Buse et al 2009, Chase et al 2008, De Leeuw et al 2005, Fritsche et al 2003, Garber et al 2007, Haak et al 2005, Heller et al 2009, Hermansen et al 2004, Hermansen et al 2006, Home et al 2004, Horvath et al 2007, Kølendorf et al 2006, Lee et al 2012, Montañana et al 2008, Pan et al 2007, Pieber et al 2005, Philis-Tsimikas et al 2006, Raslová et al 2007, Ratner et al 2000, Riddle et al 2003, Robertson et al 2007, Rosenstock et al 2005, Russell-Jones et al 2004, Siegmund et al 2007, Standl et al 2004, Tan et al 2004, Tricco et al 2014, Vague et al 2003, Yenigun et al 2009, Yki-Järvinen et al 2000, Yki-Järvinen et al 2006).*
- The safety and efficacy of the long-acting analog Toujeo (insulin glargine U-300) have been compared to that of Lantus (insulin glargine U-100) in OL, randomized, active-controlled, parallel studies of up to 26 weeks in patients with T1DM and T2DM. The reductions in HbA1c and fasting plasma glucose with Toujeo were found to be similar to that of Lantus, including patients aged ≥ 65 years *(Home et al 2018, Bolli et al 2015, Home et al 2015, Riddle et al 2014[b], Ritzel et al 2018, Yki-Järvinen et al 2014).*
- A 2018 meta-analysis comparing Toujeo with Lantus in patients with T1DM and T2DM found that Toujeo was associated with a reduced risk of nocturnal hypoglycemia (RR, 0.81; 95% CI, 0.69 to 0.95) and a slight benefit in HbA1 reduction (effect size, -0.08; 95% CI, -0.14 to -0.01) (*Diez-Fernandez et al 2018*).
- Tresiba (insulin degludec) was evaluated in more than 5,600 T1DM and T2DM patients throughout 9 pivotal studies and 5 extension studies (BEGIN clinical program).
  - In 8 of the pivotal trials, Tresiba was non-inferior to Lantus (insulin glargine U-100) or Levemir (insulin detemir) in lowering HbA1c from baseline, with similar rates of hypoglycemia; in 5 trials, the rate of nocturnal hypoglycemia was significantly lower with Tresiba compared to Lantus or Levemir *(Davies et al 2014, Garber et al 2012, Gough et al 2013, Heller et al 2012, Mathieu et al 2013, Meneghini et al 2013[a], Onishi et al 2013, Zinman et al 2012).* It is

noteworthy that 2 of the 8 Tresiba trials resulted in a nominally lower reduction in HbA1c for Tresiba compared to the active comparator basal insulin agents *(Davies et al 2014, Heller et al 2012).* The HbA1c and hypoglycemia trends were also observed in the published extension trials *(Bode et al 2013, Davies et al 2016, Hollander et al 2015, Rodbard et al 2013).* In the ninth pivotal trial, Tresiba lowered HbA1c significantly more than oral sitagliptin 100 mg once daily in patients with T2DM who were receiving 1 or 2 concomitant background OAD agents (treatment difference, -0.43; 95% CI, -0.61 to -0.24; p < 0.001), but there were significantly more episodes of overall confirmed hypoglycemia (p < 0.0001) *(Philis-Tsimikas et al 2013).*

- Across the BEGIN trials, a consistently increased risk of major adverse cardiovascular events (MACE) was observed with Tresiba. At the request of an FDA Advisory Committee, Novo Nordisk conducted a pre-specified meta-analysis of MACE, which included a pooled analysis of 8,068 patients from 16 Phase 3 trials conducted for Tresiba monotherapy and insulin degludec/insulin aspart (Ryzodeg). According to the 2012 analysis, there was a consistent trend towards harm in the pooled insulin degludec groups compared to active comparators (hazard ratio [HR], 1.67; 95% CI, 1.01 to 2.75). Additional post-hoc analyses consistently trended towards harm regardless of endpoint, effect measure, analysis method, and subgroup analyses *(FDA Briefing Document 2012, Novo Nordisk Briefing Document 2012).*
- The large, DB, active-comparator DEVOTE trial was subsequently initiated to prospectively and rigorously compare the cardiovascular (CV) safety of Tresiba to Lantus in patients with T2DM at high risk for CV events. The primary composite endpoint of death from CV causes, nonfatal myocardial infarction (MI), or nonfatal stroke occurred in 8.5% of the Tresiba group and 9.3% of the Lantus group (HR, 0.91; 95% CI, 0.78 to 1.06; p < 0.001 for non-inferiority), confirming non-inferiority of Tresiba to Lantus in terms of CV safety. Tresiba also demonstrated statistically significantly lower rates of severe hypoglycemia (odds ratio [OR] for severe hypoglycemic events, 0.73; 95% CI, 0.60 to 0.89; p < 0.001 for superiority) *(Marso et al 2017).*

- The efficacy of Tresiba vs Lantus in reducing the rate of symptomatic hypoglycemic episodes in patients with T1DM and T2DM was examined in the SWITCH 1 and SWITCH 2 trials, respectively. These 65-week, DB, crossover trials enrolled patients with hypoglycemia risk factors to receive Tresiba or Lantus. In both trials, Tresiba was found to cause fewer symptomatic hypoglycemic episodes (SWITCH 1: estimated rate ratio [ERR], 0.89; p < 0.001; SWITCH 2: ERR, 0.70; p < 0.001) and nocturnal hypoglycemic episodes (SWITCH 1: ERR, 0.64; p < 0.001; SWITCH 2: ERR, 0.58; p < 0.001) during the maintenance period than Lantus *(Lane et al 2017, Wysham et al 2017)*.
- A meta-analysis of 18 trials with 16,791 patients compared the safety and efficacy of Tresiba to Lantus, and similarly found that Tresiba was associated with a significant reduction in risk for all confirmed hypoglycemia during the maintenance treatment period (ERR, 0.81; 95% CI, 0.72 to 0.92; p=0.001), nocturnal confirmed hypoglycemia during the entire (ERR, 0.71; 95% CI, 0.63 to 0.80; p,0.001) and maintenance treatment periods (ERR, 0.65; 95% CI, 0.59 to 0.71; p,0.001), and a significantly lower fasting plasma glucose level (ETD -0.28 mmol/L; 95% CI, -0.44 to -0.11 mmol/L; p=0.001). Tresiba was found to reduce the incidence of severe hypoglycemia in patients with T2D, but not T1D (*Zhang et al 2018)*.
- Additionally, Tresiba was evaluated for safety and efficacy in pediatric patients (ages 1 to 17) (N = 350) with T1DM in a 26-week, randomized, OL trial. Tresiba was non-inferior to Lantus with a difference in HbA1c reduction from baseline of 0.15% (95% CI, -0.03 to 0.33%) between the groups (pre-specified non-inferiority margin, 0.4%) *(Tresiba prescribing information 2016).*
- The safety and efficacy of Basaglar (insulin glargine U-100) compared to Lantus (insulin glargine U-100) were evaluated in 2 pivotal studies enrolling 534 and 744 patients with T1DM (ELEMENT 1 trial) and T2DM (ELEMENT 2 trial), respectively. Both trials were multicenter, parallel group, randomized controlled trials (RCTs); ELEMENT 1 was OL and ELEMENT 2 was DB. Both trials were conducted over 24 weeks; however, ELEMENT 1 also included a 28-week comparative safety extension period. Mealtime insulin lispro was administered 3 times daily in both groups within the ELEMENT 1 trial. OAD medication was permitted in conjunction with insulin treatment within the ELEMENT 2 trial. The primary efficacy endpoint tested the non-inferiority of agents by the reduction in HbA1c from baseline to 24 weeks. In both ELEMENT 1 and ELEMENT 2, Basaglar and Lantus had similar and significant (p < 0.001) within-group decreases in HbA1c values from baseline. Basaglar met non-inferiority criteria compared to Lantus for change in HbA1c from baseline to 24 weeks in both trials (ELEMENT 1: -0.35% vs -0.46%, respectively; LSMD, 0.108%; 95% CI, -0.002 to 0.219; p > 0.05; ELEMENT 2: -1.29% vs -1.34%, respectively; LSMD, 0.052%; 95% CI, -0.07 to 0.175; p > 0.05). There were no statistically significant differences between treatment groups for the rate of each category of hypoglycemia (total, nocturnal, severe) at 24 or 52 weeks in ELEMENT 1 and at 24 weeks in ELEMENT 2 (p > 0.05 for all treatment comparisons). No significant differences between treatment groups were seen for change from baseline in body weight (ELEMENT 1, week 24 and 52: both p > 0.05; ELEMENT 2, week 24: p > 0.05) *(Blevins et al 2015, Rosenstock et al*

2015[b]). Basaglar has also been compared to Lantus when used in combination with OADs in patients with T2DM. ELEMENT 5 was a 24-week trial and included predominately Asian (48%) and White (46%) patients. Basaglar met non-inferiority criteria compared to Lantus for change in HbA1c from baseline to 24 weeks (-1.25% vs -1.22%; LSMD, -0.04%; 95% CI, -0.22 to 0.15). Other 24-week efficacy and safety outcomes were similar between groups (*Pollom et al 2019*).

- At this time, there is a lack of substantial head-to-head data demonstrating the superiority of one long-acting insulin analog over another. When comparing the long-acting insulin analogs head-to-head, several trials have demonstrated non-inferiority among the products when used in the management of T1DM and as add-on therapy in patients with T2DM *(Heller et al 2009, Hollander et al 2008, Pieber et al 2007, Raskin et al 2009, Rosenstock et al 2008, Swinnen et al 2010).*
  - In one head-to-head trial of Lantus and metformin vs Levemir and metformin, Lantus had greater HbA1c lowering, but Levemir demonstrated less weight gain and hypoglycemia *(Meneghini et al 2013[b]).*
  - A 2011 Cochrane review (included 4 trials; N = 2250) concluded that Lantus and Levemir are equally effective in achieving and maintaining glycemic control (HbA1c). The review also found no differences in overall, nocturnal, and severe hypoglycemic events *(Swinnen et al 2011).* A 2018 meta-analysis similarly found no differences in HbA1c reduction between insulin degludec, determir, or glargine in T1DM and T2DM patients, but the incidence of hypoglycemia was less with degludec as compared to glargine (nocturnal hypoglycemia; T1DM: RR, 0.68; 95% CI, 0.56 to 0.81; T2DM: RR, 0.73; 95% CI, 0.65 to 0.82) (*Holmes et al 2018).*
  - To further inform the differences between basal insulin agents, a network meta-analysis (included 41 trials, of which 25 trials included patients on basal-oral therapy; N = 15,746) evaluated the safety and efficacy of Toujeo (insulin glargine U-300) vs other basal insulin therapies in the treatment of T2DM. The authors found that the change in HbA1c was comparable between Toujeo and Levemir (difference, -0.08; 95% credible interval [CrI], -0.4 to 0.24) and Tresiba (difference, -0.12; CrI, -0.42 to 0.2). Additionally, there were no differences in nocturnal or documented symptomatic hypoglycemic events *(Freemantle et al 2016).*

Combination Insulins

- A direct comparative trial evaluating 2 types of premixed biphasic insulin (insulin lispro 50/50 and insulin aspart 70/30) demonstrated similar results in terms of reducing HbA1c *(Domeki et al 2014).* Another trial comparing biphasic insulin to basal plus prandial insulin in T2DM demonstrated that basal plus prandial insulin therapy was slightly more effective than premixed insulin with less hypoglycemia *(Riddle et al 2014[a]).*

Other Evidence

- A systematic review that included 11 studies and compared the efficacy and safety of biosimilar insulins (Basaglar and Admelog) to their reference products found comparable pharmacokinetic and/or pharmacodynamic parameters, clinical efficacy and immunogenicity, and adverse events between the biosimilar agents and their reference products (*Tieu et al 2018)*.
- Insulin therapies have been compared to GLP-1 agonists with mixed study results. A study comparing glycemic control with Lantus vs exenatide demonstrated that better glycemic control was sustained with exenatide *(Diamant et al 2012).* Other studies have demonstrated that GLP-1 agonists are statistically non-inferior to Lantus for change in HbA1c *(Inagaki et al 2012, Weissman et al 2014).* Studies comparing the addition of GLP-1 agonists to Lantus were found to be non-inferior to the addition of thrice daily insulin lispro to Lantus *(Diamant et al 2014, Rosenstock et al 2014).*
- In terms of clinical outcomes, the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) have demonstrated that intensive glycemic control with insulin significantly reduces the rate of onset and progression of diabetic complications when compared to standard therapy (DCCT 1993, UKPDS 1998). Neither trial indicated the specific insulin formulations utilized; however, in the UKPDS, the risk reduction in microvascular complications was related more toward tight glycemic control rather than to one specific therapy (UKPDS, 1998).

Combination Products: Long-Acting Insulin and GLP-1 Receptor Agonist

- A 2017 systematic review and meta-analysis evaluated the efficacy and safety of insulin degludec/liraglutide vs insulin glargine/lixisenatide treatment in T2DM (*Cai 2017*). The analysis included 8 trials. The absolute HbA1c change relative to baseline with insulin glargine/lixisenatide was -1.50% and -1.89% with insulin degludec/liraglutide; comparisons

between the groups revealed no significant differences. Additionally, there was no significant difference between the groups with regard to body weight changes.

Soliqua (insulin glargine/lixisenatide)

- The efficacy and safety of insulin glargine/lixisenatide were evaluated over 30 weeks in 2 Phase 3, active-comparator (AC), OL, RCTs, titled the LIXILAN trials:
  - T2DM patients uncontrolled on basal insulin: The LIXILAN-L trial was a 2-treatment arm study in 731 T2DM patients. At baseline, patients were receiving basal insulin for at least 6 months at stable daily doses ± OADs. Patients who had an insulin glargine daily dose of 20 to 50 U were randomized to either insulin glargine/lixisenatide 100/33 (n = 366) or insulin glargine 100 U/mL (n = 365). The maximum dose of insulin glargine allowed in the trial was 60 U for both groups. For the primary endpoint, HbA1c reduction after 30 weeks of treatment, the LSMD between insulin glargine/lixisenatide and insulin glargine was statistically significant favoring combination therapy over monotherapy (LSMD, −0.5%; 95% CI, −0.6 to −0.4; p < 0.0001) *(Aroda et al 2016, FDA briefing document [Soliqua] 2016, FDA summary review [Soliqua] 2016).*
  - Comparative data vs GLP-1 receptor agonists: The LIXILAN-O trial was a 3-treatment arm study in 1167 patients with T2DM who were inadequately controlled on metformin ± OADs. Patients who met HbA1c goals based on prior therapy were then randomized to either insulin glargine/lixisenatide 100/33 (n = 468), insulin glargine 100 U/mL (n = 466), or lixisenatide (n = 233). The maximum dose of insulin glargine allowed in the trial was 60 U. For the primary endpoint, insulin glargine/lixisenatide required a non-inferior HbA1c reduction over 30 weeks compared to insulin glargine (non-inferiority upper margin of 0.3%). After 30 weeks of treatment, the LSMD in HbA1c reduction met non-inferiority compared to insulin glargine (LSMD, −0.3%; 95% CI, −0.4 to −0.2; p < 0.0001) and also demonstrated superiority for the endpoint (p < 0.0001). At week 30, the LSMD in HbA1c reduction between insulin glargine/lixisenatide and lixisenatide was also statistically significant (LSMD, −0.8%; 95% CI, −0.9 to −0.7; p < 0.0001) *(Rosenstock et al 2016, FDA briefing document [Soliqua] 2016, FDA summary review [Soliqua] 2016).*
  - Weight and hypoglycemic events: Treatment with insulin glargine/lixisenatide was associated with mean weight losses of up to 0.7 kg from baseline across the aforementioned trials. Hypoglycemic rates were comparable for insulin glargine/lixisenatide and insulin glargine; however, fewer lixisenatide-treated patients experienced documented symptomatic hypoglycemic events compared to insulin glargine/lixisenatide (6.4% vs 25.6%, respectively) *(Aroda et al 2016, Rosenstock et al 2016, FDA summary review [Soliqua] 2016).*

Xultophy (insulin degludec/liraglutide)

- The efficacy and safety of insulin degludec/liraglutide were evaluated over 26 weeks in 9 Phase 3, parallel-group, AC, RCTs, titled the DUAL trials *(Xultophy dossier 2016).* Currently, results from DUAL I through VII are available, and DUAL VIII and IX trials are ongoing; therefore, these trials will not be discussed. The DUAL I, IV, VI, and VII trials were conducted in patients uncontrolled while administered OADs, and since insulin degludec/liraglutide is not FDA-approved for use in patients previously uncontrolled on OADs, these trials have been excluded from this review:
  - T2DM patients uncontrolled on basal insulin and OADs:
    - The DUAL II trial was a 2-treatment arm, DB study in 413 T2DM patients that compared insulin degludec/liraglutide (n = 207) to insulin degludec (n = 206). Prior to randomization, uncontrolled patients were receiving basal insulin (20 to 40 U) and metformin ± OADs. The maximum dose of insulin degludec allowed in the trial was 50 U, and the maximum allowed dose of liraglutide was 1.8 mg. HbA1c reduction from baseline after 26 weeks of treatment, the primary endpoint, was 1.9% for insulin degludec/liraglutide and 0.9% for insulin degludec. The estimated treatment difference (ETD) for HbA1c statistically favored combination injectable therapy over monotherapy (ETD, −1.1%; 95% CI, −1.3 to −0.8; p < 0.0001) *(Buse et al 2014).*
    - The DUAL V trial was a 2-treatment arm, OL, non-inferiority study in 557 T2DM patients that compared insulin degludec/liraglutide (n = 278) to insulin glargine (n = 279) and metformin. Prior to randomization, uncontrolled patients were receiving insulin glargine (20 to 50 U) and metformin. The trial maximum dose of insulin degludec/liraglutide was 50 U of insulin degludec and 1.8 mg of liraglutide; there was no maximum dose for insulin glargine. For the primary endpoint, an upper bound of the 95% CI < 0.3% was required for non-inferiority, which was achieved. The HbA1c reduction from baseline after 26 weeks of treatment was -1.8% for insulin degludec/liraglutide and -1.1% for insulin glargine. The ETD for HbA1c statistically favored combination injectable therapy over monotherapy (ETD, −0.59%; 95% CI, −0.74 to −0.45; p < 0.001 for non-inferiority) *(Lingvay et al 2016).*
  - T2DM patients uncontrolled on GLP-1 receptor agonists:

- The DUAL III trial was a 2-treatment arm, OL study in 438 T2DM patients that compared insulin degludec/liraglutide (n = 292) to the currently administered maximum dose of GLP-1 receptor agonist (n = 146) and metformin ± OAD therapy. Prior to randomization, patients were receiving maximum doses of liraglutide once daily or exenatide twice daily, according to the local labeling, and metformin ± OADs. The trial maximum dose of insulin degludec/liraglutide was 50 U of insulin degludec and 1.8 mg of liraglutide. HbA1c reduction from baseline after 26 weeks of treatment, the primary endpoint, was 1.4% for insulin degludec/liraglutide and 0.3% for unchanged doses of GLP-1 receptor agonists. The ETD for HbA1c statistically favored combination injectable therapy over monotherapy (ETD, −0.94%; 95% CI, −1.1 to −0.8; p < 0.001) *(Linjawi et al 2017).*

- Weight and hypoglycemic events: Treatment with insulin degludec/liraglutide was associated with mean weight losses of up to 2.7 kg and weight gain of 2 kg from baseline across the aforementioned trials. Hypoglycemia rates with insulin degludec/liraglutide were comparable to insulin degludec. However, compared to GLP-1 receptor agonists, the estimated rate ratio (ERR) was 25.36 (95% CI, 10.63 to 60.51; p < 0.001), demonstrating a statistically significantly higher rate of hypoglycemic episodes in the insulin degludec/liraglutide group vs the GLP-1 receptor agonist group. Conversely, the ERR favored insulin degludec/liraglutide over insulin glargine with a statistically significantly higher rate of hypoglycemic episodes in the insulin glargine group (ERR, 0.43; 95% CI, 0.3 to 0.61; p < 0.001) *(Buse et al 2014, Lingvay et al 2016, Linjawi et al 2017, Xultophy dossier 2016).*

Cardiovascular (CV) outcomes

- A number of key CV studies have been conducted with insulin glargine, insulin degludec, liraglutide, and lixisenatide; of these, only liraglutide has demonstrated CV-positive outcomes. Studies with adequate power have not been conducted with the long-acting insulin and GLP-1 receptor agonist combination products.
  - The ORIGIN trial was a randomized trial without blinding conducted in 12,612 patients with CV risk factors plus impaired fasting glucose, impaired glucose tolerance, or T2DM. Patients were randomized to receive insulin glargine or standard of care therapy, which included continuing their pre-existing glycemic control regimen. CV risk factors at baseline included previous MI, stroke, angina, or revascularization. After a median 6.2 year follow-up, no significant difference in the co-primary outcomes of nonfatal MI, nonfatal stroke, or death from CV causes, and these events plus revascularization or hospitalization for heart failure (HF), were observed. The rates of incident CV outcomes were similar in the insulin glargine and standard care groups: 2.94 and 2.85 per 100 person-years, respectively, for the first co-primary outcome (HR, 1.02; 95% CI, 0.94 to 1.11; p = 0.63) and 5.52 and 5.28 per 100 person-years, respectively, for the second co-primary outcome (HR, 1.04; 95% CI, 0.97 to 1.11; p = 0.27) *(Gerstein et al 2012).*
  - ELIXA, a multi-center (MC), DB, randomized, placebo-controlled (PC) trial (N = 6068) was conducted to evaluate the long-term effects of lixisenatide vs placebo on CV outcomes in patients with T2DM who had a recent acute coronary syndrome event within 180 days of screening. The primary endpoint was 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. The median follow-up was 25 months. It was found that the primary endpoint event 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 non-inferiority 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)*.
  - LEADER, a MC, DB, randomized, PC 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, nonfatal MI, or nonfatal stroke) occurred in fewer patients in the liraglutide group (13%) 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). Mortality from CV causes was lower in the liraglutide group (4.7%) vs the placebo group (6%) (HR, 0.78; 95% CI, 0.66 to 0.93; p = 0.007). Additionally, 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 2016).*

CLINICAL GUIDELINES

- Insulin is the mainstay of therapy for adult and pediatric patients with T1DM. Current guidelines recommend that most people with T1DM be treated with multiple daily injections (3 to 4 injections per day of basal and prandial insulin) or continuous subcutaneous insulin infusion. Either multiple daily injections or a continuous infusion can be considered,

with some recent data demonstrating modest advantages with pump therapy such as increased HbA1c lowering and reduced severe hypoglycemia rates. In addition, the guidelines suggest that most people with T1DM should use insulin analogs to reduce hypoglycemia risk *(ADA 2019, Chiang 2018, Handelsman et al 2015).*

- According to current clinical guidelines regarding the management of T2DM, consideration should be given to initiating insulin therapy (with or without other agents) at the outset of treatment in newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or HbA1c. Insulin therapy is usually started once patients are not achieving glycemic goals with noninsulin therapies *(ADA 2019, Davies 2018, Garber et al 2019, Handelsman et al 2015).*
- Guidelines suggest that an insulin treatment program be designed specifically for an individual patient, to match the supply of insulin to his or her dietary/exercise habits and prevailing glucose trends, as revealed through self-monitoring. Anticipated glucose-lowering effects should be balanced with the convenience of the regimen in the context of an individual's specific therapy goals *(ADA 2019, Davies 2018, Garber et al 2019, Handelsman et al 2015).*
  - The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACA) T2DM management algorithm identifies lifestyle therapies such as weight loss, comprehensive management of lipids and blood pressure, safety, and simplicity as crucial factors of a T2DM regimen. The guideline notes that patients are unlikely to achieve glycemic targets with a third oral antihyperglycemic agent if their HbA1c level > 8% or in those with long-standing disease. A GLP-1 agent may be considered, but many patients will eventually require insulin. The guideline suggests basal (long-acting) insulin for those who are symptomatic with an entry HbA1c > 9.0%. Basal insulin analogs are preferred over NPH. If an intensified regimen is needed, the addition of a GLP-1 agonist, SGLT2 inhibitor, or DPP-4 inhibitor can be considered. The combination of basal insulin with a GLP-1 receptor agonist may offer greater efficacy than the oral agents. Prandial (rapid-acting) insulin prior to meals can be considered when the total daily dose of basal insulin exceeds 0.5 U/kg *(Garber et al 2019).*
    - The guideline also states that newer basal insulin formulations (glargine U-300, and degludec U-100 and U-200) have more prolonged and stable pharmacokinetic and pharmacodynamic characteristics than glargine U-100 and detemir. RCTs have reported equivalent glycemic control and lower rates of severe or confirmed hypoglycemia, particularly nocturnal hypoglycemia, compared to glargine U-100 and detemir insulin; however, no recommendation for specific insulin products is given.
  - The ADA and European Association for the Study of Diabetes (EASD) offer similar emphasis on lifestyle modifications and CV disease risk management. In the 2019 update to the ADA standards of medical care in diabetes, the pharmacologic treatment of T2DM was significantly changed to align with the ADA-EASD consensus report. The ADA guideline states that insulin therapy (with or without additional agents) should be initiated in patients with newly diagnosed T2DM with evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when HbA1c levels (≥ 10%) or blood glucose levels (≥ 300 mg/dL) are very high. The ADA and EASD recommend that, in most patients who require an injectable therapy, a GLP-1 agonist should be the first choice ahead of insulin. Due to the progressive nature of the disease, patients may eventually require insulin therapy (*ADA 2019, Davies 2018)*.
    - Certain patient factors can influence the choice of insulin therapy. For patients with established atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease (CKD), insulin therapies with demonstrated CV disease safety (degludec and glargine U-100) should be considered. For patients with hypoglycemia issues, a basal insulin with lower risk of hypoglycemia should be considered (risk of hypoglycemia: degludec/glargine U-300 < glargine U-100/detemir < NPH).
    - A basal insulin/GLP-1 agonist combination can be considered when first intensifying therapy to injectable products in patients with a HbA1c > 10% and/or if the patient is above the target HbA1c by > 2%. The combination can also be considered in patients who require additional control after the addition of a GLP-1 agonist in the intensification algorithm.
- The American College of Cardiology published an expert consensus decision pathway for patients with T2DM and ASCVD (*Das 2018*). For the GLP-1 agonists, liraglutide is the only agent in the class with 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 considers liraglutide as the preferred GLP-1 agent (*ADA 2019, Das 2018*).

SAFETY SUMMARY

Insulins

- Contraindications:

- Insulins are contraindicated during episodes of hypoglycemia and with hypersensitivity to any ingredient of the product.
- In addition, Afrezza is also contraindicated in patients with chronic lung disease, such as asthma or chronic obstructive pulmonary disease (COPD), because of the risk of acute bronchospasm.

- Boxed Warnings:
  - Afrezza has a Boxed Warning for the risk of acute bronchospasm in patients with chronic lung disease. Before initiating Afrezza, a detailed medical history, physical examination, and spirometry should be performed to identify potential lung disease in all patients.
- Warnings/Precautions:
  - Insulin pens must never be shared between patients, even if the needle is changed. Patients using insulin vials must never reuse or share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.
  - Frequent glucose monitoring and insulin dose reduction may be required in patients with renal or hepatic impairment.
  - All insulins can cause hypokalemia, which if untreated, may result in respiratory paralysis, ventricular arrhythmia, and death.
  - Long-term use of insulin can cause lipodystrophy at the site of repeated insulin injections.
  - Accidental mix-ups between basal insulin products and other insulins, particularly rapid-acting insulins, have been reported. To avoid medication errors, patients should be instructed to always check the insulin label before each injection.
  - Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products. If hypersensitivity reactions occur, the insulin product should be discontinued.
  - Administration of Humulin R U-500 in syringes other that U-500 insulin syringes has resulted in dosing errors. Patients should be prescribed U-500 syringes for use with Humulin R U-500 vials. The prescribed dose should always be expressed in units of insulin.
  - Afrezza has additional respiratory-related warnings and precautions associated with its use including acute bronchospasm in patients with chronic lung disease, decline in pulmonary function, and lung cancer.
- Adverse Events (AEs):
  - Hypoglycemia is the most commonly observed AE. Hypoglycemia can impair concentration ability and reaction time which may place an individual and others at risk in situations where these abilities are important. Severe hypoglycemia can cause seizures, may be life-threatening, or cause death. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia.
  - Weight gain, sodium retention and edema, and injection site reactions can occur.
  - Additional AEs observed with the inhaled insulin, Afrezza, include cough, throat pain or irritation, headache, diarrhea, productive cough, fatigue, nausea, decreased pulmonary function test, bronchitis, and urinary tract infection.
- Drug Interactons:
  - β-blockers, clonidine, guanethidine, and reserpine may mask hypoglycemic reactions.
  - Thiazolidinediones can cause dose-related fluid retention, particularly when used in combination with insulin.
  - Refer to the prescribing information for all drugs that can increase or reduce the glucose-lowering ability of insulin.
- Risk Evaluation and Mitigation Strategy (REMS)
  - The FDA previously required a communication plan to inform health care professionals about the serious risk of acute bronchospasm associated with Afrezza; however, in April 2018, the FDA determined that the communication plan has been completed and REMS is no longer needed. (https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/022472Orig1s017ltr.pdf).

Combination, Long-Acting Insulin and GLP-1 Receptor Agonist

- Contraindications:
  - Both combination agents are contraindicated in patients with hypersensitivity to any component of the products and during episodes of hypoglycemia.
  - Xultophy (insulin degludec/liraglutide) is also contraindicated in and has a boxed warning for patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- Warnings/Precautions:

- Warnings and precautions are consistent with each individual agent and include pancreatitis, serious hypersensitivity reactions/allergic reactions, hypoglycemia or hyperglycemia, the potential for overdose due to medication errors, acute kidney injury, hypokalemia, and the potential for fluid retention and heart failure with use of thiazolidinediones. Prefilled pens should never be shared between patients (even if the needle is changed) due to the risk of transmission of blood-borne pathogens.
- Additional warnings and precautions for Soliqua include immunogenicity risks associated with the development of antibodies to insulin glargine and lixisenatide resulting in a loss of glycemic control and a lack of clinical studies showing macrovascular risk reduction. Additional warnings for Xultophy include a potential increased risk for acute gallbladder disease.

- AEs:
  - The most common AEs reported with these agents include nausea, nasopharyngitis, diarrhea, headache, and upper respiratory tract infection.
  - Additional common AEs include hypoglycemia and allergic reactions with Soliqua and increased lipase with Xultophy.
- Drug Interactions:
  - The GLP-1 receptor agonist components may cause delayed gastric emptying of oral medications. Certain medications may require administration 1 hour before (ie, antibiotics, acetaminophen, oral contraceptives, or other medications dependent on threshold concentrations for efficacy) or 11 hours after (ie, oral contraceptives) administration of the GLP-1 receptor agonist.
  - Monitor use closely when administered concomitantly with other medications that may affect glucose metabolism.
  - Antiadrenergic medications (ie, beta blockers, clonidine, guanethidine, and reserpine) may mask the signs and symptoms of hypoglycemia.
- REMS programs:
  - The FDA previously required a REMS program for Xultophy, which included a communication plan for alerting healthcare professionals about the risk of acute pancreatitis and the potential risk of MTC; however, in December 2017, the FDA determined that the communication plan is no longer necessary and that a REMS is no longer required (https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/208583Orig1s001ltr.pdf).
- Lixisenatide and liraglutide slow gastric emptying. Patients with gastroparesis were excluded from trials; therefore, agents are generally not recommended in cases of severe gastroparesis.

DOSING AND ADMINISTRATION

- Injection sites should be rotated within the same region (abdomen, thigh or upper arm) from one injection to the next to reduce the risk of lipodystrophy.
- Dose adjustments in patients with renal and/or hepatic dysfunction may be required with the insulin products.
- In elderly patients, caution should be taken with initial insulin dosing and subsequent dose changes to avoid hypoglycemic reactions.

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
Rapid-Acting Insulins				
Admelog (insulin lispro)	100 U/mL: SoloStar pen, vial	SC, IV	Administer within 15 minutes before a meal or immediately after a meal. Use in a regimen with intermediate- or long-acting insulin when administered by SC injection.	Safety and efficacy in children < 3 years with T1DM and in children with T2DM have not been established. Use SoloStar pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Afrezza (insulin human)	Single-use cartridges: 4, 8, 12 units Available in cartons	Inhalation	Generally given 3 times daily at the beginning of a meal	Safety and efficacy in pediatric patients or in renal or hepatic dysfunction have not been established.

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
	with a single dosage and in titration packs with multiple dosages			
Apidra (insulin glulisine)	100 U/mL: SoloStar pen, vial	SC, IV	Administer within 15 minutes before a meal or within 20 minutes after starting a meal. Dose and frequency are individualized per patient needs. Use in a regimen with intermediate- or long-acting insulin when administered by SC injection.	Safety and efficacy in children < 4 years with T1DM or in children with T2DM have not been established. Use SoloStar pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Fiasp (insulin aspart)	100 U/mL: FlexTouch pen, vial, PenFill cartridges	SC, IV	Administer at the start of a meal or within 20 minutes after starting a meal. Use in a regimen with intermediate- or long-acting insulin when administered by SC injection.	Safety and efficacy have not been established in children. Use FlexTouch pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Humalog (insulin lispro)	100 U/mL: Cartridge, KwikPen, Junior KwikPen, vial 200 U/mL: KwikPen	SC, IV (U-100 only)	Administer within 15 minutes before a meal or immediately after a meal. Use in a regimen with intermediate- or long-acting insulin when administered by SC injection.	Safety and efficacy in children < 3 years with T1DM and in children with T2DM have not been established. Use KwikPen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Novolog (insulin aspart)	100 U/mL: Cartridge (PenFill), FlexPen, Vial	SC, IV	Novolog: Should be injected immediately (within 5 to 10 minutes) before a meal. Use in a regimen with intermediate- or long-acting insulin when administered by SC injection.	Safety and efficacy in children < 2 years with T1DM and in children with T2DM have not been established. Use FlexPen and PenFill cartridges with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Short-Acting Insulins				
Humulin R (insulin, regular, human recombinant)	100 U/mL: Vial 500 U/mL KwikPen, vial	SC, IV (U-100 only)	When given SC, generally given 3 or more times daily before meals (within 30 minutes). U-500: Generally given 2 to 3 times daily before meals.	U-500: well-controlled studies in children not available. Dosing in pediatric patients must be individualized. Dose conversion should not be performed when using the U-

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
			U-100: Often used concomitantly with intermediate- or long-acting insulin when administered by SC injection.	500 KwikPen or a U-500 insulin syringe. Only a U-500 insulin syringe should be used with the Humulin U-500 vial. Use KwikPen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Novolin R Novolin R ReliOn (insulin, regular, human recombinant)	100 U/mL: Vial	SC, IV	Administration should be followed by a meal within 30 minutes of administration. Often used in combination with intermediate- or long-acting insulin when administered by SC injection.	Safety and efficacy in children < 2 years with T1DM or in children with T2DM have not been established. Use in pumps is not recommended due to risk of precipitation.
Intermediate-Acting Insulins				
Humulin N (insulin, NPH, human recombinant isophane)	100 U/mL: KwikPen, vial	SC	Generally given in 1 to 2 injections per day 30 to 60 minutes before a meal or bedtime.	Has not been studied in children. Dosing in pediatric patients must be individualized. Use KwikPen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Novolin N Novolin N ReliOn (insulin, NPH, human recombinant isophane)	100 U/mL: Vial	SC	Generally given in 1 to 2 injections per day 30 to 60 minutes before a meal or bedtime.	
Long-Acting Insulins				
Basaglar (insulin glargine)	100 U/mL: KwikPen	SC	Daily May be administered at any time of day, but at same time every day.	Safety and efficacy in children < 6 years with T1DM and in children with T2DM have not been established. Use with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Lantus (insulin glargine)	100 U/mL: SoloStar pen, vial	SC	Daily May be administered at any time of day, but at same time every day.	Safety and efficacy in children < 6 years with T1DM and in children with T2DM have not been established. Use SoloStar pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Levemir (insulin	100 U/mL:	SC	Daily to twice daily	Safety and efficacy in children <

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
detemir)	FlexTouch pen, vial		Once daily administration should be given with evening meal or at bedtime. Twice daily administration should be given in the morning and then 12 hours later with evening meal or at bedtime.	2 years with T1DM and in children with T2DM have not been established. Use FlexTouch pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Toujeo (insulin glargine U-300)	300 U/mL: SoloStar pen, Max SoloStar pen	SC	Daily Administer at the same time each day.	Safety and efficacy in children have not been established. To minimize the risk of hypoglycemia, the dose of Toujeo should be titrated no more frequently than every 3 to 4 days. The Toujeo Max SoloStar pen carries 900 U of Toujeo U-300 (twice as many as the regular SoloStar pen) and is recommended for patients that require at least 20 U per day Use with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Tresiba (insulin degludec)	100 U/mL: FlexTouch pen, vial 200 U/mL: FlexTouch pen	SC	Daily May be administered at any time of day (should be same time of day in pediatric patients).	Safety and efficacy in children < 1 year have not been established (use in children ≥ 1 year with T2DM is supported by evidence from adult T2DM studies). The recommended number of days between dose increases is 3 to 4 days. Pediatric patients requiring < 5 units daily should use the U-100 vial. Use FlexTouch pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Combination Insulins, Rapid-Acting and Intermediate-Acting				
Humalog Mix 50/50 Humalog Mix 75/25	100 U/mL: KwikPen, vial	SC	Administer within 15 minutes before meals. Typically	Safety and efficacy in children have not been established.

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
(insulin lispro protamine/insulin lispro)			dosed twice daily.	Use Humalog Mix KwikPen and Novolog Mix FlexPen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Novolog Mix 70/30 (insulin aspart protamine/insulin aspart)	100 U/mL: FlexPen, vial	SC	Twice daily T1DM: administer within 15 minutes before meals T2DM: administer within 15 minutes before or after meal	
Combination Insulins, Short-Acting and Intermediate-Acting				
Humulin 70/30 (NPH, human insulin isophane/regular human insulin)	100 U/mL: KwikPen, vial	SC	Twice daily 30 to 45 minutes before a meal	Safety and efficacy in children have not been established. Use KwikPen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Novolin 70/30 Novolin 70/30 ReliOn (NPH, human insulin isophane/regular human insulin)	100 U/mL: FlexPen, vial	SC	Twice daily 30 to 60 minutes before a meal	
Combination Products, Long-Acting Insulin and GLP-1 Receptor Agonist				
Soliqua 100/33 (insulin glargine/lixisenatide)	100 U/mL; 33 mcg/mL: SoloStar pen	SC	Once daily within the hour prior to the first meal of the day	The pen delivers doses from 15 to 60 U of insulin glargine with each injection. Not recommended for use in end-stage renal disease (ESRD). Frequent BG monitoring and dose adjustment may be necessary in hepatic impairment.
Xultophy 100/3.6 (insulin degludec/liraglutide)	100 U/mL; 3.6 mg/mL: pen	SC	Once daily at the same time each day with or without food	The pen delivers doses from 10 to 50 U of insulin degludec with each injection. Has not been studied in patients with renal or hepatic impairment.

Abbreviations: BG = blood glucose, IV = intravenous, SC = subcutaneous, T1DM = type 1 diabetes mellitus, T2DM = type 2 diabetes mellitus, U = unit

(Clinical Pharmacology 2019)

*Dose and frequency of insulin products should be individualized per patient needs.
See the current prescribing information for full details

CONCLUSION

Insulins

- The insulin products are approved for use in the management of both T1DM and T2DM. The primary differences between commercially available insulin products revolve around pharmacodynamic and pharmacokinetic properties, particularly onset and duration of action.
- Individual insulin products are classified by their onset and duration of actions and may fall into one of four categories: rapid-, short-, intermediate-, or long-acting insulins. Insulin therapy is usually administered by SC injection, which allows for prolonged absorption and less pain compared to IM injection. No generic insulin products are currently available.
- Afrezza is a rapid-acting inhaled insulin. The inhalation route offers a less invasive alternative route of administration and improved convenience of administration compared with injectable rapid-acting insulins. Due to this different route of administration, the most common AEs associated with Afrezza in clinical trials were hypoglycemia, cough, and throat pain or irritation.
- The safety and efficacy of insulin therapy in the management of diabetes are well established. Clinical trials have demonstrated that the newer rapid- and long-acting insulin analogs are as effective as regular and isophane (NPH) insulin in terms of glucose management. The data also suggest that long-acting insulin analogs are superior to NPH in decreasing HbA1c and are associated with a lower incidence of hypoglycemic events. Furthermore, head-to-head data do not consistently demonstrate the superiority of one rapid- or long-acting insulin analog over another.
- In terms of clinical outcomes, intensive glycemic control with insulin has been shown to significantly reduce the rate of onset and progression of diabetic complications when compared to standard therapy.
- Insulin is the mainstay of therapy for adult and pediatric patients with T1DM. Current guidelines recommend that most people with T1DM be treated with multiple daily injections (3 to 4 injections per day of basal and prandial insulin) or continuous subcutaneous insulin infusion. In addition, the guidelines suggest that most people with T1DM should use insulin analogs to reduce hypoglycemia risk *(ADA 2019, Chiang 2018, Handelsman et al 2015).*
- According to current clinical guidelines regarding the management of T2DM, consideration should be given to initiating insulin therapy (with or without other agents) at the outset of treatment in newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or HbA1c. Insulin therapy is usually started once patients are not achieving glycemic goals with noninsulin therapies *(ADA 2019, Davies 2018, Garber et al 2019, Handelsman et al 2015).*
- Guidelines suggest that an insulin treatment program be designed specifically for an individual patient, to match the supply of insulin to his or her dietary/exercise habits and prevailing glucose trends, as revealed through self-monitoring. Anticipated glucose-lowering effects should be balanced with the convenience of the regimen in the context of an individual's specific therapy goals *(ADA 2019, Davies 2018, Garber et al 2019, Handelsman et al 2015).*
- The ADA and EASD recommend that in most patients who require an injectable therapy a GLP-1 agonist should be the first choice, ahead of insulin. Certain patient factors can influence the choice of insulin therapy and recommendations for certain products are made for those with ASCVD, CKD, and those with hypoglycemia issues (*ADA 2019, Davies 2018)*.

Combination, Long-Acting Insulin and GLP-1 Receptor Agonist

- Insulin glargine/lixisenatide (Soliqua) and insulin degludec/liraglutide (Xultophy) are long-acting insulin and incretin-based antidiabetic combination therapies that are FDA-approved as adjunctive therapy to diet and exercise to improve glycemic control in adult T2DM patients.
- The medications are administered through a fixed ratio pen. Soliqua may be administered in doses of 15 to 60 U of insulin glargine and 5 to 20 mcg of lixisenatide, while Xultophy may be administered in doses of 10 to 50 U of insulin degludec and 0.36 to 1.3 mcg of liraglutide SC once daily depending on prior treatment and dosages. Individualized dosing is recommended based on metabolic needs, blood glucose monitoring, glycemic control, type of diabetes, and prior insulin use of the patient.
- These agents have been studied in combination with metformin, sulfonylureas, pioglitazone, and meglitinides. In studies, Soliqua demonstrated HbA1c reductions ranging from 0.3 to 0.5% vs insulin glargine and 0.8% vs lixisenatide. Xultophy demonstrated estimated treatment differences in HbA1c reductions of 1% vs insulin degludec monotherapy, 0.6% vs insulin glargine monotherapy, and 0.9% vs a GLP-1 receptor agonist (eg, liraglutide or exenatide twice daily). Across trials, Xultophy and Soliqua were associated with both weight losses and gains. Hypoglycemia rates were mostly similar to those observed within the basal insulin monotherapy arms; however, the GLP-1 receptor agonists were associated with less hypoglycemic events *(Aroda et al 2016, Buse et al 2014, FDA summary review [Soliqua] 2016, Lingvay et al 2016, Linjawi et al 2017, Rosenstock et al 2016).* Several CV outcomes trials have been conducted in patients with T2DM who were administered basal insulin monotherapy or GLP-1 receptor agonist monotherapy. Of these trials, the

only trial which demonstrated a reduced CV risk was the LEADER trial, which compared liraglutide to placebo *(Gerstein et al 2012, Marso et al 2016, Marso et al 2017, Pfeffer et al 2015).*

- Overall, the safety profiles of these agents are similar. Xultophy has a boxed warning regarding the risk of thyroid C-cell tumors and is contraindicated in patients with a history of MTC or MEN 2. Other key warnings for these products include increased risks of pancreatitis, hypoglycemia or hyperglycemia, the potential for overdose due to medication errors, acute kidney injury, hypokalemia, and the potential for fluid retention and heart failure with use of thiazolidinediones. Soliqua has an additional warning and precaution regarding immunogenicity risks associated with the development of antibodies which may result in the loss of glycemic control. Common AEs include gastrointestinal effects (eg, nausea, diarrhea, etc), nasopharyngitis, headache, and upper respiratory tract infection.
- The ADA and EASD guidelines note that a basal insulin/GLP-1 agonist combination can be considered when first intensifying therapy to injectable products in patients with a HbA1c > 10% and/or if above the target HbA1c by over 2%. The combination can also be considered in patients who require additional control after the addition of a GLP-1 agonist in the intensification algorithm (*ADA 2019, Davies 2018).*

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Therapeutic Class Overview
Antidepressants, SSRI

INTRODUCTION

- Major depressive disorder (MDD) is a highly prevalent and disabling disorder characterized by symptoms such as depressed mood, anhedonia, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, low energy, poor concentration, thoughts of worthlessness or guilt, and recurrent thoughts about death or suicide (*Simon 2015*).
  - MDD is associated with higher rates of chronic disease, impaired functioning, and increased healthcare utilization. The condition is more prevalent among females and persons aged 40 to 59. From 2009 to 2012, 7.6% of Americans 12 years of age or older had depression (moderate or severe symptoms in the past 2 weeks) (*Pratt and Brody 2014*).
  - Current guidelines recommend first-line treatment with a second-generation antidepressant (SGA) and/or cognitive behavioral therapy (CBT). The effectiveness of SGAs is generally comparable between and within classes of antidepressants, including selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). SSRIs, SNRIs, mirtazapine, and bupropion are considered optimal for the treatment of MDD in most patients (*American Psychiatric Association [APA] 2010, Qaseem et al 2016, Veteran's Affairs/Department of Defense [VA/DoD] 2016*).
- SSRIs inhibit the serotonin reuptake pump and increase postsynaptic serotonin receptor occupancy. This initial action may cause subsequent changes involved in treating depression. SSRIs are selective in that they have relatively little affinity for other types of receptors. Reuptake inhibition occurs soon after SSRIs are started, and the full therapeutic effects of SSRIs may not appear for 3 to 8 (or more) weeks after treatment has started (*Hirsch and Birnbaum 2017*).
- Some of the SSRIs are also used to treat other psychiatric disorders besides MDD, including panic disorder, obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD), social anxiety disorder, posttraumatic stress disorder (PTSD), premenstrual dysphoric disorder(PMDD)/premenstrual syndrome (PMS), and bulimia nervosa.
  - GAD is characterized by excessive anxiety and worry. Symptoms of GAD include restlessness, being easily fatigued, irritability, difficulty concentrating, muscle tension, and sleep disturbances (*Bandelow et al 2012*).
  - OCD is characterized by recurrent intrusive thoughts, images, or urges (obsessions) that typically cause anxiety or distress, and by repetitive mental or behavioral acts (compulsions) that the individual feels driven to perform, either in response to an obsession or according to rules that he or she believes must be applied rigidly *(Simpson 2016)*.
  - Panic disorder is characterized by recurrent unexpected panic attacks followed by concern about subsequent panic attacks or maladaptive change in behavior related to the attacks. Panic attacks are discrete periods of intense fear or discomfort accompanied by somatic and psychic symptoms (eg, palpitations, sweating, trembling, dyspnea, chest pain, nausea) (*APA 2009, Bandelow et al 2012*).
  - PMS is characterized by the presence of both physical and behavioral (including affective) symptoms that occur repetitively in the second half of the menstrual cycle and interfere with some aspects of the woman's life. The APA defines PMDD as a severe form of PMS in which symptoms of anger, irritability, and internal tension are prominent *(Yonkers and Casper 2016).*
  - PTSD is a clinically-significant condition with symptoms that have persisted for more than 1 month after exposure to a traumatic event and caused significant distress or impairment in social, occupational, or other important areas of functioning. PTSD can appear alone as the only diagnosis, or more commonly, with another co-occurring disorder, such as a substance use disorder or mood disorder *(Veterans Affairs [VA]/Department of Defense [DoD] 2017)*.
  - Social anxiety disorder is characterized by persistent fear of being observed or evaluated negatively by others in social performance or interaction situations. Patients with social anxiety disorder often avoid social interactions or endure them with intense anxiety or distress (*Bandelow et al 2012*).
  - Bulimia nervosa is characterized by recurrent episodes of binge eating and inappropriate compensatory behaviors, as well as frequent comorbid psychopathology *(Engel et al 2017)*.
- The scope of this review will be the safety and efficacy of the SSRIs in the treatment of MDD and other psychiatric Food and Drug Administration (FDA)-approved indications. The SSRIs include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline.
  - Brisdelle, a low dose (7.5 mg) paroxetine mesylate formulation, is only FDA-approved for the treatment of moderate to vasomotor symptoms (VMS) associated with menopause. This indication will not be addressed in this review.
- Medispan Therapeutic Class: Selective Serotonin Reuptake Inhibitors

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Brisdelle (paroxetine mesylate) capsules	✔
Celexa (citalopram) oral solution, tablets*	✔
fluoxetine delayed-release (DR) capsules‡	✔
fluoxetine tablets‡	✔
fluvoxamine tablets‡	✔
fluvoxamine ER capsules‡	✔
Lexapro (escitalopram) oral solution, tablets*	✔
Paxil (paroxetine hydrochloride) oral suspension, tablets	✔ †
Paxil CR (paroxetine hydrochloride ER) tablets	✔
Pexeva (paroxetine mesylate) tablets	--
Prozac (fluoxetine) capsules, oral solution*	✔
Sarafem (fluoxetine) capsules‡, tablets	✔
Zoloft (sertraline) oral solution, tablets	✔

*Brand Celexa, Lexapro, and Prozac oral solution are no longer marketed.
†Paxil oral suspension does not have a generic available.
‡Brand Luvox (fluvoxamine) tablets/capsules, Prozac Weekly (fluoxetine) capsules, Prozac (fluoxetine) tablets, and Sarafem (fluoxetine) capsules are no longer marketed.

(*Drugs@FDA 2017, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

INDICATIONS

Table 2. FDA Approved Indications for SSRIs

Indication	Citalopram	Escitalopram	Fluoxetine	Fluoxetine (Sarafem)	Fluoxetine DR	Fluvoxamine	Fluvoxamine ER	Paroxetine hydrochloride	Paroxetine hydrochloride ER	Paroxetine mesylate (Brisdelle)	Paroxetine mesylate (Pexeva)	Sertraline
GAD		✔						✔			✔	
MDD	✔	✔	✔		✔			✔	✔		✔	✔
OCD			✔			✔	✔	✔			✔	✔
Moderate to VMS associated with menopause										✔		
Panic disorder			✔					✔	✔		✔	✔
PMDD				✔					✔			✔
PTSD								✔				✔
Social anxiety disorder								✔	✔			✔
Bulimia nervosa			✔									

(*Prescribing information: Brisdelle 2017, Celexa tablets 2017, citalopram oral solution 2017, fluoxetine delayed-release 2015, fluoxetine tablets 2016, fluvoxamine 2017, fluvoxamine extended-release 2015, Lexapro 2017, Paxil 2016, Paxil CR 2016, Pexeva 2017; Prozac 2017, Sarafem 2017, Zoloft 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

GAD

- There is a lack of data available directly comparing different serotonergic reuptake inhibitors (including SSRIs vs SNRIs) for GAD. Trials have generally shown that all serotonergic reuptake inhibitors studied have the same degree of effectiveness, ie, response rates of approximately 60 to 70% for the serotonergic reuptake inhibitors vs. 40% for the placebo. SSRIs that have been shown in randomized control trials (RCTs) to be efficacious for GAD include paroxetine, sertraline, citalopram, and escitalopram. Uncontrolled trials and our clinical experience suggest other SSRIs (eg, fluoxetine and fluvoxamine) are effective for GAD as well (*Bystritsky 2016*).

MDD

- A large body of literature supports the superiority of SSRIs compared with placebo in the treatment of MDD. Although a few analyses suggest small advantages of SNRIs over SSRIs in rates of remission, a preponderance of the data finds no significant evidence of the superiority of any other class or agents over SSRIs. Most individual trials and meta-analyses show no differences in efficacy among individual SSRIs (*APA 2010, VA/DoD 2016*).
- A 2011 Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review evaluated bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine in the treatment of adults with depressive disorders (*Gartlehner et al 2011*).

- Overall, treatment effects were similar among SGAs. Some analyses yielded statistically significant differences among treatments, but the magnitudes of differences were modest and probably not clinically relevant.
  - Meta-analyses of head-to-head trials showed statistically significantly greater response rates for escitalopram than citalopram (1 unpublished study and 5 published studies involving 1802 patients) (odds ratio [OR], 1.49, 95% confidence interval [CI], 1.07 to 2.01), and sertraline than fluoxetine (4 studies involving 960 patients) (OR, 1.42, 95% CI, 1.08 to 1.85).
- In several head-to-head trials, overall efficacy in maintaining remission did not significantly differ between escitalopram and desvenlaxafine, escitalopram and paroxetine, fluoxetine and sertraline, fluoxetine and venlafaxine, fluvoxamine and sertraline, and trazodone and venlafaxine.
- For patients with MDD and accompanying anxiety, 4 head-to-head trials suggested that antidepressants have similar antidepressive efficacy. Two of these studies compared SSRIs (fluoxetine, paroxetine, and sertraline).
- Overall, SGAs caused similar adverse events (AEs); however, the frequency of specific events differed among some drugs. In addition, Discontinuation rates were similar between SSRIs and other SGAs (range of means, 15% to 25%).

- A multiple-treatments meta-analysis of 117 RCTs (n = 25,928) found clinically important differences when comparing bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine (not approved in the United States), sertraline, and venlafaxine for the acute treatment of adults with MDD. (*Cipriani et al 2009*).
  - Patients on mirtazapine, escitalopram, venlafaxine, and sertraline were significantly more likely to respond to therapy than those on duloxetine (OR 1.39, 1.33, 1.30 and 1.27, respectively), fluoxetine (OR 1.37, 1.32, 1.28, and 1.25, respectively), fluvoxamine (OR 1.41, 1.35, 1.30, and 1.27, respectively), and paroxetine (OR 1.35, 1.30, 1.27, and 1.22, respectively).
  - Escitalopram and sertraline showed the best profile of acceptability, leading to significantly fewer discontinuations than did duloxetine, fluvoxamine, paroxetine, and venlafaxine.

OCD

- A Cochrane review of 17 RCT and quasi RCT studies (n = 3097) evaluated the efficacy and AEs of SSRIs vs placebo for OCD in adults. SSRIs as a group were more effective than placebo in reducing the symptoms of OCD between 6 and 13 weeks post-treatment, measured using the Yale-Brown Obsessive Compulsive Scale (YBOCS) (weighted mean difference [WMD] -3.21, 95% CI -3.84 to -2.57). The WMD for individual SSRI drugs were similar and not statistically different. Based on 13 studies (2697 participants), SSRIs were more effective than placebo in achieving clinical response at post-treatment (relative risk [RR] 1.84, 95% CI 1.56 to 2.17). The pooled RR was shown to be similar between individual SSRI drugs. Although reported AEs data were more limited, with few exceptions, the overall and individual AEs for the different SSRIs were always worse than for placebo and, in the majority of cases, the difference was statistically significant. Nausea, headache and insomnia were always reported amongst the most common AEs in clinical trials for each of the drugs (*Soomro et al 2008*).

Panic Disorder

- A Cochrane review of 35 RCTs (n = 6785) evaluated antidepressants and benzodiazepines as monotherapy for adults with panic disorder. An analysis of 2 studies (n = 1316) directly comparing paroxetine with venlafaxine demonstrated similar response rates for panic disorder (RR 0.96; 95% CI, 0.75 to 1.23; 2 studies; 991 participants; I^2 = 1%; high quality of evidence). Additionally, no difference in response rate was detected between antidepressants and benzodiazepines for panic disorder (RR 0.99; 95% CI, 0.67 to 1.47; 2 studies; 215 participants; low quality of evidence) (*Bighelli et al 2016*).
- In a meta-analysis of 50 studies (n = 5236) of antidepressants for panic disorder, the following antidepressants demonstrated superiority over placebo in the reduction from baseline of overall anxiety symptoms (in increasing order of effectiveness): citalopram, sertraline, paroxetine, fluoxetine, and venlafaxine for panic symptoms and paroxetine, fluoxetine, fluvoxamine, citalopram, venlafaxine, and mirtazapine (*Andrisano et al 2013*).

PMDD

- A Cochrane review of 31 RCTs (n = 6785) evaluated the effectiveness and safety of SSRIs for treating PMS. The review compared fluoxetine, paroxetine, sertraline, escitalopram and citalopram vs. placebo. SSRIs reduced overall self-rated symptoms significantly more effectively than placebo. The effect size was moderate when studies reporting end scores were pooled (for moderate dose SSRIs: SMD -0.65, 95% CI -0.46 to -0.84; n = 9 studies, 1276 women; moderate heterogeneity I^2 = 58%; low quality evidence). SSRIs were effective for symptom relief whether taken only in the luteal

phase or continuously, with no clear evidence of a difference in effectiveness between these modes of administration. However, few studies directly compared luteal and continuous regimens and more evidence is needed on this question. Withdrawals due to AEs were significantly more likely to occur in the SSRI group. In secondary analyses, SSRIs were effective for treating specific types of symptoms (eg, psychological, physical and functional symptoms, and irritability) (*Marjoribanks et al 2013*).

PTSD

- A systematic review and meta-analysis of RCTs (n = 51 studies) evaluated the efficacy of all types of pharmacotherapy, as monotherapy, in reducing symptoms of PTSD. SSRIs were found to be statistically superior to placebo in reduction of PTSD symptoms but the effect size was small (standardized mean difference -0.23, 95% CI -0.33 to -0.12). Three drugs were significantly superior to placebo on either clinician- and self-rated PTSD symptom severity combined (paroxetine) or clinician-rated PTSD symptom severity alone (fluoxetine and venlafaxine). Insufficient evidence was found to support the preferential use of individual agents in either combat-related or non-combat-related trauma (*Hoskins et al 2015*).

Social Anxiety Disorder

- A systematic review and meta-analysis of RCTs (41 studies) aimed to identify optimal treatments for social phobia (ie, social anxiety disorder) (*Canton et al 2012*).
  - SSRIs were the most extensively tested in patients with social phobia, with 17 placebo-controlled acute treatment RCTs reported. Almost half of the studies studied paroxetine, with 2 to 3 studies each for escitalopram, fluoxetine, fluvoxamine, and sertraline. The pooled OR for response to each SSRI ranged between 1.98 (95% CI, 1.07 to 3.67) for fluoxetine and 3.41 (95% CI, 2.51 to 4.69) for paroxetine. The overall OR was 2.73 (95% CI, 1.67 to 4.48). With 1 exception, SSRIs had significantly greater Clinical Global Impressions (CGI) response rates compared with placebo.
  - In general, SSRIs showed separation from placebo by weeks 4 to 6 on a number of response or other outcome measures; however SSRI-placebo differences tended to increase out to 12 weeks of treatment.
  - There have been 4 studies assessing the effect of continuation treatment with SSRIs in patients who have responded to acute treatment. In these relapse prevention studies, patients were randomized to remain on their SSRI or were switched to placebo, under double-blind conditions. All 4 studies showed robust effects of the SSRIs in preventing relapse of social phobia (pooled OR 0.25, 95% CI, 0.18 to 0.35).

CLINICAL GUIDELINES

GAD

- **World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Pharmacological Treatment of Anxiety Disorders, OCD and PTSD in Primary Care** *(Bandelow et al 2012)*
  - The first-line pharmacologic therapies for GAD are SSRIs, SNRIs and pregabalin. Other treatment options include buspirone and hydroxyzine. Benzodiazepines should only be used for long-term treatment when other drugs or CBT have failed.

MDD

- **VA/DoD Clinical Practice Guideline for the Management of MDD** *(VA/DoD 2016)*
  - As first-line treatment for uncomplicated mild to moderate MDD, evidence-based psychotherapy or evidence-based pharmacotherapy should be offered. Selection should be based on patient preference, safety/side effect profile, history of prior response to a specific medication, family history of response to a medication, concurrent medical illnesses, concurrently prescribed medications, cost of medication, and provider training/competence.
    - Evidence-based pharmacotherapy includes SSRIs (except fluvoxamine), SNRIs, mirtazapine, and bupropion.
    - The evidence does not support recommending a specific psychotherapy or pharmacotherapy over another.
    - In patients who have demonstrated partial or no response to initial maximized monotherapy after a minimum of 4 to 6 weeks of treatment, switching to another monotherapy (medication or psychotherapy) or augmenting with a second medication or psychotherapy is recommended.
  - In cases of severe MDD, combined pharmacotherapy and psychotherapy is recommended if initial monotherapy with an antidepressant did not achieve a response or remission. In patients who have demonstrated a partial response and are tolerating the current antidepressant, augmentation with another medication or psychotherapy is reasonable.

- **Nonpharmacologic Versus Pharmacologic Treatment of Adult Patients With MDD: A Clinical Practice Guideline From the American College of Physicians (ACP)** (*Qaseem et al 2016*)
  - Clinicians are recommended to select between either cognitive behavioral therapy or SGAs (SSRIs, SNRIs) to treat patients with MDD after discussing treatment effects, AE profiles, cost, accessibility, and preferences with the patient (Grade: Strong recommendation, moderate-quality evidence).
  - There are reported differences among SGAs in mild (constipation, diarrhea, dizziness, headache, insomnia, nausea, and somnolence) to major (sexual dysfunction and suicidality) AEs. Bupropion is associated with a lower rate of sexual AEs than fluoxetine and sertraline, whereas paroxetine has higher rates of sexual dysfunction than fluoxetine, fluvoxamine, nefazodone, and sertraline. Physicians and patients should discuss AE profiles before selecting a medication.
- **American Psychiatric Association (APA) Practice Guideline for the Treatment of MDD: 3rd Edition** (*APA 2010*)
  - The effectiveness of antidepressant medications is generally comparable between classes and within classes of medications. Thus, the initial selection of an antidepressant medication should be based on various factors such as anticipated AEs, the safety or tolerability of these AEs for the individual patient, pharmacological properties of the medication, medication response in prior episodes, cost, and patient preference.
  - For most patients, an SSRI, an SNRI, mirtazapine, or bupropion is optimal. In general, the use of MAOIs should be restricted to patients who do not respond to other treatments.

OCD

- **APA Practice Guideline for the Treatment of OCD** *(APA 2013)*
  - The guideline recommends CBT or a serotonin reuptake inhibitor (ie, SSRIs or clomipramine) as first-line treatments for OCD. Choice of treatment modality depends on many factors, including the nature and severity of the patient's symptoms, the nature of any co-occurring psychiatric and medical conditions and their treatments, the availability of CBT, and the patient's past treatment history, current medications, and preferences.
  - The guideline notes that all SSRIs appear to be equally effective in treating OCD, even though citalopram and escitalopram are not FDA-approved for this indication.
  - The guideline notes the importance, when selecting among the SSRIs, of considering the safety and acceptability of particular side effects for a given patient. Paroxetine was noted to be the SSRI most associated with weight gain.

Panic Disorder

- **WFSBP Guidelines for the Pharmacological Treatment of Anxiety Disorders, OCD and PTSD in Primary Care** *(Bandelow et al 2012*)
  - In acute panic attacks, reassurance of the patient may be sufficient in most cases. In severe attacks, short-acting benzodiazepines may be needed (eg, melting tablets). SSRIs and venlafaxine are the first-line treatments for panic disorder. After remission, treatment should continue for at least several months in order to prevent relapses. SSRIs, venlafaxine, TCAs, benzodiazepines and other drugs have shown long-term efficacy in these studies.

- **APA Practice Guideline for the Treatment of Panic Disorder** *(APA 2009)*
  - The use of a SSRI, SNRI, TCA, or CBT as the initial treatment for panic disorder is strongly supported by demonstrated efficacy in numerous RCTs. In the absence of a co-occurring mood disorder, monotherapy with a benzodiazepine is also an appropriate initial treatment.
    - The relatively favorable safety and side-effect profile of SSRIs and SNRIs makes them the best initial pharmacotherapy choice for many patients with panic disorder.
  - A particular form of psychodynamic psychotherapy, panic-focused psychodynamic psychotherapy (PFPP), was effective in 1 RCT and could be offered as an initial treatment.
  - There is insufficient evidence to recommend any of these pharmacological or psychosocial interventions as superior to another, or to routinely recommend a combination of treatments over monotherapy, although a combination may be chosen based on individual circumstances.

PMDD

- **American Family Physician – PMS and PMDD** (*Hofmeister and Bodden 2016*)
  - SSRIs are first-line treatment for severe symptoms of PMS and PMDD. Sertraline, paroxetine, fluoxetine, citalopram, and escitalopram can be used to treat the psychiatric symptoms of PMS and PMDD and have been shown to relieve some of the physical symptoms.

  - A 2013 Cochrane review analyzed 31 RCTs that compared SSRIs with placebo for symptom relief of PMS. Each of the 5 SSRIs studied had statistically significant benefits on patient-reported symptoms when taken continuously or only during the luteal phase, but more direct studies comparing luteal phase administration with continuous administration are needed.
- SNRIs such as venlafaxine have been used off-label to treat PMDD in women with predominantly psychological symptoms. The effect is achieved over a relatively short period, 3 to 4 weeks, and sustained throughout subsequent menstrual cycles.

PTSD

- **VA/DoD Clinical Practice Guideline for the Management of PTSD** *(VA/DoD 2017*)
  - For those patients who choose not to engage in or are unable to access trauma-focused psychotherapy, the use of sertraline, paroxetine, fluoxetine, or venlafaxine as monotherapy is recommended based on the results of 3 systematic reviews. Each of these 3 meta-analyses concluded that sertraline, paroxetine, fluoxetine, and venlafaxine each had stronger evidence to support use in the treatment of PTSD compared to the other SSRIs and SNRIs. The benefits of these medications also outweigh the potential harms.
- **APA Practice Guideline for the Treatment of Acute Stress Disorder and PTSD** *(APA 2004, APA 2009 [update])*
  - The 2004 guideline recommended the SSRIs as a first-line medication treatment for patients with PTSD. The trials reviewed in the 2009 update suggest that the SSRIs may no longer be recommended with the same level of confidence for veterans with combat-related PTSD as for patients with non-combat-related PTSD. Further research is needed to answer why these populations have been shown to have differential responses to SSRI treatment.
  - No significant differences among antidepressants, including the SSRIs, were found in the few head-to-head studies then available.

Social Anxiety Disorder

- **WFSBP Guidelines for the Pharmacological Treatment of Anxiety Disorders, OCD and PTSD in Primary Care** *(Bandelow et al 2012*)
  - The guideline recommends SSRIs and venlafaxine for first-line pharmacologic therapy for social anxiety disorder. There is insufficient evidence to recommend benzodiazepines or TCAs. Exposure therapy and CBT are also effective psychotherapies.

Bulimia Nervosa

- **APA Practice Guideline for the Treatment of Eating Disorders** *(APA 2012)*
  - In a 2011 systematic review for the WFSBP, *Aigner et al* identified 36 RCTs of medications for the treatment of bulimia nervosa. They reported that for TCA, Grade A evidence exists with a moderate risk-benefit ratio. For fluoxetine, Grade A evidence exists with a good risk-benefit ratio, and for topiramate, there is Grade A evidence with a moderate risk-benefit ratio. These findings and recommendations were consistent with the 2006 APA guideline, which recommends antidepressants, particularly the SSRIs, as one effective component of the initial treatment program for most patients with bulimia nervosa.
  - Other pharmaceutical agents, including oxcarbazepine, aripiprazole, and baclofen, have been reported to be effective for bulimia nervosa, but the results were from small case series or studies sponsored by the drug manufacturer.
  - Citalopram was studied in a small single-blind 12-week RCT. In this study, 37 patients with bulimia nervosa received fluoxetine (20 to 60 mg/day) or citalopram (20 to 40 mg/day). Both groups improved with respect to eating pathology. Patients receiving fluoxetine reported greater reductions in introjected anger, whereas those receiving citalopram reported greater reduction in depressive feelings.

SAFETY SUMMARY

- SSRIs are contraindicated in patients receiving MAOIs or within 14 days of their discontinuation.
- All SSRIs carry a boxed warning for suicidal thoughts and behaviors. The risk of suicidal thinking and behavior is increased in children, adolescents, and young adults taking SSRIs.
- The use of SSRIs with other serotonergic agent increases the likelihood of serotonergic AEs and should be monitored closely. Drugs that have serotonergic properties include meperidine, triptans, most antidepressants, amphetamines, ergot alkaloids, dopamine antagonists, St. John's wort, and others. Additionally, SSRIs should not be administered with an SNRI or another SSRI as the risk for serotonin syndrome or neuroleptic malignant syndrome is greatly increased.

- The SSRIs tend to have similar side effect profiles; however, certain SSRIs may be more likely to cause specific side effects. Thus, some patients who cannot tolerate one SSRI may do well with another. Common AEs are summarized in the table below *(Hirsch and Birnbaum 2017)*.

Table 3. AEs of SSRIs

Drug	Anticholinergic	Drowsiness	Insomnia/ agitation	Orthostatic hypotension	QTc prolongation*	Gastrointestinal toxicity¶	Weight gain	Sexual dysfunction
Citalopram	0	0	1+	1+	1+Δ	1+	1+	3+
Escitalopram	0	0	1+	1+	1+	1+	1+	3+
Fluoxetine	0	0	2+	1+	1+	1+	1+	3+
Fluvoxamine	0	1+	1+	1+	0 to 1+	1+	1+	3+
Paroxetine	1+	1+	1+	2+	0 to 1+	1+	2+	4+
Sertraline	0	0	2+	1+	0 to 1+	2+◊	1+	3+

* Risk of QTc prolongation or torsades de pointes is also elevated with advanced age, female sex, heart disease, congenital long QT syndrome, hypokalemia or hypomagnesemia, elevated serum drug concentrations (eg, drug overdose, interacting drugs, organ failure) and combination of drugs with QTc prolonging effects.

¶ All SSRIs are associated with transient nausea and gastrointestinal discomfort upon initiation or dose increase.

Δ Based upon reports of dose related QTc prolongation and arrhythmia, the maximum recommended dose of citalopram is 20 mg for patients at increased risk of elevated citalopram serum concentrations.

◊ Sertraline is associated with higher rates of diarrhea.

DOSING AND ADMINISTRATION

Table4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Brisdelle (paroxetine mesylate)	Capsules	Oral	Once daily at bedtime	--
Celexa (citalopram)	Oral solution, tablets	Oral	Once daily, in the morning or evening	• Dosing adjustment in hepatic impairment; use with caution in severe renal impairment
fluoxetine DR	Capsules	Oral	Once weekly	• Initiate fluoxetine DR capsules 7 days after the last daily dose of fluoxetine 20 mg • Dosing adjustment in hepatic impairment
Fluvoxamine	ER capsules, tablets	Oral	Capsules: once daily at bedtime Tablets: once daily at bedtime for total daily doses ≤ 50 mg (pediatric) or ≤ 100 mg (adults); divided in 2 doses for total daily doses > 50 mg (pediatric) or > 100 mg (adults)	• Dosing adjustment in hepatic impairment
Lexapro (escitalopram)	Oral solution, tablets	Oral	Once daily, in the morning or evening	• Dosing adjustment in hepatic impairment; use

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				with caution in severe renal impairment
Paxil (paroxetine hydrochloride)	Oral suspension, tablets	Oral	Once daily, usually in the morning	• Dosing adjustment in renal or hepatic impairment
Paxil CR (paroxetine hydrochloride)	Tablets	Oral	Once daily, usually in the morning	• Dosing adjustment in renal or hepatic impairment
Pexeva (paroxetine mesylate)	Tablets	Oral	Once daily, usually in the morning	• Dosing adjustment in severe renal or hepatic impairment
Prozac (fluoxetine)	Capsules, oral solution, tablets	Oral	Once daily, in the morning or twice a day	• Dosing adjustment in hepatic impairment
Sarafem (fluoxetine)	Capsules, tablets	Oral	Once daily, given continuously (every day of the menstrual cycle) or intermittently (defined as starting a daily dose 14 days prior to the anticipated onset of menstruation through the first full day of menses and repeating with each new cycle)	• Dosing adjustment in hepatic impairment
Zoloft (sertraline)	Oral solution, tablets	Oral	Once daily	• Dosing adjustment in mild hepatic impairment; not recommended in moderate to severe hepatic impairment

See the current prescribing information for full details

CONCLUSION

- SSRIs are frequently used as first-line antidepressants because of their efficacy, tolerability, and general safety in overdose.
- According to clinical practice guidelines, CBT and SGAs are equally effective first-line monotherapies in the initial treatment of patients with MDD. There is insufficient evidence to recommend a specific psychotherapy or pharmacotherapy over another. The effectiveness is generally comparable between classes and within classes of SGAs. Thus, the initial selection of an antidepressant medication should be based on various factors such as anticipated AEs, the safety or tolerability of these AEs for the individual patient, pharmacological properties of the medication, medication response in prior episodes, cost, and patient preference (*APA 2010, Qaseem et al 2016, VA/DoD 2016*).
- Some of the SSRIs are also FDA-approved to treat other psychiatric disorders besides MDD, including panic disorder, OCD, GAD, social anxiety disorder, PTSD, PMDD, and bulimia nervosa. For these various indications, there are generally no significant differences among the SSRIs; however, some products do have a stronger level of evidence or more clinical data available.
- The SSRIs tend to have similar side effect profiles; however, certain SSRIs may be more likely to cause specific side effects. Thus, some patients who cannot tolerate 1 SSRI may do well with another. AEs include: drowsiness, insomnia, QTc prolongation, orthostatic hypotension, weight gain, and sexual dysfunction.
- All SSRIs carry a boxed warning for suicidal thoughts and behaviors, with an increased risk in children, adolescents, and young adults taking SSRIs. The use of SSRIs with other serotonergic agent increases the likelihood of serotonergic AEs and should be monitored closely.

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Therapeutic Class Overview
Respiratory Beta-Agonists

INTRODUCTION

- Respiratory beta$_2$-agonists are primarily used to treat reversible airway disease. They are Food and Drug Administration (FDA)-approved for the treatment of asthma, chronic obstructive pulmonary disease (COPD), exercise-induced asthma/bronchospasm, and/or reversible bronchospasm.
- Asthma is a chronic lung disease that inflames and narrows the airways, making it difficult to breathe. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing. Asthma affects people of all ages, but most often starts during childhood. In the United States, more than 25 million people are known to have asthma, including about 7 million children. The exact cause(s) of asthma are unknown. A combination of factors such as genetics, certain respiratory infections during childhood, and contact with airborne allergens can contribute to its development. Most patients with asthma have allergies (*National Heart, Lung, and Blood Institute [NHLBI] 2014*).
  - Current pharmacologic options for asthma management are categorized as: (1) long-term control medications to achieve and maintain control of persistent asthma, and (2) quick-relief medications used to treat acute symptoms and exacerbations.
  - Long-term control medications for asthma include (*NHLBI 2007*):
    - Corticosteroids (inhaled corticosteroids [ICSs] for long-term control; short courses of oral corticosteroids to gain prompt control of disease, long-term oral corticosteroids for severe persistent asthma)
    - Cromolyn sodium and nedocromil
    - Immunomodulators (ie, omalizumab)
    - Leukotriene modulators
    - Long-acting beta$_2$-agonists (LABAs)
    - Methylxanthines (ie, theophylline)
  - Quick-relief medications for asthma include (*NHLBI 2007*):
    - Anticholinergics (ie, ipratropium bromide), as an alternative bronchodilator for those not tolerating a short-acting beta$_2$-agonist (SABA)
    - SABAs (therapy of choice for relief of acute symptoms and prevention of exercise-induced bronchospasm)
    - Systemic corticosteroids (not short-acting, but used for moderate and severe exacerbations)
  - In recent years, additional medications have been made available for select subsets of patients with asthma, including the interleukin-5 (IL-5) antagonists benralizumab, mepolizumab, and reslizumab, and the interleukin-4 (IL-4) antagonist dupilumab, for the management of severe asthma with an eosinophilic phenotype (*Prescribing information: Cinqair 2018, Dupixent 2018, Fasenra 2017, Nucala 2017*). Additionally, tiotropium, long used for COPD, has been FDA-approved for the treatment of asthma (*Spiriva Respimat prescribing information 2018*).
  - ICSs are the most effective, most commonly recommended long-term control medications used for the treatment of asthma. The LABAs should not be used as monotherapy for the management of asthma due to increased risk for serious adverse events, including death. However, they are effective adjunctive therapy in patients who are not adequately controlled with an ICS alone. Theophylline and mast-cell stabilizers have weak to low efficacy in asthma. Theophylline has an unfavorable side-effect profile and may be life-threatening at high doses. Mast-cell stabilizers have a more favorable safety profile. Tiotropium is an option for add-on therapy in patients ≥ 12 years old with a history of exacerbations. An IL-5 antagonist or the immunoglobulin E (IgE) antagonist, omalizumab, may be added if patients require a higher level of care. Omalizumab is used in patients with moderate to severe allergic asthma while IL-5 antagonists are used for severe eosinophilic asthma. SABAs are the medication of choice for the relief of bronchospasm during acute exacerbations of asthma (*Fasenra prescribing information 2017, NHLBI 2007, Global Initiative for Asthma [GINA] 2018*).
- COPD is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities. The abnormalities are usually caused by exposure to noxious particles or gases. Airflow limitation is caused by a combination of small airway disease (eg, obstructive bronchiolitis) and parenchymal destruction (emphysema); the relative contributions of each component vary between patients. The most common symptoms of COPD include dyspnea, cough, and sputum production (*Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2019*).

- COPD affects 6.4% of the United States (U.S.) population and is the major contributor to mortality from chronic lower respiratory diseases, the third leading cause of death in the U.S. (*Centers for Disease Control and Prevention 2017*). Globally, COPD is the fourth leading cause of death and is expected to be the third leading cause of death by 2020; the burden of COPD continues to increase due to continued exposure to risk factors and aging of the population (*GOLD 2019*).
- Cigarette smoking is the main risk factor for COPD; other risk factors include biomass fuel exposure (such as from cooking and heating in poorly ventilated dwellings) and air pollution. Host factors such as genetic abnormalities, abnormal lung development, and accelerated aging can predispose individuals to COPD development (*GOLD 2019*).
- Patients with COPD may experience exacerbations, which are periods of acute worsening of respiratory symptoms (*GOLD 2019*).
- Pharmacologic therapy for COPD can reduce symptoms, reduce the frequency and severity of exacerbations, and improve patients' health status and exercise tolerance. There is no conclusive evidence that COPD medications modify the long-term decline in lung function characteristics of COPD (*GOLD 2019*).
- Pharmacologic options for COPD treatment comprise several classes, including beta$_2$-agonists, anticholinergics, methylxanthines, ICSs, various combination products, and the phosphodiesterase (PDE)-4 inhibitor, roflumilast. Pharmacologic treatments should be individualized based on symptom severity, risk of exacerbations, side effects, comorbidities, drug availability, and cost, as well as the patient's response, preference, and ability to use various drug delivery devices (*GOLD 2019*).
- Inhaled bronchodilators are central to COPD symptom management, and are usually given on a regular basis to prevent or reduce symptoms. Several long-acting inhaled bronchodilators are available, and use of short-acting bronchodilators on a regular basis is not generally recommended (*GOLD 2019*).
- Beta$_2$-agonists differ in their dosing requirements, pharmacokinetic parameters, and potential adverse effects. Several of the SABAs are available generically in at least 1 strength or formulation; however, there are no generic formulations for the LABAs.

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

Table 1. Medications Included Within Class Review

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

Abbreviations: HFA = hydrofluoroalkane
*No A-rated generics have been approved by the FDA; however, an authorized generic is available.
†Formoterol was previously available as a dry powder inhaler (Foradil Aerolizer); however, this formulation is no longer marketed.

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

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

Abbreviations: COPD = chronic obstructive pulmonary disease; HFA = hydrofluoroalkane
*Age ≥ 4 years (HFA inhalation aerosols and dry powder inhaler); age ≥ 2 (solution for nebulization); age ≥ 2 years (syrup); age ≥ 6 years (tablets and extended-release tablets)
†Inhalation aerosols and dry powder inhaler only
‡Age ≥ 4 years (Xopenex HFA); age ≥ 6 years (Xopenex inhalation solution)
§Age ≥ 12 years
‖Only as a concomitant therapy with a long-term asthma control medication, such as an ICS
¶Age ≥ 4 years
**Indicated for long-term, once-daily maintenance treatment

(*Prescribing information: albuterol solution 2017, albuterol syrup 2016, albuterol tablets 2014, albuterol extended-release tablets 2015, Arcapta Neohaler 2013, Brovana 2014, metaproterenol syrup 2014, metaproterenol tablets 2016, Perforomist 2018, ProAir HFA 2018, ProAir RespiClick 2018, Proventil HFA 2017, Serevent Diskus 2016, Striverdi Respimat 2018, terbutaline injection 2011, terbutaline tablets 2016, Ventolin HFA 2018, Xopenex HFA 2017, Xopenex inhalation solution 2017*)

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

CLINICAL EFFICACY SUMMARY

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

SABAs: Asthma and COPD

- In the clinical trials that evaluated SABAs for the treatment of mild asthma, all SABAs have been shown to be efficacious in improving forced expiratory volume in 1 second (FEV_1). In the clinical trials that compared albuterol to levalbuterol, inconsistent results were found (*Carl et al 2003, Gawchik et al 1999, Milgrom et al 2001, Nelson et al 1998, Nowak et al 2004, Nowak et al 2006, Qureshi et al 2005, Schreck et al 2005, Sepracor Trial 1, Sepracor Trial 2, Skoner et al 2001*).
  - In 2 studies (1 retrospective, 1 prospective), levalbuterol resulted in a significantly lower hospitalization rate compared to albuterol (*Carl et al 2003, Schreck et al 2005*).
  - In another trial, when the 2 agents were given in the emergency department, there was no significant difference in the time to discharge (*Skoner et al 2001*).
  - *Nowak et al* also reported that there was no difference in the time to discharge from the emergency room with albuterol compared to levalbuterol (76 and 78.5 minutes; p = 0.74) (*Nowak et al 2006*).

- Overall, studies have shown no significant differences between the 2 agents in the peak change in FEV_1 and the number and incidence of adverse events experienced (*Carl et al 2003, Gawchik et al 1999, Milgrom et al 2001, Nelson et al 1998, Nowak et al 2004, Nowak et al 2006, Qureshi et al 2005, Schreck et al 2005, Sepracor Trial 1, Sepracor Trial 2, Skoner et al 2001*).
  - In an unpublished study, the difference in peak FEV_1 was statistically significant for albuterol hydrofluoroalkanes (HFA) compared to levalbuterol HFA ($p = 0.018$) (*Sepracor Trial 2*).

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

LABAs: Asthma

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

LABAs: COPD

- A systematic review concluded that in patients with COPD, there was no difference in the rate of mild exacerbations between patients treated with an ICS or LABA (odds ratio, 1.63; 95% confidence interval [CI], 0.49 to 5.39) or in the rate of moderate or severe COPD exacerbations (rate ratio, 0.96; 95% CI, 0.89 to 1.02) (*Spencer et al 2011*).
- The safety and efficacy of indacaterol were evaluated in randomized controlled trials that compared it to placebo and other agents used in the management of COPD (*Balint et al 2010, Buhl et al 2011, Chapman et al 2011, Dahl et al 2010, Donohue et al 2010, Feldman et al 2010, Korn et al 2011, Kornmann et al 2011, Magnussen et al 2010, Vogelmeier et al 2010*). Notably, most of these trials evaluated indacaterol in doses of 150, 300 and 600 mcg once daily, rather than the FDA-approved dosing of 75 mcg once daily (*Balint et al 2010, Buhl et al 2011, Chapman et al 2011, Dahl et al 2010, Donohue et al 2010, Feldman et al 2010, Korn et al 2011, Kornmann et al 2011, Magnussen et al 2010, Vogelmeier et al 2010*). However, results from placebo-controlled trials of indacaterol 75 mcg have also been published, lending support to the use of the 75 mcg dose (*Gotfried et al 2012, Kerwin et al 2011*).
- Overall, data from published clinical trials demonstrated that treatment with indacaterol consistently results in significantly higher mean trough FEV_1 after 12 weeks of treatment compared to placebo, formoterol, salmeterol and tiotropium. Patients treated with indacaterol also achieved significant improvements in COPD symptoms, as well as health-related quality of life compared to those treated with placebo. Compared to placebo, indacaterol significantly reduces the use of rescue medications, increases the days of no rescue medication use, and improves diary card-derived symptom variables (eg, nights with no awakenings, days with no daytime symptoms, days able to perform usual activities). In general, treatment with indacaterol is favored over other long-acting bronchodilators for these outcomes, but statistical superiority is not consistently achieved (*Balint et al 2010, Buhl et al 2011, Chapman et al 2011, Dahl et al 2010, Donohue et al 2010, Feldman et al 2010, Gotfried et al 2012, Kerwin et al 2011, Korn et al 2011, Kornmann et al 2011, Magnussen et al 2010, Vogelmeier et al 2010*). Recent meta-analyses comparing indacaterol to tiotropium and to twice-daily LABAs (salmeterol or formoterol) demonstrated that patients treated with indacaterol had higher trough FEV_1 and greater improvements in the use of rescue medications and achieving improvements in dyspnea and health status compared to the alternative treatments. However, the trials included in this meta-analysis used indacaterol doses higher than FDA-approved daily doses of 75 mcg (*Cope et al 2013, Rodrigo et al 2012*).
- Placebo-controlled trials demonstrate that within 5 minutes after administration of indacaterol, significant improvements in bronchodilation are achieved (*Balint et al 2010, Donohue et al 2010, Gotfried et al 2012, Kerwin et al 2011,*

Magnussen et al 2010, Vogelmeier et al 2010). These results have also been observed when comparing indacaterol to salmeterol, salmeterol/fluticasone, and tiotropium (*Buhl et al 2011, Korn et al 2011, Vogelmeier et al 2010*).

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

EIA

- For the treatment of EIA, albuterol, metaproterenol, and formoterol have demonstrated an improvement in FEV_1 compared to placebo (*Berkowitz et al 1986, Bonini et al 2013, Edelman et al 2000, Richter et al 2002, Shapiro et al 2002, Storms et al 2004*).
  - In 1 study, albuterol- and metaproterenol-treated patients had a lower incidence of exercise-induced bronchospasm compared to placebo (*Cote et al 2009*).

- In another study comparing albuterol, formoterol and placebo for EIA, both active treatment groups provided a statistically significant decrease in mean maximum percent of FEV_1 compared to placebo ($p < 0.01$) (*Shapiro et al 2002*).

CLINICAL GUIDELINES

Asthma

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

COPD

- The 2018 GOLD guidelines state that the management strategy for stable COPD should be predominantly based on an assessment of the patient's symptoms and future risk of exacerbations. The risk of exacerbations is now based solely on the exacerbation history, whereas in previous versions of the guideline, risk assessment also included consideration of airflow limitation assessed by spirometry. Key recommendations from the GOLD guidelines are as follows (*GOLD 2019*):
  - Inhaled bronchodilators are recommended over oral bronchodilators.
  - LAMAs and LABAs are preferred over short-acting agents except for patients with only occasional dyspnea.
  - Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on 1 bronchodilator, treatment should be escalated to 2.
  - Long-term monotherapy with ICSs is not recommended. Long-term treatment with ICSs may be considered in association with LABAs for patients with a history of exacerbations despite treatment with long-acting bronchodilators.
  - Treatment recommendations are given for patients with COPD based on their GOLD patient group (see Table 3 below).
    - Group A: Patients should be offered bronchodilator treatment (short- or long-acting), based on its effect on breathlessness. This should be continued if symptomatic benefit is documented.
    - Group B: Initial therapy should consist of a long-acting bronchodilator (LAMA or LABA). For patients with persistent breathlessness on monotherapy, use of 2 bronchodilators is recommended (LAMA + LABA). For patients with severe breathlessness, initial therapy with 2 bronchodilators may be considered. If the addition of a second bronchodilator does not improve symptoms, it is suggested that treatment could be stepped down to a single bronchodilator; switching to another device or molecules can also be considered.
    - Group C: Initial therapy should be a LAMA. Patients with persistent exacerbations may benefit from adding a second long-acting bronchodilator (LAMA + LABA, preferred) or using an ICS + LABA. For patients who have a history and/or findings suggestive of asthma-COPD overlap or blood eosinophil count ≥ 300 cells/µL, ICS + LABA is preferred.
    - Group D: In general, it is recommended to start therapy with a LAMA. For patients with more severe symptoms, especially dyspnea and/or exercise limitation, LAMA/LABA may be considered for initial treatment. In some patients, initial therapy with an ICS + LABA may be the first choice; these patients may have a history and/or findings suggestive of asthma-COPD overlap or blood eosinophil count ≥ 300 cells/µL. In patients who develop further exacerbations on LAMA + LABA therapy, alternative pathways include escalation to a LAMA + LABA + ICS

(preferred) or a switch to an ICS + LABA. If patients treated with a LAMA + LABA + ICS still have exacerbations, options for selected patients may include addition of roflumilast, addition of a macrolide, or stopping the ICS.

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

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

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

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

Exercise-induced bronchoconstriction

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

SAFETY SUMMARY

- Contraindications:
  - Serevent Diskus and ProAir RespiClick are contraindicated in patients with a severe hypersensitivity to milk proteins.
  - LABAs should generally not be used as a primary treatment of status asthmaticus or other acute episodes of asthma or COPD that require intensive measures; this is listed as a contraindication for Serevent Diskus.
  - All LABAs are contraindicated for use in patients with asthma without concomitant use of a long-term asthma control medication.
- Key warnings and precautions:
  - All LABAs have a boxed warning describing the increased risk of asthma-related deaths. Because of this risk, use of LABAs for the treatment of asthma without a concomitant long-term asthma control medication, such as an ICS, is contraindicated. LABAs should be used only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an ICS.
  - Beta$_2$-agonists may also lead to:
    - paradoxical bronchospasm
    - fatalities with excessive use
    - cardiovascular effects such as increased heart rate, blood pressure, and/or electrocardiogram changes
    - central nervous system effects and/or seizures
  - LABAs should not be used to treat acute symptoms or initiated in the setting of acutely deteriorating asthma or COPD.
- Adverse events
  - Commonly-reported adverse events (≥ 5% for at least 1 medication in the class) include chest pain, palpitations, tachycardia, dizziness, excitement, fatigue, headache, nervousness, shakiness, somnolence, tremor, rash, diarrhea,

nausea, vomiting, pain, asthma exacerbation, bronchitis, cough, influenza, nasal congestion, nasopharyngitis/pharyngitis, respiratory disorder, rhinitis, throat irritation, upper respiratory tract infection, viral respiratory infection, accidental injury, fever, and viral infection.

- Albuterol, levalbuterol, metaproterenol, terbutaline, arformoterol, indacaterol, and salmeterol are Pregnancy Category C; ProAir RespiClick, formoterol, and olodaterol are not currently assigned a Pregnancy Category.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

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

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

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

See the current prescribing information for full details.

CONCLUSION

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

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