BRIAN SANDOVAL
Governor

RICHARD WHITLEY, MS
Director

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
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NOTICE OF PUBLIC MEETING – PHARMACY AND THERAPEUTICS COMMITTEE

AGENDA

Date of Publication:	**February 24, 2017**
Date and Time of Meeting:	**Thursday, March 23, 2017 at 1:00 PM**
Name of Organization:	**The State of Nevada, Department of Health and Human Services (DHHS), Division of Health Care Financing and Policy (DHCFP)**
Place of Meeting:	**North Nevada Location:** **Silver State Health Insurance Exchange** **2310 S. Carson Street, Suite 3A** **Carson City, Nevada 89701**
Place of Video-Conference:	**South Nevada Location:** **Silver State Health Insurance Exchange** **150 N. Stephanie Street, Suite 100** **Henderson, Nevada 89074** **Please check with staff to verify room location**
Webinar Registration:	https://catamaranrx.webex.com/catamaranrx/onstage/g.php?MTID=e9e4f7b1984f04c07fb657784c2c7802d OR www.webex.com, select "Join," enter Meeting Number 749 549 205, your name and email and then select, "Join." A Password should not be necessary, but if asked, enter "Medicaid"

Event Number: **749 549 205**

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

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

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

Public comment is limited to 5 minutes per individual, organization, or agency, but may be extended at the discretion of the Chairperson.

AGENDA

1. Call to Order and Roll Call

2. Public Comment

3. Administrative

a. **For Possible Action**: Review and Approve Meeting Minutes from December 8, 2016

b. Status Update by DHCFP

i. Public Comment

4. Established Drug Classes

a. Psychotropic Agents: Atypical Antipsychotics - Oral

i. Public Comment

ii. Drug Class Review Presentation – OptumRx

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

1. Approve Clinical/Therapeutic Equivalency of Agents in Class

2. Identify Exclusions/Exceptions for Certain Patient Groups

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

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

b. Respiratory Agents: Short-Acting Respiratory Beta-Agonists

i. Public Comment

ii. Drug Class Review Presentation – OptumRx

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

1. Approve Clinical/Therapeutic Equivalency of Agents in Class

2. Identify Exclusions/Exceptions for Certain Patient Groups

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

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

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

a. Cardiovascular Agents: Antihypertensive Agents: Vasodilators - Oral

i. Public Comment

ii. Drug Class Review Presentation – OptumRx

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

1. Approve Clinical/Therapeutic Equivalency of Agents in Class

2. Identify Exclusions/Exceptions for Certain Patient Groups

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

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

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

i. Public Comment

ii. Drug Class Review Presentation – OptumRx

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

1. Approve Clinical/Therapeutic Equivalency of Agents in Class

2. Identify Exclusions/Exceptions for Certain Patient Groups

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

v.

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

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

i. Public Comment

ii. Drug Class Review Presentation – OptumRx

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

1. Approve Clinical/Therapeutic Equivalency of Agents in Class

2. Identify Exclusions/Exceptions for Certain Patient Groups

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

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

6. Proposed New Classes

a. Ophthalmic Agents: Opthalmics for Dry Eye Disease

i. Public Comment

ii. Drug Class Review Presentation – OptumRx

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

1. Approve Clinical/Therapeutic Equivalency of Agents in Class

2. Identify Exclusions/Exceptions for Certain Patient Groups

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

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

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

8. Closing Discussion

a. Public comments on any subject

b. Date and location of the next meeting

c. Adjournment

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

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

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

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

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

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

	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 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®		OXYCONTIN® QL XTAMPZA ER®

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

Preferred Products	PA Criteria	Non-Preferred Products
PEGASYS® CONVENIENT PACK PEG-INTRON® and REDIPEN		
Anti-hepatitis Agents		
Polymerase Inhibitors/Combination Products		
EPCLUSA® HARVONI® 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
Ribavirins		
RIBAVIRIN		RIBASPHERE RIBAPAK® MODERIBA® REBETOL®
Anti-Herpetic Agents		
ACYCLOVIR FAMVIR® VALCYCLOVIR		
Influenza Agents		
AMANTADINE TAMIFLU® RIMANTADINE RELENZA®		
Cephalosporins		
Second-Generation Cephalosporins		
CEFACLOR CAPS and SUSP CEFACLOR ER CEFUROXIME TABS and SUSP CEFPROZIL SUSP		CEFTIN® CECLOR® CECLOR CD® CEFZIL
Third-Generation Cephalosporins		
CEFDINIR CAPS / SUSP CEFPODOXIME TABS and SUSP		CEDAX® CAPS and SUSP CEFDITOREN OMNICEF® SPECTRACEF® SUPRAX® VANTIN®
Macrolides		
AZITHROMYCIN TABS/SUSP		BIAXIN®

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

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

Preferred Products	PA Criteria	Non-Preferred Products
LABETALOL METOPROLOL (Regular Release) NADOLOL PINDOLOL PROPRANOLOL PROPRANOLOL/HCTZ SOTALOL TIMOLOL		
Calcium-Channel Blockers		
AFEDITAB CR® AMLODIPINE CARTIA XT® DILTIA XT® DILTIAZEM ER DILTIAZEM HCL DYNACIRC CR® EXFORGE® EXFORGE HCT® FELODIPINE ER ISRADIPINE LOTREL® NICARDIPINE NIFEDIAC CC NIFEDICAL XL NIFEDIPINE ER NISOLDIPINE ER TAZTIA XT® VERAPAMIL VERAPAMIL ER		
Direct Renin Inhibitors		
TEKAMLO® TEKTURNA® TEKTURNA HCT® VALTURNA®		AMTURNIDE®
Vasodilators		
Inhaled		
VENTAVIS® TYVASO®		
Oral		
LETAIRIS® ORENITRAM® SILDENAFIL TRACLEER®		ADCIRCA® ADEMPAS® OPSUMIT® REVATIO ®

Preferred Products	PA Criteria	Non-Preferred Products
Antilipemics		
Bile Acid Sequestrants		
COLESTIPOL CHOLESTYRAMINE WELCHOL®		QUESTRAN®
Cholesterol Absorption Inhibitors		
ZETIA®		
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® LESCOL® LESCOL XL® LIPITOR® LIPTRUZET® LIVALO® MEVACOR® PRAVACHOL® SIMCOR® VYTORIN® ZOCOR®
Niacin Agents		
NIASPAN® (Brand only) NIACIN ER (ALL GENERICS)		NIACOR®
Omega-3 Fatty Acids		
LOVAZA® VASCEPA®		OMEGA-3-ACID OMTRYG®
Dermatological Agents		
Antipsoriatic Agents		
Topical Vitamin D Analogs		
CALCIPOTRIENE		CALCITENE® DOVONEX® CREAM

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

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

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

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

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

Preferred Products	PA Criteria	Non-Preferred Products
VICTOZA® *		
Insulins (Vials, Pens and Inhaled)		
APIDRA® HUMALOG® HUMULIN® LANTUS® LEVEMIR ® NOVOLIN® NOVOLOG® TRESIBA FLEX INJ		AFREZZA® 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 NEW SYNJARDY® XIGDUO XR®
Sulfonylureas		
AMARYL® CHLORPROPAMIDE DIABETA® GLIMEPIRIDE (Amaryl®) GLIPIZIDE (Glucotrol®) GLUCOTROL® GLUCOVANCE® GLIPIZIDE EXT-REL (Glucotrol XL®) GLIPIZIDE/METFORMIN (Metaglip®) GLYBURIDE MICRONIZED (Glynase®) GLYBURIDE/METFORMIN (Glucovance®) GLUCOTROL XL® GLYBURIDE (Diabeta®) GLYNASE® METAGLIP® TOLAZAMIDE TOLBUTAMIDE		

Preferred Products	PA Criteria	Non-Preferred Products
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®
Musculoskeletal Agents		
Antigout Agents		
ALLOPURINOL COLCHICINE TAB/CAP NEW PROBENECID NEW PROBENECID/COLCHICINE NEW ULORIC® NEW		COLCRYS® TAB NEW MITIGARE® CAP NEW ZURAMPIC® NEW ZYLOPRIM® NEW
Bone Resorption Inhibitors		
Bisphosphonates		
ALENDRONATE TABS FOSAMAX PLUS D®		ACTONEL® ALENDRONATE SOLUTION ATELVIA® BINOSTO® BONIVA® DIDRONEL® ETIDRONATE IBANDRONATE SKELID®
Nasal Calcitonins		
MIACALCIN®		FORTICAL® CALCITONIN-SALMON

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

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

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

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

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

Preferred Products	PA Criteria	Non-Preferred Products
RITALIN LA® STRATTERA® VYVANSE®		
Antidepressants		
Other		
BUPROPION BUPROPION SR BUPROPION XL DULOXETINE * MIRTAZAPINE MIRTAZAPINE RAPID TABS PRISTIQ® TRAZODONE VENLAFAXINE (ALL FORMS)	PA required for members under 18 years old * PA required *No PA required if ICD-10 - M79.1; M60.0-M60.9, M61.1.*	APLENZIN® BRINTELLIX® CYMBALTA® * DESVENLAFAXINE FUMARATE EFFEXOR® (ALL FORMS) FETZIMA® FORFIVO XL® KHEDEZLA® VIIBRYD® WELLBUTRIN®
Selective Serotonin Reuptake Inhibitors (SSRIs)		
CITALOPRAM ESCITALOPRAM FLUOXETINE PAROXETINE PEXEVA® SERTRALINE	PA required for members under 18 years old	CELEXA® FLUVOXAMINE QL LEXAPRO® LUVOX® PAXIL® PROZAC® SARAFEM® ZOLOFT®
Antipsychotics		
Atypical Antipsychotics - Oral		
ARIPIPRAZOLE CLOZAPINE FANAPT® LATUDA® NUPLAZID®* Preferred for ICD-10 code G31.83 OLANZAPINE QUETIAPINE REXULTI® RISPERIDONE SAPHRIS®	**PA required for Ages under 18 years old** **PA Forms:** https://www.medicaid.nv.gov/Downloads/provider/FA-70A.pdf (ages 0-5) 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®

Preferred Products	PA Criteria	Non-Preferred Products
SEROQUEL XR® ZIPRASIDONE		SEROQUEL® VRAYLAR® ZYPREXA®
Anxiolytics, Sedatives, and Hypnotics		
ESTAZOLAM FLURAZEPAM ROZEREM® * TEMAZEPAM TRIAZOLAM ZALEPLON NEW ZOLPIDEM ZOLPIMIST® NEW	*(PA not required for ICD-10 code G47.0 and F51.0)	AMBIEN® AMBIEN CR® BELSOMRA® DORAL® ESZOPICLONE EDLUAR® HETLIOZ® INTERMEZZO® LUNESTA® SILENOR® SOMNOTE®
	PA required for members under 18 years old	SONATA® ZOLPIDEM CR
Psychostimulants		
Narcolepsy Agents		
Provigil® *	* (No PA required for ICD-10 code G47.4)	MODAFINIL NUVIGIL® XYREM®
Respiratory Agents		
Nasal Antihistamines		
ASTEPRO® DYMISTA® PATANASE®		AZELASTINE OLOPATADINE
Respiratory Anti-inflammatory Agents		
Leukotriene Receptor Antagonists		
MONTELUKAST ZAFIRLUKAST		ACCOLATE® SINGULAIR®
Respiratory Corticosteroids		
ARNUITY ELLIPTA® ASMANEX® FLOVENT DISKUS® QL FLOVENT HFA® QL PULMICORT FLEXHALER® PULMICORT RESPULES®* QVAR®	*No PA required if < 4 years old	ALVESCO® AEROSPAN HFA® BUDESONIDE NEBS*
Nasal Corticosteroids		
FLUTICASONE NASONEX®		BECONASE AQ® FLONASE®

	Preferred Products	PA Criteria	Non-Preferred Products
			FLUNISOLIDE NASACORT AQ® OMNARIS® QNASL® RHINOCORT AQUA® TRIAMCINOLONE ACETONIDE VERAMYST® ZETONNA®
Phosphodiesterase Type 4 Inhibitors			
	DALIRESP® QL	PA required	
Respiratory Antimuscarinics			
	ATROVENT® COMBIVENT RESPIMAT® IPRATROPIUM/ALBUTEROL NEBS QL IPRATROPIUM NEBS SPIRIVA®	Only one agent per 30 days is allowed	INCRUSE ELLIPTA ® SEEBRI NEOHALER® SPIRIVA RESPIMAT® TUDORZA®
Respiratory Beta-Agonists			
Long-Acting Respiratory Beta-Agonist			
	FORADIL® SEREVENT DISKUS® QL STRIVERDI RESPIMAT®		ARCAPTA NEOHALER® BROVANA® PERFOROMIST NEBULIZER®
Short-Acting Respiratory Beta-Agonist			
	ALBUTEROL NEB/SOLN LEVALBUTEROL NEBS PROVENTIL® HFA XOPENEX® HFA* QL	* PA required	PROAIR® HFA PROAIR RESPICLICK® VENTOLIN HFA® XOPENEX® Solution* QL
Respiratory Corticosteriod/Long-Acting Beta-Agonist Combinations			
	ADVAIR DISKUS® ADVAIR HFA® DULERA® SYMBICORT®		BREO ELLIPTA®
Respiratory Long-Acting Antimuscarinic/Long-Acting Beta-Agonist Combinations			
	ANORO ELLIPTA® STIOLTO RESPIMAT®		UTIBRON NEOHALER ®
Toxicology Agents			
Antidotes			
Opiate Antagonists			
	EVZIO ® NALOXONE NARCAN® NASAL SPRAY		

	Preferred Products	PA Criteria	Non-Preferred Products
Substance Abuse Agents			
Mixed Opiate Agonists/Antagonists			
	BUNAVAIL® SUBOXONE® ZUBSOLV®	PA required for class	BUPRENORPHINE/NALOXONE

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

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

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

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

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

(b) Antirejection medications for organ transplants;

(c) Antihemophilic medications; and

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

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

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

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

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

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

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

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

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

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

(b) Maintains continuous eligibility for Medicaid; and

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

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

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

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

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

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

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

(c) Anticonvulsant medications;

(d) Antirejection medications for organ transplants;

(e) Antidiabetic medications;

(f) Antihemophilic medications; and

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

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

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

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

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

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

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

Definition of "Therapeutic Alternative"

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

Appendix D – Quantity Limits (effective October 17, 2016)

Brand Name	Generic Name	Strength	Dosage Form	Limit
ADD/ADHD Agents				
Adderall XR®	Amphetamine/Dextroamphetamine Mixed salts ER	5mg 10mg 15mg 20mg 25mg 30mg	Capsule	30 caps/30 days
Aptensio XR®	Methylphenidate ER	10mg 15mg 20mg 30mg 40mg 50mg 60mg	Capsule	30 caps/30 days
Concerta®	Methylphenidate ER	18mg 27mg 36mg 54mg	Tablet	30 tabs/30 days
Daytrana®	Methylphenidate Patch	10mg 15mg 20mg 30mg	Patch	30 patches/30 days
Dexedrine Spansule®	Dextroamphetamine ER	5mg 10mg 15mg	Capsule	60 caps/30 days
Dyanavel XR	Amphetamine ER suspension	2.5mg/ml	Oral Suspension	240 ml/30 days
Focalin XR®	Dexmethylphenidate ER	5mg 10mg 15mg 20mg 25mg 30mg 35mg 40mg	Capsule	30 caps/30 days
Intuniv®	Guanfacine ER	1mg 2mg 3mg 4mg	Tablet	30 tabs/30 days
Kapvay®	Clonidine ER	0.1mg	Tablet	60 tabs/30 days
Metadate CD®	Methylphenidate ER	10mg 20mg 30mg 40mg 50mg 60mg	Capsule	30 caps/30 days
Metadate ER®	Methylphenidate ER	20mg	Tablet	60 tabs/30 days
Quillichew XR®	Methylphenidate ER	20mg 30mg 40mg	Chew Tab	30 tabs/30 days
Quillivant XR®	Methylphenidate ER	25mg	Oral Susp	360 ml/30 days
Ritalin LA®	Methylphenidate ER	10mg 20mg 30mg 40mg 60mg	Capsule	30 caps/30 days

Appendix D – Quantity Limits (effective October 17, 2016)

Brand Name	Generic Name	Strength	Dosage Form	Limit
Ritalin SR®	Methylphenidate ER	10mg 20mg	Tablets	30 tabs/30 days
Strattera®	Atomoxetine	10mg 18mg 25mg 40mg 60mg 80mg 100mg	Capsule	60 caps/30 days
Vyvanse®	Lisdexamfetamine	10mg 20mg 30mg 40mg 50mg 60mg 70mg	Capsule	30 caps/30 days
Analgesics				
Celebrex® (COX-II)	Celecoxib	All Strengths	Capsule	400mg per day
Lidoderm®	Lidocaine	5%	Transdermal patch	90 patches per rolling 30 days
Toradol	Ketorolac	10mg	Tablet	20 tablets per 6 months
Acetaminophen containing products		All Strengths	All	3,000mg Acetaminophen per day
Anticoagulants				
Lovenox®	Enoxaparin	30mg/0.3ml	Solution for Injection	18ml/Rx
Lovenox®	Enoxaparin	40mg/0.4ml	Solution for Injection	24ml/Rx
Lovenox®	Enoxaparin	60mg/0.6ml	Solution for Injection	36ml/Rx
Lovenox®	Enoxaparin	80mg/0.8ml	Solution for Injection	48ml/Rx
Lovenox®	Enoxaparin	100mg/ml	Solution for Injection	60ml/Rx
Lovenox®	Enoxaparin	120mg / 0.8ml	Solution for Injection	48ml/Rx
Lovenox®	Enoxaparin	150mg/ml	Solution for Injection	60ml/Rx
Pradaxa®	Dabigatran	75mg and 150mg	Capsule	60 tabs/30 days
Antiemetics				
Aloxi®	Palonosetron HCL	0.25mg/5ml	Solution for Injection	35 mls/30 days
Anzemet®	Dolasetron	50 mg	Tablet	4 tabs/Rx
Anzemet®	Dolasetron	100 mg	Tablet	2 tabs/Rx
Anzemet®	Dolasetron	20mg/ml	Solution for Injection	35 mls/30 days
Cesamet®	Nabilone	1 mg	Capsule	180 caps/30 days
Kytril®	Granisetron	1 mg	Tablet	2 tabs/Rx

Appendix D – Quantity Limits (effective October 17, 2016)

Brand Name	Generic Name	Strength	Dosage Form	Limit
Kytril®	Granisetron	1 mg/5 ml, 30 ml per bottle	Oral Solution	1 bottle/Rx
Sancuso®	Granisetron transdermal	3.1 mg/24 hr (7 day patch)	Transdermal patch	1 patch/Rx
Zofran®	Ondansetron	4 mg	Tablet and ODT	12 tabs/Rx
Zofran®	Ondansetron	8 mg	Tablet and ODT	6 tabs/Rx
Zofran®	Ondansetron	24 mg	Tablet	1 tab/Rx
Zofran®	Ondansetron	4 mg/5 ml, 50 ml per bottle	Oral Solution	1 bottle/Rx
Zofran®	Ondansetron	2mg/ml	Solution for Injection	350 mls/30 days
Zofran®	Ondansetron	4mg/2ml	Solution for Injection	6 mls/claim
Zofran®	Ondansetron	40mg/20ml	Solution for Injection	20 mls/claim
Zuplenz®	Ondansetron	4 mg	Dissolving Film	12 films/Rx
Zuplenz®	Ondansetron	8 mg	Dissolving Film	6 films/Rx
Emend®	Aprepitant	80mg	Capsule	2 caps/Rx
Emend®	Aprepitant	125mg	Capsule	1 cap/Rx
Zofran®	Ondansetron	4mg	ODT	12 tabs/Rx
Zofran®	Ondansetron	8mg	ODT	6 tabs/Rx
Antimigraine Agents				
Amerge®	Naratriptan	1mg	Tablet	9 tabs/month
Amerge®	Naratriptan	2.5mg	Tablet	9 tabs/month
Axert®	Almotriptan	6.25mg	Tablet	6 tabs/month
Axert®	Almotriptan	12.5mg	Tablet	6 tabs/month
Frova®	Frovatriptan	2.5mg	Tablet	9 tabs/month
Imitrex®	Sumatriptan	25mg	Tablet	18 tabs/month
Imitrex ®	Sumatriptan	50mg	Tablet	9 tabs/month
Imitrex ®	Sumatriptan	100mg	Tablet	9 tabs/month
Imitrex®	Sumatriptan	6mg	Injection Kit	4 injections/month
Imitrex®	Sumatriptan	5mg	Nasal Spray	12 units/month
Imitrex®	Sumatriptan	20mg	Nasal Spray	6 units/month
Maxalt®	Rizatriptan	5mg	Tablet	12 tabs/month
Maxalt	Rizatriptan	10mg	Tablet	12 tabs/month
Maxalt-MLT	Rizatriptan	5mg	ODT	12 tabs/month
Maxalt-MLT	Rizatriptan	10mg	ODT	12 tabs/month
Zomig®	Zolmitriptan	2.5mg	Tablet	12 tabs/month
Zomig®	Zolmitriptan	5mg	Tablet	6 tabs/month
Zomig-ZMT	Zolmitriptan	2.5mg	ODT	12 tabs/month
Zomig-ZMT	Zolmitriptan	5 mg	Nasal Spray	12 tabs/month

Appendix D – Quantity Limits (effective October 17, 2016)

Brand Name	Generic Name	Strength	Dosage Form	Limit
Chemotherapy Agents				
Avastin®	Bevacizumab	100mg/4ml	Solution for Injection	12 mls/claim
Avastin®	Bevacizumab	400mg/16ml	Solution for Injection	32 mls/claim
	Bleomycin Sulfate	All Strengths	Vial	30 vials/7 days
	Cytarabine	20mg/ml 5ml vial	Solution for Injection	15 mls/claim
	Cytarabine	20mg/ml 50ml vial	Solution for Injection	250 mls/claim
Herceptin®	Trastuzumab	440mg vial	Solution for Injection	3 vials/claim
Lupron®	Leuprolide Acetate Kit	All Strengths	Solution for Injection	2 kits/30 days
Navelbine®	Vinorelbine Tartrate	All Strengths	Solution for Injection	36 mls/30 days
Taxol	Paclitaxel	100mg/16.7 ml	Solution for Injection	50.1mls/claim
Taxol	Paclitaxel	150mg/25ml	Solution for Injection	75mls/claim
Taxol	Paclitaxel	30mg/5ml	Solution for Injection	15mls/claim
Taxol	Paclitaxel	300mg/50ml	Solution for Injection	150mls/claim
Colony Stimulating Hormones				
Granix®	TBO-Filgrastim	300mcg/0.5 ml 480mcg/0.8 ml	Solution for Injection	0.8 ml/day
Neulasta®	Pegfilgrastim	6mg/0.6ml	Solution for Injection Onpro Kit	1.2 mls/7 days
Neupogen®	Filgrastim	300mcg/0.5 ml 480mcg/0.8 ml	Solution for Injection	8.5 ml/day
Zarxio®	Filgrastim	300mcg/0.5 ml 480mcg/0.8 ml	Solution for Injection	8.5 ml/day
Diabetic Supplies				
	Lancets			200 lancets/month
	Alcohol Swabs			200 swabs/month
	Battery for Monitor			1 battery/year
	Blood Glucose Monitor			1 meter every 2 years
	Blood Glucose Strips			200 strips/month
	Insulin Syringes			100 syringes/month
	Keto-Stix			100 strips/month
	Control Solution			1 solution set/month

Appendix D – Quantity Limits (effective October 17, 2016)

Erythropoiesis Stimulating Agents				
Aranesp®	Darbepoetin Alfa	All Strengths	Solution for Injection	1500 mcg/30 days or 3 ML per claim
Epogen®/Procrit®	Epoetin Alfa	All Strengths	Solution for Injection	500,000 units/30 days or 3 ML per claim
Omontys®	Peginesatide	10mg/ml	Solution for Injection	3 ML per claim
Omontys®	Peginesatide	20mg/2ml	Solution for Injection	4 ML per claim
Hepatitis C Agents				
Daklinza®	Daclatasvir		Tablet	14 days supply first fill, 28 tabs per rolling 25 days on subsequent fills
Harvoni®	Ledipasvir-Sofosbuvir		Tablet	14 days supply first fill, 28 tabs per rolling 25 days on subsequent fills
Incivek®	Telaprevir	375 mg	Tablet	168 tabs per rolling 25 days
Olysio®	Simprevir		Capsule	14 days supply first fill, 28 caps/rolling 25 days on subsequent fills
Sovaldi®	Sofosbuvir		Capsule	14 days supply first fill, 28 caps/rolling 25 days on subsequent fills
Technivie®	Ombitasvir / Paritaprevir / Ritonavir		Tablet	14 days supply first fill, 2 boxes of tablets, 56/28 days
Victrelis®	Boceprevir	200 mg	Capsule	336 caps per rolling 25 days
Viekira Pak®	Ombitas-Paritapre-Riton-Dasab		Pack	14 days supply first fill, 1 pack/28 days
Multiple Sclerosis Agents				
Copaxone®	Glatiramer Acetate	20mg	Solution for Injection	30 ml/30 days
Rebif®	Interferon Beta-1A	All Strengths	Solution for Injection	6 vials/Rx
Ampyra®	dalfampridine	10mg	Tablet	60 tabs/30 days
Opioids				
Actiq®	Fentanyl	All Strengths	Lozenge	120 lozenges per rolling 30 days
Avinza®	Morphine Sulfate	All Strengths	Capsule	1 capsule/day

Butrans®	Buprenorphine transdermal patch	All Strengths	Transdermal patch	4 patches/30 days
Demerol	Meperidine Hydrochloride	All Strengths	Solution for Injection	30 mls/day
Duragesic®	Fentanyl	All Strengths	Transdermal patch	1 patch every 3 days
Duragesic®	Fentanyl	All Strengths	Patch	1 patch every 2 days if failure to achieve pain relief is documented and clinical notes are provided to the clinical call center.
Embeda®	Morphine-Naltrexone	All Strengths	Capsule	2 capsules per day
Exalgo®	Hydromorphine ER	All Strengths	Tablet	1 tablet per day
Fentora®	Fentanyl	All Strengths	Buccal tablet	120 tabs per rolling 30 days
Hysingla® ER	Hydrocodone ER	All Strengths	Tablet	1 tablet per day
Kadian®	Morphine Sulfate	All Strengths	Capsule	2 caps/day
MS Contin	Morphine Sulfate	All Strengths	Tablet	3 tabs/day
Nucynta® ER	Tapentadol ER	All Strengths	Tablet	2 tablets/day
Opana® ER	Oxymorphone ER	All Strengths	Tablet	2 tablets/day
OxyContin®	Oxycodone	All Strengths	Tablet	3 tabs/day
Stadol®	Butorphanol	All Strengths	Nasal Spray	2 per rolling 30 days
Xartemis® XR	Oxycodone/APAP ER	All Strengths	Tablet	4 tabs/day
Zohydro® ER	Hydrocodone ER	All Strengths	Tablet	2 tabs/day
Oral Contraceptives				
Oral Contraceptives	All Products	All Strengths	Tablet	28 tablets (when provided in a physician's office)
Respiratory				
Daliresp®	Roflumilast	500mcg	Tablet	30 tabs/25 days
Duoneb	Ipratropium/Albuterol	0.5-2.5mg / 3ml	Nebulizer Solution	360 ml/month
Flovent®	Fluticasone	100mcg	Rotadisk	1 inhaler/month
Flovent®	Fluticasone	250mcg	Rotadisk	1 box/month
Flovent®	Fluticasone	50mcg	Rotadisk	1 box/month
Serevent® Diskus®	Salmeterol	50mcg	Diskus	1 box (60 inhalations per month)
Xopenex®	Levalbuterol	(All Strengths)	Nebulizer Solution	4 boxes (288ml) per month
Xopenex	Levalbuterol	0.31 and 0.63mg		Every 6 hours (see monthly max above)
Xopenex	Levalbuterol	1.25mg		Every 8 hours (see monthly max above)
Sedative/Hypnotics				
Ambien®	Zolpidem	5mg and 10mg	Tab	30 tabs/30 days

Ambien CR®	Zolpidem ER	6, 6.25, 12, 12.5mg	Tab CR	30 tabs/30 days
Belsomra®	Suvorexant	5, 10, 15 and 20mg	Tab	30 tabs/30 days
Dalmane®	Flurazepam	15mg and 30mg	Capsule	30 caps/30 days
Doral®	Quazepam	15mg	Tab	30 tabs/30 days
Edluar®	Zolpidem	5mg and 10mg	SL Tab	30 tabs/30 days
Halcion	Triazolam	0.125 and 0.25 mg	Tab	30 tabs/30 days
Hetlioz®	Tasimelteon	20mg	Capsule	30 caps/30 days
Intermezzo®	Zolpidem	1mg and 3mg	SL tab	30 tabs/30 days
Prosom®	Estazolam	1mg and 2mg	Tab	30 tabs/30 days
Restoril®	Temazepam	7, 7.5, 15, 22, 22.5, and 30mg	Capsule	30 caps/30 days
Rozerem®	Ramelteon	8mg	Tab	30 tabs/30 days
Silenor®	Doxepin	3mg and 6mg	Tab	30 tabs/30 days
Sonata®	Zaleplon	5mg and 10mg	Capsule	30 caps/30 days
Zolpimist®	Zolpidem	5mg	Oral Spray	1 Unit/30 days
Buprenorphine/ Naloxone				
Subutex®	Buprenorphine	2mg	SL Tab	90 tabs/30 days
Subutex®	Buprenorphine	8mg	SL Tab	60 tabs/30 days
Suboxone®	Buprenorphine/ Naloxone	2mg/0.5mg	SL Tab/Film	90 tabs/30 days
Suboxone®	Buprenorphine/ Naloxone	4mg/1mg	SL Tab/Film	30 tabs/30 days
Suboxone®	Buprenorphine/ Naloxone	8mg/2mg	SL Tab/Film	60 tabs/30 days
Suboxone®	Buprenorphine/ Naloxone	12mg/3mg	SL Tab/Film	30 tabs/30 days
Zubsolv®	Buprenorphine/ Naloxone	1.4mg/0.36mg	SL Tab	90 tabs/30 days
Zubsolv®	Buprenorphine/ Naloxone	5.7mg / 1.4mg	SL Tab	60 tabs/30 days
Miscellaneous				
Adenocard	Adenosine	All Strengths	Solution for Injection	255 ml/30 days
Benadryl®	Diphenhydramine HCL	All Strengths	Solution for Injection	5 mls/day
Botox®	Onabotulinumtoxina	All Strengths	Solution for Injection	4 vials/30 days
Brilinta®	ticagrelor	All Strengths	Tablet	60 tabs/25 days

Appendix D – Quantity Limits (effective October 17, 2016)

Colcrys®	Colchicine	0.6mg	Tablet	90 tabs/30 days - FMF 60 tabs/30 days - Chronic Gout
Corlanor®	Ivabradine	5mg 7.5mg	Tablet	60 tabs/30 days
Crestor®	Rosuvastatin	10mg	Tablet	2 tabs/day
Crestor®	Rosuvastatin	20mg	Tablet	1 tab/day
Depo-Provera	Medroxyprogesterone	150 mg	Solution for Injection	2 ml/3 months
Duexis®	Ibuprofen/famotidine	800/26.6mg	Tablet	3 tabs/day
Effient®	Prasugrel		Tablet	30 tabs/30 days
Elidel®	Pimecrolimus	1%	Tube	30 GM per rolling 30 days with a 25% tolerance for refills
Entresto®	Sacubitril/Valsartan	24-26mg 49-51mg 97-103mg	Tablets	60 tabs/30 days
Haldol®	Haloperidol Decanoate	All Strengths	Solution for Injection	20 ml/30 days
Jublia®	Efinaconazole	10%	Topical Solution	1 bottle/30 days
Kalydeco™	Ivacaftor	50 mg 75mg 150mg	Tablet Packets	60 tabs or packs/25 days
Kerydin®	Tavaborole	5%	Topical Solution	1 bottle/30 days
Lamisil® Granules	Terbinafine	125mg 187.5mg	Granules Packet	60 packs/30 days
Makena®	Hydroxyprogesterone Caproate	250mg/ml	Solution for Injection	1 vial/30 days
Mitigare®	Colchicine	0.6mg	Tablets	60 tabs/30 days
Nuvigil®	Armodafinil	50mg 150mg 200mg 250mg	Tablet	1 tablet per day
Onmel®	Itraconazole	200mg	Tablet	30 tabs/30 days
Orkambi®	Lumacaftor/Ivacator	200-125mg	Tablet	112 tabs/28 days
Phenergan/Codeine	Promethazine/Codeine	6.25-10 mg/5 ml	Syrup	120 ml/fill, 3 fills per rolling 12 months
Phenergan VC/Codeine	Promethazine VC/Codeine	6.25-10 mg/5 ml	Syrup	120 ml/fill, 3 fills per rolling 12 months
Praluent®	Alirocumab	75mg 150mg	Pen/Syringe	2 pens/syringes per rolling 28 days
Protopic®	Tacrolimus	All Strengths	Tube	30 gm per rolling 30 days with a 25% tolerance for refills

Appendix D – Quantity Limits (effective October 17, 2016)

Provigil®	Modafinil	100mg 200mg	Tablet	1 tablet per day
Regranex®	Becaplermin	0.01%	Tube	15 gm tube per claim, 2 tubes in lifetime
Repatha®	Evolocumab	140mg/ml	Pen/Syringe	3 pens/syringes per rolling 28 days
Smoking Cessation Products				180 days/year
Solu-Medrol®	Methylprednisolone	All Strengths	Solution for Injection	12 ml/30 days
Synagis®	Palivizumab	100mg	Vial	4 vials/Rx
Versed	Midazolam Hydrochloride	All Strengths	Solution for Injection	100 mls/day
	Triamcinolone Acetonide	All Strengths	Solution for Injection	16 mls/30 days
	Blood Factor per unit (Antihemophilic Factor, Human or Recombinant)	All Strengths	Unit	10,000 units/day
Viberzi®	Eluxadoline	75mg 100mg	Tablet	2 tablets per day
Xolair®	Omalizumab	150mg	Vial	6 vials/28 days
Xyrem®	Sodium oxybate	500mg/ml	Solution	540 ml/30 days

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Governor

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Nevada Medicaid

PHARMACY AND THERAPEUTICS COMMITTEE

DRAFT MEETING MINUTES

The Division of Health Care Financing and Policy (DHCFP) Pharmacy and Therapeutics Committee held a public meeting on December 8, 2016 beginning at **1:00 p.m.** at the following location:

Springs Preserve
Desert Living Center
333 S. Valley View Blvd
Las Vegas, NV 89107
Phone: (702) 822-7700

Committee Members Present:
Mark Decerbo, Pharm.D.; Shamim Nagy, MD; Mike Hautekeet, Pharm.D.; Joseph Adashek, MD; Nikki Beck, Pharm.D.; Christopher Highley, MD; Weldon Havins, MD

Committee Members Absent:
Adam Zold, Pharm.D.; Evelyn Chu, Pharm.D.

Others Present:
DHCFP:
Mary Griffith, RN, Pharmacy Services Specialist; Shannon Richards, Deputy Attorney General; Shannon Sprout, DHCFP

HPES:
Beth Slamowitz, Pharm.D.

Optum:
Carl Jeffery, Pharm.D.; Kevin Whittington, RPh; Daniel Medina (via teleconference)

Others: Joey Sturgeon, Silvergate; Dan Tubridy, BI; Nana Namapau, BI; Mark Schwartz, GSK; Charissa Anne, J&J; Scott Black, Daiichi Sankyo; Melissa Walsh, Novartis; Sean Pascoe, Novartis; Jennifer Lauper, BMS; David Crosby, BMS; Chris Amstead, Amgen; Terry Turner, Shionogi; Akvile Garcia, Roseman; Neggy Ghalchi, Roeman; Michael Faithe, Amgen; Lee Stout, Chiesi; Sandy Sierawski, Pfizer; Lovell Robinson, Abbvie; Laura Hill, Abbvie; Jill Suag, UCB; Michelle Mui, UCB; Joe Busby, Lilly; Laura Litzenberger, Janssen; Marc Rueckert, Pfizer; Chad Macgreger, UCB; Kerry Bonilla, AZ

AGENDA

1. Call to Order and Roll Call

Meeting called to order at 1:00 PM

Roll Call:

Carl Jeffery, OptumRx
Kevin Whittington, OptumRx
Mary Griffith, DHCFP
Shannon Sprout, DHCFP
Beth Slamowitz, Hewlett Packard Enterprises
Weldon Havins, MD
Joseph Adashek, MD
Shamim Nagy, MD, Chair
Shannon Richards, Deputy Attorney General
Mark Decerbo, Pharm.D.
Christopher Highley, MD
Nikki Beck, Pharm.D.
Michael Hautekeet, Pharm.D.

2. Public Comment

None.

3. Administrative

a. **For Possible Action**: Review and Approve Meeting Minutes from September 22, 2106.

Shamim Nagy, Chair: Our first item is to approve the minutes from the last meeting.

Mark Decerbo: Move to approve as posted.

Michael Hautekeet: Second.

Voting: Ayes across the board. The motion carries.

b. Status Update by DHCFP.

i. Public Comment.

Shamim Nagy, Chair: Public comment on any matter? No.

Shamim Nagy, Chair: Status update from DHCFP.

Mary Griffith: Thank you everyone for coming. My name is Mary Griffith. I have a couple updates. At the October DUR Committee meeting the Committee voted to add some quantity for long and short acting opioids. The initial prescriptions will be limited to seven days. Any script over 7 days will require a prior authorization. The seven day prescriptions will be limited to 13 per rolling 12 months. The daily quantity will also be limited to 60 mg morphine equivalents. This is all in line with the Governor's task force to address prescription opioid abuse. We are hoping this will be implemented March or April of next year.

The next P&T meeting we will be video conferencing. The members will be split with the members in the North attending the meeting at the Health Exchange office in Carson City and the Southern Nevada members will be at the Health Exchange office in Henderson. We hope this will make things easier for the Northern Nevada members, so they don't have to travel. Voting might be a little trickier, it will be an adjustment.

Weldon Havins: I have a question. For someone with cancer and cancer pain, you are saying they can't get the higher dose?

Mary Griffith: No, there are some exceptions, patients with cancer, malignancy, palliative care, post-operative recovery that is expected to exceed 3 months, residents in long-term care facilities and recipients that are being treated for HIV or AIDs. Others will require a PA.

4. Established Drug Classes

a. Musculoskeletal Agents: Antigout Agents

Shamim Nagy, Chair: Any public comments? None.

Shamim Nagy, Chair: Established drug classes. Musculoskeletal Agents. Any public comment? No.

Carl Jeffery: Good afternoon. We are talking about the antigout agents. It has been a long time since we last reviewed this class and we have a few changes. A couple new agents, Zurampic and Uloric have been introduced since we last looked at this class. Looking at the indications, this chart shows which agents are used for chronic or acute treatments. The new one, Zurampic, is only indicated for combination with other agents. Colchine was approved based on some old studies looking at different doses and some studies for preventing attacks. The common

theme is they all have studies showing they decrease uric acid levels, but have not demonstrated a decrease in the number of attacks. The guidelines all start with diet and lifestyle modifications and then move to different treatments, for acute episodes NSAIDs and colchicine. The DUR Committee did update the criteria for colchicine, they need to try some other agents before they can exceed the common dose of colchicine. Optum recommends the Committee consider these clinically and therapeutically equivalent.

Joseph Adashek: I make the motion to accept these as clinically and therapeutically equivalent.

Weldon Havins: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: Optum recommends we include the most commonly used medications currently. Uloric is considered first-line and the DUR Board criteria refers to Uloric too. The non-preferred drugs are either brand name agents or only used in combinations. This is Optum's recommendation.

Weldon Havins: I move that we accept Allopurinol, Colchicine tab and cap, probenecid and probenecid with Colchine and Uloric as preferred.

Joseph Adashek: Second.

Mark Decerbo: Just a quick question before voting, I'm just curious, did the DUR Committee discuss any criteria with Zurampic? As you pointed out, all the data with this agent is in combination with other agents. Was there any discussion about adding a PA to assure the recipient is on another agent?

Carl Jeffery: At the time the DUR Committee discussed this, Zurampic was not available. My understanding was that this should not be used alone because of some potential renal damage.

Voting: Ayes across the board, the motion carries.

b. Hematological Agents: Anticoagulants – Oral

Shamim Nagy, Chair: Our next topic is Oral Anticoagulants.

Is there any public comment? No.

Carl Jeffery: At the last meeting we brought this up and made Savaysa as preferred. We are not going to come back and try to change your mind. This slide shows the current indications, new ones are being added all the time. Unless the Committee wants to discuss this more, we are just bringing it up at the request of the Committee. Optum recommends these be considered clinically and therapeutically equivalent.

Weldon Havins: I move they be considered clinically and therapeutically equivalent.

Joseph Adashek: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: Optum recommends no changes at this time, unless the Committee sees something to move non-preferred.

Joseph Adashek: I move we accept the recommendations.

Weldon Havins: Second.

Voting: Ayes across the board, the motion carries.

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

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

Shamim Nagy, Chair: The next topic is established drug classes being reviewed due to the release of new drugs.

ACE inhibitors. Do we have any public comment?

Joey Sturgeon: My name is Joey Sturgeon, I am a pharmacist and National Account Director for Silvergate. We just released Qbrelis, a lisinopril oral solution. It was made available to pharmacies last month. ACE inhibitors have been available for a long time. Qbrelis is an oral solution, 1mg/ml which allows the titration for weight based dosing as recommended in pediatric patients. Statistics, and guidance documents from the FDA regarding compounded drugs were presented. I ask the Committee to remove barriers to obtaining this medication. I ask the Committee to add an age edit to allow for patients under the age of 18.

Shamim Nagy, Chair: Thank you. Any other public comment?

Weldon Havins: If a child needs an ACE inhibitor, what is the common generic?

Mark Decerbo: Most commonly for an oral solution would be enalapril now that there is a commercially available product and is on the PDL.

Carl Jeffery: We just heard about Qbrelis and that is what brought this class back. It has similar indications, stored at room temperature. We were comparing it to the compounded alternative. This slide shows the list of currently available ACE inhibitors. Optum recommends the Committee consider these clinically and therapeutically equivalent.

Mark Decerbo: I move the agents be considered clinically and therapeutically equivalent.

Christopher Highley: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: With the Epaned we made it preferred for 10 and under, right now we recommend Qbrelis be non-preferred, the Epaned would be available for children.

Weldon Havins: I move to accept the ACE inhibitor classifications as noted.

Joseph Adashek: Second.

Voting: Ayes across the board, the motion carries.

b. Psychotropic Agents: Anxiolytics, Sedatives, and Hypnotics

Shamim Nagy, Chair: The next class is psychotropic agents, anxiolytics, sedatives and hypnotics. Is there any public comment? No.

Carl Jeffery: This is a pretty easy class too. We haven't looked at it for a while, there have been a few new generics on the market since we last reviewed it. The generic for Sonata, zaleplon is available now. It is a good medication and well established. There is a study that shows there not be as much of a residual drowsiness compared to zolpidem. The other medication we are talking about is Zolpimist, an oral spray of zolpidem. It is good for fast bed-time activity, within about 15 minutes. Nothing else has changed in the class. Optum recommends this class be considered clinically and therapeutically equivalent.

Joseph Adashek: I move we consider them clinically and therapeutically equivalent

Weldon Havins: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: The new generic zaleplon and Zolpimist is recommended preferred and then keep the rest of the class the same.

Weldon Havins: I move the preferred products be approved as recommended adding zaleplon and Zolpimist.

Joseph Adashek: Second.

Voting: Ayes across the board the motion carries.

c. Otic Agents: Otic Antiinfectives – Otic Quinolones

Shamim Nagy, Chair: The next class is otic quinolones.

Any public comment? No.

Carl Jeffery: This is another class with some newer agents. Ofloxacin and Ciprodex are currently preferred. We have all the current indications covered. There is one injectable agent that is not covered on the PDL because it is only used in physician offices. Otovel is a combination of ciprofloxacin and fluocinolone, very similar indications to the other agents for otitis media down to children 6 months old. It was evaluated in two studies compared to oral amoxicillin. The other one is Cipro HC, it is new since the last review, ciprofloxacin and hydrocortisone also have similar indications. It was compared to the ingredients separately. Optum recommends the Committee consider these clinically and therapeutically equivalent.

Christopher Highley: I move these products be considered clinically and therapeutically equivalent.

Michael Hautekeet: Second.

Voting: Ayes - 6, Nay – 1, the motion carries.

Weldon Havins: I am just curious about the Nay vote.

Mark Decerbo: It is a formality with the antidiabetics themselves, but when we have diabetics and steroid combinations, it is hard to call a monotherapy equivalent to the combination therapy.

Joseph Adashek: Is the whole purpose to the category to lump together drugs that treat the same thing?

Carl Jeffery: Yes, going back to this slide with the indications, we categorize them based on what they are used for. We could call it otic quinolones and combination agents. But that is the basis of why we have this class.

Christopher Highley: Didn't you mention it in one of the studies with a shorter duration?

Carl Jeffery: I talked about Otovel, it was compared to oral amoxicillin. They didn't compare it to another otic agent. The Cipro HC, they compared to the ingredients separately.

Mark Decerbo: To clarify, functionally I agree with the process, but it is just semantics. The naming is difficult because you could sub-categorize many classes. If we want to get really picky, we could vote "no" on all of these.

Carl Jeffery: Optum recommends Cipro HC be included as preferred and Cetraxal, a branded ciprofloxacin, Otovel and the generic ciprofloxacin as non-preferred.

Nikki Beck: Is there a reason you put two of the antibiotics steroid combinations as preferred?

Carl Jeffery: The Ciprodex and Cipro HC, they have slightly different indications, we are trying to catch as many as possible. This gives prescribers a few more options.

Mark Decerbo: I move we consider the changes to the PDL of Otic Quinolones and combinations as presented.

Weldon Havins: Second

Voting: Ayes across the board, the motion carries.

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

Shamim Nagy, Chair: The next class is antidiabetic agents, sodium-glucose co-transporter 2 inhibitors.

Do we have public comment?

Laura Litzenberger: Good afternoon, I'm Laura Litzenberger from Janssen Scientific Affairs. I want to provide an update of the cardiovascular safety program for Invokana. We have heard a lot about cardiovascular safety within the SGLT2 class. Janssen is also studying the cardiovascular safety of Invokana as the FDA requires. The program has over 10,000 patients with a follow-up of 6 to 7 years. We believe the results will be available during the first half of 2017. Specifics for efficacy information were presented.

Nana Numapau: My name is Nana Numapau, I am the Associate Director for Health Economics and Outreach for Boehringer Ingleheim. I wanted to make the Committee aware last Friday, Jardiance received approval for the redaction of cardiovascular death and cardiovascular heart disease.

Carl Jeffery: Invokamet XR is the new product in this class. This slide shows the agents in this class have similar indications. Invokamet XR is an extended release version of Invokana and metformin. No studies showing that this agent is better than any other, just pharmacokinetic data showing they are bioequivalent. There is some new information about Jardiance and some of the other warnings as Laura mentioned. From a class standpoint, Optum recommends the Committee consider these clinically and therapeutically equivalent.

Joseph Adashek: I move we consider these clinically and therapeutically equivalent.

Weldon Havins: Second.

Voting: Ayes – 6, Nay – 1, the motion carries.

Carl Jeffery: Optum recommends with the theme of keeping the combination products as non-preferred. That way patients are supposed to be titrated individually and then moved to the combination agents. I know this isn't always how it works. Keep in mind that they only have to try one agent before moving to a non-preferred for the diabetic class. Optum recommends Invokamet XR be added as non-preferred.

Nikki Beck: I motion we accept the recommendations.

Christopher Highley: I second.

Voting; Ayes across the board, the motion carries.

e. Biologic Response Modifiers: Targeted Immunomodulators

Shamim Nagy, Chair: The next class is Biologic Response Modifiers, Immunomodulators.

Public comment?

David Crosby: I am David Crosby, a medical science liaison with Bristol Myers Squibb here to speak on Orencia. An overview of indications, clinical trials for safety and efficacy, and guidelines that have been updated to include non-traditional DMARDS were presented. There is no black box warning. Please consider adding Orencia as a first line option on the preferred drug list.

Nikki Beck: Did I hear you say there is not increased risk of infection with Orencia?

David Crosby: In the Ample study, the rates were comparable.

Weldon Havins: You stated you would also like this considered second-line, would that be different than non-preferred?

David Crosby: I would ask to remove the step-edit for Orencia, right now it needs to go through Enbrel or Humira.

Nikki Beck: Can you explain the step therapy Carl? Do they have to fail two of the others?

Carl Jeffery: Right, they would need to try the two preferred agents or have some unique indication for a non-preferred.

Weldon Havins: Are any of the preferred non-TNF agents?

Carl Jeffery: I'm not familiar enough with the class to know for sure. We are recommending some changes, right now Enbrel and Humira are preferred.

Nikki Beck: And Orencia is the only T-cell activator?

David Crosby: Correct, it has a unique mechanism of action.

Weldon Havins: Carl, you're recommending moving everything but Enbrel and Humira?

Carl Jeffery: Right, everything in yellow is what we are recommending as changes.

Laura Hill: My name is Laura Hill I am with Medical Affairs at AbbVie. Humira is one of the preferred agents recommended. I wanted to make you aware of a new approved indication, non-infectious intermediate pan uveitis in adult patients. This brings the number of indications up to 10.

Weldon Havins: Is this an approved use of uveitis or only for rheumatic disease?

Carl Jeffery: This will be across the board, it would be for all indications.

Mark Decerbo: Do you know what the PA is for in this drug class?

Carl Jeffery: Most of them follow the FDA approved indications, I'm not aware of any step therapy requirements from the DUR Board.

Michael Faith: I am Michael Faith with Amgen Scientific Affairs. I wanted to update the Committee of a new indication for Enbrel. It is approved for patients four years of age and older for chronic moderate to severe psoriasis who are candidates for system and phototherapy. Previously that lower limit was 18 years of age. Enbrel is the only agent approved for the pediatric indication.

Eva Ehrlich: My name is Eva Ehrlich, I am a Board Certified Rheumatologist here in Las Vegas. I was with the University of Nevada, School of Medicine, but recently resigned and now have a private practice. My UCB colleagues asked me to come and share my experience with Cimzia but I am happy to answer any questions. Cimzia is unique because it is an anti-TNF but it is PEGylated so it has some other unique features. Because of the loading dose, it works quickly. The dose is more flexible, every two weeks or every month. And data shows it may be safer in women during pregnancy. I know my GI colleagues also use Cimzia for inflammatory bowel disease and they would like to have it available for the Medicaid recipients.

Weldon Havins: The Cimzia is being proposed as preferred.

Eva Ehrlich: I just want to make sure all questions are answered. I also wanted to comment that we rheumatologists would like access to different medications, even though they may be in the same class. Some patients lose their response or may not qualify for some medications. Having the flexibility is important.

Nikki Beck: Have you used Orencia in your practice?

Eva Ehrlich: Yes, Orencia is good because it has a different mechanism of action. A study compared it to Remicade, Orencia was shown to be safer. The response varies among different patients, but overall Orencia is considered to be safer than some of the others, especially in older patients.

Nikki Beck: In what ways is it safer?

Eva Ehrlich: For example, a patient that has been exposed to TB, Orencia is my preferred drug. Anti-TNF inhibition is less safe in this population. Overall, frequent or severe infections, I reach for Orencia in these patients or patients with diabetes.

Carl Jeffery: This class was requested class to be brought back at the last meeting. It is a complicated class because the pathophysiology with the immunomodulators is very complex. There are all sorts of factors with the inflammatory process. The indications vary widely from uveitis, rheumatoid arthritis and GI diseases. These are important medications for a lot of patients. This slide shows the common indications. I had to remove some of the more rare indications so I could get it to fit on the slide. The green highlighted agents are what we are proposing as preferred. We tried to pick the drugs that would get the most coverage for our patients. We think the selection here provides options for indications and dosage forms for providers. The new ones I want to highlight. Inflectra is biosimilar to Remicade and Taltz is new on the market available in March. On this slide the different types are shown. The TNF and others are shown. Generally this is a hard class to combine into one, there are all sorts of indications and classes. Optum recommends the Committee consider these clinically and therapeutically equivalent.

Mark Decerbo: This is another tough one, but I support the recommendations. I think it is better that we rename the class to the Targeted Immunomodulators. I sometimes wonder if we should break these down by TNF vs. non-TNF. Is this the first biosimilar that we are mentioning?

Weldon Havins: Yes, I think so.

Mark Decerbo: I think we are still waiting for the FDA to provide some more information on these as far as being interchangeable.

Weldon Havins: Is that your motion?

Mark Decerbo: I move that these be considered clinically and therapeutically equivalent.

Weldon Havins: Second.

Shamim Nagy, Chair: When will we be reviewing this class again?

Carl Jeffery: There are some biosimilars that will be coming out within the year. I'm sure we will see this again. We will see what the FDA says and see how the pharmacies treat these.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: Our intention is to change the class up. About a year ago we made the decision to stick with anything with an indication for rheumatology to narrow down the class. Here we are changing it back to Targeted Immunomodulators and adding some of the drugs back. We have a wide variety of indications and mechanisms of action. We feel this proposal gives the providers a lot of options. The non-preferred agents can be obtained for unique indications.

Nikki Beck: If Orencia has the ability to be used with patients with immune dysfunction like diabetes or TB, I would like to see that medication be available. I haven't personally seen the data showing that Orencia has a lower risk of infection, but we have heard from a provider that uses it on her patients. It is a different class than everything that is proposed as preferred. We have several TNF agents, an interleukin inhibitor and Xeljanz is a different agent, a kinase inhibitor. Orencia is one more niche.

Carl Jeffery: You can certainly make Orencia preferred. We did our best to choose what we thought would work well.

Nikki Beck: I would make a motion to move Orencia as preferred.

Joseph Adashek: Second.

Mark Decerbo: As a committee, we can stratify this class pretty far down, but how many different options should we provide? I'm not aware of any real reduction in infection for Orencia.

Nikki Beck: I would be comfortable doing some research and getting back for the next meeting. But the infection rate is something that is important in my practice. Infection is the ultimate killer, not the rheumatoid arthritis.

Eva Ehrlich: If I may say something. I don't know a lot of data comparing the safety of Orencia compared to a TNF. Orencia is approved in Europe as first-line therapy even before methotrexate. There is some data in the early RA patients showing that actually some of these patients can go in remission and have much better results than starting them on methotrexate first. I think that tells you where this stands with our European colleagues. I think it would be very valuable to have that drug available as preferred. I don't expect it to be available before methotrexate, but maybe first line biologic?

Shamim Nagy, Chair: What patient is best for this?

Eva Ehrlich: The patients that are CCP positive or have a poor prognosis, when they are started on Orencia early, they have better results compared to the patients started on methotrexate. That would be the patient population, plus the ones that have a higher risk of infection. For these patients, I would want to use Orencia first before an anti-TNF.

Joseph Adashek: In our practice, we prefer Orencia first over an anti-TNF.

Shamim Nagy, Chair: Could we repeat the motion?

Nikki Beck: I move that we move Orencia to preferred.

Joseph Adashek: I second the motion.

Voting: Ayes - 5, Nay -1, the motion carries.

Weldon Havins: I move that including Orencia, the preferred products be accepted as recommended by Optum. We just voted to move Orencia.

Joseph Adashek: Second.

Voting: Ayes across the board the motion carries.

6. Proposed New Classes

a. Functional Gastro-intestinal Disorder Drugs

Shamim Nagy, Chair: The next class is New Drug Classes, Functional Gastro-intestinal Disorder Drugs.

Public comment? No.

Carl Jeffery: This is a new class of medication to introduce to our Preferred Drug List. We call it the Functional Gastro-intestinal Disorder Drugs because it encompasses different classes. There are four in the list now, but there is another agent coming out soon maybe March or July. This slide shows the indications, they are all constipation predominant like opioid induced constipation, chronic idiopathic constipation and irritable bowel syndrome – constipation predominant. The agents are Amitiza, Linzess, Movantik and Relistor. They have similar indications. A quick overview of each of the medication. Amitiza is a CIC2, the chloride channel in the intestinal lumen increases fluid to help the motility. Three studies for the OIC vs. placebo. The first two show some good significance, the third wasn't as good but they also included methadone. They don't know if this works as well for patients on methadone. For the IBS-C, a couple studies show improvement in abdominal pain and discomfort and stool consistency. For chronic idiopathic constipation, several studies showing this is better vs. placebo. Relistor is like naloxone with an additional chain to stop it from getting into the blood stream. Movantik is another naloxone type medication. This one is PEGylated. Two studies showing it is effective. Linzess is a different mechanism of action. A guanylate cyclase-C agonist, this increases chloride and bicarbonate in the GI lumen. A couple studies showing this is more effective than placebo. As presented, Optum recommends the Committee consider these clinically and therapeutically equivalent.

Weldon Havins: I move they be considered clinically and therapeutically equivalent.

Joseph Adashek: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: For us to start things off, we are proposing Amitiza and Linzess as preferred. We think we capture the majority of the available indications.

Joseph Adashek: I move we accept the recommendations.

Weldon Havins: Second.

Voting: Ayes across the board, the motion carries.

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

Shamim Nagy, Chair: Report on new drugs to the market.

Carl Jeffery: We have a couple new drug approvals. The immunomodulators will be coming back soon because of the Xeljanz and a new drug for opioid-induced constipation. A couple new generics that are coming out, Zetia, Proventil HFA and Proair HFA. Remicade and Advair Diskus are both coming out as generic. We will bring these back, both highly used medications. Strattera is coming soon too.

Nikki Beck: What about Lantus? I have heard it called a generic or it could be a biosimilar.

Carl Jeffery: You're right, I didn't include that one. We have insulin products for the next meeting because there are a couple new products coming out. There are also some new combinations with incretin mimetics with insulins. It could be a whole new class. That is it for my discussion.

8. Closing Discussion

Shamim Nagy, Chair: Closing discussion.

Mark Decerbo: Going back to the naming of the classes, maybe something that might be good for next time. Could Optum look at the nomenclature and the combination products? We have several classes where we state combinations are included and other classes where we have combinations in the class, but not listed in the class title.

Carl Jeffery: That's a good point. I use Clinical Pharmacology for the category, but everything doesn't always fit into a neat category, so we have to shoehorn them in. But I think at least adding the combination reference to the names is a good idea.

Shamim Nagy, Chair: The date of the next meeting?

Carl Jeffery: We are scheduled for March 22nd. It will be a split meeting with North Nevada people in Carson City and the Southern Nevada members at the Nevada Health Exchange in Henderson.

Shamim Nagy, Chair: Meeting adjourned at 2:15 PM.

N. Psychotropic Medications for Children and Adolescents

Therapeutic Class: Psychotropic Agents
Last Reviewed by the DUR Board: September 3, 2015

Psychotropic medications for children and adolescents are subject to prior authorization based on the Application of Standards in Section 1927 of the Social Security Act (SSA) and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for billing information.

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

1. Coverage and Limitations

The Division of Health Care Financing and Policy (DHCFP) requires prior authorization approval for children and adolescents for the psychotropic therapeutic classes below and medication combinations considered to be poly-pharmacy. The DHCFP has adopted the following practice standards to strengthen treatment outcomes for our children and adolescents.

a. The psychotropic therapeutic classes subject to this policy are:

2. Antipsychotics

2. Antidepressants

3. Mood Stabilizers (including lithium and anticonvulsants used for behavioral health indications.)

4. Sedative hypnotics

5. Antianxiety agents

b. For all children under 18 years of age, the following must be documented in the medical record for authorization.

1. For psychotropic medications in this age group, when possible, be prescribed by or in consultation with a child psychiatrist.

2. Psychotropic medication must be part of a comprehensive treatment plan that addresses the education, behavioral management, living home environment and psychotherapy.

3. Physician and/or prescriber monitoring is required while the recipient is utilizing any psychotropic medication.

a. For recipients who are in initial treatment (have not received any doses previously) or are continuing therapy but are considered unstable (has had a dose change in the last three months), medical documentation must support a monthly or more frequent visit with the physician and/or precsriber. If the recipient was discharged from an institution on the medication, the follow-up visit(s) can be with their treating physician and/or prescriber.

b. For recipients who are considered stable in their medication therapy, medical documentation must support visits with the treating physician at least every three months.

c. Poly-pharmacy: Each psychotropic medication prescribed must be independently treating a specific symptom and/or diagnosis.

1. Poly-pharmacy (intra-class) is defined as more than one drug within the same therapeutic class within a 60-day time period.

a. Prior authorization approval is required for two or more drugs in the same therapeutic class within a 60-day period.

2. Poly-pharmacy (inter-class) is defined as more than one drug across different therapeutic classes within a 60-day time period.

a. Prior authorization approval is required for four or more drugs across all psychotropic therapeutic classes listed in this policy within a 60-day time period.

3. Approval for poly-pharmacy may be given in situations where the requested medication(s) will be used for cross tapering and situations where the recipient will be discontinuing the previously prescribed agent. A 30-day cross-taper will be allowed.

4. Approval for poly-pharmacy may be given for a medication to augment the effect of another psychotropic medication as long as the purpose of the poly-pharmacy is clearly documented in the recipient's medical record and each agent is supported by individual authorizations.

5. The recipient must have a trial of each individual medication alone. The reasons for an inadequate response must be documented in the medical record.

6. For intra-class and inter-class poly-pharmacy, all psychotropic medications must be utilized for a medically accepted indication as established by the Food and Drug Administration (FDA), and/or peer reviewed literature.

d. For children under six years of age, in addition to the Coverage and Limitation requirements, all psychotropic medications require a prior authorization approval and must be utilized for a medically accepted indication as established by the FDA and/or peer-reviewed literature.

e. Continuity of Care. In an effort to improve recipient safety and quality of care:

1. For recipients under 18 years of age, who have been discharged from an institutional facility, they will be allowed to remain on their discharge medication regimen for up to six months to allow the recipient time to establish outpatient mental health services. The initial prior authorization after discharge must document the name of the discharge institution and the date of discharge.

2. For all other recipients under the age of 18, a six month prior authorization will be granted to cover current medication(s) when it is documented that the recipient has been started and stabilized. This will allow the recipient time to establish services if necessary and to transition to medication(s) per Nevada Medicaid policy.

2. Exceptions to this criteria for Anticonvulsants and ADD/ADHD medications:

a. Treatment for seizure disorders with anticonvulsants are not subject to this policy. The ICD Codes for Epilepsy and/or Convulsions will bypass the prior authorization requirement at the pharmacy POS if the correct ICD Code is written on the prescription and transmitted on the claim. Or the prior authorization requirement will be overridden for anticonvulsant medications when the prescriber has a provider specialty code of 126, neurology or 135, pediatric neurology, in the POS system.

b. The current policy for treatment of ADD/ADHD is to be followed. Refer to this Chapter's Appendix A.

3. Prior Authorization Guidelines:

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

INTRODUCTION

- Antipsychotic medications have been used for over 50 years to treat schizophrenia and a variety of other psychiatric disorders (Miyamato et al, 2005).
- Antipsychotic medications exert their effect in part by blocking D_2 receptors. It is the blockade of these receptors in the mesolimbic pathway that is believed to contribute to desired antipsychotic effects, especially improvement of positive symptoms associated with schizophrenia (Farah, 2005).
- Antipsychotics are divided into 2 distinct classes based on their affinity for D_2 and other neuroreceptors: typical antipsychotics, also called first generation antipsychotics, and atypical antipsychotics, also called second generation antipsychotics (SGAs) (Miyamato et al, 2005).
- There are a number of atypical antipsychotic formulations available as both branded and generic products. Food and Drug Administration (FDA)-approved indications for the atypical antipsychotics include autism, bipolar disorder, Tourette's disorder, major depressive disorder (MDD), schizophrenia, and schizoaffective disorder. FDA-approved atypical agents include (Drugs@FDA, 2017):
  - Generic agents – aripiprazole, clozapine, iloperidone, olanzapine, paliperidone, quetiapine immediate- and extended-release, risperidone, ziprasidone, and olanzapine/fluoxetine
  - Branded agents –GEODON® (short-acting injection only), LATUDA®, REXULTI®, SAPHRIS®, VERSACLOZ® (oral suspension), and VRAYLAR™
  - Long-acting injections – ABILIFY MAINTENA®, ARISTADA™ , INVEGA SUSTENNA®, INVEGA TRINZA®, RISPERDAL CONSTA®, and ZYPREXA RELPREVV®
- Autism
  - Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by impairment in socialization, communication, and behavior (Weissman and Bridgemohan, 2016).
  - ASD are more common in males than females and estimates of prevalence vary based on populations studied.
  - Data from the Autism and Developmental Disabilities Monitoring Network in the United States report a prevalence of 14.6 per 1,000 children at age 8 in 2012 (Morbidity and Mortality Weekly Report [MMWR], 2016).
  - The pathogenesis of ASD is not completely understood but is believed to have a genetic component which alters brain development (Augustyn, 2016).
  - Overall treatment goals include maximization of functioning, improvement in quality of life and helping the patient achieve and maintain independence.
  - Specific treatment goals include improving social, communication and adaptation skills, improving academic functioning, and decreasing nonfunctional behaviors.
  - Treatments include educational and behavioral therapies, and pharmacologic interventions to treat targeted symptoms including aggression, impulsivity, hyperactivity, anxiety, sleep disturbances and depression (Weissman and Bridgemohan, 2016).
- Bipolar disorder
  - Bipolar disorder is characterized by discrete mood instability. The lifetime prevalence of bipolar disorder is reported to be approximately 1%, although the true prevalence is uncertain (Stovall, 2016[a]).
  - Genetics, in addition to environmental factors, appears to play an important role in the pathogenesis of bipolar disorder.
  - Drugs commonly used to treat acute mania or hypomanias include lithium, anticonvulsants, and antipsychotics. Benzodiazepines may be helpful when adjunctive treatment is needed for insomnia, agitation, or anxiety (Stovall, 2016[b]).
- Major depressive disorder (MDD)
  - MDD manifests with symptoms of depressed mood, loss of interest or pleasure in almost all activities, altered sleep, change in appetite or weight, poor energy and/or concentration, thoughts of worthlessness, and potentially thoughts of death or suicide (Gelenberg et al, 2010).
  - For the diagnosis of MDD, patients must have ≥ 5 symptoms that have been present during the same 2-week period or represent a change from previous functioning; at least one of the symptoms is either (1) depressed

mood or (2) loss of interest or pleasure. The goal of treatment is full remission (Diagnostic and Statistical Manual of Mental Disorders [DSM] V, 2013).
    - Based on data from 2006 to 2008, approximately 9% of US adults meet the criteria for current depression, including 3.4% who have MDD. Women are more likely to experience major depression in their lifetime as compared to men (11.7 vs 5.6%), and major depression is most prevalent in patients aged 45 to 64 years old (CDC, 2013; MMWR, 2010).
- Schizophrenia
    - Schizophrenia is a disorder involving chronic or recurrent psychosis and is associated with significant functional impairment. Schizophrenia is believed to be caused by an increase in the cerebral activity of dopamine D_2 in the mesolimbic and/or mesocortical regions of the brain (Lehman et al, 2004).
    - The disease includes positive symptoms such as hallucinations, delusions, and disorganized speech, as well as negative symptoms including flat affect, cognitive impairment, and impairment in executive functioning (DSM V, 2013; Lehman et al, 2004).
    - For the diagnosis of schizophrenia, patients must have ≥ 2 symptoms that have been present for a significant portion of time during a one-month period and continuous signs of the disturbance persist for at least 6 months. Symptoms must include one of the following: delusions, hallucinations, and disorganized speech, but may also include grossly disorganized or catatonic behavior, and negative symptoms (DSM V, 2013).
    - The prevalence of schizophrenia is approximately 0.3 to 0.66%, and the lifetime incidence is 10.2 to 22 per 100,000 person-years (McGrath et al, 2008; van Os et al, 2009).
- Tourette's disorder
    - Tourette's disorder ranges greatly in terms of symptom severity and is often associated with comorbidities (Murphy et al, 2013).
    - Tourette's disorder is characterized by persistent and repetitive motor and/or vocal tics, and onset is typically observed in childhood. For diagnosis, tics need to be present for at least one year. The pathophysiology of chronic tic disorders is not known but believed to be due to motor issues at both cortical and subcortical levels that are not properly modulated at the cortico-striatal-thalamo-cortical circuits.
    - Other comorbidities often observed with Tourette's disorder include attention-deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD).
    - The prevalence of chronic tic disorders has been estimated as 0.5 to 3%, with approximately 7% of school age children having had tics in the previous year.
- The agents included in this review are listed in Table 1 by brand name. Since there are multiple branded agents that contain the same generic component the remaining tables in the review are organized by generic name. This review is restricted to the atypical antipsychotic agents and their respective FDA-approved indications.

Table 1. Medications Included Within Class Review

Drug	Formulation	Manufacturer	FDA Approval Date	Generic
Single Entity Agents				
ABILIFY® (aripiprazole)	tab; sol	Otsuka (brand); various (generic)	11/15/2002 (tab) 12/12/2004 (sol)	✔
ABILIFY® DISCMELT™ (aripiprazole)	ODT	various (generic)	06/07/2006	✔
CLOZARIL® (clozapine)	tab	Heritage (brand); various (generic)	09/26/1989	✔
FANAPT® (iloperidone)	tab; titrate pack	Vanda and Inventia (brand)	05/06/2009	-*
FAZACLO® (clozapine)	ODT	Jazz (brand); various (generic)	02/09/2004	✔
GEODON® (ziprasidone hydrochloride)	cap	Pfizer (brand); various (generic)	02/05/2001	✔
GEODON® (ziprasidone mesylate)	inj (short-acting)	Pfizer	06/21/2002	-

Drug	Formulation	Manufacturer	FDA Approval Date	Generic
INVEGA® (paliperidone)	tab	Janssen (brand); various (generic)	12/19/2006	✔
LATUDA® (lurasidone)	tab	Sunovion	10/28/2010	-
REXULTI® (brexpiprazole)	tab	Otsuka	07/10/2015	-
RISPERDAL® (risperidone)	tab; sol	Janssen (brand); various (generic)	12/29/1993	✔
RISPERDAL® M-TAB® (risperidone)	ODT	Janssen (brand); various (generic)	04/02/2003	✔
SAPHRIS® (asenapine)	SL tab	Forest Pharma	08/13/2009	-
SEROQUEL® (quetiapine)	tab	AstraZeneca (brand); various (generic)	09/26/1997	✔
SEROQUEL XR® (quetiapine extended-release)	tab	AstraZeneca	05/17/2007	✔
VERSACLOZ® (clozapine)	susp	Jazz	02/06/2013	-
VRAYLAR™ (cariprazine)	cap; titrate pack	Allergan	09/17/2015	-
ZYPREXA® (olanzapine)	tab; inj (short-acting)	Eli Lilly (brand); various (generic)	09/30/1996 (tab) 03/29/2004 (inj)	✔
ZYPREXA ZYDIS® (olanzapine)	ODT	Eli Lilly (brand); various (generic)	04/06/2000	✔
Long-Acting Injectable Products				
ABILIFY MAINTENA® (aripiprazole extended-release)	inj	Otsuka	02/28/2013	-
ARISTADA™ (aripiprazole lauroxil extended-release)	inj	Alkermes	10/5/2015	-
INVEGA SUSTENNA® (paliperidone palmitate)	inj	Janssen	07/31/2009	-
INVEGA TRINZA® (paliperidone palmitate)	inj	Janssen	05/18/2015	-
RISPERDAL CONSTA® (risperidone microspheres)	inj	Janssen	10/29/2003	-
ZYPREXA RELPREVV® (olanzapine pamoate)	inj	Eli Lilly	12/11/2009	-
Combination Products				
SYMBYAX® Olanzapine/ fluoxetine	cap	Eli Lilly (brand); various (generic)	12/24/2003	✔

Abbrv: cap = capsule; inj = injection; ODT = oral disintegrating tablet; SL = sublingual; sol = solution; susp = suspension; tab = tablet; titrate pak = titration pack

*Vanda filed a patent infringement lawsuit against Inventia for Fanapt generic products. In December 2016, Vanda and Inventia entered into a confidential stipulation regarding any potential launch date of the generic products. Currently, Inventia is only manufacturing the Fanapt titration pack (ME staff press release, 2016).

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

INDICATIONS

- The following summarizes all FDA-approved indications:
  - Autism: Aripiprazole and risperidone are the only agents indicated for the treatment of irritability associated with autistic disorder in pediatric patients (aged 6 to 17 years, and 5 to 17 years, respectively).
  - Bipolar disorder: All oral agents in class are indicated for use in bipolar disorder, except clozapine, iloperidone, paliperidone, and REXULTI. RISPERDAL CONSTA is the only long-acting injectable indicated for the treatment of bipolar disorder.
    - Aripiprazole, olanzapine/fluoxetine, risperidone, quetiapine, and SAPHRIS are approved for use in pediatric patients ≥ 10 years of age with bipolar disorder. Olanzapine is approved for use in patients ≥ 13 years of age with bipolar disorder.
  - Depression: Aripiprazole, REXULTI, and SEROQUEL XR are indicated as adjunctive treatment for major depressive disorder in patients already taking an antidepressant. Olanzapine when prescribed in combination with fluoxetine is indicated for treatment resistant depression.
  - Schizophrenia: All agents in class are indicated for use in schizophrenia with the exception of the combination agent, SYMBYAX (olanzapine/fluoxetine). Clozapine and paliperidone products, excluding INVEGA TRINZA, are indicated for the treatment of schizoaffective disorder. Clozapine is the only agent in class FDA-approved for treatment-resistant schizophrenia.
    - Aripiprazole, olanzapine, quetiapine and risperidone are approved for use in patients ≥ 13 years of age and paliperidone oral products are approved for patients ≥ 12 years of age with schizophrenia.
  - Tourette's Disorder: Aripiprazole is the only agent indicated for the treatment of Tourette's disorder in pediatric patients, aged 6 to 18 years.
- Table 2 highlights FDA-approved indications at a high level. Please refer to Tables 4 and 5 for a detailed explanation of indications by agent, age, formulation, and use as an adjunct or monotherapy.

Table 2. Food and Drug Administration Approved Indications

Agent	Autism	Bipolar Disorder: manic/mixed	Bipolar Disorder: depressive	Depression – treatment-resistant	MDD: adjunct	Schizoaffective disorder	Schizophrenia	Schizophrenia: treatment-resistant	Tourette's Disorder
Oral Products									
aripiprazole	✔ *	✔ *	-	-	✔	-	✔ *	-	✔ *
asenapine	-	✔ *	-	-	-	-	✔	-	-
brexpiprazole	-	-	-	-	✔	-	✔	-	-
cariprazine	-	✔	-	-	-	-	✔	-	-
clozapine	-	-	-	-	-	✔	✔	✔	-
iloperidone	-	-	-	-	-	-	✔	-	-
lurasidone	-	-	✔	-	-	-	✔	-	-
olanzapine	-	✔ *	-	-	✔ †	-	✔ *	-	-
olanzapine/ fluoxetine	-	-	✔ *	✔	-	-	-	-	-
paliperidone	-	-	-	-	-	✔	✔ *	-	-
quetiapine	-	✔ *	✔	-	✔ †	-	✔ *	-	-
risperidone	✔ *	✔ *	-	-	-	-	✔ *	-	-
ziprasidone	-	✔	-	-	-	-	✔	-	-
Long-Acting Injectable Products									
aripiprazole ER	-	-	-	-	-	-	✔	-	-
aripiprazole lauroxil ER	-	-	-	-	-	-	✔	-	-
paliperidone palmitate (SUSTENNA)	-	-	-	-	-	✔	✔	-	-
paliperidone palmitate (TRINZA)	-	-	-	-	-	-	✔	-	-
risperidone microspheres	-	✔	-	-	-	-	✔	-	-
olanzapine pamoate	-	-	-	-	-	-	✔ ‡	-	-

*FDA-approved indications for pediatric patients; †Extended-release formulation; ‡ Patients must be observed by a health care professional for 3 hours post-dose administration

(Prescribing information: ABILIFY, 2016; ABILIFY MAINTENA, 2016; ARISTADA, 2016; CLOZARIL, 2016; FANAPT, 2016; FAZACLO, 2015; GEODON, 2015; INVEGA, 2016; INVEGA SUSTENNA, 2016; INVEGA TRINZA, 2016; LATUDA, 2013; REXULTI, 2016; RISPERDAL, 2016; RISPERDAL CONSTA, 2016; SAPHRIS, 2017; SEROQUEL, 2013; SEROQUEL XR, 2016; SYMBYAX, 2016; VERSACLOZ, 2015; VRAYLAR, 2016; ZYPREXA, 2016; ZYPREXA RELPREVV, 2016)

CLINICAL EFFICACY SUMMARY

- The goal of this review is to evaluate key published literature regarding atypical antipsychotics for FDA-approved indications in children, adolescents, and adults. Numerous studies evaluating the efficacy of antipsychotic medications have been conducted. In clinical practice, the role of the atypical antipsychotics has been clearly established for the treatment of bipolar disorder and schizophrenia. In general, clinical consensus guidelines do not differentiate one agent from another, supporting the concept that all patients will require an individualized approach to treatment selection, taking into account the agent's safety profile and patient's individual risk factors.
- Key clinical studies evaluating the roles of atypical antipsychotic agents in the treatment of FDA-approved indications are included in the review. However, in recognition of the vast number of published studies of older atypical antipsychotics in adults, only a selection of randomized controlled studies (RCTs), systematic reviews (SR), and meta-analyses (MAs) are included in this review.

CHILDREN/ADOLESCENTS

- The Agency for Healthcare Research and Quality (AHRQ) conducted a SR of literature on the safety and efficacy of antipsychotics in children and adolescents. The review included studies of atypical antipsychotics (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, paliperidone, and ziprasidone), conducted in patients 24 years of age or younger, used for the following FDA-approved and off-label indications: pervasive developmental disorder, attention deficit hyperactivity disorder/disruptive behavior disorders, bipolar disorder, schizophrenia, psychosis, Tourette's syndrome, OCD, post-traumatic stress disorder, anorexia nervosa, and miscellaneous behavioral issues. Overall, indications associated with moderate strength evidence for the use of atypical antipsychotics included disruptive behavior disorder, bipolar disorder, schizophrenia, and Tourette's syndrome. No significant differences between the different atypical antipsychotics were noted in the identified head-to-head comparisons. The risks of weight gain (weight gain, 4.6 kg) and dyslipidemia were highest with olanzapine. Weight gain with ziprasidone was not significantly different from placebo. The other atypical antipsychotics were associated with intermediate weight gain. Risperidone was associated with the greatest incidence of prolactin-related adverse events (consistent with adult data). Extrapyramidal adverse events were significantly more common with risperidone and aripiprazole compared to placebo (Seida et al, 2012[a]; Seida et al, 2012[b]).

Autism Spectrum Disorder

- For the treatment of irritability associated with autistic disorder in patients, risperidone has been approved in pediatric patients aged 5 to 17 years and aripiprazole has been approved in patients aged 6 to 17 years. Very few RCTs have been conducted evaluating safety and efficacy and only one low-quality study has been conducted evaluating comparative effectiveness. The primary outcome measure in trials was the change from baseline to endpoint in the Aberrant Behavior Checklist-Irritability subscale of the ABC (ABC-I), which measured symptoms of irritability in autistic disorder. One risperidone trial measured the Clinical Global Impression-Change (CGI-C) scores as a co-primary outcome measure.
- The safety and efficacy of aripiprazole was evaluated in 2 placebo-controlled (PC), 8-week trials. Over 75% of these subjects were under 13 years of age. In one of these trials, children and adolescents with autistic disorder (N = 98) received daily doses of placebo or aripiprazole 2 to 15 mg/day. The mean daily dose of aripiprazole at the end of 8-week period was 8.6 mg/day. Aripiprazole significantly improved ABC-I subscale scores, including emotional and behavioral symptoms of irritability, aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods (Owen et al, 2009). In the second of these trials in children and adolescents with autistic disorder (N = 218), 3 fixed doses of aripiprazole (5, 10, or 15 mg/day) were compared to placebo. ABC-I subscale scores were significantly decreased by 12.4 points with 5 mg/day, 13.2 with 10 mg/day, and 14.4 with 15 mg/day compared with 8.4 for placebo. Clinical Global Impressions (CGI)-Improvement scores were significantly improved: 2.6 points for 5 mg/day, 2.5 for 10 mg/day, and 2.5 for 15 mg/day compared with 3.3 for placebo. At the higher doses, ABC stereotypy, hyperactivity, CGI-S (Severity of Illness) scores, and other secondary measures were also improved (Marcus et al, 2009).
- In one MA of 3 trials evaluating pediatric patients (N = 316) treated with aripiprazole, results demonstrated a greater increase in weight vs placebo (weight gain,1.13 kg; 95% confidence interval [CI], 0.71 to 1.54; P < 0.00001), and had a higher relative risk (RR) for sedation (RR, 4.28; 95% CI, 1.58 to 11.6; P = 0.004) and tremor (RR, 10.26; 95% CI, 1.37 to 76.63; P = 0.02) (Hirsch et al, 2016).
- The safety and efficacy of risperidone was evaluated in two 8-week and one 6-week, PC pivotal trials (McCracken et al, 2002; Shea et al, 2004). Approximately 90% of these subjects were under 12 years of age. In the two 8-week trials, the efficacy and safety of risperidone were measured in patients aged 5 to 16 years (N = 101) in weight-based, twice-

daily doses of 0.5 to 3.5 mg/day (the RUPP trial) and in patients aged 5 to 12 years (N = 79) who received 0.02 to 0.06 mg/kg/day given once or twice daily (McCracken et al, 2002; Shea et al, 2004). The 6-week trial measured efficacy and safety in patients using lower than FDA-approved recommended dosing, and outcomes did not demonstrate efficacy (RISPERDAL prescribing information, 2014). In the RUPP trial, risperidone-treated patients exhibited a 56.9% reduction in the mean ABC-I score from baseline, compared to a 14.1% reduction observed in the placebo group (P < 0.001) (McCracken et al, 2002). Risperidone was generally well tolerated, and most adverse events were mild and transient. Due to the uncertainty of a clear benefit with regard to the core symptoms of autism, the authors recommend that risperidone be reserved for the treatment of moderate-to-severe behavioral problems accompanying autism. In the second 8-week trial, risperidone patients demonstrated a 64% improvement in ABC-I subscale vs 31% improvement with placebo, which was a significant positive finding for hyperactivity (Shea et al, 2004). Somnolence was the most frequently reported adverse event (72.5 vs 7.7%), and risperidone-treated subjects experienced statistically greater increases in weight (2.7 vs 1 kg), pulse rate, and systolic blood pressure.

- In an extension of the RUPP trial, 63 responders received open-label (OL) risperidone for another 16 weeks. Risperidone dose adjustments were allowed up to a maximum total daily dose of 3.5 mg/day. At the end of the 4-month extension, an intention-to-treat analysis revealed a minor, but clinically insignificant increase in ABC-I score. There was also a significant time effect on the ABC-I scale at the end of the 4-month extension phase (P = 0.02) (McDougle et al, 2005).
- Additional trials have been conducted measuring effects of risperidone; however, most trials included less than 50 patients per trial. The outcomes of these trials are more sensitive to variability within the trials due to the small effect size (Aman et al, 2008; Capone et al, 2008; Gagliano et al, 2004; Gencer et al, 2008; Luby et al, 2006; Miral et al, 2008; Nagaraj et al, 2006).
- One head-to-head, prospective, 8-week trial was conducted comparing the effects of aripiprazole ≤ 10 mg/day (mean dose, 5.5 mg/day) to risperidone ≤ 3 mg/day (mean dose, 1.12 mg/day) in patients (N = 59) aged 4 to 18 years of age. Approximately 65% of patients were diagnosed with autism, and additional diagnoses included Asperger syndrome, pervasive developmental disorder, and disruptive behavior disorder. Study authors stated double-blind (DB) techniques were not enforced for all patients. At the end of the trial, the mean baseline ABC-I subscale was not statistically different (P = 0.06), but numerically favored risperidone. No differences were detected between groups for each adverse event or in the rate of discontinuations due to adverse events. Study authors concluded the safety and efficacy of both agents were comparable (Ghanizadeh et al, 2014).

Bipolar Disorder

Manic/Mixed Episodes

- Aripiprazole, olanzapine, olanzapine/fluoxetine, risperidone, quetiapine and SAPHRIS (asenapine) have FDA-approved indications for the treatment of pediatric patients diagnosed with bipolar disorder. All agents are approved for ages ≥ 10 years, except olanzapine which is approved in patients aged ≥ 13 years. In pediatric patients with bipolar disorder, evidence is extremely limited.
- Based on a 2012 AHRQ SR of 81 trials evaluating typical and atypical antipsychotics, a total of 11 trials measured efficacy and safety in adolescents with bipolar disorder. Compared to placebo, aripiprazole, olanzapine, ziprasidone, quetiapine and risperidone were associated with greater improvements in response rates in analysis of 7 trials with 1,006 patients (RR, 1.76; 95% CI, 1.46 to 2.13); number needed to treat [NNT], 3 to 7). Increased remission rates were observed with atypical antipsychotic use in 6 trials with 976 patients (RR, 2.4; 95% CI, 1.5 to 3.83; NNT, 2 to 12); however, significant heterogeneity was noted across trials. Comparing olanzapine to risperidone, olanzapine was associated with significantly smaller improvement in Young Mania Rating Scale (YMRS) score and a non-significant lower response rate (RR, 0.72; 95% CI, 0.5 to 1.03) in analysis of 2 trials with 92 patients. Risperidone significantly improved YMRS score vs ziprasidone in 1 trial with 84 patients. Overall, atypical antipsychotics may improve remission rates compared to placebo in adolescents with bipolar disorder (Seida et al, 2012[a]; Seida et al, 2012[b]).
- In a 21-day, DB, PC trial, 403 patients aged 10 to 17 years with bipolar I disorder were randomized to placebo, asenapine 2.5 mg, 5 mg, or 10 mg twice daily. The primary endpoint, change from baseline in YMRS score, demonstrated a statistically significant and dose-dependent mean difference in YMRS scores at 21 days for all asenapine groups vs placebo (2.5mg, -3.2; P = 0.0008 vs 5mg, -5.3; P < 0.001 vs 10mg, -6.2; P < 0.001). Weight gain was higher across the asenapine groups, with 8 to 12% of patients experiencing ≥ 7% weight gain vs 1.1% of patients in the placebo group (P < 0.05). Fasting glucose, insulin and cholesterol changes were also numerically higher in the asenapine groups vs placebo (P = not reported). Overall, asenapine was well tolerated and showed efficacy in the treatment of this pediatric population, although the duration of the study period was brief (Findling et al, 2015).

Depressive Episodes

- Clinical trials measuring the safety and efficacy of atypical antipsychotics in depressive episodes in pediatric patients diagnosed with bipolar disorder are limited. Two trials examined efficacy of quetiapine in this population. In a small trial, a total of 32 patients aged 12 to 18 years were randomized to quetiapine 300 to 600 mg/day or placebo and followed over a period of 8 weeks. The primary endpoint was change in the Children's Depression Rating Scale, Revised Version (CDRS-R) score, in which both quetiapine and placebo groups exhibited statistically significant reductions in the CDRS-R scores from baseline (P < 0.001), with no difference between groups (19 vs 20; P = 0.89). All other efficacy measures were not statistically different from placebo (DelBello et al, 2009). A similar 8-week trial enrolled 193 patients aged 10 to 17 years with acute bipolar depression. Patients were randomized to placebo or quetiapine XR 150 to 300 mg/day. The primary endpoint was change in CDRS-R score from baseline, with mean CDRS-R scores decreasing from baseline in both placebo (-29.6) and treatment (-27.3) groups. The difference between groups was not statistically significant (95% CI, -6.22 to 1.65; P = 0.25). Triglyceride levels were elevated in 9.3% of the quetiapine XR group vs 1.4% of the placebo group. Mean weight gain was 1.3 kg in the quetiapine XR group vs 0.6 kg in the placebo group (P = not reported) (Findling et al, 2014).
- In a DB, PC trial, 291 patients aged 10 to 17 with bipolar I disorder and depressive episodes were randomized 2:1 to olanzapine/fluoxetine or placebo for 8 weeks. Doses of olanzapine/fluoxetine were titrated to 12/50mg daily over 2 weeks. The olanzapine/fluoxetine group had a 5-point greater mean decrease in CDRS-R score from baseline vs placebo (-28.4 vs -23.4; P = 0.003). A total of 78.2% olanzapine/fluoxetine patients achieved response (defined as ≥ 50% reduction of CDRS-R score from baseline and a YMRS item 1 score ≤ 2) vs 59.2% of placebo group patients (P = 0.003). Weight gain was more common in the olanzapine/fluoxetine group vs placebo (4.4 vs 0.5 kg; P < 0.001), as well as increase in fasting total cholesterol, LDL cholesterol and triglycerides (all P < 0.001). Mean prolactin increase was higher in the olanzapine/fluoxetine group vs placebo (P < 0.001) and increase in heart rate was also statistically significantly higher in the treatment group (P = 0.013). This trial demonstrated efficacy in pediatric patients, but also demonstrated serious adverse effects (Detke et al, 2015).

Schizophrenia and/or Schizoaffective Disorder

- In pediatric patients diagnosed with schizophrenia, FDA-approved treatments include aripiprazole, olanzapine, quetiapine and risperidone for use in patients ≥ 13 years of age and paliperidone oral products in patients aged ≥ 12 years. Many trials include a small sample size of patients, or are not well-designed. However, efficacy has been demonstrated and results are similar to adult trials.
- Based on a 2012 AHRQ SR of 81 trials evaluating typical and atypical antipsychotics, a total of 23 randomized trials and 2 cohort studies measured efficacy and safety in adolescents with schizophrenia. Clozapine, olanzapine, and risperidone were associated with greater improvements compared to haloperidol in Brief Psychiatric Rating Scale (BPRS) score in analysis of 3 trials with 71 patients. Risperidone significantly improved Positive and Negative Syndrome Scale (PANSS) score in 1 trial with 8 patients. There was no significant difference in PANSS score comparing olanzapine vs haloperidol in 1 trial with 19 patients. Overall, clozapine, olanzapine, and risperidone may be more effective than haloperidol in adolescents with schizophrenia (Seida et al, 2012[a]; Seida et al, 2012[b]).
- A Cochrane review compared atypical antipsychotic medications to placebo, typical antipsychotics, or another atypical antipsychotic in adolescents with psychosis. Compared to typical antipsychotics, there were no significant differences in BPRS scores in an analysis of 5 trials with 236 patients. There was no evidence to suggest the superiority of atypical antipsychotics over typical antipsychotics; however, fewer adolescents dropped out due to adverse effects when administered an atypical antipsychotic (RR, 0.65; 95% CI, 0.36 to 1.15). Minimal evidence was available comparing one atypical antipsychotic to another. In terms of the number of patients who did not respond (defined as ≤ 30% reduction in BPRS score), results significantly favored clozapine, but increases in salivation, sweating, and higher glucose levels were observed vs olanzapine in 1 trial with 39 patients. Treatment with olanzapine, risperidone and clozapine was associated with weight gain. Aripiprazole was not associated with increased prolactin or dyslipidemia. Low-dose risperidone significantly decreased improvement in PANSS total score but also reduced the rate of extrapyramidal symptoms (EPS) vs standard-dose risperidone in 1 trial with 255 patients. Overall, efficacy between atypical and typical antipsychotics may be similar; however, safety benefits may favor treatment with atypical antipsychotics (Kumar et al, 2013).

Tourette's Disorder

- Aripiprazole is the only agent indicated for the treatment of Tourette's disorder. Efficacy and safety is based on low quality evidence in one fixed dose and one flexible dose trial. There is minimal evidence of safety and efficacy in this population.

- In one published, DB, PC, 10-week trial, aripiprazole significantly reduced total tic score (Yale Global Tic Severity Scale [YGTSS-TTS]; -15 vs -9.6) and phonic tic score (YGTSS-PTS; -7.4 vs -4.2), but not motor tic score, compared with placebo in patients aged 6 to 18 years with Tourette's disorder. The response rate (score of 1 or 2 on the Tourette's syndrome CGI-Improvement scale) was 66 vs 45%, respectively (Yoo et al, 2013).
- In another similarly designed, unpublished, 8-week trial in patients aged 7 to 17 years who received weight-based aripiprazole, significant improvements compared with placebo were seen on YGTSS-TTS with a change of -13.4 and -16.9 points with low- and high-dose aripiprazole compared to -7.1 in placebo (ABILIFY prescribing information, 2015).
- Aripiprazole was associated with increased body weight compared to placebo (range, 0.4 to 1.5 kg). Additional adverse reactions (incidence ≥ 5% and at least twice that for placebo) were sedation, somnolence, nausea, headache, nasopharyngitis, fatigue, and increased appetite (ABILIFY prescribing information, 2015). In one safety trial, aripiprazole had a safer cardiovascular profile vs pimozide, and was associated with a lower frequency of QT prolongation (Gulisano et al, 2011).

ADULTS

- The AHRQ conducted a SR of literature on the safety and efficacy of antipsychotics in adults comparing first- (typical antipsychotics) and second-generation (atypical antipsychotics). The review included studies of atypical antipsychotics (aripiprazole, asenapine, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone), conducted in patients 18 to 64 years of age, and used for the following FDA-approved indications: bipolar disorder, schizophrenia, and schizophrenia-related psychoses. The most frequent comparisons involved haloperidol, with 43 studies comparing haloperidol with risperidone and 37 studies comparing haloperidol with olanzapine. Nevertheless, the number of studies available for each comparison and outcome was often limited. Overall, indications associated with moderate to low strength evidence for the use of atypical antipsychotics included schizophrenia and schizophrenia-related psychoses. Bipolar disorder was associated with low strength of evidence. Few differences of clinical importance for outcomes of effectiveness were found. Patient-important outcomes were rarely assessed. Data were sparse for the 4 key adverse events deemed to be most clinically important. In terms of efficacy, few differences were found between typical and atypical antipsychotic agents, specifically when compared to haloperidol and clinical significance (defined as ≥ 20% difference between interventions) was rarely found. The evidence regarding safety, particularly those adverse events of most interest (ie, diabetes, tardive dyskinesia, metabolic syndrome, and mortality) were insufficient to draw firm conclusions about the risks among treatment groups. No differences were found in mortality for chlorpromazine vs clozapine and haloperidol vs aripiprazole, or in metabolic syndrome for haloperidol vs olanzapine. The most frequently reported adverse events with significant differences were EPS; in most cases, the atypical antipsychotic had fewer EPS than haloperidol (Abou-Setta et al, 2012).

<u>Bipolar Disorder</u>

Manic/Mixed Episodes

- All oral atypical antipsychotic agents in class are indicated for use in bipolar disorder, except clozapine, iloperidone, paliperidone, and REXULTI (brexpiprazole). The following summarizes direct comparative evidence and recent MAs and SRs.
- Based on a 2012 AHRQ SR of 125 trials evaluating typical and atypical antipsychotics, a total of 11 measured efficacy and safety in adults with bipolar disorder. Compared to haloperidol, there was no difference in YMRS score for manic episodes when compared to aripiprazole, olanzapine, and risperidone, and difference in Montgomery-Asberg Depression Rating Scale (MADRS) score compared to aripiprazole in a total of 9 trials. In one trial of 350 patients, haloperidol was favored in terms of YMRS score over ziprasidone. Haloperidol produced lower relapse rates than aripiprazole in one trial with 347 patients and provided better response rates than ziprasidone in one trial of 350 patients. The most frequently reported adverse effects with significant differences were in the category of EPS and most often involved haloperidol. Haloperidol appears to be an equally effective treatment compared with the atypical antipsychotics; however, it is associated with more incidences of EPS compared to other agents (Abou-Setta et al, 2012).
- One SR of 9 RCTs (N = 1,289) compared the effectiveness of atypical antipsychotics to placebo, either as monotherapy or as adjunctive treatment with a mood stabilizer. Atypical antipsychotics, either alone or in combination with mood stabilizers, had superior efficacy in treating manic symptoms of mixed episodes compared to placebo in short term trials lasting 3 to 6 weeks ($P < 0.00001$). Atypical antipsychotics also had superior efficacy in treating depressive symptoms of mixed episodes ($P < 0.001$) (Muralidharan et al, 2013).
- The efficacy and safety of asenapine in the treatment of manic or mixed bipolar I disorder were evaluated in 5 PC, and active-controlled (olanzapine) studies in adult patients, with or without psychotic features (McIntyre et al, 2009[a];

McIntyre et al, 2010[a]; McIntyre et al, 2009[b]; McIntyre et al, 2010[b]; Szegedi et al, 2011). In a pooled analysis of patients experiencing bipolar mania, asenapine and olanzapine were comparable in terms of reduction from baseline in YMRS scores at week 52 of therapy (McIntyre et al, 2010[b]). A meta-analysis of various anti-manic therapy options found that asenapine was associated with a statistically significant improvement in YMRS scores from baseline compared to placebo (mean difference [MD], -0.3; 95% CI, -0.53 to -0.07), though it was less effective compared to olanzapine (0.22; 95% CI, 0.08 to 0.37) (Cipriani et al, 2011). The most commonly reported adverse events reported with asenapine included sedation, dizziness, somnolence and weight gain. Of note, it was calculated that for every 9 patients treated with olanzapine over asenapine, one would experience clinically significant weight gain with olanzapine (19 vs 31%) (McIntyre et al, 2009[b]).

- The approval of the newest FDA-approved agent, cariprazine, was based on the efficacy and safety from 3 flexible dose, DB, PC 3-week trials (Calabrese et al, 2015; Durgam et al, 2015[a]; Sachs et al, 2014). A total of 1,047 adult patients with acute manic or mixed episodes were administered placebo or cariprazine 3 to 12 mg per day based on tolerability. Across trials, the mean daily dose was 8.8 mg per day and the mean final dose was 10.4 mg per day (FDA/CBER summary review, 2015). All doses were superior to placebo in reducing YMRS and CGI-S scores and a significant reduction in YMRS was observed as early as 4 days in some studies and persisted until week 3. The proportion of YMRS remitters was significantly higher in the cariprazine group than placebo (difference range, 15 to 19%) (Calabrese et al, 2015; Durgam et al, 2015[a]; Sachs et al, 2014). Of note, doses higher than 6 mg had similar efficacy, but adverse events were less tolerable. Due to the long half-life and pharmacokinetics of the active metabolite, DDCAR, the steady state was not achieved in trials (FDA/CBER summary review, 2015). It is anticipated that late-onset of adverse reactions would be observed if assessed for a longer period. In bipolar studies, 4% of patients with normal hemoglobin A1c developed elevated levels (≥ 6.5%). According to pooled analysis (n = 1,940 cariprazine-treated patients) within the FDA summary review, the most frequently observed adverse events include akathisia (14.2%), EPS (20.8%), constipation (7.6%), and nausea/vomiting (6 to 8%). The proportion of patients with weight increase ≥ 7% from baseline ranged from 1 to 3% across cariprazine doses.
- The efficacy and safety of risperidone 1 to 6 mg/day compared to olanzapine 5 to 20 mg/day were evaluated in a 3-week, DB, RCT in patients hospitalized for bipolar I disorder, manic or mixed episode, without psychotic features. Olanzapine and risperidone mean doses were 14.7 mg/day and 3.9 mg/day, respectively. There was no difference between groups in many outcome measures in remission or response in YMRS, 21-item Hamilton Rating Scale for Depression (HAM-D-21), or MADRS scales. More patients given olanzapine completed the trial compared with patients given risperidone (78.7 vs 67%, respectively). In total, 62.1% of patients in the olanzapine group and 59.5% of patients in the risperidone group were categorized as responders (defined as ≥ 50% reduction in the YMRS score at endpoint). Olanzapine-treated patients experienced significantly greater elevations in liver function enzymes and weight gain (2.5 vs 1.6 kg). Risperidone-treated patients experienced significantly more prolactin elevations and sexual dysfunction (Perlis et al, 2006[a]).

Depressive Episodes

- Placebo-controlled trials measuring effects for the treatment of bipolar depression have demonstrated efficacy with lurasidone, quetiapine (immediate- and extended-release [ER]), and olanzapine/fluoxetine as monotherapy and adjunctive treatment (Calabrese et al, 2005; Corya et al, 2006; McElvoy et al, 2010; Loebel et al, 2014[a]; Loebel et al, 2014[b]; Shelton et al, 2005; Suppes et al, 2010; Thase et al, 2007; Young et al, 2010).
- Treatment with olanzapine/fluoxetine was superior to monotherapy with olanzapine and lamotrigine in achieving greater improvements in MADRS and CGI-BP (bipolar version) (Tohen et al, 2003; Brown et al, 2009). Patients treated with olanzapine/fluoxetine had significantly greater rates of treatment response and remission compared to those receiving olanzapine monotherapy (Tohen et al, 2003). It is not clear if quetiapine outperforms lithium in terms of treatment of bipolar depression, as various studies have produced different results (Chiesa et al, 2012; Young et al, 2010).
- MAs have found that combination treatment with olanzapine/fluoxetine may be the optimal treatment for bipolar depression compared to other treatment options. However, the overall evidence quality was considered low, trials had limited durations, and a high placebo effect was observed. Olanzapine, quetiapine, lurasidone, valproate, selective-serotonin reuptake inhibitors (SSRIs), lithium, and tricyclic antidepressants (TCAs) also appeared to be effective, but with varied acceptability (Fornaro et al, 2016; Silva et al, 2013; Taylor et al, 2014; Vieta et al, 2010). No notable efficacy differences were identified between atypical antipsychotics, suggesting that lurasidone, quetiapine, and olanzapine/fluoxetine may be reasonable choices.

<u>Major Depressive Disorder (MDD)</u>

Key MDD Meta-Analyses

- A number of MAs and SRs have been conducted evaluating the safety and efficacy of atypical antipsychotics to augment treatment for MDD. Aripiprazole, REXULTI (brexpiprazole), and SEROQUEL XR (quetiapine ER) are indicated for the treatment of MDD as adjunctive treatment; and olanzapine, in combination with fluoxetine, is indicated for the treatment of treatment-resistant depression. The most recent, well-designed MAs have been summarized for efficacy and safety evaluations.
- One meta-analysis, which followed Cochrane methodologies, evaluated 17 trials of short-term duration ranging from 4 to 12 weeks. The analysis compared adjunctive atypical antipsychotics treatment in combination with a SSRI/serotonin-norepinephrine reuptake inhibitor (SNRI) to SSRI or SNRI monotherapy in patients with refractory or treatment-resistant MDD. Results demonstrated that the augmentation of antidepressants with atypical antipsychotics (olanzapine, quetiapine, aripiprazole, and risperidone [Note: risperidone is not FDA-approved for this indication]) was more effective than antidepressant monotherapy in improving response and remission rates. However, adjunctive atypical antidepressant therapy was associated with a higher discontinuation rate due to adverse effects (9.1 vs 2.6%). The attributable risk for the discontinuation rate due to adverse effects was 0.07 (number needed to harm [NNH], 16; 95% CI, 12 to 20) (Wen et al, 2014).
- Another meta-analysis evaluated 14 trials in patients with current MDD and an inadequate response to at least one course of antidepressant medication treatment. Compared to placebo, the atypical antipsychotics significantly improved remission rates: aripiprazole (odds ratio [OR], 2.01; 95% CI, 1.48 to 2.73), olanzapine/fluoxetine (OR, 1.42; 95% CI, 1.01 to 2), quetiapine (OR, 1.79; 95% CI, 1.33 to 2.42) and risperidone (OR, 2.37; 95% CI, 1.31 to 4.3). In terms of remission, all atypical antipsychotics were efficacious; however, olanzapine/fluoxetine had a higher NNT compared to other agents (NNT for olanzapine/fluoxetine, 19 vs NNT for aripiprazole, quetiapine, risperidone, 9). Treatment was associated with several adverse events, including akathisia (aripiprazole), sedation (quetiapine, olanzapine/fluoxetine and aripiprazole), abnormal metabolic laboratory results (quetiapine and olanzapine/fluoxetine), and weight gain (all 4 drugs, especially olanzapine/fluoxetine). However, little to no information was provided in detail regarding the adverse events (Spielmans et al, 2013).

Adjunctive treatment for MDD

- Aripiprazole, REXULTI, and SEROQUEL XR are indicated for the treatment of MDD as adjunctive treatment. The following information describes the pivotal trials used for FDA-approval.
- The FDA-approval of aripiprazole for the adjunctive treatment of MDD was based on 2 PC, 6-week trials in adult patients (N = 381; N = 362) who had failed 1 to 3 courses of antidepressant therapy, including an inadequate response to 8 weeks of antidepressant treatment. Aripiprazole was superior to placebo in reducing the mean MADRS total scores and remission rates. The NNT to reduce remission rates (defined as MADRS total score ≤ 10 and ≥ 50% reduction in MADRS) was 10 (Berman et al, 2007; Marcus et al, 2008). Increased incidences of akathisia were seen across trials with one trial reporting a NNH of 4 (Marcus et al, 2008). One pooled analysis of 3 similarly designed trials (N = 409) measured the effects of aripiprazole in older vs younger patients. Results demonstrated adjunctive aripiprazole was effective in improving depressive symptoms in older patients, 50 to 67 years and akathisia was the most commonly reported adverse event in both the older (17.1%) and younger (26%) patient groups (Steffens et al, 2011). Other trials have demonstrated similar results (Kamijima et al, 2013; Papakostas et al, 2005). In a 12-week, randomized, DB, PC trial evaluating the safety and efficacy of aripiprazole for adjunctive MDD treatment in patients over the age of 60 (N = 181), a higher percentage of patients achieved remission (defined as a MADRS score of ≤ 10) in the aripiprazole group as compared to placebo (44% vs 29 %; P = 0.03; NNT 6.6). Similar to other studies, akathisia was the most common side effect in the aripiprazole group (26% vs 12%), and Parkinsonism was also more often reported (17% vs 2%) (Lenze et al, 2015).
- The safety and efficacy of brexpiprazole was evaluated in 2 DB, PC, pivotal, 6-week trials in adult patients as an adjunct to antidepressant therapy for MDD. In the pivotal studies, brexpiprazole 2 mg daily doses significantly reduced the mean MADRS score, the primary endpoint, compared with placebo (Study 1 [N = 353], -8.4 points with brexpiprazole 2 mg vs -5.2 points with placebo). In an FDA analysis, the brexpiprazole 1 mg and 3 mg dose did not reduce the mean MADRS score; however, an FDA analysis found evidence of efficacy based on phase 2 data, and per protocol and intention-to-treat analyses of Study 2 (Thase et al, 2015; FDA briefing document, 2015). The most common adverse reactions in MDD trials were akathisia (NNH, 15), increased weight (NNH, 20) and somnolence (NNH, 22); and in schizophrenia trials were increased weight (NNH, 48) and tremor (NNH, 51) (Correll et al, 2015; Kane et al, 2015[a]; Thase et al, 2015).
- The FDA-approval of quetiapine fumarate ER as an adjunct to antidepressant therapy for the treatment of MDD was based on two 6-week, PC, fixed dose trials (N = 939) in doses of 150 mg or 300 mg/day. A pooled analysis of the 2 RCTs demonstrated that quetiapine fumarate 300 mg/day (58.3%; P < 0.01; NNT, 9) dose significantly improved the MADRS response (defined as ≥ 50% decrease in MADRS total score), but the quetiapine fumarate 150 mg/day

(53.7%; P = 0.06) did not compared to placebo (46.2%). However, MADRS remission was significantly improved for both the quetiapine fumarate 300 mg/day (36.5%; P < 0.001; NNT, 8) and 150 mg/day dose (35.6%; P < 0.01; NNT, 9) vs placebo (24.1%). The most common adverse events leading to discontinuation were somnolence and sedation. For the quetiapine fumarate 300 mg/day, 150 mg/day, and placebo treatment, the mean weight gain was 1.3, 0.9, and 0.2 kg, and the incidence of EPS was 6.4, 3.8, and 4.2%, respectively (Bauer et al, 2010).

Treatment-resistant depression

- Olanzapine, combined with fluoxetine, is the only agent in class indicated for treatment-resistant depression. Approval of olanzapine/fluoxetine for the acute treatment of treatment-resistant depression was based on 3 clinical trials of 8- (2 trials) and 12-week duration. Treatment with olanzapine/fluoxetine was generally more effective than monotherapy with either olanzapine or fluoxetine in improving MADRS scores; however, results in trials have been mixed (Corya et al, 2006; Shelton et al, 2005; Thase et al, 2007). In one 12-week, DB trial, olanzapine/fluoxetine was compared to olanzapine, fluoxetine, or venlafaxine monotherapy. Olanzapine/fluoxetine demonstrated a statistical MADRS advantage over all monotherapy agents after week 1 which was maintained up to week 6; however, this effect was only sustainable over olanzapine monotherapy at week 12 (Corya et al, 2006). Other trial data demonstrated that olanzapine/fluoxetine was not significantly different compared to other antidepressants such as nortriptyline and fluoxetine monotherapy in improving MADRS scores (Corya et al, 2006; Shelton et al, 2005).
- Treatment with olanzapine/fluoxetine has consistently demonstrated increases in the incidence (≥ 10%) of weight gain, increased appetite, somnolence, and dry mouth. Additional adverse events have varied in trials. Compared to fluoxetine and olanzapine monotherapy, the most common adverse events for olanzapine/fluoxetine (incidence ≥ 10%) included peripheral edema and hypersomnia, which were significantly higher than that of fluoxetine monotherapy (P < 0.001) (Thase et al, 2007). Compared to olanzapine, fluoxetine or venlafaxine monotherapy, the most common adverse events for olanzapine/fluoxetine (incidence ≥ 10%) included dizziness, asthenia, peripheral edema, and headache. More patients in the combination therapy group discontinued due to weight gain (Corya et al, 2006). Compared to fluoxetine, olanzapine, and nortriptyline monotherapy, the most common adverse events for olanzapine/fluoxetine combination therapy (incidence ≥ 10%) were asthenia, headache, anxiety, tremor, nervousness, insomnia, and nausea (Shelton et al, 2005).

<u>Schizophrenia and/or Schizoaffective Disorder</u>

- All oral atypical antipsychotic agents in class are indicated for use in schizophrenia with the exception of combination agent SYMBYAX (olanzapine/fluoxetine). Clozapine and paliperidone products, excluding INVEGA TRINZA, are indicated for the treatment of schizoaffective disorder. The following summarizes recent MAs and SRs, landmark trials in schizophrenia, and study evidence related to newer atypical antipsychotic agents (ie, asenapine, brexpiprazole, Iloperidone, and lurasidone) that do not have extensive trial evidence.
- Based on a 2012 AHRQ SR of 125 trials evaluating typical and atypical antipsychotics, a total of 113 measured efficacy and safety in adults with schizophrenia or schizophrenia-related psychoses. Compared to haloperidol, there was no difference in PANSS (and/or Scale for the Assessment of Positive Symptoms [SAPS]) score for positive symptoms vs aripiprazole, clozapine, olanzapine, quetiapine, and risperidone. Outcomes measuring negative symptoms demonstrated a significant difference in PANSS scores favoring aripiprazole for 1,701 patients in 3 trials, risperidone for 4,043 patients in 20 trials, and olanzapine-treatment for 3,742 patients in 14 trials. When compared with haloperidol, risperidone yielded lower relapse rates for 1,405 patients in 6 trials and olanzapine provided better response rates for 4,099 patients in 14 trials and remission rates for 582 patients in 3 trials. The most common adverse effects with significant differences were in the category of EPS and most often involved haloperidol. Haloperidol appears to be equally effective to treatment with the atypical antipsychotics in terms of positive symptoms; however, for negative symptom scores aripiprazole, risperidone, and olanzapine may be better options for treatment. Olanzapine and risperidone may be better options when remission/relapse rates are considered (Abou-Setta et al, 2012).
- One large, recent Bayesian meta-analysis of 212 RCTs compared 15 antipsychotic medications for efficacy and safety outcomes in patients with schizophrenia or related disorders in short term trials. The primary endpoint was efficacy measured by mean overall change in symptoms after 6 weeks and all antipsychotics were significantly more effective than placebo. Clozapine had the greatest mean difference in the change in symptom scores and was significantly superior to all other antipsychotics, including olanzapine and risperidone which have demonstrated some efficacy in treatment-resistant patients. After clozapine, olanzapine, and risperidone were significantly more effective than the other antipsychotics apart from paliperidone. Overall, effect sizes were small and there were some inconsistencies between results, but the authors did not consider that this was substantial enough to change the results. Safety assessment for the FDA-approve agents indicated that EPS was lowest for clozapine and highest for

haloperidol; sedation was lowest for risperidone and highest for clozapine; weight gain was lowest for haloperidol and highest for olanzapine; prolactin increase was lowest for aripiprazole and highest for paliperidone; and QT prolongation was lowest for lurasidone and highest for ziprasidone. The authors concluded that the properties of antipsychotic drugs differed greatly among agents and that treatment should be fit to individual patients' needs. As the meta-analysis had many limitations, including substantial differences between studies, and uncertainties surround indirect comparisons, generalizability of the findings and authors' conclusions are limited. This is similar to many large atypical antipsychotic MAs (Leucht et al, 2013).

- One Cochrane SR evaluated aripiprazole vs other atypical antipsychotics for the treatment of schizophrenia. Differences in efficacy between aripiprazole and other atypical antipsychotics (olanzapine, risperidone, and ziprasidone) demonstrated no advantage in terms of overall global state (defined as MD in CGI-S score) or mental state (defined as MD total change in PANSS score). When compared with any one of several new generation antipsychotic drugs in one RCT (N = 523), the aripiprazole group showed improvement in energy, mood, negative symptoms, somnolence, and weight gain. More nausea was seen in patients given aripiprazole (N = 2,881; RR, 3.13; 95% CI, 2.12 to 4.61). Weight gain with aripiprazole-treatment was less common (N = 330; RR, 0.35; 95% CI, 0.19 to 0.64). Attrition ranged from 30 to 40% (no differences between groups). Due to the high attrition rates validity is limited, thereby making it difficult to make strong conclusions. There is limited data on the safety and efficacy of aripiprazole. Based on current available evidence, efficacy of aripiprazole appears to be similar and there may be benefits in terms of weight gain, but there appears to be an increased incidence of nausea compared to other agents (Khanna et al, 2014).
- One Cochrane SR evaluated quetiapine compared to other atypical antipsychotics for the treatment of schizophrenia. Efficacy and safety were evaluated in 5,971 patients across 35 RCTs. For the primary efficacy endpoint, PANSS total score, the comparator drugs may be more effective than quetiapine, but the clinical meaning of these data is unclear. There were no significant differences in efficacy between quetiapine and clozapine, but quetiapine was associated with fewer adverse events. Quetiapine demonstrated fewer movement disorders compared to risperidone (RR, 0.5; 95% CI, 0.36 to 0.69), olanzapine (RR, 0.51; 95% CI, 0.32 to 0.81), and paliperidone (RR, 0.64; 95% CI, 0.45 to 0.91). There are limited studies; however, data provides evidence that quetiapine-treated patients may need to be hospitalized more frequently than those taking risperidone or olanzapine. Quetiapine may be slightly less effective than risperidone and olanzapine in reducing symptoms, and it may cause less weight gain and fewer side effects and associated problems (such as heart problems and diabetes) than olanzapine and paliperidone, but more than risperidone and ziprasidone (Asmal et al, 2013).
- The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) was a large, multi-center study initiated by the National Institute of Mental Health to examine the effectiveness of SGAs compared to FGAs in patients with chronic schizophrenia. It was intended to include patients treated in typical clinical settings and to reflect typical clinical practice in which individuals with schizophrenia may require multiple medication trials before finding one that is adequately both efficacious and tolerable. The study design allowed for patients who discontinued one study antipsychotic drug to enter subsequent phases of the study to receive additional antipsychotic medications (Lieberman et al, 2005; Stroupe et al, 2006; Stroupe et al, 2009). Among the unexpected outcomes was the finding that, with the exception of clozapine, the SGAs did not separate out robustly from the FGAs with respect to overall efficacy and times to treatment discontinuation. However, because of relatively high discontinuation rates across all treatment arms, potential biases regarding optimal dosing of individual drugs, and clear differences in treatment-emergent side effect profiles, the implications of CATIE are subject to interpretation which may preclude definitive guidance in developing pharmacotherapy guidelines for patients with schizophrenia as a whole.
- The efficacy of asenapine in the treatment of schizophrenia in adults was evaluated in 4 published, randomized, DB, PC, and active-controlled (haloperidol, risperidone, and olanzapine) trials, ranging in duration from 6 weeks to one year (Kane et al, 2011; Kane et al, 2010[a]; Potkin et al, 2007; Schoemaker et al, 2010). Asenapine was associated with statistically significant improvement in PANSS scores from baseline compared to placebo, starting from week 2 of therapy. CGI-I and CGI-S scores were also significantly improved with asenapine therapy compared to placebo. Moreover, an extension study demonstrated a reduced risk of relapse associated with continuation of asenapine therapy (Kane et al, 2011). However, a direct-comparison study suggests that asenapine is less effective than olanzapine in terms of changes from baseline in PANSS and CGI-S scores. Furthermore, study discontinuation due to inadequate efficacy was noted in only 14% of patients receiving olanzapine compared to 25% of patients in the asenapine group. Mean weight gain was 0.9 kg with asenapine and 4.2 kg with olanzapine (Shoemaker et al, 2010). In another study, while 17% of patients receiving risperidone experienced a weight gain of at least 7% from baseline, 9% of patients in the asenapine group were noted to exhibit clinically significant weight gain (Potkin et al, 2007).

- The safety and efficacy of brexpiprazole was evaluated in 2 DB, PC, 6-week trials in adults with schizophrenia. In the pivotal studies, brexpiprazole 2 mg and 4 mg daily doses significantly reduced the PANSS score (-20.73 and -19.65 vs -12.01 points with placebo), the primary endpoint, compared with placebo; however, in the BEACON trial, only the brexpiprazole 4 mg dose significantly reduced the PANSS score (-20 vs -13.53 points with placebo) (Correll et al, 2015; Kane et al, 2015[a]). The most common adverse reactions in MDD trials were akathisia (NNH, 15), increased weight (NNH, 20) and somnolence (NNH, 22); and in schizophrenia trials were increased weight (NNH, 48) and tremor (NNH, 51) (Correll et al, 2015; Kane et al, 2015[a]; Thase et al, 2015). The safety and efficacy of brexpiprazole for maintenance therapy of schizophrenia was evaluated in a randomized, DB, MC, PC trial. It enrolled 524 patients with an acute exacerbation of psychotic symptoms to be stabilized on brexpiprazole 1 to 4 mg daily. Patients who achieved stabilization (criteria including PANSS total score ≤ 70, CGI-S score ≤ 4 [moderately ill], no current suicidal behavior, or violent or aggressive behavior) for 12 weeks then entered a 52-week maintenance phase where they were randomized to their stabilization dose of brexpiprazole (N = 97) or placebo (N = 105). The co-primary endpoints were time to exacerbation of psychotic symptoms or impending relapse, defined as worsening of CGI-I and PANSS scores, hospitalization due to worsening of psychotic symptoms, suicidal behavior, or violent/aggressive behavior. In the maintenance phase, 13.5% of patients in the brexpiprazole group experienced impending relapse vs 38.5% of placebo patients (P < 0.0001) and time to impending relapse was statistically significantly lower (Hazard ratio [HR], 0.34; P = 0.0008). However, based on results of an interim analysis, the trial was terminated early. Only a small number of patients were exposed to brexpiprazole for the prescribed 52 weeks and, therefore, conclusions cannot be drawn for long-term use (Fleischhacker et al, 2016).
- The efficacy and safety of cariprazine in schizophrenia was based on 3 DB, randomized, PC 6-week trials (Durgam et al, 2014; Durgam et al, 2015[b]; Kane et al, 2015[b]). A total of 1,792 adult patients with acute exacerbation of schizophrenia were administered placebo or cariprazine 1.5 to 9 mg per day. Two trials were fixed-dose studies and included active comparators, risperidone 4 mg and aripiprazole 10 mg, to assess sensitivity; one study was a flexible dose study with no active comparator. In the flexible dose study, the mean daily dose ranged from 5 to 8 mg per day (Kane et al, 2015[b]). All doses were superior to placebo in reducing PANSS and CGI-S scores and a significant PANSS reduction was observed as soon as 7 days for the higher doses and 2 to 3 weeks for the lower doses (FDA/CBER summary review, 2015). Of note, higher doses do result in quicker control of symptoms; however, if high doses continue resulting in accumulation of the active metabolite DDCAR it is not clear how this may influence safety results. Delayed incidences of akathisia occurred. According to pooled analysis (n = 1,317 cariprazine-treated patients) within the FDA clinical summary, the most common adverse events reported in schizophrenia trials were EPS (28.5%) and akathisia (11.2%) (FDA/CBER summary review, 2015). The akathisia observed at cariprazine doses ≤ 6 mg is comparable to those observed with aripiprazole, but accumulation of the DDCAR metabolite may result in later-onset effects. In schizophrenia studies, 4% of patients with normal hemoglobin A1c developed elevated levels (≥ 6.5%). The proportion of patients with weight increase ≥ 7% from baseline ranged from 8 to 17% across cariprazine doses. In an OL 48-week extension (N = 97) of a 6-week trial, safety and tolerability were found to be maintained. The most common adverse events were akathisia (14%), insomnia (14%), and weight gain (11.8%) (Durgam et al, 2014; Durgam et al, 2016[b]). Another study evaluated cariprazine for maintenance therapy for schizophrenia relapse in 765 patients. A flexible-dose, OL, 8-week, run in phase was followed by a 12-week, fixed-dose, stabilization phase. Patients completing the OL phase (N = 264) entered a DB phase and received cariprazine (3 to 9 mg/day), or placebo for up to 72 weeks. During the DB phase, 24.8% of the cariprazine group experienced relapse vs 47.5% of the placebo group (HR, 0.45; 95%CI, 0.28 to 0.73). Time to relapse was statistically significantly longer for the cariprazine group vs placebo (25th percentile time to relapse, 224 vs 92 days, respectively; P < 0.001). The long-term safety profile of cariprazine was found to be consistent with findings from previous trials (Durgam et al, 2016[a].)
- Iloperidone has been studied as monotherapy for the treatment of adults with an acute or subacute exacerbation of schizophrenia. Three 6-week, randomized, DB, placebo- and active comparator (risperidone and haloperidol)-controlled studies found iloperidone to be significantly more effective than placebo (Potkin et al, 2008). Another 4-week, placebo- and active comparator- (ziprasidone) controlled study found a significant improvement in PANSS scores with iloperidone therapy compared to placebo (Cutler et al, 2008). Two MAs of these 4 studies corroborated earlier data, finding iloperidone more effective than placebo in terms of improvement from baseline in various subscales of the PANSS scale and BPRS scores (Citrome et al, 2011; Citrome et al, 2012). The long-term efficacy and safety of iloperidone in the treatment of schizophrenia was evaluated in a meta-analysis that pooled the follow-up data (up to 52 weeks) from 3 prospective RCTs. The meta-analysis found the long-term efficacy of Iloperidone, assessed via the time to relapse endpoint, to be comparable to haloperidol (P = 0.85), with a more favorable long-term safety profile (Kane et al, 2008). Moreover, another meta-analysis designed to evaluate the short-term safety of iloperidone found the following dose-related adverse effects: dry mouth, dizziness, somnolence and dyspepsia. EPS

was noted in association with iloperidone but was more common with haloperidol and risperidone therapies. Iloperidone was also associated with QTc prolongation and weight gain (1.5 to 2.1 kg) (Weiden et al, 2008). The efficacy of iloperidone for relapse-prevention during maintenance phase of schizophrenia treatment was evaluated in a DB, PC, randomized withdrawal study. Patients were not blinded and were stabilized for 24 weeks. If clinically stable for 12 weeks, they were then randomized to iloperidone (8 to 24 mg/day) (N = 153) or placebo (N = 150) for 26 weeks. The primary endpoints were time to relapse and proportion of patients experiencing relapse (defined as hospitalization due to worsening schizophrenia, worsening of PANSS and CGI-I scores, suicidal or aggressive behavior, or treatment escalation [ie, dose increases or additional medications]). The trial was stopped early due to superior iloperidone relapse prevention. Time to relapse was statistically significantly longer with iloperidone vs placebo (140 vs 95 days, respectively; P < 0.0001). The relapse rate for placebo was 64% vs 17.9% for iloperidone (P < 0.0001). The safety was comparable to other trial results, with dizziness, insomnia, headache, dry mouth, and somnolence being the most common adverse events. Weight gain ≥ 7% occurred in 25.2% of iloperidone-treated patients in the relapse-prevention phase. Mean change in QTcF from baseline was 4.9 ms in the iloperidone group (vs 1 ms in placebo) during the relapse-prevention phase. Rates of EPS (2.5% in stabilization phase/1.3% in relapse-prevention phase) and akathisia (3.7% and 1%, respectively) were consistently low in iloperidone-treated patients as well (Weiden et al, 2016).

- Lurasidone was investigated for the treatment of adult patients with acute and chronic symptoms of schizophrenia in 2 PC, 6-week studies and two 21-day studies directly comparing the safety and efficacy of lurasidone 120 mg once daily with ziprasidone 80 mg twice daily. In PC studies, lurasidone dosed 40, 80, or 120 mg once daily was associated with significant improvements from baseline in PANSS and the BPRS scores, compared to placebo (Meltzer et al, 2011; Nakamura et al, 2009). The 2 direct-comparison studies demonstrated comparable improvements in the lurasidone and ziprasidone groups in terms of the reduction in total PANSS, PANSS positive symptom, PANSS general symptom, CGI-S scores, and several cognition scales. Likewise, the 2 groups were comparable in terms of rates of discontinuation for any reason and discontinuation due to adverse events (Harvey et al, 2011; Potkin et al, 2011). Of note, lurasidone was more effective in improving negative symptom PANSS scores compared to ziprasidone (P = 0.046). Both therapies were associated with a small weight loss from baseline and neither therapy was associated with a clinically significant electrocardiogram abnormality. Extrapyramidal adverse events were noted in 3.3% of patients in the ziprasidone group and in 3.3% of patients receiving lurasidone (Potkin et al, 2011). The efficacy of lurasidone in maintenance treatment was evaluated in a DB, PC, RCT. Patients (N = 676) with schizophrenia experiencing an acute exacerbation entered into an OL stabilization phase for 12 to 24 weeks. Patients achieving stabilization for 12 weeks (N = 285) were randomized into a 28-week, DB phase to receive lurasidone (40 to 80 mg/day), or placebo. The probability of relapse at the 28-week point was 42.2% vs 51.2% in the lurasidone and placebo groups, respectively (NNT = 12). Lurasidone statistically significantly delayed the time to relapse vs placebo (P = 0.039). In patients receiving lurasidone in both the OL and DB phases, the most common adverse events were akathisia (16.7%), insomnia (12.5%), and headache (11.8%) (Tandon et al, 2016).

Long-Acting Injectable Atypical Antipsychotics:

Bipolar Disorder

- Risperidone long-acting injection is the only long-acting injection FDA-approved for bipolar I disorder as monotherapy or in combination with lithium or valproate for maintenance therapy. Compared to placebo, risperidone long-acting injection has demonstrated superior efficacy in acute and non-acute patients with similar safety effects to that of oral risperidone (Mcfadden et al, 2009; Quiroz et al, 2010; Vieta et al, 2012; Yatham et al, 2007).
- For maintenance therapy, risperidone long-acting injection monotherapy has demonstrated inconsistent results regarding the endpoint of delayed time to recurrence of any mood episode compared to placebo (Quiroz et al, 2010; Vieta et al, 2012). When risperidone long-acting injection was used in combination with mood stabilizers (eg, lithium and valproate), antidepressants, or anxiolytics, the time to relapse was significantly longer with fewer proportions of patients relapsing compared to placebo (Mcfadden et al, 2009). An exploratory post hoc analysis showed that the time to recurrence of any mood episode was also significantly longer with oral olanzapine compared with risperidone long-acting injection (P = 0.001) (Vieta et al, 2012). The adverse effect profile of long-acting injection therapy is not fully understood; however, EPS, weight gain, hyperprolactinemia, and cardiovascular events were observed in risperidone long-acting injection therapy trials (Mcfadden et al, 2009; Quiroz et al, 2010; Vieta et al, 2012; Yatham et al, 2007).

Schizophrenia

- All 6 long-acting injectable atypical antipsychotics are FDA-approved for the treatment of schizophrenia in adults. These agents include ABILIFY MAINTENA (aripiprazole ER), ARISTADA (aripiprazole lauroxil), ZYPREXA

RELPREVV (olanzapine pamoate), INVEGA SUSTENNA (paliperidone palmitate once-a-month injection), INVEGA TRINZA (paliperidone palmitate once-every-3-months injection), and RISPERDAL CONSTA (risperidone microspheres). INVEGA SUSTENNA is the only agent FDA-approved for the treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers or antidepressants.

- A number of MAs and SRs have been conducted evaluating long-acting injection atypical antipsychotics compared to oral antipsychotics for the treatment of schizophrenia. Comparative effectiveness data between long-acting injectable atypical antipsychotics are lacking and there is insufficient evidence to draw firm conclusions. The most recent, well-designed MAs have been summarized for efficacy and safety evaluations.
- One meta-analysis of atypical antipsychotics included 13 RCTs measuring the efficacy and safety of long-acting injection atypical antipsychotics vs oral antipsychotics or placebo in patients with schizophrenia. Long-acting injectable atypical antipsychotics were not associated with a significant decrease in the PANSS total score from baseline from oral antipsychotics (P = 0.33); therefore, both formulations had similar efficacy. No additional significant differences were noted. The long-acting injectable atypical antipsychotics were associated with a higher incidence of EPS compared to placebo (P < 0.001) and oral antipsychotics (P = 0.048) (Fusar-Poli et al, 2013).
- One SR and meta-analysis of long-acting antipsychotic injectable agents (including typical and atypical agents) measured the safety and efficacy of treatment compared to oral antipsychotics in 21 RCTs (11 trials measured atypical antipsychotic agents). Patients with schizophrenia, schizophreniform, or schizoaffective disorder were evaluated in longer duration trials of greater than or equal to 6 months. Long-acting injectable antipsychotics were similar to oral antipsychotics for relapse prevention in outpatient studies lasting ≥ 1 year (RR, 0.93; 95% CI, 0.71 to 1.07; P = 0.03). Among individual long-acting injectable antipsychotics, only fluphenazine was superior to oral antipsychotics in drug efficacy (P = 0.02) and in preventing hospitalization (P = 0.04). There was no difference between each individual long-acting injectable antipsychotic and pooled long-acting injectable antipsychotics compared to oral antipsychotics regarding discontinuation due to adverse events (P = 0.65) (Kishimoto et al, 2013).
- One meta-analysis compared outcomes for once-monthly long acting injections of paliperidone palmitate and risperidone across 7 RCTs. Paliperidone palmitate was less likely to show no improvement in global state (defined as reduction in PANSS scores) vs placebo (RR, 0.79; 95% CI, 0.74 to 0.85). When comparing both active treatments, one trial favored paliperidone palmitate and one trial favored risperidone long-acting injection; therefore, conclusions could not be made. In terms of safety, paliperidone palmitate and risperidone long-acting injection were similar. Compared to placebo, paliperidone palmitate led to significant elevations in serum prolactin, regardless of patient gender (Nussbaum et al, 2012).
- One SR of 41 trials measuring safety concluded that long-acting injectable atypical antipsychotics are associated with similar adverse effects to that of oral formulations, and no clinically significant trends can be conclusively drawn. Data suggested that olanzapine pamoate was associated with dose-dependent weight gain, lipid and glucose metabolism issues, and may increase prolactin levels even at low doses. Post-injection syndrome, due to accidental intravascular injection of olanzapine pamoate, was characterized by delirium and/or excessive sedation (incidence, 1.2%). The risperidone long-acting injection may increase the risk of QT prolongation, although the clinical significance is unknown. Hyperprolactinemia, EPS, cardiovascular events (ie, tachycardia and orthostatic hypotension), and weight gain are known side effects of risperidone long-acting injection and paliperidone palmitate. The most common adverse event associated with paliperidone palmitate was worsening of psychotic symptoms (incidence, 3.5 to 16%) (Gentile et al, 2013).
- Two additional long-acting injectable agents were approved in 2015, ARISTADA (aripiprazole lauroxil) and INVEGA TRINZA (paliperidone palmitate once-every-3-months injection).
  - The safety and efficacy of aripiprazole lauroxil in adult patients with schizophrenia was established in one PC, DB, RCT of 622 patients over a period of 12 weeks. Oral aripiprazole was administered concomitantly for the first 3 weeks of treatment. The PANSS total score was significantly decreased at day 85 by 10.9 with monthly intramuscular (IM) injections of aripiprazole lauroxil 441 mg and by 11.9 with 882 mg IM monthly compared with placebo (P < 0.001 for both). PANSS was significantly improved as early as day 8 and maintained throughout the study. In terms of safety, more than double the proportion of patients taking aripiprazole lauroxil experienced akathisia (441 mg, 11.6%; 882 mg, 11.5%) compared to placebo (4.3%). The majority of the akathisia (75%) was experienced before the second injection within the first 3 weeks. Additional treatment-emergent adverse effects (incidence ≥ 2%) included insomnia, headache, and anxiety (Meltzer et al, 2015).
  - The FDA-approval of INVEGA TRINZA, the 3-month IM paliperidone palmitate injection, was based on one PC, OL/DB trial of 305 patients with schizophrenia experiencing acute symptoms. Prior to administration of paliperidone palmitate once every 3 months injection, patients were administered flexible oral doses for 17 weeks, and then administered the paliperidone palmitate once monthly injection for 12 weeks. If stable, patients were

then administered the once every 3 month injection. Paliperidone palmitate once every 3 months injection significantly lengthened the median time to first relapse vs placebo. The mean change in PANSS total scores showed greater improvement in the paliperidone group compared to placebo (P < 0.001). Due to the low percentage of relapse in treated patients (7.4%), the median time was not estimated; however, in the placebo group, 23% experienced relapse, with a median time of 274 days. The trial was stopped early due to demonstration of efficacy. Those adverse events noted more frequently in the group receiving paliperidone palmitate vs the placebo group included headache (9 vs 4%), weight increased (9 vs 3%), nasopharyngitis (6 vs 1%), and akathisia (4 vs 1%) (Berwaerts et al, 2015).

SAFETY SUMMARY

- All atypical antipsychotic agents have a boxed warning of increased mortality in elderly patients with dementia-related psychosis. Those agents (ie., ABILIFY, LATUDA, REXULTI, SEROQUEL, SEROQUEL XR, and SYMBYAX) indicated for depressive episodes carry a boxed warning of an increased risk of suicidal thoughts and behaviors. ZYPREXA RELPREVV has a boxed warning of incidences of post-injection delirium and/or sedation syndrome. Lastly, clozapine-containing agents (ie., CLOZARIL, FAZACLO, and VERSACLOZ) have boxed warnings of severe neutropenia, orthostatic hypotension, bradycardia, syncope, seizures, myocarditis, and cardiomyopathy.
- GEODON is contraindicated in patients with recent acute myocardial infarction (MI), history of QT prolongation or with drugs that prolong QT, and uncompensated heart failure (HF). LATUDA is contraindicated for concomitant use with strong CYP3A4 inducers and/or inhibitors. Lastly, SAPHRIS is contraindicated in patients with severe hepatic impairment.
- Clozapine-containing products and ZYPREXA RELPREVV are a part of the Risk Evaluation and Mitigation Strategies (REMS) program. Registry, training, and counseling is required as part of both programs. Clozapine products also require certain laboratory levels prior to prescribing. ZYPREXA RELPREVV requires patients to be observed in clinic for 3 hours after administration. In December 2016, the FDA announced that the full clozapine REMS program would not be implemented in 2016 due to technical and logistical challenges. The date of full launch is unknown (FDA safety communication [clozapine], 2016).
- A vast number of Warnings and Precautions are assigned to the atypical antipsychotic agents. The following outlines the most recent FDA safety communications:
    - In May 2016, the FDA warned that impulse-control problems had been associated with the use of aripiprazole. Uncontrollable urges to gamble, binge eat, shop, and have sex were reported. New warnings were added to the drug labels and patient Medication Guides (FDA safety communication [aripiprazole], 2016).
    - In September 2015, the FDA made modifications to the clozapine REMS program. The absolute neutrophil count (ANC) requirements were modified to a lower ANC level. Benign ethnic neutropenia (BEN) patients were also included as now eligible for clozapine-treatment (FDA safety communication [clozapine], 2015).
    - In March 2015, the FDA concluded their study after 2 unexplained deaths were reported as a result of high plasma drug concentrations after the appropriate doses of ZYPREXA RELPREVV were administered. Study results were inconclusive; therefore, the FDA did not make recommendations to change treatment (FDA safety communication [ZYPREXA RELPREVV], 2015).
    - In May 2016, the FDA warned that olanzapine can cause a Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). In December 2014, 6 patients reported incidences of DRESS with GEODON use. If DRESS is suspected, use should be discontinued immediately. As a result, DRESS was added as a Warning and Precaution to both products (FDA safety communication [olanzapine], 2016; FDA safety communication [ziprasidone], 2014).
    - In September 2011, 52 cases of Type I hypersensitivity reactions were reported with SAPHRIS use. A Warning and Precaution of hypersensitivity reactions was added to the SAPHRIS prescribing information (FDA safety communication [asenapine], 2011).
    - In February 2011, a safety warning for all atypical antipsychotics was communicated after increases in the risk of EPS and withdrawal symptoms were observed in newborns whose mothers were administered antipsychotics in the third trimester of pregnancy (FDA safety communication, 2011).
- Many factors are taken into consideration when prescribing an atypical antipsychotic, including co-morbid conditions and safety risks. Common adverse events observed within the class include EPS, sedation, increased prolactin levels, autonomic effects, metabolic effects, and cardiac risks including the risk of ventricular arrhythmias (QT prolongation). Table 3 outlines the relative adverse event trends observed between the various atypical antipsychotic agents:

Table 3. Relative Adverse Event Risk Observed in Trials for Atypical Antipsychotic Agents

Adverse Event	Aripiprazole	Asenapine	Brexpiprazole	Cariprazine	Clozapine*	Iloperidone	Lurasidone	Olanzapine	Paliperidone	Quetiapine	Risperidone	Ziprasidone
Sedation – sleepiness	Low	Moderate	Low	Low	High	Low	Moderate	Moderate	Low	Moderate	Low	Low
Diabetes	Low	Moderate	Low	Low	Very high	Moderate	Negligible to low	High	Moderate	Moderate	Moderate	Negligible to low
EPS – akathisia (motor restlessness), parkinsonism (tremor, rigidity, and slow movements), dystonia (continuous muscle spasms or contractions), and tardive dyskinesia (jerky movements).	Low	Low to moderate	Low	Low to moderate	Negligible to low	Negligible to low	Moderate	Low	High	Negligible to low	High	Low to moderate
Anticholinergic – blurred vision, constipation, dry mouth, drowsiness, memory impairment, etc.	Negligible	Negligible	Negligible to low	Negligible to low	High	Low	Negligible	Moderate	Negligible	Moderate	Low	Negligible
Orthostasis – low blood pressure resulting in dizziness when standing up.	Negligible	Low	Negligible to low	Negligible to low	High	High	Low	Low	Moderate	Moderate	Low	Low
Weight Gain	Low	Moderate	Low	Low	Very high	Moderate	Negligible to low	High	Moderate	Moderate	Moderate	Negligible to low
Prolactin – high levels linked to gynecomastia, sexual dysfunction, menstrual disruption, acne, amenorrhea, hirsutism, osteoporosis, increased risk of hip fracture, etc.	Low	Moderate	Negligible to low	Negligible to low	Negligible to low	Negligible to low	Negligible to low	Low	High	Negligible to low	High	Low
QT prolongation	Negligible to low	Low	Low	Negligible to low	Low	Moderate	Negligible to low	Low	Low	Low	Low	Moderate

Abbrv: EPS = extrapyramidal side effects
Note: Information is based on indirect comparisons and expert assessments; however, more head-to-head trials are warranted to substantiate observations
*Granulocytopenia or agranulocytosis has been reported in 1%. Clozapine associated with excess risk of myocarditis and venous thromboembolism (VTE), including fatal pulmonary embolism (PE).

(Altinbas et al, 2013; FDA/CBER summary review [VRAYLAR], 2015; Jibson et al, 2016)

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
Aripiprazole (ABILIFY,†† ABILIFY DISMELT, ABILIFY MAINTENA)	Orally disintegrating tablet: 10 mg 15 mg Oral Tablet: 2 mg 5 mg 10 mg 15 mg 20 mg 30 mg Long-acting injection (vial or syringe): 300 mg 400 mg Oral Solution: 1 mg/mL	Bipolar disorder – manic or mixed episodes: Oral formulations and monotherapy: initial, 15 mg PO daily; recommended dose, 15 mg PO daily; max, 30 mg PO daily tablet Adjunct to lithium or valproate (oral formulations): initial dose may range from 10 mg to 15 mg PO daily Schizophrenia: Oral formulations: initial or target, 10 to 15 mg PO daily; max, 30 mg PO daily tablet; dose increases should generally not be made before 2 weeks; daily doses > 15 mg were not shown to be more efficacious than 15 mg PO daily Long-acting injection: initial or maintenance, 400 mg IM once a month; max, 400 mg/month; take 14 days of concurrent oral aripiprazole (10 to 20 mg) or current oral antipsychotic in conjunction with the first injection Adjunctive treatment of major depressive disorder: Oral formulations: initial, 2 to 5 mg PO daily; recommended dose, 2 to 15 mg (or 5 to 10 mg) PO daily; max, 15 mg PO daily; dose adjustments up to 5 mg/day should occur at intervals of ≥ 1 week. Dosing of oral solution: May be substituted for tablets on an mg-per-mg basis up to 25 mg. Tablet doses of 30 mg should receive 25 mg of solution.	Bipolar mania – manic or mixed episodes as monotherapy or as adjunct to lithium or valproate (10 to 17 years): Oral formulations: initial, 2 mg PO daily; target dose, 10 mg PO daily; max, 30 mg PO daily tablet; titrate every 2 days Schizophrenia (13 to 17 years): Oral formulations: initial, 2 mg PO daily; target dose, 10 mg PO daily; max, 30 mg PO daily tablet; titrate every 2 days; daily doses of 30 mg daily were not shown to be more efficacious than 10 mg daily Autistic disorder with irritability (6 to 17 years): Oral formulations: initial, 2 mg PO daily; target dose, 5 to 15 mg PO daily; max, 15 mg PO daily; dose adjustments up to 5 mg/day should occur at intervals of ≥ 1 week. Tourette's Disorder (6 to 18 years): Oral formulations: initial, 2 mg PO daily; recommended dose, 5 mg PO daily for patients < 50 kg and 10 mg PO daily for patients ≥ 50 kg; max, 10 mg PO daily for patients < 50 kg and 20 mg PO daily for patients ≥ 50 kg; dose adjustments should occur gradually at intervals of ≥ 1 week.	Dose adjustments are recommended in known CYP2D6 poor metabolizers, or with concomitant CYP2D6 inhibitors, and/or CYP3A4 inhibitors/inducers.*	Oral formulations should be administered once daily without regard to meals. Aripiprazole-naïve patients should establish tolerability with oral formulations prior to initiating long-acting injections. Long-acting injection may be administered in the deltoid or gluteus by a healthcare professional only.

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
			Dosing of oral solution: May be substituted for tablets on a mg-per-mg basis up to 25 mg. Tablet doses of 30 mg should receive 25 mg of solution.		
Aripiprazole lauroxil (ARISTADA)	Long-acting injection (pre-filled syringe): 441 mg 662 mg 882 mg	Schizophrenia: Initial or maintenance, 441 mg, 662 mg, or 882 mg IM once a month or 882 mg IM once every 6 weeks; take 21 days of concurrent oral aripiprazole in conjunction with the first injection	Not FDA-approved	Dose adjustments are recommended in known CYP2D6 poor metabolizers, or in patients taking concomitant CYP2D6 inhibitors, and/or CYP3A4 inhibitors/inducers for more than 2 weeks.*	Aripiprazole-naïve patients should establish tolerability with oral formulations prior to initiating long-acting injections. The 441 mg dose can be injected into the deltoid or gluteal muscle, but the 662 mg and 882 mg doses can only be administered in the gluteal muscle by a healthcare professional.
Asenapine (SAPHRIS)	Sublingual tablet: 2.5 mg 5 mg 10 mg	Bipolar disorder– manic or mixed episodes: Acute and maintenance monotherapy: initial, target and max dose, 10 mg SL twice daily; dose can be decreased to 5 mg SL twice daily if adverse effects occur. Adjunct to lithium or valproate: initial dose, 5 mg SL twice daily; max dose, 10 mg SL twice daily Schizophrenia: Acute treatment: initial, 5 mg SL twice daily; target dose, 5 mg SL twice daily; max dose, 10 mg SL twice daily; the safety of doses above 10 mg SL twice daily has	Bipolar disorder– manic or mixed episodes (10 to 17 years): Initial, 2.5 mg SL twice daily; target dose, 2.5 to 10 mg SL twice daily; max dose, 10 mg SL twice daily; titrate 2.5 to 5 mg every 3 days	Pediatric patients appear to be more sensitive to dystonia with initial dosing when the recommended titration schedule is not followed.	Do not swallow sublingual tablets. Sublingual tablets should be placed under the tongue and left to dissolve completely. The sublingual tablet will dissolve in saliva within seconds. Eating and drinking should be avoided for 10 minutes after

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
		not been evaluated Maintenance treatment: initial, 5 mg SL twice daily; target dose, 5 to 10 mg SL twice daily; max dose, 10 mg SL twice daily			administration.
Brexpiprazole (REXULTI)	Oral Tablet: 0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg	Adjunctive treatment of major depressive disorder: Initial, 0.5 to 1 mg PO once daily; maintenance, 2 mg once daily; max, 3 mg once daily Schizophrenia: Initial, 1 mg PO once daily; maintenance, 2 to 4 mg once daily; max, 4 mg once daily	Not FDA-approved	Dose adjustments are recommended in known CYP2D6 poor metabolizers, concomitant moderate to strong CYP2D6 and/or CYP3A4 inhibitors, and/or CYP3A4 inducers.*	Take with or without food
Cariprazine (VRAYLAR)	Capsule: 1.5 mg 3 mg 4.5 mg 6 mg Titration pack: 1.5 mg and 3 mg	Schizophrenia: Initial, 1.5 mg PO once daily; maintenance, 1.5 to 6 mg PO once daily; titrate by 1.5 to 3 mg once daily to target dose; max, 6 mg once daily. Bipolar disorder – manic or mixed episodes: Initial, 1.5 mg PO once daily; maintenance, 3 to 6 mg PO once daily; titrate by 1.5 to 3 mg once daily to target dose; max, 6 mg once daily.	Not FDA-approved	Due to the long half-life, dose changes may not be reflected for several weeks. Monitor for adverse events and response for several weeks. Dose adjustments are recommended with concomitant CYP3A4 inhibitors.*	Take with or without food Discontinuation of treatment may not be immediately reflected in the patient. No data addressing switching patients to another treatment is available.
Clozapine (CLOZARIL, FAZACLO, VERSACLOZ)	Orally disintegrating tablet: 12.5 mg 25 mg 100 mg 150 mg 200 mg Tablet: 25 mg	Treatment-resistant schizophrenia: Initial, 12.5 mg PO once or twice daily;* target dose, 300 to 450 mg daily (in divided doses); max, 900 mg PO daily; titrate by 25 to 50 mg daily to target dose by the end of 2 weeks, after 2 weeks then may titrate by ≤ 100 mg no more frequently than once or twice weekly. Reduce the risk of recurrent suicidal behavior in schizophrenia or	Not FDA-approved	In the event of planned termination of therapy, gradual reduction in dose is recommended over a 1 to 2 week period. Dose adjustments are recommended in patients with renal/hepatic	Prior to initiating, a baseline ANC must be ≥ 1,500/µL (≥ 1,000/µL for patients with Benign Ethnic Neutropenia [BEN]). To continue treatment, ANC must be monitored regularly. Shake oral suspension for 10 seconds prior to

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
	50 mg 100 mg 200 mg Suspension: 50 mg/mL	schizoaffective disorder: Same dosing as above. Mean dose is ~300 mg daily.		impairment, CYP2D6 poor metabolizers, taking concomitant CYP2D6, CYP1A2, CYP3A4 inhibitors and/or CYP3A4, CYP1A2 inducers.*	each use.
Iloperidone (FANAPT)	Tablet: 1 mg 2 mg 4 mg 6 mg 8 mg 10 mg 12 mg	Schizophrenia: Initial, 1 mg twice daily; maintenance, increase to reach the target dose range of 6 to 12 mg twice daily with daily dosage adjustments not to exceed 2 mg twice daily; max, 12 mg twice daily	Not FDA-approved	Dose adjustments are recommended in patients with renal/hepatic impairment, CYP2D6 poor metabolizers, taking concomitant CYP2D6 and/or CYP3A4 inhibitors.*	Control of symptoms may be delayed during the first 1 to 2 weeks. Some adverse effects are dose related.
Lurasidone (LATUDA)	Tablet: 20 mg 40 mg 60 mg 80 mg 120 mg	Schizophrenia: Initial, 40 mg PO once daily;† max, 160 mg PO once daily Bipolar disorder - depressive episodes: Monotherapy or as adjunct to lithium or valproate: initial, 20 mg PO once daily; maintenance 20 to 120 mg once daily; max, 120 mg once daily; in the monotherapy study, daily doses of 80 to 120 mg were not shown to be more efficacious than 20 to 60 mg daily.	Not FDA-approved	Recommended starting dose is 20 mg and the max dose is 80 mg with concomitant use with a moderate CYP3A4 inhibitor, or moderate to severe hepatic or renal impairment.	Administer with food (≥ 350 calories).
Olanzapine (ZYPREXA, ZYPREXA ZYDIS, ZYPREXA RELPREVV)	Orally disintegrating tablet: 5 mg 10 mg 15 mg 20 mg Tablet:	Schizophrenia: Oral formulations: initial, 5 to 10 mg PO daily; maintenance, 10 mg PO daily; max, 20 mg PO daily; adjust in increments of 5 mg daily. Long-acting injection: initial (during the first 8 weeks), 210 to 300 mg IM every 2 weeks or 405 mg IM every 4 weeks depending	Schizophrenia (13 to 17 years): Oral formulations: initial, 2.5 to 5 mg PO daily; target, 10 mg PO daily; max, 20 mg PO daily; adjust in increments of 2.5 to 5 mg. Bipolar disorder– manic or mixed episodes (13 to 17 years):	Lower starting dose recommended in debilitated or pharmaco-dynamically sensitive patients or patients with predisposition to hypotensive	Be aware that there are 2 olanzapine injectable formulations with different dosing schedules. Administer ZYPREXA without regard to meals.

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
	2.5 mg 5 mg 7.5 mg 10 mg 15 mg 20 mg Short-acting injection (vial): 10 mg Long-acting injection (vial): 210 mg 300 mg 405 mg	upon target oral olanzapine dose; maintenance (after the first 8 weeks of ZYPREXA RELPREVV), 150 to 300 mg IM every 2 weeks or 300 to 405 mg IM every 4 weeks depending upon target oral olanzapine dose; doses > 405 mg every 4 weeks or > 300 mg every 2 weeks have not been evaluated.* <u>Bipolar disorder– manic or mixed episodes:</u> Monotherapy (oral formulations): initial, 10 or 15 mg PO daily; maintenance, 5 to 20 mg PO daily; max, 20 mg PO daily; adjust in increments of 5 mg daily. Adjunct to lithium or valproate (oral formulations): initial, 10 mg PO daily; maintenance, 5 to 20 mg PO daily; max, 20 mg PO daily. <u>Bipolar disorder - depressive episodes (in combo with fluoxetine):</u> Oral formulations: initial, 5 mg PO daily in combination with fluoxetine 20 mg PO daily; maintenance, 5 to 12.5 mg PO daily in combination with fluoxetine 20 to 50 mg PO daily; doses > 18 mg olanzapine with 75 mg of fluoxetine have not been evaluated. <u>Agitation associated with schizophrenia and bipolar I mania</u>: Short-acting injection: initial, 2.5 to 10 mg IM up to every 2 hours; target dose, 10 mg IM (lower dose to 5 to 7.5 mg when clinical factors warrant); max, 30 mg IM daily <u>Treatment-resistant depression (in combo</u>	Oral formulations: initial, 2.5 or 5 mg PO daily; target, 10 mg PO daily; max, 20 mg PO daily; adjust in increments of 2.5 to 5 mg. <u>Bipolar disorder - depressive episodes (in combo with fluoxetine) (10 to 17 years)</u>: Oral formulations: initial, 2.5 mg PO daily in combination with fluoxetine 20 mg PO daily; maintenance, 2.5 to 12 mg PO daily in combination with fluoxetine 20 to 50 mg PO daily; doses > 12 mg olanzapine with 50 mg of fluoxetine have not been evaluated.	reactions, or with potential slowed metabolism. Recommended dosing for the powder for injection is based on correspondence to oral olanzapine doses.	ZYPREXA RELPREVV is available only through a restricted distribution program and must be administered by a healthcare professional; patient observation required for at least 3 hours after injection due to the potential for Post-Injection Delirium/Sedation Syndrome. Establish tolerability with oral olanzapine prior to initiating therapy with ZYPREXA RELPREVV.

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
		with fluoxetine): Oral formulations: initial, 5 mg PO daily in combination with fluoxetine 20 mg PO daily; maintenance, 5 to 20 mg PO daily in combination with fluoxetine 20 to 50 mg PO daily; doses > 18 mg olanzapine with 75 mg of fluoxetine have not been evaluated.			
Olanzapine/ fluoxetine (SYMBYAX)	Capsule: 3/25 mg 6/25 mg 6/50 mg 12/25 mg 12/50 mg	Bipolar disorder - depressive episodes and treatment-resistant depression: Initial, 6/25 mg once daily in the evening; maintenance, adjust dosage according to efficacy and tolerability; max, doses > 18/75 mg have not been evaluated	Bipolar disorder - depressive episodes (10 to 17 years): Capsule: initial, 3/25 mg once daily in the evening; maintenance, adjust dosage according to efficacy and tolerability; max, doses > 12/50 mg have not been evaluated	Discontinue treatment gradually.	Neonates exposed to SSRIs late in the third trimester have required prolonged hospitalizations, respiratory support, and tube feeding. Consider tapering dose for pregnant women during the third trimester.
Paliperidone (INVEGA, INVEGA SUSTENNA, INVEGA TRINZA)	Extended-release tablet: 1.5 mg 3 mg 6 mg 9 mg Long-acting injection: Once-a-month (INVEGA SUSTENNA): 39 mg 78 mg 117 mg 156 mg 234 mg Once every 3 months (INVEGA	Schizophrenia: Oral formulation:† initial, 6 mg PO daily; maintenance, 3 to 12 mg PO daily; max, 12 mg PO daily; titrate by 3 mg, increases > 6 mg should occur at intervals > 5 days and only after reassessment. Long-acting injection (INVEGA SUSTENNA): initial, 234 mg administered on treatment day one, followed by 156 mg one week later; maintenance, 117 mg (range, 39 to 234 mg) administered once monthly; max, 234 mg administered once monthly. Long-acting injection (INVEGA TRINZA): To be initiated only after 4 months of INVEGA SUSTENNA. INVEGA TRINZA dose depends on INVEGA SUSTENNA dose; INVEGA SUSTENNA 78 mg, 117 mg, 156 mg, or 234 mg doses	Schizophrenia (12 to 17 years) weighing < 51 kg: Oral formulation:† initial, 3 mg PO daily; maintenance, 3 to 6 mg PO daily; max, 6 mg PO daily; titrate by 3 mg at intervals > 5 days and only after reassessment; in one study, daily doses of 6 mg were not shown to be more efficacious. Schizophrenia, adolescents (12 to 17 years) weighing ≥ 51 kg: Oral formulation:† initial, 3 mg PO daily; maintenance, 3 to 12 mg PO daily; max, 12 mg PO daily; titrate by 3 mg at intervals > 5 days and only after reassessment; in one study, daily doses of 12 mg were not shown to be more efficacious.	For patients who have never taken oral paliperidone or oral or injectable risperidone, tolerability should be established with oral paliperidone or risperidone prior to initiating treatment with long-acting injectable paliperidone.	Tablets should be swallowed whole and should not be chewed, divided, or crushed. Administer the first 2 INVEGA SUSTENNA doses in the deltoid muscle. Following the second INVEGA SUSTENNA dose, doses can be administered in either the deltoid or gluteal muscle.

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
	TRINZA): 273 mg 410 mg 546 mg 819 mg	administered once monthly should be converted to INVEGA TRINZA 273 mg, 410 mg, 546 mg, or 819 mg doses administered once every 3 months, respectively; conversion from the INVEGA SUSTENNA 39 mg dose has not been studied. Schizoaffective disorder (monotherapy or adjunct to mood stabilizers or antidepressants): Oral formulation:† initial, 6 mg PO daily; maintenance, 3 to 12 mg PO daily; max, 12 mg PO daily; titrate by 3 mg in increments of > 4 days and only after reassessment. Long-acting injection (INVEGA SUSTENNA): initial, 234 mg administered on treatment day one, followed by 156 mg one week later; maintenance, 78 to 234 mg administered once monthly; max, 234 mg administered once monthly; the 39 mg dose has not been studied.			
Quetiapine (SEROQUEL, SEROQUEL XR)	Extended-release tablet: 50 mg 150 mg 200 mg 300 mg 400 mg Immediate-release tablet: 25 mg 50 mg 100 mg 200 mg 300 mg	Bipolar disorder - depressive episodes: Immediate-release tablet: initial, 50 mg PO once daily at bedtime; maintenance, 300 mg PO daily*; max, 300 mg PO daily Extended-release tablet: initial, 50 mg PO once daily; maintenance, 300 mg once PO daily*; max, 300 mg PO daily Bipolar disorder - manic episodes: Immediate-release tablet (monotherapy or as an adjunct to lithium or divalproex): initial, 50 mg PO twice daily; maintenance, 400 to 800 mg PO daily*; max, 800 mg PO daily	Bipolar disorder - manic episodes (10 to 17 years): Immediate-release tablet (monotherapy): initial, 25 mg PO twice daily; maintenance, 200 to 300 mg PO twice daily*; max, 600 mg PO daily Extended-release tablet (monotherapy): initial, 50 mg PO daily; recommended, 400 to 600 mg PO daily*; max, 600 mg PO daily Schizophrenia (13 to 17 years):	Dose titration is required.	Extended-release tablets should be swallowed whole and not split, chewed, or crushed. Administer extended-release tablets without food or with a light meal. Extended-release tablets should be administered once daily, preferably in the

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
	400 mg	Bipolar disorder – manic or mixed episodes: Extended-release tablet (monotherapy or as an adjunct to lithium or divalproex): initial, 300 mg PO once daily; maintenance, 400 to 800 mg PO once daily*; max, 800 mg PO daily Major depressive disorder: Extended-release tablet (as an adjunct to antidepressants): initial, 50 mg PO once daily; maintenance, 150 to 300 mg PO once daily*; max, 300 mg PO daily Schizophrenia: Immediate-release tablet: initial, 25 mg PO twice daily; maintenance, 150 to 750 mg PO daily*; max, 750 mg PO daily for acute treatment (≤ 6 weeks) and 800 mg PO daily for maintenance dosing Extended-release tablet: initial, 300 mg PO once daily; maintenance, 400 to 800 mg PO once daily*; max, 800 mg PO daily	Immediate-release tablet: initial, 25 mg PO twice daily; recommended, 200 to 400 mg PO twice daily*; max, 800 mg PO daily Extended-release tablet: initial, 50 mg PO daily; recommended, 400 to 800 mg PO daily*; max, 800 mg PO daily		evening. Administer immediate-release tablets without regard to food.
Risperidone (RISPERDAL, RISPERDAL CONSTA, RISPERDAL M-TAB)	Orally disintegrating tablet: 0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg Solution: 1 mg/mL Tablet:	Bipolar – manic or mixed episodes:‡: Oral formulations: initial, 2 to 3 mg PO daily; target, 1 to 6 mg PO daily; max, 6 mg PO daily Long-acting injection (monotherapy or as an adjunct to lithium or valproate): 25 mg IM every 2 weeks; maintenance, 25 to 50 mg IM every 2 weeks; max, 50 mg IM every 2 weeks Schizophrenia: Long-acting injection: 25 mg IM every 2 weeks; maintenance, 25 to 50 mg IM every	Bipolar – manic or mixed episodes (10 to 17 years): Oral formulations: initial, 0.5 mg PO once daily; dosage adjustments, if indicated, at intervals not less than 24 hours, in increments of 0.5 mg or 1 mg PO daily, as tolerated, to a recommended dose of 2.5 mg PO daily; no additional benefit was seen above 2.5 mg PO daily; doses higher than 6 mg PO daily were not studied	For the treatment of bipolar mania in adults, there is no clinical data supporting maintenance dosing. For the treatment of bipolar mania in children and adolescents, no additional benefit was seen with	For the treatment of bipolar mania, risperidone should be administered once daily. For the treatment of schizophrenia, risperidone should be administered once or twice daily. Oral RISPERDAL (or another antipsychotic)

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
	0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg Long-acting injection: 12.5 mg 25 mg 37.5 mg 50 mg	2 weeks; max, 50 mg IM every 2 weeks Oral formulations: initial, 2 mg PO once daily or 1 mg PO twice daily; target, 4 to 16 mg PO per day (divided into once or twice daily dosing); maintenance therapy, 2 to 8 mg PO daily; max, 16 mg PO daily; daily doses of > 6 mg per day for twice daily dosing were not were not shown to be more efficacious than lower doses.	Irritability associated with autistic disorder, children and adolescents aged 5 to 16 years§: Orally disintegrating tablet, oral solution, tablet: initial, 0.25 mg PO daily for patients < 20 kg and 0.5 mg daily for patients ≥ 20 kg; max, 1 mg PO daily in patients < 20 kg, 2.5 mg in patients ≥ 20 kg Schizophrenia, adolescents aged 13 to 17 years: Orally disintegrating tablet, oral solution, tablet: initial, 0.5 mg PO once daily; dosage adjustments, if indicated, at intervals not less than 24 hours, in increments of 0.5 mg or 1 mg PO daily, as tolerated, to a recommended dose of 3 mg PO daily; max, 6 mg PO daily	doses > 2.5 mg/day, and doses > 6 mg/day were not evaluated. Titrate the dose of RISPERAL CONSTA no sooner than every 4 weeks; clinical effects are observed ≥ 3 weeks after injection.	should be given with the first injection of RISPERDAL CONSTA, and continued for 3 weeks (and then discontinued) to ensure adequate concentrations of RISPERDAL CONSTA.
Ziprasidone (GEODON)	Capsule: 20 mg 40 mg 60 mg 80 mg Short-acting injection: 20 mg/mL	Acute agitation in schizophrenia: Injection: initial, 10 mg IM every 2 hours or 20 mg every 4 hours; max, 40 mg IM daily¶ Bipolar disorder – manic or mixed episodes: Capsule (monotherapy): initial, 40 mg PO twice daily; maintenance (monotherapy), 60 to 80 mg PO twice daily on day 2; maintenance (adjunct to lithium or valproate), 40 to 80 mg PO twice daily Schizophrenia: Capsule: initial, 20 mg PO twice daily; maintenance, 20 to 80 mg PO twice daily; max, 100 mg PO twice daily; no additional benefit for doses > 20 mg twice daily	Not FDA-approved	Not applicable.	Administer capsules with food. Administration of short-acting injection for more than 3 consecutive days has not been studied. If long term therapy is indicated, oral therapy should replace the injection as soon as possible. Coadministration of capsules and injection

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
					is not recommended.

Abbrv: ANC = absolute neutrophil count, BEN = Benign Ethnic Neutropenia, CBC = complete blood count, CYP = cytochrome isoenzyme, IM = intramuscularly, PO = orally, SL = sublingually, WBC = white blood count

*Please refer to individual package insert for dose titration and/or tapering guidance.

†Initial dose titration is not required.

‡There is no clinical data supporting maintenance dosing.

§No dosing data is available for children who weighed less than 15 kg.

¶Administration for more than 3 consecutive days has not been studied.

**In combination with fluoxetine 20 mg (adults and children)

††Short-acting injection is FDA-approved and guidance outlined in prescribing information; however, formulation has been discontinued.

SPECIAL POPULATIONS

Table 5. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy/ Nursing
Aripiprazole*	No dosage adjustment is recommended for elderly patients. Safety and effectiveness of aripiprazole lauroxil extended-release injection in patients > 65 years of age have not been evaluated.	Safety and effectiveness in pediatric patients < 13 years with schizophrenia, patients < 10 years with bipolar mania, and patients < 6 years with Tourette's or with irritability associated with autism have not been established. PK in patients aged 10 to 17 years was similar to adults. The long-acting injections have not been studied in children.	No dosage adjustment is required in subjects with renal impairment.	No dosage adjustment is required in subjects with hepatic impairment.	May cause EPS and/or withdrawal symptoms in neonates with third trimester exposure; discontinue drug or nursing.
Asenapine	Clinical studies did not include sufficient numbers of elderly patients to determine whether or not they respond differently than younger patients.	Safety and efficacy in the treatment of bipolar disorder in patients < 10 years of age, and patients with schizophrenia aged < 12 years have not been evaluated.	No dosage adjustment is required in subjects with renal impairment.	Contraindicated in patients with severe hepatic impairment.	May cause EPS and/or withdrawal symptoms in neonates with third trimester exposure; discontinue drug or nursing.
Brexpiprazole*	Has not been studied in patients aged ≥ 65 years; PK studies showed similar results to adults for MDD.	Safety and effectiveness have not been established. Antidepressants increase the risk of suicidal thoughts and behaviors in pediatric patients.	In moderate, severe, or end-stage renal impairment (CrCL < 60 mL/min), the max dose for MDD is 2 mg once daily and in schizophrenia is 3 mg once daily.	In moderate to severe hepatic impairment, the max dose for MDD is 2 mg once daily and in schizophrenia is 3 mg once daily.	May cause EPS and/or withdrawal symptoms in neonates with third trimester exposure; discontinue drug or nursing.
Cariprazine	Clinical studies did not include sufficient numbers of elderly patients to determine whether or not they respond differently	Safety and effectiveness have not been established.	Not recommended in severe renal impairment (CrCL < 30 mL/min).	Not recommended in severe hepatic impairment (Child-Pugh 10 to 15).	No adequate studies in pregnant women; use only if clearly needed. Drug is present in the milk

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy/ Nursing
	than younger patients.				of animal models; discontinue drug or nursing.
Clozapine*†	Clinical studies did not include sufficient numbers of elderly patients to determine whether or not they respond differently than younger patients. Elderly are more susceptible to hypotension, tachycardia, anticholinergic effects, and tardive dyskinesia.	Safety and effectiveness in pediatric patients have not been established.	Dose reductions may be needed in patients with renal impairment.	Dose reductions may be needed in patients with hepatic impairment.	No adequate studies in pregnant women; however, in general neonates with third trimester exposure have EPS and/or withdrawal symptoms with antipsychotic use. Drug is present in human milk; discontinue drug or nursing.
Iloperidone*	Clinical studies did not include sufficient numbers of elderly patients to determine whether or not they respond differently than younger patients.	Safety and effectiveness in pediatric patients have not been established.	Renal impairment (CrCL < 30 mL/min) had minimal effect on PK parameters.	Not recommended in severe impairment.	No adequate studies in pregnant women; use only if clearly needed. Drug is present in the milk of animal models; do not breastfeed.
Lurasidone	Clinical studies did not include sufficient numbers of elderly patients to determine whether or not they respond differently than younger patients.	Safety and effectiveness in pediatric patients have not been established.	PK bounds varied moderately in mild to severe impairment; dose should not exceed 80 mg/day in patients with CrCL < 50.	In severe impairment AUC was much higher than in mild to moderate impairment; dose reduction to max 40 mg/day recommended.	No adequate studies in pregnant women; use only if benefit outweighs risk. Discontinue drug or nursing.
Olanzapine	Consider a lower starting dose (2.5 mg to 5 mg short-acting injection) for any elderly patient if factors are present that might decrease PK clearance or increase the PD response. Clinical studies did not include sufficient numbers of elderly	Safety and effectiveness in pediatric patients with schizophrenia or manic/mixed bipolar I disorder < 13 years of age and < 10 years in combination with fluoxetine for acute treatment of depressive episodes have not been established.	No dosage adjustment is required in subjects with renal impairment. Has not been studied in long-acting injection formulations.	May reduce clearance; however a small study (N = 6) of cirrhosis patients showed very little PK effects. Has not been studied in long-acting injection formulations.	No adequate studies in pregnant women; use only if benefit outweighs risk. May cause EPS and/or withdrawal symptoms in neonates with third trimester exposure. Drug is present in human milk; do not breastfeed.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy/ Nursing
	patients in long-acting injection studies to determine whether or not they respond differently than younger patients.	Safety and effectiveness of the long-acting injection have not been established. Adolescents treated with oral olanzapine are more prone to weight gain, sedation, metabolic changes, prolactin, and AST increases.			
Olanzapine/ fluoxetine	Clinical studies did not include sufficient numbers of elderly patients to determine whether or not they respond differently than younger patients. Certain factors might decrease PK clearance or increase PD response; consider a lower starting dose (3/25 mg or 6/25 mg).	Safety and efficacy in pediatric patients with bipolar depression < 10 years have not been established. Safety and efficacy in treatment resistant depression has not been established. Adolescents treated with oral olanzapine are more prone to weight gain, sedation, metabolic changes, prolactin, and AST increases.	No dosing recom-mendations	Consider lower initial doses of SYMBYAX (3/25 mg or 6/25 mg) in hepatic impairment. Caution is advised when using SYMBYAX in patients with diseases or conditions that could affect its metabolism.	No adequate studies in pregnant women; fluoxetine exposure in the first trimester has had inconsistent results and the third trimester have resulted in complications requiring prolonged hospitalizations, respiratory support, and tube feeding. Use only if benefit outweighs risk. Drug is present in human milk; do not breastfeed.
Paliperidone Paliperidone palmitate‡	Because elderly patients may have diminished renal function, dose adjustment may be required according to their renal function status. In general, the recommended dosing for elderly patients with healthy renal function is the same as for younger adult patients with	Safety and effectiveness in pediatric patients with schizophrenia < 12 years of age have not been established. Safety and effectiveness in pediatric patients with schizoaffective disorder and other conditions have not been established. Safety and	Adjust dose to 3 to 6 mg once daily in mild renal impairment (CrCL 50 to 80 mL/ min); 1.5 to 3 mg once daily in moderate to severe impairment (CrCL 10 to 50 mL/ min). For mild impairment, SUSTENNA should be dosed at 156 mg on day 1 followed by 117	For patients with mild to moderate hepatic impairment no dose adjustment is recom-mended. Not studied in patients with severe hepatic impairment.	No adequate studies in pregnant women; however, in general neonates with third trimester exposure have EPS and/or withdrawal symptoms with antipsychotic use. Drug is present in human milk; discontinue drug or nursing.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy/ Nursing
	healthy renal function.	effectiveness of the long-acting injection in patients < 18 years of age have not been established.	mg one week later; subsequent dose should be 78 mg every month. TRINZA should be transitioned after stabilized on SUSTENNA. For moderate to severe impair-ment, long-acting injections are not recommended.		
Quetiapine	For elderly patients, consider a slower rate of dose titration and a lower target dose; when indicated, dose escalation should be performed with caution in these patients.	Safety and effectiveness in pediatric patients with schizophrenia < 13 years, and bipolar mania < 10 years have not been established. Increases in systolic and diastolic BP occurred in pediatric patients. Safety and effectiveness in bipolar depression have not been established.	Dosage adjustment not needed.	Start at a low dose of 50 mg for extended-release (XR) and 25 mg immediate-release (IR). Increase by 25 to 50 mg for IR and 50 mg for XR formulations.	Based on animal data, may cause fetal harm. Limited human data; only use if the benefit justifies the risk. Drug is present in human milk; discontinue drug or nursing.
Risperidone‡	Clinical studies did not include sufficient numbers of elderly patients to determine whether or not they respond differently than younger patients. Lower doses may be considered as elderly are susceptible to hypotension and risperidone is highly excreted by the kidneys.	Safety and effectiveness in pediatric patients with schizophrenia < 13 years, bipolar disorder < 10 years, and autistic disorder < 5 years have not been established. Pediatric patients treated with oral risperidone are prone to tardive dyskinesia, weight gain, somnolence,	For severe impairment (CrCL < 30 mL/min), start at 0.5 mg twice daily (see PI for dose titration). Long-acting injection should be initiated after patient is stable on the oral formulation.	For severe impairment (Child-Pugh C), start at 0.5 mg orally twice daily (see PI for dose titration). Long-acting injection should be initiated after patient is stable on the oral formulation.	Reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, feeding disorder, and corpus callosum were reported in neonates exposed in the third trimester. No data is available in humans with the long-acting injection. Drug is present in human milk; discontinue drug or

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy/ Nursing
		and elevated prolactin levels. Safety and efficacy of the long-acting injection in pediatric patients have not been established.			nursing.
Ziprasidone	Consider a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients. Ziprasidone IM has not been studied in this group.	Safety and effectiveness in pediatric patients have not been established.	Caution should be used in renal impairment with administration of IM formulations due to cyclodextrin, which is renally filtered.	Dose adjustments are not required but PK changes have been observed. Ziprasidone IM has not been studied in this group.	Based on animal data, may cause fetal harm. Limited human data; only use if the benefit justifies the risk. Drug is present in the milk of animal models; do not breastfeed.

Abbrv: AST = hepatic aminotransferase, ANC = absolute neutrophil count, AUC = area under the curve, BP=blood pressure, CrCL = creatinine clearance, EPS = extrapyramidal symptoms, IM = intramuscular, MDD = major depressive disorder, NMS = neuroleptic malignant syndrome, PD = pharmacodynamic, PI = prescribing information, PK = pharmacokinetic
*For CYP2D6 poor metabolizers dosage adjustments are recommended.
†For hospice patients (life expectancy ≤ 6 months), consider reducing the ANC monitoring frequency to once every 6 months.
‡Patients with Parkinson's disease or Dementia with Lewy Bodies can have increased sensitivity to long-acting injections, which may result in confusion, EPS, NMS, obtundation, and instability with frequent falls.

CONCLUSION

- The antipsychotics are divided into 2 distinct classes: typical antipsychotics, also called first generation antipsychotics, and atypical antipsychotics, also called second generation antipsychotics (Miyamato et al, 2005).
- There are a number of atypical antipsychotics formulations available as both branded and generic products. These agents are available in various dosage forms including capsules, tablets, injections, oral solutions, sublingual tablets, and orally disintegrating tablets. FDA-approved indications for the atypical antipsychotics include autism, bipolar disorder, Tourette's disorder, major depressive disorder, schizophrenia, and schizoaffective disorder. FDA-approved atypical agents include (Drugs@FDA, 2017):
  - Generic agents – aripiprazole, clozapine, iloperidone, olanzapine, paliperidone, quetiapine immediate- and extended-release, risperidone, ziprasidone, and olanzapine/fluoxetine
  - Branded agents – GEODON® (short-acting injection only), LATUDA®, REXULTI®, SAPHRIS®, VERSACLOZ® (oral suspension), and VRAYLAR™
  - Long-acting injections – ABILIFY MAINTENA®, ARISTADA™ , INVEGA SUSTENNA®, INVEGA TRINZA® (the only once every 3 months injection), RISPERDAL CONSTA®, and ZYPREXA RELPREVV®
- In terms of the pharmacology of the atypical antipsychotics, different chemical entities have different properties. Most atypical antipsychotics have a fairly long half-life (≥ 24 hours), except lurasidone, quetiapine, and ziprasidone. Aripiprazole lauroxil is the prodrug of aripiprazole, and paliperidone is the active metabolite of risperidone. The newly FDA-approved agent, cariprazine, has the longest half-life in the oral class (1 to 3 weeks for active metabolite); therefore, delayed adverse events have been reported. Clozapine can be highly toxic; therefore, clinicians should check plasma levels before exceeding a 600 mg dose. For the long-acting injectable agents, drug tolerability should be established prior to initiating the long-acting injectable treatment; a patient's response to an adjusted dose may not be seen for some time due to the long half-life. RISPERDAL CONSTA serum concentrations may not be seen until

approximately 3 weeks after injection. In certain slow metabolizers careful dose adjustment should be made as is the case with iloperidone and CYP2D6 slow metabolizers (Clinical Pharmacology, 2016; Micromedex 2.0, 2016).

- FDA-approved indications vary by diagnosis, age, or by use as mono- or adjunctive-therapy. All agents in class are indicated for use in schizophrenia with the exception of combination agent SYMBYAX (olanzapine/fluoxetine). Clozapine and paliperidone products, excluding INVEGA TRINZA, are indicated for the treatment of schizoaffective disorder, and clozapine is the only agent in class FDA-approved for treatment-resistant schizophrenia. Aripiprazole, olanzapine, quetiapine and risperidone are approved for use in patients ≥ 13 years of age and paliperidone oral products are approved for patients ≥ 12 years of age with schizophrenia. All oral agents in class are indicated for use in bipolar disorder, except clozapine, iloperidone, paliperidone, and REXULTI. RISPERDAL CONSTA is the only long-acting injectable indicated for the treatment of bipolar disorder. Aripiprazole, olanzapine/fluoxetine, risperidone, quetiapine, and SAPHRIS are approved for use in pediatric patients ≥ 10 years of age with bipolar disorder. Olanzapine is approved for use in patients ≥ 13 years of age with bipolar disorder. Aripiprazole and risperidone are the only agents indicated for the treatment of irritability associated with autistic disorder in pediatric patients (aged 6 to 17 years, and 5 to 17 years, respectively). Aripiprazole is the only agent indicated for the treatment of Tourette's disorder in pediatric patients, aged ≥ 6 years. Aripiprazole, REXULTI, and SEROQUEL XR are indicated as adjunctive treatment for major depressive disorder in patients already taking an antidepressant. Olanzapine, when prescribed in combination with fluoxetine, is indicated for treatment-resistant depression.
- Comparative effectiveness data is most available for the treatment of schizophrenia and schizophrenia-like psychosis in adults; however, outcomes are often inconsistent. Study evidence demonstrates that there are no consistent differences in the efficacy between the atypical antipsychotics in acute or short-term trials, although clozapine has often been touted as significantly more effective for patients with treatment-resistant schizophrenia compared to all other atypical antipsychotics (Leucht et al, 2013; Lieberman et al, 2005; Stroupe et al, 2006; Stroupe et al, 2009). In general, clozapine is often followed by olanzapine and risperidone in terms of improved efficacy (Lehman et al, 2004; Leucht et al, 2013). There is also very little evidence evaluating the long-acting injection agents and newer agents brexpiprazole, cariprazine, iloperidone, and lurasidone. Challenges associated with comparative effectiveness reviews are mainly due to high attrition rates, internal validity study concerns, and small sample sizes within trials.
- Each atypical antipsychotic has a distinctive chemical structure, mechanism of action, and neuropharmacologic and adverse event profile. It should be noted that paliperidone is an active metabolite of risperidone and therefore carries some similarity in chemical structure and pharmacologic effects with the parent drug. Plasma levels of cariprazine and its metabolite accumulate over time; adverse reactions may not appear until after several weeks of drug administration.
- Safety profiles vary between agents and are often an important component of treatment selection. The long-acting injection antipsychotics are often prescribed for patients who demonstrate adherence issues with oral formulations. Common adverse events observed within the class include extrapyramidal symptoms (EPS), increased prolactin levels, autonomic effects, metabolic effects, and cardiac risks including risk of ventricular arrhythmias (QT prolongation). When compared to the typical antipsychotics, the atypical antipsychotics are associated with a lower risk of EPS and tardive dyskinesia (with the exception of clozapine), making them a generally better-tolerated treatment option (Abou-Setta et al, 2012; Lehman et al, 2004; Seida et al, 2012[a]; Seida et al, 2012[b]; VA Pharmacy Benefits Management Services, 2012). However, certain atypical antipsychotic agents appear to have varying levels of risk according to the side effect profile (Jibson et al, 2016; Micromedex 2.0, 2016). The following factors may be considered when selecting certain agents in patients:
  - o Metabolic syndrome – Metabolic effects influencing weight gain, glycemic effects, and lipid profiles have been reported to fluctuate with all atypical antipsychotics. Clozapine and olanzapine have been associated with the highest risks; aripiprazole, lurasidone, and ziprasidone have been associated with lower risks. Despite the stratified risks, routine monitoring of metabolic measures is recommended for patients on all antipsychotics.
  - o EPS or tardive dyskinesia – Atypical antipsychotics have a lower risk of these side effects compared to typical antipsychotic agents. Tardive dyskinesia risks have been reported to be similar to the prevalence of EPS. Risperidone has been associated with a higher risk of EPS (up to 25% in adults); clozapine and quetiapine carry the lowest risk.
  - o Anticholinergic effects – Anticholinergic side effects include dry mouth, constipation, blurred vision, and urinary retention. Clozapine has the strongest affinity for muscarinic receptors among the agents in class; therefore, anticholinergic side effects are reported most often. This is followed by olanzapine and quetiapine.

- QT prolongation – QT prolongation has been reported with a number of atypical antipsychotic agents, but to a lesser degree than other classes of medications. Iloperidone and ziprasidone have been reported to prolong the QT interval (average increase in QTc of 9 to 10 msec) most often, and should be avoided in high risk patients. Those less likely to cause cardiac arrhythmias include aripiprazole, lurasidone, and cariprazine; however, very few studies have been conducted with lurasidone and cariprazine.
- Myocarditis and cardiomyopathy – Clozapine has been associated with fatal cases, often within the first few months of treatment.
- Orthostatic hypotension and tachycardia – Changes in heart rate and blood pressure are most frequently observed with clozapine (9 to 25%) and iloperidone (3 to 12%). In pediatric patients, quetiapine has been associated with increased systolic/diastolic pressure in 15 to 41% of patients, but in adults orthostatic hypotension and tachycardia have been reported in up to 7% of patients. Tachycardia has been reported in up to 16% of paliperidone-treated adult patients. Hypotension has been reported less frequently with aripiprazole, asenapine, brexpiprazole, cariprazine, and lurasidone. However, fewer studies have been conducted with the newer agents.
- Seizure – All atypical antipsychotics carry a risk for seizures; however, this appears to be associated with lowering the seizure threshold versus new-onset seizures. Incidences of seizure are most often reported with clozapine (3 to 5%), and to a lesser degree risperidone (0.3%)
- Prolactin levels and sexual side effects – Elevations of prolactin have been most associated with risperidone and paliperidone. This is particularly concerning in pediatric patients as it is associated with changes in estrogen and testosterone levels and may result in gynecomastia and menstrual disturbances. In pediatric patients administered risperidone, hyperprolactinemia has been reported in 49 to 87% of patients versus adults in which incidences range from 1 to 4% depending on formulation (IM or oral routes). Abnormal prolactin levels have also been associated with sexual dysfunction, infertility and galactorrhea. Of the atypical antipsychotics that are well studied, prolactin abnormalities are less frequently reported with olanzapine and ziprasidone. For patients in which sexual dysfunction is a concern, a number of MAs have referred to aripiprazole as the drug of choice (Serretti et al, 2011).
- Sedation – Clozapine is most associated with sedation (46%), followed by olanzapine (20 to 52%) and quetiapine (18 to 57%). In class, aripiprazole is unique as insomnia was reported in ≥ 10% of adult patients, but somnolence/fatigue and insomnia were reported in ≥ 10% of pediatric patients.
- Agranulocytosis – Agranulocytosis, leukopenia, and neutropenia are associated with use of clozapine. Within the first few months of treatment, this is particularly evident in patients with pre-existing low blood counts or those who had prior drug-induced blood dyscrasias. In 2015, the FDA made changes to the recommended monitoring within the clozapine REMS program around severe neutropenia (FDA Drug Safety Communication [clozapine], 2015).
- Hypersensitivity – Olanzapine and ziprasidone have a specific warning for a fatal drug reaction with eosinophilia and systemic symptoms or DRESS. In 2011, the FDA issued an alert on serious allergic reactions after 52 cases of Type I hypersensitivity reactions were reported with asenapine use (FDA Drug Safety Communication [Saphris], 2011).

- Newly FDA-approved agent, cariprazine, has demonstrated safe and effective use in doses ≤ 6mg/day for the treatment of bipolar disorder or schizophrenia in short-term adult trials (Calabrese et al, 2015; Durgam et al, 2015[a]; Durgam et al, 2014; Durgam et al, 2015[b]; FDA/CBER summary review, 2015; Kane et al, 2015[b]; Sachs et al, 2014). The most common adverse events with treatment are EPS and akathisia. The clinical implications of the long half-life have not been well characterized and some experts have cited safety concerns associated with the accumulating active metabolite. Although, one 72-week (N = 264) and one 48-week (N = 97) extension trial in patients with schizophrenia have demonstrated comparable results to short-term trials of 6 weeks. Patients who are able to persist on treatment maintained efficacy and tolerability at cariprazine doses of 1.5 to 9 mg daily during maintenance therapy (Durgam et al, 2016[a]; Durgam et al, 2016[b]).
- For the treatment of Tourette's disorder, aripiprazole has demonstrated safe and effective use compared to placebo in trials of 8 to 10 weeks in pediatric patients aged ≥ 6 years. Adverse events most frequently observed included sedation-like effects, nausea, headache, nasopharyngitis, and increased appetite (ABILIFY prescribing information, 2015; Gulisano et al, 2011; Yoo et al, 2013).
- For the treatment of irritability associated with autism, one small, low quality study (N = 59) compared the effects of aripiprazole and risperidone in patients aged 4 to 18 years over a period of 8 weeks, although FDA-approval

stipulates therapy should be initiated for ages 5 to 6 years. No differences were detected in terms of safety or efficacy; however, the ABC-I scores numerically favored risperidone (P = 0.06) (Ghanizadeh et al, 2014). Both agents have demonstrated safe and effective use in placebo controlled trials (Marcus et al, 2009; McCracken et al, 2002; Owen et al, 2009; Shea et al, 2004; McDougle et al, 2005). Based on current data, both agents appear to have similar efficacy and safety.

- For the treatment of major depressive disorder (MDD), aripiprazole, REXULTI (brexpiprazole), and SEROQUEL XR (quetiapine ER) have demonstrated effectiveness when combined with adjunctive treatment, generally in trials with a 6-week duration and combined with an SSRI or SNRI. Olanzapine/fluoxetine (SYMBYAX) has also demonstrated effectiveness in treatment-resistant depression. Most studies have been PC trials. REXULTI is the newest agent FDA-approved and has not been included in MAs. Primary efficacy results demonstrate efficacy vs placebo, and the safety profile appears to be similar to aripiprazole (Thase et al, 2015). One meta-analysis found all agents were more effective than antidepressant monotherapy in improving response and remission rates, although adjunctive atypical antidepressant therapy was associated with a higher discontinuation rate due to adverse effects (Wen et al, 2014). Another meta-analysis concluded aripiprazole and quetiapine may have an advantage in reducing remission (NNT, 9) compared to olanzapine/fluoxetine (NNT, 19) (Spielmans et al, 2013). More well-designed, head-to-head trials are needed to validate conclusions. Treatment was associated with several medication-specific adverse events, including akathisia (aripiprazole), sedation (quetiapine, olanzapine/fluoxetine, and aripiprazole), abnormal metabolic laboratory results (quetiapine and olanzapine/fluoxetine), and weight gain (all drugs, especially olanzapine/fluoxetine).
- For the treatment of bipolar disorder, a number of atypical antipsychotics have demonstrated effective use for managing symptoms associated with manic or mixed episodes; however, only a few agents have demonstrated efficacy for depressive episodes. In adolescents and children, aripiprazole, olanzapine, olanzapine/fluoxetine, risperidone, quetiapine, and SAPHRIS are FDA-approved for manic or mixed episodes, although only quetiapine and olanzapine/fluoxetine have been studied for depressive episodes. In an AHRQ SR, aripiprazole, olanzapine, ziprasidone, quetiapine, and risperidone were associated with greater improvements in response rates (NNT, 3 to 7) and increased remission rates (NNT, 2 to 12) compared to placebo (Seida et al, 2012[a]; Seida et al, 2012[b]). For depressive episodes, evidence is less clear, but point to efficacy with the FDA approved agents (Findling et al, 2014; Detke et al, 2015). In adult patients with bipolar disorder, selection of agents should be based on the adverse event profile and individual patient characteristics as all FDA-approved agents have demonstrated efficacy (Abou-Setta et al, 2012; Muralidharan et al, 2013). RISPERDAL CONSTA is the only long-acting injection agent in class that has demonstrated safe and effective use (McFadden et al, 2009; Quiroz et al, 2010; Vieta et al, 2012; Yatham et al, 2007). Although only lurasidone, quetiapine (immediate- and extended-release), and olanzapine/fluoxetine have demonstrated efficacy for depressive episodes, MAs have concluded that olanzapine/fluoxetine may be the optimal treatment compared to other treatment options for depressive episodes (Fornaro et al, 2016; Silva et al, 2013; Taylor et al, 2014; Vieta et al, 2010).
- For the treatment of schizophrenia, MAs evaluating the roles of available atypical antipsychotics in the treatment of schizophrenia suggest that all agents are significantly more effective than placebo. Most analyses and studies have demonstrated that with the exception of clozapine, the atypical antipsychotics do not separate out robustly from the typical antipsychotics with respect to overall efficacy and times to treatment discontinuation. The trends for respective efficacy suggest that clozapine, olanzapine, and risperidone may be more effective agents based on relapse and remission rates compared to typical antipsychotics or placebo; however, many atypical antipsychotics haven't been studied to the same extent as these agents. In general, due to high attrition rates in trials, validity is limited, thereby making it difficult to make strong conclusions (Abou-Setta et al, 2012; Asenjo Lobos et al, 2010; Asmal et al, 2013; Cipriani et al, 2011; Citrome et al, 2009; Durgam et al, 2014; Durgam et al, 2015[b]; Glick et al, 2011; Jones et al, 2010; Kane et al, 2015[b]; Khanna et al, 2014; Klemp et al, 2011; Komossa et al, 2009[a], Komossa et al, 2010[a]; Komossa et al, 2009[b]; Komossa et al, 2010[b]; Komossa et al, 2011; Kumar et al, 2013; Leucht et al, 2009[a]; Leucht et al, 2009[b]; Leucht et al, 2013; Lieberman et al, 2005; Perlis et al, 2006[b]; Riedel et al, 2010; Seida et al, 2012[a]; Seida et al, 2012[b]; Stroupe et al, 2006; Stroupe et al, 2009; Tarr et al, 2011; Vieta et al, 2010; Yildiz et al, 2011).
- The use of these agents for the treatment of schizophrenia is recognized by national and international guidelines as a mainstay in therapy. Guidelines vary by indication and the following outlines use in children, adolescents, and adults:

Adults

- Bipolar disorders – Guidelines recommend the use of drugs such as lithium, anticonvulsants and/or antipsychotics for the treatment of bipolar disorders (Hirschfeld et al, 2002; Hirschfeld et al, 2005; VA/DoD, 2010).
  - Drugs likely to be beneficial for bipolar mania include lithium, anticonvulsants (eg, valproate, carbamazepine), and atypical antipsychotics. Lithium or valproate may be combined with an atypical antipsychotic.
  - Treatment options for bipolar depression include lithium, lamotrigine, and certain atypical antipsychotics (eg, quetiapine, olanzapine in combination with fluoxetine, and lurasidone).
- MDD – In general, guidelines state that no particular antidepressant agent is superior to another in efficacy or time to response. Choice can be guided by matching patient's symptoms to side effect profile, presence of medical and psychiatric comorbidity, and prior response (VA/DoD, 2016; Gelenberg et al, 2010).
  - For the majority of patients, an SSRI, SNRI, bupropion or mirtazapine is optimal for first-line treatment. Atypical antipsychotics may be useful to augment antidepressant therapy (Gelenberg et al, 2010).
- Schizophrenia – Guidelines recommend that agents should be chosen based on clinical circumstances and side effects. Clozapine has the greatest efficacy on persistent hostility, aggressive behavior, suicidal behavior, and should be considered in patients with suicidal ideation; recent evidence has also demonstrated there may be lower rates of overall mortality with clozapine use. Clozapine should be used to treat persistent psychotic symptoms or treatment-resistant patients. A minimum of 6 weeks is needed for an adequate trial to establish efficacy. If a patient is non-adherent to treatment or has chronic relapse, a long-acting injectable antipsychotic agent may be considered (Dixon et al, 2009; Lehman et al, 2004; VA Pharmacy Benefits Management Services, 2012).

Children and Adolescents

- Use of atypical antipsychotics - According to guidelines from the American Academy of Child and Adolescent Psychiatry (AACAP), prior to the initiation of antipsychotic therapy, patients should undergo a thorough diagnostic assessment and evaluation for comorbid medical conditions and concomitant medications. Furthermore, a multidisciplinary plan that includes education and psychotherapy should be established. The prescriber should also have a thorough discussion about the risks and benefits of psychotropic treatment (Findling et al, 2011).
- Autism Spectrum Disorders (ASD) – AACAP guidelines state that pharmacotherapy may be considered in children with ASD when there is a specific target symptom or comorbid condition. Risperidone and aripiprazole are FDA-approved for irritability associated with autism; other drugs that have been studied include: clonidine, olanzapine, valproic acid, lamotrigine, levetiracetam, clomipramine, amantadine, pentoxifylline (in combination with risperidone), and naltrexone (Volkmar et al, 2014).
- Bipolar disorder – According to AACAP guidelines for treatment of children and adolescents with bipolar disorder, pharmacotherapy is the primary treatment for bipolar mania. Standard therapy includes lithium, valproate, and/or atypical antipsychotic agents, with other adjunctive medications used as indicated (McClellan et al, 2007).
- Schizophrenia – According AACAP guidelines, antipsychotics are a primary treatment for schizophrenia spectrum disorders in children and adolescents. The choice of agent is typically based on factors such as FDA-approval status, side effect profile, patient and family preference, and cost (McClellan et al, 2013).
- Tourette's disorder– According to AACAP guidelines for the treatment of children and adolescents with tic disorders, pharmacotherapy should be considered for moderate to severe tics causing severe impairment in quality of life, or when psychiatric comorbidities are present that can also be targeted. Most clinicians use atypical antipsychotics before first-generation agents and some prefer α-agonists over antipsychotic medications due to the adverse effect profile. Commonly used drugs include risperidone, aripiprazole, and clonidine (Murphy et al, 2013). The European Society for the Study of Tourette Syndrome guideline recommends risperidone as first-line treatment, aripiprazole for treatment-refractory patients, and clonidine for patients with co-morbid ADHD (Roessner et al, 2011).

- Pharmacologic therapy treatment is highly individualized and dependent on a number of patient characteristics and response to treatment. In certain patient groups, such as pediatric patients, liquid formulations are useful for better dose-control, so clinicians may titrate and taper doses in those that may have sensitive responses to treatment. Agents with different chemical structures have different clinical responses and adverse events; therefore, access to the atypical antipsychotic medication class is important in order to tailor therapies to individual patients.

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U. Xopenex® (Levalbuterol)

Therapeutic Class: Beta Adrenergic Agents
Last Reviewed by the DUR Board: July 26, 2012

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

1. Coverage and Limitations

   a. Authorization only for recipients experiencing side effects on one other beta-adrenergic agent of any formulation.

   b. Authorization for patients whose cardiovascular status is considered to be in severe deteriorating condition.

2. Prior Authorization Guidelines

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

Therapeutic Class Overview
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-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-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 mepolizumab and reslizumab for the management of severe asthma with an eosinophilic phenotype (Prescribing information: CINQAIR, 2016; NUCALA, 2015). Additionally, tiotropium, long used for COPD, has been FDA approved for the treatment of asthma (SPIRIVA RESPIMAT prescribing information, 2016).
- ICSs are the most effective, most commonly recommended long-term control medications used for the treatment of asthma. Alternative long-term control medications include leukotriene modifiers, mast-cell stabilizers, and methylxanthines; however, these agents are considered less effective as monotherapy compared to ICSs. The LABAs should not be used as monotherapy for the management of asthma; however, they are considered the most effective adjunctive therapy in patients who are not adequately controlled with an ICS alone. Tiotropium is an option for add-on therapy in certain patients requiring an additional controller medication. SABAs are the medication of choice for the relief of bronchospasm during acute exacerbations of asthma (NHLBI, 2007; GINA, 2016).
- 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], 2017).

- COPD affects more than 5% of the adult 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, 2012). 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, 2017).
- 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, 2017).
- Patients with COPD may experience exacerbations, which are periods of acute worsening of respiratory symptoms (GOLD, 2017).
- 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 characteristic of COPD (GOLD, 2017).
- 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, 2017).
- 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, 2017).
- Beta$_2$-agonists differ in their dosing requirements, pharmacokinetic parameters, and potential adverse effects. Several of the SABAs are available generically in at least one 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.
- The tables in this review are organized by whether the drug product is short- or long-acting. Note that extended-release albuterol is categorized as short-acting for the purposes of this review, along with the other albuterol products.
- Medispan class/subclass: Sympathomimetics/Beta Adrenergics

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	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)	Various	08/15/1996*	-
Albuterol solution for nebulization	Various	02/21/1992	✔
Albuterol, oral tablets, extended-release tablets, and syrup (VOSPIRE® ER and generics)	Various	varied	✔
Levalbuterol inhalation aerosol (XOPENEX® HFA and generic)	Various	03/11/2005	-†
Levalbuterol solution for nebulization (XOPENEX® and generics)	Various	03/25/1999	✔
Metaproterenol, oral tablets and syrup	Various	05/13/1974	✔
Terbutaline, oral tablet and injection	Various	04/22/1975	✔
Long-Acting beta$_2$-agonists (Inhaled)			
Arformoterol solution for nebulization (BROVANA®)	Sunovion	10/06/2006	-
Formoterol solution for nebulization (PERFOROMIST®)‡	Mylan	05/11/2007	-

Drug	Manufacturer	FDA Approval Date	Generic Availability
Indacaterol (ARCAPTA® NEOHALER)	Novartis	07/01/2011	-
Olodaterol (STRIVERDI® RESPIMAT®)	Boehringer Ingelheim	07/31/2014	-
Salmeterol (SEREVENT® DISKUS)	GlaxoSmithKline	09/19/1997	-

*PROVENTIL HFA

†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, 2016; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2016)

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	✔ ¶**	✔ **	✔	

*Age ≥4 years (HFA inhalation aerosols and dry power inhaler); age 2 to 12 years (solution for nebulization); age ≥2 years (syrup); age ≥6 years (tablets and extended-release tablets)

†Inhalation aerosols and powder only

‡Age ≥4 years (XOPENEX HFA); age ≥6 years (XOPENEX inhalation solution)

§Age ≥12 years

¶Only as a concomitant therapy with a long-term asthma control medication, such as an ICS

**Age ≥4 years

***Indicated for long-term, once daily maintenance treatment

(Prescribing information: albuterol solution, 2014; albuterol syrup, 2009; albuterol tablets, 2006; ARCAPTA NEOHALER, 2012; BROVANA, 2014; metaproterenol syrup, 2014; metaproterenol tablets, 2010; PERFOROMIST, 2013; PROAIR HFA, 2016; PROAIR RESPICLICK, 2016; PROVENTIL HFA, 2012; SEREVENT DISKUS, 2016; STRIVERDI RESPIMAT, 2016; terbutaline injection, 2011; terbutaline tablets, 2011; VENTOLIN HFA, 2014; VOSPIRE ER, 2012; XOPENEX HFA, 2015; XOPENEX inhalation solution, 2015)

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

- Clinical trials have demonstrated the efficacy of short-acting and long-acting beta$_2$-agonists in providing relief from asthma exacerbations, COPD exacerbations and exercise-induced asthma (EIA). In the clinical trials that evaluated these products 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; Schreck et al, 2005; Qureshi et al, 2005; Skoner et al, 2001; Nowak et al, 2006; Nelson et al, 1998; Gawchik et al, 1999; Milgrom et al, 2001; Sepracor Trial 1; Sepracor Trial 2; Nowak et al, 2004). In two studies (one retrospective, one prospective), levalbuterol resulted in a significantly lower hospitalization rate compared to albuterol (Carl et al, 2003; Schreck et al, 2005). In another trial, when the two 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). 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). Additionally, studies have shown no significant differences between the two agents in the peak change in FEV_1 and the number and incidence of adverse events experienced (Carl et al, 2003; Schreck et al, 2005; Qureshi et al, 2005; Skoner et al, 2001; Nowak et al, 2006; Nelson et al, 1998; Gawchik et al, 1999; Milgrom et al, 2001; Sepracor Trial 1; Sepracor Trial 2; Nowak et al, 2004).
- 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).
- 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 by Salpeter et al, salmeterol and formoterol both demonstrated an increase in severe exacerbations that required hospitalization, life-threatening exacerbations and asthma-related deaths in adults and children alike when compared to placebo (Salpeter et al, 2006). Due to the results of these studies, all LABAs are assigned a boxed warning stating that these agents may increase the risk of asthma-related death.
- A systematic review concluded that in patients with COPD, there was no difference in the rate of mild exacerbations between patients treated with an ICS or LABA (odd ratio, 1.63; 95% confidence interval [CI], 0.49 to 5.39) or in the rate of moderate or severe COPD exacerbations (rate ratio, 0.96; 95% CI, 0.89 to 1.02) (Spencer et al, 2011).
- The safety and efficacy of indacaterol were evaluated in randomized controlled trials that compared it to placebo and other agents used in the management of COPD (Feldman et al, 2010; Kornmann et al, 2011; Dahl et al, 2010; Korn et al, 2011; Magnussen et al, 2010; Balint et al, 2010; Donohue et al, 2010; Vogelmeier et al, 2010; Buhl et al, 2011; Chapman et al, 2011). Notably, most of these trials evaluated indacaterol in doses of 150, 300 and 600 µg once daily, rather than the FDA-approved dosing of 75 µg once daily (Feldman et al, 2010; Kornmann et al, 2011; Dahl et al, 2010; Korn et al, 2011; Magnussen et al, 2010; Balint et al, 2010; Donohue et al, 2010; Vogelmeier et al, 2010; Buhl et al, 2011; Chapman et al, 2011). However, results from placebo-controlled trials of indacaterol 75 µg have also been published, lending support to the use of the 75 µg dose (Kerwin et al, 2011; Gotfried et al, 2012).
- Overall, data from published clinical trials demonstrate 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 significant superiority is not consistently achieved (Feldman et al, 2010; Kornmann et al, 2011; Dahl et al, 2010; Korn et al, 2011; Magnussen et al, 2010; Balint et al, 2010; Donohue et al, 2010; Vogelmeier et al, 2010; Buhl et al, 2011; Chapman et al, 2011; Kerwin et al, 2011; Gotfried et al, 2012). 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 µg (Rodrigo et al, 2012; Cope et al, 2013).

- Placebo-controlled trials demonstrate that within five minutes after administration of indacaterol, significant improvements in bronchodilation are achieved (Magnussen et al, 2010; Balint et al, 2010; Donohue et al, 2010; Vogelmeier et al, 2010; Kerwin et al, 2011; Gotfried et al, 2012). These results have also been observed when comparing indacaterol to salmeterol, salmeterol/fluticasone, and tiotropium (Korn et al, 2011; Vogelmeier et al, 2010; Buhl et al, 2011).
- In two 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 five 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 versus 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 significantly improved FEV_1 AUC_{0-3} versus placebo in both studies (P<0.0001 for all comparisons) and trough FEV_1 versus 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 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, four-way cross-over group, Phase 3 studies investigated the long-term efficacy and safety of once-daily olodaterol via Respimat soft-mist inhaler versus placebo and formoterol over six 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 six 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}]) versus placebo in both studies (for all comparisons P<0.0001). No statistically significant differences were reported between the three active comparators (Feldman et al, 2014).
- A meta-analysis compared LABAs (salmeterol, formoterol, and indacaterol) to tiotropium and 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 was somewhat limited, but demonstrated a significant improvement in health-related quality of life, FEV_1 and exacerbations (Farne et al, 2015).

- For the treatment of EIA, albuterol, metaproterenol, and formoterol have demonstrated an improvement in FEV_1 compared to placebo (Berkowitz et al, 1986; Shapiro et al, 2002; Richter et al, 2002; Edelman et al, 2000; Storms et al, 2004, Bonini et al, 2013). In one 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

- 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, 2016).
- The Institute for Clinical Systems Improvement (ICSI) guideline follows a similar stepwise approach for asthma management (Sveum et al, 2012).
- The 2017 GOLD guidelines underwent a significant update from prior guideline versions. The 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, 2017):
    - 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 one bronchodilator, treatment should be escalated to two.
    - Long-term monotherapy with ICSs is not recommended. Long-term treatment with ICSs may be considered in association with LABAs for patients with a history of exacerbations despite treatment with long-acting bronchodilators.
    - Treatment recommendations are given for patients with COPD based on their GOLD patient group (see Table 3 below).
        - Group A: Patients should be offered bronchodilator treatment (short- or long-acting). This should be continued if symptomatic benefit is documented.
        - Group B: Initial therapy should consist of a long-acting bronchodilator (LAMA or LABA). For patients with persistent breathlessness on monotherapy, use of two bronchodilators is recommended (LAMA + LABA). For patients with severe breathlessness, initial therapy with two bronchodilators may be considered. If the addition of a second bronchodilator does not improve symptoms, it is suggested that treatment could be stepped down to a single bronchodilator.

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

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

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

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).
- 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-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

- Beta-agonists are generally contraindicated in patients with hypersensitivity to the drug or components of the formulation. SEREVENT 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-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

- It is also important to note that 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 one 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.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Generic Name	Available Formulations	Usual Recommended Dose (Adults)	Usual Recommended Dose (Pediatric)
Albuterol	Metered dose aerosol inhaler (HFA): 120 µg albuterol sulfate* (60† or 200 inhalations) Metered dose dry powder inhaler: 117 µg albuterol sulfate*/actuation (200 actuations) Solution for nebulization: 0.63 mg/3 mL 1.25 mg/3 mL 2.5 mg/3 mL 2.5 mg/0.5 mL Sustained-release tablet: 4 mg 8 mg Syrup: 2 mg/5 mL Tablet: 2 mg 4 mg	Treatment or prevention of bronchospasm in patients with asthma: Metered dose aerosol inhaler (HFA): 1 to 2 inhalations every 4 to 6 hours; maximum, 12 inhalations/day Dry powder inhaler: 2 inhalations every 4 to 6 hours; 1 inhalation every 4 hours may be sufficient for some patients Solution for nebulization: 2.5 mg three to four times daily Sustained-release tablet: 4 to 8 mg twice daily; maximum, 32 mg/day Syrup, tablet: 2 to 4 mg three to four times daily; maximum, 8 mg four times daily Exercise-induced bronchospasm: Aerosol and powder inhaler (HFA and dry powder): 2 inhalations 15 to 30 minutes before exercise	Treatment or prevention of bronchospasm in patients with asthma: Metered dose aerosol inhaler (HFA): 4 years of age and older: 1 to 2 inhalations every four to six hours; maximum, 12 inhalations/day Dry powder inhaler: 4 years of age and older: 2 inhalations every 4 to 6 hours: 1 inhalation every 4 hours may be sufficient for some patients Solution for nebulization: 2 to 12 years of age: 0.63 to 1.25 mg three to four times daily; maximum, 2.5 mg three to four times daily Sustained-release tablet: 6 to 12 years of age: 4 mg twice daily; maximum, 24 mg/day Syrup: 2 to 5 years of age: 0.1 mg/kg of body weight three times daily; maximum, 4 mg three times daily; 6 to 14 years of age: 2 mg three to four times daily; maximum, 24 mg/day Tablet: 6 to 12 years of age: 2 mg three to four times daily; maximum 24 mg/day

Generic Name	Available Formulations	Usual Recommended Dose (Adults)	Usual Recommended Dose (Pediatric)
			Exercise-induced bronchospasm: Metered dose aerosol inhaler (HFA): 4 years of age and older: 2 inhalations 15 to 30 minutes before exercise Dry powder inhaler: 4 years of age and older: 2 inhalations 15 to 30 minutes before exercise
Levalbuterol	Metered dose aerosol inhaler (HFA): 59 µg‡ (80 or 200 inhalations) Solution for nebulization: 0.31 mg 0.63 mg 1.25 mg (0.5 and 3 mL vials)	Treatment or prevention of bronchospasm in patients with asthma: Metered dose aerosol inhaler (HFA): 1 to 2 inhalations every 4 to 6 hours Solution for nebulization: 0.63 mg three times daily every 6 to 8 hours; maximum, 1.25 mg three times daily	Treatment or prevention of bronchospasm in patients with asthma: Metered dose aerosol inhaler (HFA): 4 years of age and older: 1 to 2 inhalations every 4 to 6 hours Solution for nebulization: 6 to 11 years of age: 0.31 mg three times daily; maximum, 0.63 mg three times daily
Metaproterenol	Syrup: 10 mg/5 mL Tablet: 10 mg 20 mg	Treatment or prevention of bronchospasm in patients with asthma and treatment of reversible bronchospasm occurring in association with emphysema and bronchitis: Syrup, tablet: 20 mg three to four times daily	Treatment or prevention of bronchospasm in patients with asthma: Syrup, tablet: 6 to 9 years of age (or weight under 60 lb): 10 mg three to four times daily
Terbutaline	Injection: 1 mg/mL (2 mL vial) Tablet: 2.5 mg 5 mg	Treatment or prevention of bronchospasm in patients with asthma: Injection: 0.25 mg subcutaneously in the lateral deltoid area, may repeat in 15 to 30 minutes if improvement does not occur; maximum, 0.5 mg in 4 hours Tablet: 2.5 to 5 mg three times daily, 6 hours apart; maximum, 15 mg in 24 hours Treatment of reversible bronchospasm occurring in association with emphysema and bronchitis: Injection: 0.25 mg subcutaneously in the lateral deltoid area, may repeat in 15 to 30 minutes if improvement does not occur; maximum, 0.5 mg in 4 hours	Treatment or prevention of bronchospasm in patients with asthma: Injection: Safety and efficacy in children less than 12 years of age have not been established. Tablet: 12 to 15 years of age: 2.5 mg three times daily, 6 hours apart; maximum, 7.5 mg in 24 hours

Generic Name	Available Formulations	Usual Recommended Dose (Adults)	Usual Recommended Dose (Pediatric)
		Tablet: 2.5 to 5 mg three times daily, 6 hours apart; maximum, 15 mg in 24 hours	
Arformoterol	Solution for nebulization: 15 µg (2 mL)	Maintenance treatment of bronchoconstriction in COPD: Solution for nebulization: 15 µg twice daily	Safety and efficacy in children have not been established.
Formoterol	Solution for nebulization: 20 µg/2 mL	Maintenance treatment of bronchoconstriction in COPD: Solution for nebulization: 20 µg twice daily; maximum 40 µg/day	Safety and efficacy in children have not been established.
Indacaterol	Capsule for inhalation: 75 µg	Maintenance treatment of airway obstruction in COPD: Capsule for inhalation: 75 µg daily	Safety and efficacy in children have not been established.
Olodaterol	Inhalation spray: 2.5 µg per actuation	Long-term, maintenance treatment of airway obstruction in COPD: 5 µg (two inhalations) once daily at the same time of day	Safety and efficacy in children have not been established.
Salmeterol	Dry powder inhaler: 50 µg (28 or 60 inhalations)	Treatment or prevention of bronchospasm in patients with asthma: Dry powder inhaler: 1 inhalation twice daily Exercise-induced bronchospasm: Dry powder inhaler: 1 inhalation at least 30 minutes before exercise Maintenance treatment of bronchoconstriction in COPD: Dry powder inhaler: 1 inhalation twice daily	Treatment or prevention of bronchospasm in patients with asthma: Dry powder inhaler: 1 inhalation twice daily Exercise-induced bronchospasm: Dry powder inhaler: 1 inhalation at least 30 minutes before exercise

*Delivering 108 µg of albuterol (90 µg albuterol base).
†VENTOLIN HFA available as 60 and 200 inhalations; other albuterol inhalers available only as 200 inhalations.
‡Delivering 45 µg levalbuterol base.

SPECIAL POPULATIONS

Table 4. Special Populations

Generic Name	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
Short Acting beta$_2$-agonists					
Albuterol	Limit initial dose to 2 mg three to four times daily in the elderly population (oral IR dosage forms) Not sufficiently studied in patients 65 years of age and older (inhalation dosage forms)	Approved for use in children 2 years of age and older (oral IR and solution for nebulization dosage forms) Approved for use in children 4 years of age and older (HFA inhaler and dry powder inhaler) Approved for use in children 6 years of age and older (oral ER tablet)	No dosage adjustment required	No dosage adjustment required	Pregnancy Category C† Unknown whether excreted in breast milk
Levalbuterol	Not sufficiently studied in patients 65 years of age and older	Approved for use in children 4 years of age and older (HFA inhaler) Approved for use in children 6 years of age and older (solution for nebulization)	Decrease in racemic albuterol clearance; use caution	Not studied	Pregnancy Category C Unknown whether excreted in breast milk
Metaproterenol	Not sufficiently studied in patients 65 years of age and older	Tablets not recommended for children under 6 years Syrup has been studied in a limited number of children under 6 years; daily doses of 1.3 to 2.6 mg/kg were well-tolerated	Not reported	Not reported	Pregnancy Category C Unknown whether excreted in breast milk
Terbutaline	Not sufficiently studied in patients 65 years of age and older	Approved in children 12 years of age and older	Not reported	Not reported	Pregnancy Category C Unknown whether excreted in

Generic Name	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
					breast milk
Long Acting beta$_2$-agonists					
Arformoterol	Dosage adjustment not required in the elderly population	Safety and efficacy in children not established	No dosage adjustment required	Use with caution	Pregnancy Category C Unknown whether excreted in breast milk
Formoterol	Dosage adjustment not required in the elderly population	Safety and efficacy in children not established	Not studied	Not studied	Pregnancy Category C Unknown whether excreted in breast milk
Indacaterol	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients	Safety and efficacy in children not established	Not studied	No dosage adjustment required for mild or moderate impairment; not studied in severe impairment	Pregnancy Category C Unknown whether excreted in breast milk
Olodaterol	Dosage adjustment not required in the elderly population	Safety and efficacy have not been established	No dosage adjustments required in patients with severe renal impairment	No dosage adjustment required for mild or moderate impairment; not studied in severe impairment	Pregnancy Category C Probable that STRIVERDI RESPIMAT is excreted in breast milk; use with caution
Salmeterol	Dosage adjustment not required in the elderly population	Approved in children 4 years of age and older	Not studied	Not studied; however, since drug is cleared through hepatic metabolism, impairment may lead to accumulation. Monitor closely	Pregnancy Category C Unknown whether excreted in breast milk

ER=extended-release, IR=immediate-release

*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.

†Although most albuterol products are in Pregnancy Category C, the FDA's Pregnancy and Lactation Labeling Rule (PLLR) directs that pregnancy categories be replaced with a risk summary, clinical considerations, and other data. Labeling changes will be phased in gradually; currently, PROAIR RESPICLICK is not assigned a pregnancy category. Please see prescribing information for additional details.

CONCLUSION

- The single-entity respiratory beta$_2$-agonists are FDA-approved for the treatment of asthma, COPD, reversible airway obstruction and/or exercise-induced bronchospasm. The agents in this class are classified as short-acting or long-acting beta$_2$-agonists based on their onset and duration of action. These agents are available in a variety of dosage forms, including solution for nebulization, aerosol inhaler, dry powder inhaler, oral solution, tablet, and solution for injection. The SABAs are generally dosed multiple times per day for the treatment or prevention of symptoms. When used for maintenance treatment of COPD, the LABAs are typically administered twice daily, with the exception of indacaterol and olodaterol, which are administered once daily.
- The National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program guidelines, as well as other national and international guidelines, recommend the use of SABAs for patients in all stages of asthma, for symptomatic relief of reversible airway disease and for exercise-induced bronchospasm. These medications should generally be used on an as-needed or "rescue" basis. Guidelines recommend that in the 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 dose of the ICS. LABAs can 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 β_2-agonist can lead to tolerance, and daily use of LABA monotherapy is not recommended (NHLBI, 2007; GINA, 2016; Sveum et al, 2012; Parsons et al, 2013; Weiler et al, 2016).
- The 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 β_2-agonist and/or an anticholinergic agent (GOLD, 2017).
- Overall, SABAs have demonstrated similar efficacy and safety. Similarly, guidelines do not recommend one LABA over another, and head-to-head clinical trials have been inconclusive to determine superiority of any one agent. All LABAs have a boxed warning stating that these agents may increase the risk of asthma-related death. It is important to note that 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.

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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 (UptoDate, 2016).
  - 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 owing to heart disease
  - Group 3 – PH owing 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 seven to 26 cases per million adults (Pogue et al, 2016). The disease has a poor prognosis and an approximate mortality rate of 15% within one year on therapy (McLaughlin et al, 2009). The median survival in the 1980s was 2.8 years; this has improved to seven 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 three pathways critical to its pathobiology: the prostacyclin, endothelin, and nitric oxide pathways (Wu et al, 2013). There are currently 10 molecular entities within five therapeutic classes that are Food and Drug Administration (FDA)-approved for the treatment of PAH (Facts and Comparisons, 2016).
  - 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. ADEMPAS (riociguat) has the additional FDA approval for treating adults with persistent/recurrent CTEPH (WHO Group 4) after surgical treatment or inoperable CTEPH. ADEMPAS is the first and only drug to be FDA-approved in the treatment of CTEPH. Pulmonary endarterectomy is curative for CTEPH, but it is technically demanding which may limit access to its use as a treatment (Archer, 2013).
- In PAH, prostacyclin synthase is reduced resulting in inadequate production of prostacyclin I_2, a potent vasodilator with antiproliferative effects and an inhibitor of platelet aggregation (McLaughlin et al, 2009). PCAs, iloprost and treprostinil, were developed as chemically stable alternatives to epoprostenol, which requires continuous IV infusion due to its lack of stability (Asaki et al, 2015). ORENITRAM™ (treprostinil) is the first FDA-approved oral PCA. It may represent a more convenient dosage form to the other treprostinil formulations (REMODULIN® and TYVASO®). However, patients with more severe PAH are likely to receive infused PCA rather than oral therapy (McLaughlin et al, 2009). Among these agents, epoprostenol IV is the only agent which has demonstrated improved patient survival in high risk PAH patients (Galiè et al, 2015[b]). UPTRAVI® (selexipag) works at the same pathway as the PCAs, but activates the IP receptor, also known as the prostacyclin receptor. ORENITRAM and UPTRAVI are the only orally administered agents that work within the prostacyclin pathway (Asaki et al, 2015).
- Endothelial dysfunction in PAH causes increased production of endothelin-1 resulting in vasoconstriction, which is mediated by the endothelin receptors, ET_A and ET_B. Stimulation of ET_A causes vasoconstriction and cell proliferation, while stimulation of ET_B results in vasodilatation, antiproliferation and endothelin-1 clearance. The ERAs (LETAIRIS® [ambrisentan], OPSUMIT® [macitentan], and TRACLEER® [bosentan]) competitively bind to both receptors with different affinities. LETAIRIS and OPSUMIT are highly selective for the ET_A receptor, while TRACLEER is slightly selective for the ET_A receptor over the ET_B receptor. In addition, OPSUMIT has a pharmacologically active metabolite and is considered “tissue-targeting” because it displays high affinity and sustained occupancy at the ET receptors in human pulmonary arterial smooth muscles. However, the clinical significance of receptor affinities of the ERAs has not been established (McLaughlin et al, 2009).
- In patients with PAH, there is also an impaired release of nitric oxide by the vascular endothelium, thereby reducing cGMP concentrations. The PDE-5 enzyme is the predominant phosphodiesterase in the pulmonary vasculature and is responsible for the degradation of cGMP. The PDE-5 inhibitors, REVATIO® (sildenafil) and ADCIRCA® (tadalafil), increase the concentrations of cGMP resulting in relaxation of the pulmonary vascular bed.
- Medispan class: Cardiovascular Agents, Miscellaneous – Prostaglandin Vasodilators; Pulmonary Hypertension: Endothelin Receptor Antagonists, Phosphodiesterase Inhibitors, Prostacyclin Receptor Agonist, and Soluble Guanylate Cyclase Stimulator

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
ERAs			
LETAIRIS (ambrisentan)	Gilead	06/15/2007	-
OPSUMIT (macitentan)	Actelion	10/18/2013	-
TRACLEER (bosentan)	Actelion	11/20/2001	-
PDE-5 inhibitors			
ADCIRCA (tadalafil)	Eli Lilly	05/22/2009	-
REVATIO (sildenafil)	Pfizer	06/03/2005	✔ *
Prostacyclin receptor agonist			
UPTRAVI (selexipag)	Actelion Pharmaceuticals	12/21/2015	-
PCAs			
FLOLAN (epoprostenol)	GlaxoSmithKline	4/14/2000	✔
VELETRI (epoprostenol)	Actelion Pharmaceuticals	8/25/2010	-
ORENITRAM (treprostinil)	United Therapeutics	12/20/2013	-
REMODULIN (treprostinil)	United Therapeutics	5/21/2002	-
TYVASO (treprostinil)	United Therapeutics	7/30/2009	-
VENTAVIS (iloprost)	Actelion Pharmaceuticals	12/29/2004	-
sGC stimulator			
ADEMPAS (riociguat)	Bayer Healthcare	10/08/2013	-

*REVATIO tablet and IV formulations are currently available generically; however, the oral suspension is brand-only.

(Drugs@FDA, 2016; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2016)

INDICATIONS

Table 2. FDA-approved Indications

Indication	ADCIRCA (tadalafil)	ADEMPAS (riociguat)	FLOLAN (epoprostenol)	LETAIRIS (ambrisentan)	OPSUMIT (macitentan)	ORENITRAM (treprostinil)	REMODULIN (treprostinil)	REVATIO (sildenafil)	TRACLEER (bosentan)	TYVASO (treprostinil)	UPTRAVI (selexipag)	VELETRI (epoprostenol)	VENTAVIS (iloprost)
Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening				✔ *				✔ §	✔ †				
Treatment of PAH (WHO Group I) to improve exercise ability	✔ ¶		✔ ≠			✔ ¶¶	✔ ₴			✔ Ω		✔ ₳	
Treatment of PAH (WHO Group I) to delay disease progression and reduce hospitalization					✔ **						✔ ‡		
Treatment of PAH (WHO Group I) to improve exercise capacity, to improve WHO FC, and to delay clinical worsening		✔											✔ ¥

Indication	ADCIRCA (tadalafil)	ADEMPAS (riociguat)	FLOLAN (epoprostenol)	LETAIRIS (ambrisentan)	OPSUMIT (macitentan)	ORENITRAM (treprostinil)	REMODULIN (treprostinil)	REVATIO (sildenafil)	TRACLEER (bosentan)	TYVASO (treprostinil)	UPTRAVI (selexipag)	VELETRI (epoprostenol)	VENTAVIS (iloprost)
Treatment of persistent/recurrent CTEPH (WHO Group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO FC		✔											
Treatment of PAH (WHO Group I), in combination with ADCIRCA to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability				✔ *									

Abbrv: NYHA=New York Heart Association, PAH=pulmonary arterial hypertension, WHO=World Health Organization, CTEPH=chronic thromboembolic pulmonary hypertension

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

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

‡Studies included predominantly WHO FC II to III. Patients had idiopathic PAH (58%), PAH associated with connective tissue diseases (29%), and PAH associated with congenital systemic-to-pulmonary shunts (10%).

§Studies included predominately patients with NYHA class II or III symptoms and etiologies of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%).

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

¥Studies included predominately patients with NYHA class III or IV symptoms and etiologies of idiopathic or heritable PAH (65%) or PAH associated with connective tissue diseases (23%).

ΩStudies included predominately patients with NYHA class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

₳Studies included predominately patients with NYHA class III or IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.

≠Studies included predominately patients with NYHA class III or IV symptoms and etiologies of idiopathic or heritable PAH (49%) or PAH associated with connective tissue diseases (51%).

Ƨ Studies establishing effectiveness included predominately patients with New York Heart Association (NYHA) FC II to IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with connective tissue diseases (19%), and PAH associated with congenital systemic-to-pulmonary shunts (23%).** Disease progression included death, initiation of IV or SC prostacyclin vasodilators, or clinical worsening of PAH (decreased 6-minute walk distance (6MWD), worsened PAH symptoms, and need for additional PAH treatment).

¶¶The study that established effectiveness included predominantly patients with WHO FC II and III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%). As the sole vasodilator, ORENITRAM has not been shown to add to other vasodilator therapy.

(Prescribing information: ADCIRCA, 2015; ADEMPAS, 2014; FLOLAN, 2016; LETAIRIS, 2015; OPSUMIT, 2016; ORENITRAM, 2016; REMODULIN, 2014; REVATIO, 2015; TRACLEER, 2016; TYVASO, 2016; UPTRAVI, 2015; VELETRI, 2016; VENTAVIS, 2013)

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 two. 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 eight-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 one 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 one year in CHEST-2. In the observed population at one 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 one year in CHEST-2, 145 (92%) out of 157 were continuing to receive monotherapy, and 12 (8%) patients were receiving additional PH-specific medication (eight [5%] were receiving ERAs and four [3%] were receiving prostanoids). No patient required additional treatment with both an ERA and prostanoid at one 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 two 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 one of three treatment groups: placebo (n=126), an exploratory capped titration arm of ADEMPAS 1.5 mg three times daily (n=63), or a capped maximum dose of ADEMPAS 2.5 mg three 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 eight-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 two, four, six, eight, and 12, and every three months thereafter. At the March 2013 data cut-off, 324 patients (82%) were receiving ongoing treatment and 84% had received one 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 one year and 79% (95% CI, 74 to 82%) at two 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 two similar, open-label, randomized trials of eight 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 eight to 12 weeks compared with those receiving conventional therapy alone. Improvements were noted as early as week one. 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). ARIES-E was the open-label extension study for ARIES-1 and ARIES-2. After one 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 two 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 three 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 seven days. Pre-specified secondary endpoints included change from baseline to month six 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 two identical 12-week, multi-center, randomized, placebo-controlled, double-blind trials in a total of 470 patients with NYHA Class II, III, and IV PAH. REMODULIN was administered SC at an average dose of 9.3 ng/kg/min. The effect on the 6MWD was small and did not achieve statistical significance at 12 weeks. For the combined populations, the median change from baseline for patients on REMODULIN was 10 m and the median change from baseline on placebo was 0 m from a baseline of approximately 345 m. The Borg dyspnea score was significantly improved by REMODULIN during the 6-minute walk test. REMODULIN also consistently improved indices of dyspnea, fatigue, and signs and symptoms of PH. However, these results were difficult to interpret in the context of incomplete blinding to treatment assignment resulting from infusion site symptoms.

ORENITRAM (treprostinil)

- The efficacy and safety of ORENITRAM were evaluated in three 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 three-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 two 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 three months prior to study initiation. Patients received either placebo or TYVASO in four daily treatments with a target dose of nine breaths (54 mcg) per session. The primary endpoint, 6MWD, was measured at peak exposure (10 to 60 minutes post dose) and three to five 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 one, two, and three 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 seven days after the last day of treatment intake. Compared to placebo, UPTRAVI significantly reduced the composite endpoint signifying the time to progression of PAH, defined as all-cause death or a PAH complication (27% vs. 41.6%; HR, 0.6; 99% CI, 0.46 to 0.78; P<0.001); however, there were no differences in mortality between groups. The reduction in PAH complications was primarily driven by a reduction in disease progression (17.2% vs. 6.6%) and PAH-related hospitalization (18.7% vs. 13.6%). The safety of UPTRAVI compared to other agents in class is not clear. The GRIPHON pre-specified sub-group analysis did not stratify AEs by background treatment, but the study allowed stable doses of PDE-5 inhibitors and/or an ERA which accounted for ~80% of patients within the placebo baseline group. Those AEs that occurred significantly more often with UPTRAVI treatment included headache, diarrhea, jaw pain, nausea, myalgia, vomiting, extremity pain, flushing (P<0.001 for all AEs), anemia (P=0.05), and hyperthyroidism (P=0.004) (Sitbon et al, 2015).

VELETRI (epoprostenol)

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

VENTAVIS (iloprost)

- The efficacy of VENTAVIS was evaluated in a 12-week, randomized, multicenter, double-blind, placebo-controlled trial consisting of 203 patients with NYHA Class III PAH (majority), Class IV PAH, or CTEPH. Patients received 2.5 or 5 mcg of VENTAVIS six to nine 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, two year, open-label study with 63 PAH patients. Patients received VENTAVIS 2 to 4 mcg six to nine times daily. Thirty-six patients completed at least 630 days of therapy, 19 patients dropped out prematurely, and eight 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 (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 (relative risk [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).

- 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).

Treatment Guidelines

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

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

SAFETY SUMMARY

- sGC Stimulator
  - ADEMPAS has a boxed warning due to embryo-fetal toxicity. It is contraindicated in pregnancy (Pregnancy Category X) because it may cause fetal harm when administered to pregnant women.
  - Females can only receive ADEMPAS through the ADEMPAS REMS Program, a restricted distribution program that requires enrollment and certification of prescribers, patients, and pharmacies. The program also requires females of reproductive potential to comply with pregnancy testing and contraception requirements.
  - 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.
  - TRACLEER has an additional boxed warning for risks of hepatotoxicity and birth defects. Throughout treatment and for one month after stopping TRACLEER, females of reproductive potential must use two reliable methods of contraception unless the patient has had a tubal sterilization or had an intrauterine device (IUD) inserted.
  - Warnings and precautions for ADCIRCA and REVATIO include prolonged erection (for more than four hours), hearing loss, and vision loss (in one or both eyes), all of which require immediate medical attention.
  - Pulmonary edema has been reported during postmarketing surveillance of LETAIRIS and TRACLEER. Pulmonary edema may occur within weeks after starting LETAIRIS and is more common when LETAIRIS is used in combination with ADCIRCA than with LETAIRIS or ADCIRCA alone.
  - Use of OPSUMIT and TRACLEER should be avoided in patients taking potent inhibitors or inducers of CYP3A.
  - Decreases in sperm count, decreased hemoglobin and hematocrit levels, and pulmonary edema (associated with pulmonary veno-occlusive disease (PVOD) have been observed in patients taking ERAs.
- PDE-5 Inhibitors
  - All PDE-5 inhibitor products have a contraindication for use in patients on nitrates as well as a warning with concomitant alpha blocker use due to resulting hypotension. The patient should allow 48 hours to elapse between the last dose of ADCIRCA and taking nitrates. Additionally, REVATIO and ADCIRCA are contraindicated for concomitant use with the sGC stimulator, ADEMPAS.
  - In August 2012, the prescribing information for REVATIO was updated with a warning stating that the use of REVATIO in pediatric patients is not recommended due to increased mortality associated with higher doses and noted that lower doses are not effective in improving exercise capacity. The FDA clarified the warning related to pediatric use of REVATIO in March 2014, stating it was not intended to suggest that REVATIO never be used in children. The FDA acknowledged there may be situations in which the benefit-to-risk profile may be acceptable in individual children, for example, when other treatment options are limited, in which case REVATIO can be used with close monitoring (FDA Drug Safety Communication, 2014).

- Co-administration of REVATIO or ADCIRCA with potent CYP3A4 inhibitors is not recommended. Co-administration of ADCIRCA with potent CYP3A4 inducers is not recommended.
- Blood pressure lowering effects are increased when ADCIRCA is taken with alcohol.
- REVATIO and ADCIRCA are generally well tolerated with headaches, myalgia, flushing, and dyspepsia being the most common AEs reported for both products.

- 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).
  - UPTRAVI should be avoided when concomitantly administered with strong inhibitors of CYP2C8.
  - The most common AEs reported with UPTRAVI are headache, diarrhea, jaw pain, nausea, myalgia, vomiting, pain in extremity, and flushing. These AEs are more frequent during the dose titration phase.
- PCAs
  - ORENITRAM is contraindicated for use in patients with severe hepatic impairment (Child Pugh Class C).
  - FLOLAN and VELETRI are contraindicated in patients with congestive heart failure due to severe left ventricular dysfunction. Additionally, VELETRI is contraindicated in patients with pulmonary edema
  - 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.
  - 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 pulmonary edema, vasodilation reactions, and an increased risk of bleeding.
  - Both FLOLAN and REMODULIN are administered via an indwelling central venous catheter. This route of administration is associated with blood stream infections (BSI) and sepsis, which may be fatal. During long-term follow-up, sepsis was reported at a rate of 0.3 infections per patient per year in patients treated with FLOLAN. In an open-label study of IV REMODULIN (n=47), there were seven catheter-related line infections during approximately 35 patient years, or about one BSI event per five years of use. A Centers for Disease Control and Prevention survey of seven sites that used IV REMODULIN for the treatment of PAH found approximately one BSI event per three years of use. Continuous SC infusion (undiluted) is the preferred mode of administration of REMODULIN.
  - 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	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
ADCIRCA (tadalafil)	Tablet: 20 mg	40 mg once daily	Dividing the dose over the course of the day is not recommended. Use with Ritonavir: In patients receiving ritonavir for at least one week, ADCIRCA should be started at 20 mg once daily. Dose should be increased to 40 mg once daily based on tolerability. During the initiation of ritonavir, ADCIRCA should be avoided. ADCIRCA should be stopped at least 24 hours prior to starting ritonavir. After at least one week, ADCIRCA may be resumed at 20 mg once daily. Dose may be increased to 40 mg once daily based on tolerability.	With or without food
ADEMPAS (riociguat)	Tablet (film-coated): 0.5, 1, 1.5, 2, and 2.5 mg	Initial: 1 mg three times daily Maximum: 2.5 mg three times daily	Starting dose may be lowered to 0.5 mg three times daily in patients unable to tolerate the hypotensive effects and patients receiving strong CYP and P-gp/BCRP inhibitors. Dose increases should be no sooner than 2 weeks apart.	Patients who smoke may tolerate doses higher than 2.5 mg three times daily. If they stop smoking, dose decreases may be required.
FLOLAN (epoprostenol)	Powder for injection: 0.5, 1.5 mg	Initial: 2 ng/kg/min continuous infusion; dose may be increased in increments of 1 to 2 ng/kg/min every 15 minutes based on clinical response	If dose-limiting pharmacologic effects occur, the infusion rate should be decreased gradually until tolerated. 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	Initial, 5 mg once daily with or without ADCIRCA 20 mg once daily; at four-week intervals, the dose may be	Doses >10 mg once daily have not been studied.	With or without food. Tablets should not be split, crushed, or chewed.

DRUG	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		increased up to LETAIRIS 10 mg or ADCIRCA 40 mg once daily		Treatment should be initiated in women of reproductive potential only after a negative pregnancy test. Monthly pregnancy tests should be conducted during treatment.
OPSUMIT (macitentan)	Tablet: 10 mg	10 mg once daily	Doses >10 mg once daily are not recommended.	-
ORENITRAM (treprostinil)	Extended-release tablet: 0.125, 0.25, 1, and 2.5 mg	Starting dose: 0.25 mg twice daily Maximum dose is determined by tolerability.	Dose should be titrated by 0.25 or 0.5 mg twice daily or 0.125 mg three times daily, not more than every three to four days as tolerated. Coadministration with CYP2C8 inhibitors (eg, gemfibrozil) requires a reduced starting dose of 0.125 mg twice daily and can be titrated in 0.125 mg twice daily increments every three to four days.	Should be taken with food Tablets should be swallowed whole When converting from SC/IV to oral routes, use the following equation to estimate the total daily oral dose: ORENITRAM total daily dose (mg) = 0.0072 x SC or IV dose (ng/kg/min) x weight (kg); decrease the SC/IV dose up to 30 ng/kg/min/day while increasing ORENITRAM dose up to 6 mg/day, as tolerated.
REMODULIN (treprostinil)	Multi-dose vials for injection: 20, 50, 100, 200 mg	Continuous infusion should be initiated at a rate of 1.25 ng/kg/min; dose may be reduced to 0.625 ng/kg/min if initial dose cannot be tolerated	The infusion rate should be increased by increments of 1.25 ng/kg/min for the first 4 weeks of treatment and then 2.5 ng/kg/min per week for the remaining duration of infusion, depending on clinical response	SC is preferred, although it can be administered by a central IV line if SC administration is not tolerated
REVATIO (sildenafil)	Tablet: 20 mg Powder for oral suspension: 10	Tablet and powder for oral suspension: 5 or 20 mg three times daily,	Doses above 20 mg three times daily are not recommended.	Should be administered four to six hours apart.

DRUG	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	mg/mL Powder for injection: 10 mg	approximately four to six hours apart Injection: 2.5 mg or 10 mg as an IV bolus 3 times daily	A 10 mg dose of REVATIO injection is predicted to provide pharmacological effect of REVATIO and its metabolite equivalent to that of a 20 mg oral dose.	The expiration date of the reconstituted oral suspension is 60 days from the date of reconstitution.
TRACLEER (bosentan)	Tablet: 62.5 and 125 mg	Initial: 62.5 mg twice daily for four weeks Maintenance: 125 mg twice daily	Initial and maintenance dose is 62.5 mg twice daily for patients with body weight below 40 kg and over 12 years of age. In patients who have been receiving ritonavir for at least 10 days, TRACLEER should be started at 62.5 mg once daily or every other day based on tolerability. TRACLEER should be discontinued at least 36 hours prior to initiation of ritonavir. After at least 10 days following the initiation of ritonavir, TRACLEER should be resumed at 62.5 mg once daily or every other day based on tolerability.	Should be administered in the morning and evening, with or without food. Treatment should be initiated in women of reproductive potential only after a negative pregnancy test. Monthly pregnancy tests should be conducted during treatment.
TYVASO (treprostinil)	Inhalation solution: 0.6 mg/mL (1.74 mg per 2.9 mL)	Initial: Three breaths (18 mcg), per treatment session, four times a day (four hours apart) during waking hours. Maximum: Nine breaths per treatment session, four times daily.	If three breaths are not tolerated, the number of breaths may be reduced to one to two and subsequently increased to three breaths as tolerated. Dosage should be increased by an additional three breaths at approximately one to two week intervals, if tolerated, until the target dose of nine breaths (54 mcg) is reached per treatment session, four times daily.	The 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	Initial: 200 mcg orally twice daily. Dose should be titrated weekly in increments of 200 mcg twice daily.	If a patient reaches a dose that cannot be tolerated, the dose should be reduced to the previous tolerated dose.	If treatment is missed for ≥ three days, UPTRAVI should be started at a lower dose and retitrated.

DRUG	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		Maximum: 1600 mcg twice daily		
VELETRI (epoprostenol)	Powder for injection: 0.5, 1.5 mg	Initial: 2 ng/kg/min continuous infusion; dose may be increased in increments of 1 to 2 ng/kg/min every 15 minutes based on clinical response.	If dose-limiting pharmacologic effects occur, the infusion rate should be decreased gradually until tolerated. 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, 20 mcg	Initial: 2.5 mcg via inhalation. Maintenance: 2.5 to 5 mcg, based on tolerability. VENTAVIS is administered six to nine times per day (no more than once every two hours) during waking hours, according to individual need and tolerability.	Vital signs should be monitored while initiating VENTAVIS	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.

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

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
ADCIRCA (tadalafil)	No dose adjustment is required in patients >65 years of age without renal or hepatic impairment. A greater sensitivity in some older patients should be considered.	Safety and efficacy have not been established.	Mild (CrCL 51 to 80 mL/min) or moderate (CrCL 31 to 50 mL/min): Start dose at 20 mg once daily. Increase to 40 mg daily based on individual tolerability. Severe (CrCL<30 mL/min and on	Mild or moderate (Child Pugh Class A or B): Consider starting dose of 20 mg once per day due to limited clinical experience. Severe (Child Pugh Class C): Not studied, avoid use.	Pregnancy category B Unknown whether excreted in breast milk; use with caution.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
			hemodialysis): Avoid use**		
ADEMPAS (riociguat)	No dose adjustments required in older patients (65 years and older). A greater sensitivity in some older patients cannot be ruled out.	Safety and efficacy have not been established.	Not recommended in patients with CrCL <15 mL/min or on dialysis	Not recommended in patients with severe liver impairment (Child Pugh C)	Pregnancy category X Discontinue nursing or the drug.
FLOLAN (epoprostenol)	Clinical studies did not include a sufficient number of patients ≥65 years of age to determine if they respond differently from younger patients.	Safety and efficacy have not been established.	Not studied	Not studied	Pregnancy category B Unknown whether excreted in breast milk; use with caution.
LETAIRIS (ambrisentan)	The elderly (age ≥65years) showed less improvement in walk distances than younger patients. However no specific dose adjustments are needed.	Safety and efficacy have not been established.	Dose adjustment in patients with mild or moderate renal impairment is not required. There is no information for patients with severe renal impairment.	Not recommended in patients with moderate or severe hepatic impairment. Discontinue LETAIRIS if elevations of liver aminotransferases are >5x ULN or if elevations are accompanied by bilirubin >2x ULN, or by signs or symptoms of liver dysfunction and other causes are excluded.	Pregnancy category X Discontinue nursing or the drug.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
OPSUMIT (macitentan)	No dose adjustments required in patients ≥65 years.	Safety and efficacy have not been established.	Exposure to macitentan and its active metabolite in patients with severe renal impairment (CrCl 15 to 29 mL/min) compared to healthy subjects was increased by 30% and 60%, respectively. This increase is not considered clinically relevant.	Exposure to OPSUMIT was decreased by 21%, 34%, and 6% and exposure to the active metabolite was decreased by 20%, 25%, and 25% in subjects with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, and C), respectively. This decrease is not considered clinically relevant.	Pregnancy category X Discontinue nursing or the drug.
ORENITRAM (treprostinil)	Clinical studies did not include a sufficient number of patients ≥65 years of age to determine if they respond differently from younger patients.	Safety and efficacy have not been established.	No dose adjustments are required.	Mild (Child Pugh Class A): Initial, 0.125 mg twice daily. Titrate by 0.125 mg every three to four days Moderate (Child Pugh Class B): Avoid use Severe (Child Pugh Class C): Contraindicated	Pregnancy category C Discontinue nursing or the drug.
REMODULIN (treprostinil)	Clinical studies did not include a sufficient number of patients ≥65 years of age to determine if they respond differently from younger patients.	Clinical studies did not include sufficient numbers of patients aged ≤16 years to determine whether they respond differently from older patients.	Not studied	Mild to moderate: Initial dose should be decreased to 0.625 ng/kg/min ideal body weight, and monitored closely Severe: Not studied	Pregnancy category B Unknown whether excreted in breast milk; use with caution.
REVATIO (sildenafil)	Clinical studies did not include a	Use of REVATIO,	No dosage adjustment	Mild to moderate: No dose	Pregnancy category B

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
	sufficient number of patients ≥65 years of age to determine if they respond differently from younger patients. Dose selection should be cautious.	particularly chronic use, is not recom-mended in children.	required (including with severe impairment CrCL <30 mL/min)	adjustment Severe: Not studied	 Unknown whether excreted in breast milk; use with caution.
TRACLEER (bosentan)	Clinical studies of TRACLEER did not include sufficient numbers of patients ≥65 years of age to determine whether they respond differently from younger patients.	Safety and efficacy have not been established.	No dosing adjustments required	Moderate to Severe (Child Pugh Class B and C): Avoid use.	Pregnancy category X Discontinue nursing or the drug.
TYVASO (treprostinil)	Clinical studies did not include a sufficient number of patients ≥65 years of age to determine if they respond differently from younger patients.	Safety and efficacy have not been established.	Not studied	Mild to moderate: Slow up-titration is recommended. Severe: Not studied	Pregnancy category B Unknown whether excreted in breast milk; use with caution.
UPTRAVI (selexipag)	Clinical studies did not include a sufficient number of patients ≥65 years of age to determine if they respond differently from younger patients. Dose selection should be cautious.	Safety and efficacy have not been established.	No dosing adjustments required in patients with eGFR >15 mL/min/1.73 m^2. Not studied in dialysis patients or in eGFR <15 mL/min/1.73 m^2.	Mild (Child Pugh Class A): No dose adjustment necessary Moderate (Child Pugh Class B): Starting dose of 200 mcg once daily; titrate weekly by 200 mcg once daily Severe (Child Pugh Class C): Not studied, avoid use.	No human studies; animal models show no clinically relevant effects on embryofetal development. Discontinue drug or breastfeeding.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
VENTAVIS (iloprost)	Clinical studies did not include a sufficient number of patients ≥65 years of age to determine if they respond differently from younger patients. Dose selection should be cautious.	Safety and efficacy have not been established.	Not studied	Not studied	Pregnancy category C Discontinue nursing, due to the importance of the drug to the mother.
VELETRI (epoprostenol)	Clinical studies did not include a sufficient number of patients ≥65 years of age to determine if they respond differently from younger patients. Dose selection should be cautious.	Safety and efficacy have not been established.	Not studied	Not studied	Pregnancy category B Unknown; use with caution.

Abbrv: CrCL = creatinine clearance; eGFR=estimated glomerular filtration rate; ULN = upper limit of normal
*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an AE on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Pregnancy Category X = Contraindicated in pregnant women due to evidence of fetal abnormalities from AE data from investigational or marketing experience. Risks of use of the drug in pregnant women clearly outweigh potential benefits.
**Due to increased ADCIRCA exposure (AUC), limited clinical experience, and lack of ability to influence clearance by dialysis

CONCLUSION

- Pulmonary arterial hypertension (PAH) is a life-threatening disorder that is associated with a poor prognosis.
- There are five classes of drugs that are used in the management of PAH, including endothelin receptor antagonists (ERAs), phosphodiesterase (PDE)-5 inhibitors, a prostacyclin analog (PCA), a prostacyclin receptor agonist, and a soluble guanylate cyclase (sGC) stimulator.
- All of the PAH agents have shown improved pulmonary hemodynamics and exercise capacity in PAH patients as compared to placebo. Their effects on mortality have not been adequately demonstrated.
- Most trials for PAH have been relatively short-term trials (12 to 18 weeks) that evaluated changes in exercise capacity using the 6-minute walk distance (6MWD) as a primary endpoint. However, recently there has been a preference toward longer, event-driven trials that evaluate composite clinical worsening events (LeVarge et al, 2015). Published event-driven trials include SERAPHIN, GRIPHON, AMBITION, and COMPASS-2 (Galiè et al, 2015[a]; McLaughlin et al, 2015; Pulido et al, 2013; Sitbon et al, 2015).
- Clinical trials have demonstrated the safety and efficacy of the individual PAH agents; however, there is limited data comparing the agents within classes or between classes. Data is conflicting regarding the benefits of combination vs. monotherapy (Barst, 2009; McLaughlin et al, 2009; Galiè et al, 2015[b]; Taichman et al, 2014). Two recent trials evaluating this include the AMBITION and COMPASS-2 trials. The AMBITION trial has demonstrated that combination treatment with LETAIRIS and ADCIRCA resulted in reduced disease progression and hospitalization in mainly FC II and III PAH patients compared to monotherapy (Galiè et al, 2015[a]). However, the COMPASS-2 trial

demonstrated no difference between TRACLEER plus REVATIO versus REVATIO monotherapy for most endpoints with the exception of the mean 6MWD test (McLaughlin et al, 2015).

- ADEMPAS is the first and only drug to be FDA-approved in the treatment of CTEPH. Pulmonary endarterectomy can be curative for CTEPH, but it is technically demanding which may limit access to its use as a treatment. ADEMPAS is dosed three times daily, which is more frequent than several other oral treatments for PAH.
- The ERAs (LETAIRIS, OPSUMIT, and TRACLEER) competitively bind to both receptors with different affinities. LETAIRIS and OPSUMIT are highly selective for the ET_A receptor, while TRACLEER is slightly selective for the ET_A receptor over the ET_B receptor. In addition, OPSUMIT has a pharmacologically active metabolite and is considered "tissue-targeting" because it displays high affinity and sustained occupancy at the ET receptors in human pulmonary arterial smooth muscles. However, the clinical significance of receptor affinities of the ERAs has not been established.
- The PDE-5 inhibitors (ADCIRCA and REVATIO) are generally well tolerated; the most common side effects include headache, myalgia, flushing, dizziness, and gastrointestinal upset. Both products are contraindicated for use in patients on nitrates and have warnings about their use in patients on alpha-adrenergic inhibitors. Use of ADCIRCA with potent CYP3A4 inhibitors or inducers may significantly alter serum levels of ADCIRCA and is not recommended. Use of ADCIRCA in patients who are using a sGC stimulator may potentiate the hypotensive effects of sGC stimulators and is not recommended. Use of REVATIO with potent CYP3A4 inhibitors is not recommended as they may significantly alter serum levels of REVATIO.
- In addition to the oral formulation, REVATIO is available in an oral suspension formulation and an intravenous formulation. Currently, REVATIO tablets are available generically.
- ADCIRCA is taken just once a day compared to three times a day with REVATIO.
- ORENITRAM is the first oral PCA approved by the FDA. The PCAs are frequently reserved for more severe forms of PAH. As the first oral option in this subclass for treatment of PAH, ORENITRAM may offer a more convenient alternative dosage form leading to earlier PCA initiation in treatment. ORENITRAM is dosed twice daily and requires dosage titration every 3 to 4 days. ORENITRAM did not demonstrate added benefit when added to other vasodilator therapy.
- UPTRAVI is a first-in-class prostacyclin receptor agonist, which works within the same pathway as ORENITRAM. Based on results from the GRIPHON trial, UPTRAVI has reduced disease progression and hospitalization. This is in contrast to ORENITRAM, which has only improved exercise tolerability. Unlike ORENITRAM, UPTRAVI has also demonstrated efficacy when combined with a PDE-5 inhibitor and/or an ERA. The safety of UPTRAVI compared to other oral agents in class is not clear. The GRIPHON pre-specified sub-group analysis did not stratify AEs by background treatment, but the study allowed stable doses of PDE-5 inhibitors and/or an ERA throughout the trial. Background treatment was used by ~80% of patients within the placebo baseline group. Those AEs reported significantly more often with UPTRAVI treatment include headache, diarrhea, jaw pain, nausea, myalgia, vomiting, extremity pain, flushing, anemia, and hyperthyroidism (Sitbon et al, 2015). Based on indirect trial evidence, the proportion of patients discontinuing UPTRAVI vs. placebo (14% vs. 7%) due to AEs in the GRIPHON trial was higher than those within the ORENITRAM labeling vs. placebo (4% vs. 3%) (ORENITRAM prescribing information, 2014; Sitbon et al, 2015). Overall, it is not clear how the UPTRAVI safety profile compares to other agents in class due to different study populations. Head-to-head trials are needed to confirm safety risks and differences.
- The 2014 CHEST Guideline and Expert Panel Report update identifies PDE-5 inhibitors, ERAs, the oral PCA, and the sGC stimulator as viable alternatives in treating PAH adults with varying severity levels (FC II to IV) based primarily on consensus opinions (Taichman et al, 2014).
- The 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines stratifies PAH treatment by low or intermediate risk or high risk patients. In adult patients with low or intermediate risk (FC II to III), initial monotherapy or initial oral combination therapy is recommended. Based on the AMBITION trial, guidelines state that initial combination treatment with ambrisentan plus tadalafil has proven to be superior to initial monotherapy with ambrisentan or tadalafil in delaying clinical failure. In adult patients with high risk (FC IV), initial combination therapy including IV PCAs are recommended with epoprostenol IV considered first-line due to the mortality benefits in trials (Galiè et al, 2015[b]).
- Reputable society group guidelines agree that there is a lack of randomized trials in pediatric patients, making it difficult to deliver strong guidelines (Abman et al, 2015; Galiè et al, 2015[b]; Hansmann et al, 2016). The 2015 American Heart Association and American Thoracic Society guidelines recommend oral therapy with either a PDE-5 inhibitor or an ERA in lower risk PAH pediatric patients. In pediatric patients with higher-risk PAH, IV and SC PCAs should be initiated immediately with a goal to transition patients to oral or inhaled therapy after the patient is asymptomatic and stable (Abman et al, 2015). The 2015 ESC/ERS guidelines recommend that pediatric treatment follows adult guidelines taking in account risks (Galiè et al, 2015[b]). The European Pediatric Pulmonary Vascular

Disease Network, the International Society of Heart and Lung Transplantation, and the German Society of Pediatric Cardiology reaffirm much of the aforementioned guidance, but also stipulate that early combination therapy with two oral PAH drugs in treatment-naïve children who are FC II or III may be considered (Hansmann et al, 2016).

Table 5. Advantages and Disadvantages of PAH Agents

Drug	Advantages	Disadvantages
ERAs		
LETAIRIS (ambrisentan)	• Highly selective potent ET_A receptor antagonist • Indicated for treatment of PAH in patients with WHO Class II or III symptoms, to improve exercise capacity and to delay clinical worsening • Administered once daily with or without food (may require titration)	• Boxed warning for embryo-fetal toxicity and required REMS restricted distribution program • Contraindication in patients with IPF, including IPF patients with pulmonary hypertension (WHO Group III) • Not recommended for use in patients with moderate or severe hepatic impairment
OPSUMIT (macitentan)	• Newest ERA indicated to delay disease progression • "Tissue-targeting" in human pulmonary arterial smooth muscle cells • Administered once daily with or without food (no titration required)	• Boxed warning for embryo-fetal toxicity and required REMS restricted distribution program • Requires baseline and periodic lab tests prior to treatment initiation
TRACLEER (bosentan)	• First oral agent to be approved for PAH • Efficacy demonstrated as both monotherapy and in combination treatment	• Administered twice daily • Non-selectively blocks both ET_A and ET_B receptors • Boxed warning for teratogenicity with required participation in REMS restricted distribution program • Additional boxed warning related to hepatotoxicity • Use in patients with moderate to severe hepatic impairment should be avoided • Contraindication in patients receiving either cyclosporine A or glyburide • Potential teratogenic effects • Multiple drug interactions
PDE-5 inhibitors		
ADCIRCA (tadalafil)	• Administered once daily with or without food • Efficacy demonstrated as both monotherapy and in combination treatment	• Contraindicated with concomitant organic nitrates and sGC stimulator • Dose reductions needed in patients with mild and moderate renal and hepatic impairment
REVATIO (sildenafil)	• Available in multiple formulations (tablets, injection, and oral suspension) • Generic availability	• Administered three times daily • Contraindicated with concomitant organic nitrates and sGC stimulator
Prostacyclin receptor agonist		
UPTRAVI (selexipag)	• First in class, prostacyclin receptor agonist • Efficacy demonstrated as both monotherapy and in combination treatment (with an ERA and/or	• Administered twice daily • Requires dose titration between 200 mcg and 1600 mcg twice daily • Requires dose reduction in moderate hepatic impairment; not recommended for

Drug	Advantages	Disadvantages
	PDE-5 inhibitor)	use in severe hepatic impairment
PCAs		
FLOLAN (epoprostenol)	• First approved drug for the treatment of PAH, so more data and experience with this drug • Generic availability	• Risk of BSI due to use of an indwelling central venous catheter • Requires use of complex delivery system • Risk of rebound PH with abrupt discontinuation or large dose decreases • Vials must be refrigerated and infusion must be kept cool with ice packs (unless reconstituted solution was prepared with pH 12 sterile diluent for FLOLAN, in which case it is stable for 72 hours at a room temperature of up to 77°F)
ORENITRAM (treprostinil)	• First FDA-approved oral PCA	• Administered twice daily • Contraindicated in patients with Child-Pugh Class C hepatic impairment • Tablets must be swallowed whole and taken with food • Has not demonstrated benefit in combination therapy. • Abruptly lowering the dose or withdrawing the drug should be avoided
REMODULIN (treprostinil)	• Can be administered SC as an alternative to IV administration • Longer half-life compared to FLOLAN • Vials and solution are stable at room temperature (no need for ice packs), regardless of which compatible diluent is used	• Risk of BSI due to use of an indwelling central venous catheter with IV administration • Pain associated with SC administration
TYVASO (treprostinil)	• Administered via inhalation	• Must be administered 4 times daily, at equally spaced intervals • Safety and efficacy of have not been established in patients with significant underlying lung disease (eg, asthma or chronic obstructive pulmonary disease)
VELETRI (epoprostenol)	• Vials and solution are stable at room temperature (no need for ice packs), regardless of which compatible diluent is used • Reconstitution easier and more flexible	• Risk of BSI due to use of an indwelling central venous catheter • Requires use of complex delivery system • Risk of rebound PH with abrupt discontinuation or large dose reductions
VENTAVIS (iloprost)	• Administered via inhalation	• Frequent administration is required (6 to 9 times daily). • May cause bronchospasm, especially in patients with a history of hyperreactive airway disease
sGC stimulator		
ADEMPAS (riociguat)	• First in class, sGC stimulator • First FDA-approved treatment for CTEPH (WHO Group IV)	• Administered three times daily • Requires lower initial doses in patients with intolerable hypotensive effects • Requires higher doses in patients who smoke • Boxed warning for embryo-fetal toxicity and

Drug	Advantages	Disadvantages
		required REMS restricted distribution program

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Therapeutic Class Overview
Insulins

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, 2016).
- The classification of diabetes includes four clinical classes: 1) Type 1 diabetes which results from beta-cell (β-cell) destruction, usually leading to absolute insulin deficiency, 2) Type 2 diabetes 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, 2016).
- In 2012, an estimated 29.1 million people, or 9.3% of the U.S. population, had diabetes, of which, 8.1 million were estimated to be undiagnosed (ADA Diabetes Basics, 2016; Centers for Disease Control [CDC], 2014).
- The insulin products are approved for use in the management of both types 1 and 2 diabetes. Other pharmacologic options for type 2 diabetes include sulfonylureas, biguanides, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogs, 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.
- The first insulin products were derived from animal sources, primarily pork and beef; however, they are no longer available in the United States (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. 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 per milliliter (U-200).
  - Basal insulin products, also known as intermediate- or long-acting insulin, include NPH, insulin degludec, insulin detemir, and insulin glargine. Unique products within this category include a long-acting formulation of insulin glargine that provides 300 units of insulin glargine per milliliter and enables patients to utilize a higher dose in one injection. Additionally, a new insulin glargine product, BASAGLAR® (LY insulin glargine) was approved under the abbreviated 505(b)(2) pathway based on safety and effectiveness data for LANTUS® (insulin glargine). BASAGLAR was not approved as a biosimilar product, but is considered a "follow-on biologic" to LANTUS (BASAGLAR Food and Drug Administration [FDA] press release, 2015; Drugs@FDA, 2016; BASAGLAR FDA approval letter, 2015). Under a settlement agreement with Sanofi, the US launch of BASAGLAR is scheduled for December 15, 2016 (Eli Lilly press release, 2015; BASAGLAR website, 2016).
- Insulin therapy is usually administered by subcutaneous injection, which allows for prolonged absorption and less pain compared to intramuscular injection. Currently there are no generic insulin products available. Of note, insulin products are available by prescription, as well as over-the-counter (short- and intermediate-acting products only).
- This review will focus on the insulin preparations 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 (RYZODEG 70/30 FDA press release, 2015).
- Medispan class: Antidiabetics, Insulin

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
Rapid-Acting Insulins			
AFREZZA® (insulin human) inhalation powder	MannKind	07/27/2014 (4 and 8 units/inhalation) 04/17/2015 (12 units/inhalation)	-
APIDRA® (insulin glulisine)	Sanofi	04/16/2004	-
APIDRA SoloStar® (insulin glulisine)	Sanofi	02/24/2009	-
HUMALOG® (insulin lispro)	Lilly	06/14/1996	-
HUMALOG Kwikpen® (insulin lispro)	Lilly	09/06/2007 (100 units/mL) 05/26/2015 (200 units/mL)	-
NOVOLOG®, NOVOLOG PenFill® (insulin aspart)	Novo Nordisk	06/07/2000	-
NOVOLOG FlexPen® (insulin aspart)	Novo Nordisk	01/19/2001	-
NOVOLOG FlexTouch® (insulin aspart)	Novo Nordisk	10/31/2013	-
Short-Acting Insulins			
HUMULIN R (insulin, regular, human recombinant)	Lilly	10/28/1982	-
HUMULIN® R U-500 (insulin, regular, human recombinant)	Lilly	03/31/1994	-
HUMULIN R U-500 Kwikpen (insulin, regular, human recombinant)	Lilly	12/29/2015	-
NOVOLIN® R (insulin, regular, human recombinant)	Novo Nordisk	06/25/1991	-
Intermediate-Acting Insulins			
HUMULIN N, HUMULIN N Kwikpen (insulin, NPH human recombinant isophane)	Lilly	10/28/1982	-
NOVOLIN N (insulin, NPH human recombinant isophane)	Novo Nordisk	07/01/1991	-
Long-Acting Insulins			
BASAGLAR (LY insulin glargine)	Lilly	12/16/2015	-
LANTUS (insulin glargine)	Sanofi	04/20/2000	-
LANTUS SoloStar (insulin glargine)	Sanofi	04/27/2007	-
LEVEMIR® (insulin detemir)	Novo Nordisk	06/16/2005	-
LEVEMIR FlexTouch (insulin detemir)	Novo Nordisk	10/31/2013	-
TOUJEO® (insulin glargine U-300)	Sanofi	02/25/2015	-
TRESIBA® (insulin degludec)	Novo Nordisk	09/25/2015	-

Drug	Manufacturer	FDA Approval Date	Generic Availability
Combination Insulins, Rapid-Acting and Intermediate-Acting			
HUMALOG Mix 50/50™ (50% insulin lispro protamine/ 50% insulin lispro)	Lilly	12/22/1999	-
HUMALOG Mix 50/50 Kwikpen (50% insulin lispro protamine/ 50% insulin lispro)	Lilly	09/06/2007	-
HUMALOG Mix 75/25™ (75% insulin lispro protamine/ 25% insulin lispro)	Lilly	12/22/1999	-
HUMALOG Mix 75/25 Kwikpen (75% insulin lispro protamine/ 25% insulin lispro)	Lilly	09/06/2007	-
NOVOLOG Mix 70/30 (70% insulin aspart protamine/ 30% insulin aspart)	Novo Nordisk	11/01/2001	-
NOVOLOG Mix 70/30 FlexPen (70% insulin aspart protamine/ 30% insulin aspart)	Novo Nordisk	05/03/2002	-
Combination Insulins, Short-Acting and Intermediate-Acting			
HUMULIN 70/30 (70% NPH, human insulin isophane/ 30% regular human insulin)	Lilly	04/25/1989	-
NOVOLIN 70/30 (70% NPH, human insulin isophane/ 30% regular human insulin)	Novo Nordisk	06/25/1991	-

(DRUGS@FDA, 2016)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Product	Adjunct to diet and exercise to improve glycemic control in adults and children with type 1 and type 2 diabetes mellitus	Control of hyperglycemia in patients with diabetes mellitus	Improve glycemic control in patients with diabetes mellitus	Improve glycemic control in adults and children with diabetes mellitus
Rapid-Acting Insulins				
AFREZZA			✔ £	
APIDRA				✔
HUMALOG				✔
NOVOLOG				✔
Short-Acting Insulins				
HUMULIN R	✔ *			
NOVOLIN R				✔
Intermediate-Acting Insulins				
HUMULIN N				✔
NOVOLIN N			✔	
Long-Acting Insulins**				
BASAGLAR				✔ ±
LANTUS				✔ ±
LEVEMIR				✔
TOUJEO			✔	
TRESIBA			✔	

Product	Adjunct to diet and exercise to improve glycemic control in adults and children with type 1 and type 2 diabetes mellitus	Control of hyperglycemia in patients with diabetes mellitus	Improve glycemic control in patients with diabetes mellitus	Improve glycemic control in adults and children with diabetes mellitus
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. HUMULIN R U-100 may also be administered intravenously under proper medical supervision in a clinical setting for glycemic control.
**Limitations of use: Not recommended for treating diabetic ketoacidosis. Use intravenous, rapid-acting or short-acting insulin instead.
± Not indicated for children with type 2 diabetes.
£ Limitations of use: Must use with a long-acting insulin in patients with type 1 diabetes. Not recommended for treating diabetic ketoacidosis. Not recommended in patients who smoke.

(Prescribing information: AFREZZA, 2016; APIDRA, 2015; BASAGLAR, 2016; HUMALOG, 2015; HUMALOG Mix 50/50, 2015; HUMALOG MIX 75/25, 2015; HUMULIN 70/30, 2015; HUMULIN N, 2015; HUMULIN R U-100, 2015; HUMULIN R U-500, 2016; LANTUS, 2015; LEVEMIR, 2015; NOVOLIN 70/30, 2016; NOVOLIN N, 2016; NOVOLIN R, 2016; NOVOLOG, 2015; NOVOLOG Mix 70/30, 2015; TOUJEO, 2015; TRESIBA, 2016)

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 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 type 2 diabetes compared to regular insulin (Plank et al, 2005). In patients with type 1 diabetes, 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 demonstrate 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 type 1 and 2 diabetes (Dailey et al, 2004; 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 type 1or 2 diabetes (Anderson et al, 1997a; Chen et al, 2006; Dailey et al, 2004; 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 type 1 diabetes reported a 12% lower incidence of hypoglycemia with insulin lispro compared to regular insulin (P<0.001) (Anderson et al, 1997a). In another trial, significantly lower frequencies and monthly rates of severe symptomatic hypoglycemia and nocturnal hypoglycemia were reported in patients with type 2 diabetes patients with insulin glulisine compared to regular insulin (Rayman et al, 2007).
- 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 type 1 diabetes (Dreyer et al, 2005; Philotheou et al, 2011; Van Ban et al, 2011).
- In a 24-week, open-label, active-controlled, non-inferiority study, patients with type 1 diabetes on basal insulin were randomized to treatment with AFREZZA or insulin aspart administered at each meal of the day. At 24 weeks, treatment with mealtime AFREZZA provided a mean reduction in HbA1c that met the prespecified non-inferiority margin of 0.4%. However, reductions from baseline HbA1c were significantly less with AFREZZA compared to insulin aspart (-0.21% vs -0.4%, respectively; difference, 0.19%; 95% confidence interval [CI] 0.02 to 0.36). Fewer patients in the AFREZZA group achieved the HbA1c target of <7% compared to patients in the insulin aspart group (13.8% vs 27.1%, respectively; P-value not reported) (Bode et al, 2015).

- Patients with type 2 diabetes who were inadequately controlled on oral antidiabetic agents (OAD) were enrolled in a 24-week, double-blind, placebo-controlled study. Patients were randomized to receive treatment with AFREZZA or an inhaled placebo powder. At week 24, treatment with AFREZZA provided a mean reduction in HbA1c that was significantly greater compared to the reductions observed in the placebo group (-0.82 vs -0.42 respectively; difference, -0.4; 95% CI, -0.57 to -0.23; P<0.0001). A greater percentage of patients achieved the HbA1c target of ≤7% in the AFREZZA group compared to patients in the placebo group (38% vs 19%, respectively; P=0.0005) (Rosenstock et al, 2015[a]).
- 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 types 1 and 2 diabetes as demonstrated by the results of several active-comparator trials and meta-analyses (Bartley et al, 2008; Bozzano et al, 2008; Buse et al, 2009; Chase et al, 2008; De Leeuw et al, 2005; Dunbar et al, 2009; Eliaschewitz et al, 2006; 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 insulin glargine U-300 (TOUJEO) have been compared to that of insulin glargine U100 (LANTUS) in open-label randomized, active-controlled, parallel studies of up to 26 weeks in patients with type 1 and type 2 diabetes mellitus. The reduction in HbA1c and fasting plasma glucose with insulin glargine U-300 was found to be similar to that of insulin glargine. As of yet, however, only the studies in patients with type 2 diabetes are published (Bolli et al, 2015; Riddle et al, 2014[b]; Yki-Järvinen et al, 2014).
- Insulin degludec (TRESIBA) was evaluated in more than 5,600 type 1 and type 2 diabetic patients throughout nine pivotal studies and five extension studies (BEGIN clinical program). In eight of the pivotal trials, insulin degludec was non-inferior to insulin glargine (LANTUS) or insulin detemir (LEVEMIR) in lowering HbA1c from baseline, with similar rates of hypoglycemia; in five trials, the rate of nocturnal hypoglycemia was significantly lower with insulin degludec compared to insulin glargine or insulin detemir. The mean difference in HbA1c at study end for insulin degludec versus insulin glargine or detemir ranged from -0.09 to 0.17% (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 two of the eight insulin degludec trials resulted in a nominally lower reduction in HbA1c for insulin degludec 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; Mathieu et al, 2013; Rodbard et al, 2013). In the ninth pivotal trial, insulin degludec lowered HbA1c significantly more than oral sitagliptin 100 mg once daily in patients with type 2 diabetes who were receiving one or two 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 insulin degludec. At the request of an FDA Advisory Committee, Novo Nordisk conducted a pre-specified meta-analysis of MACE, which included 8,068 patients from 16 Phase 3 trials conducted for insulin degludec (TRESIBA) 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 (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 DEVOTE trial was subsequently initiated to prospectively compare the cardiovascular (CV) safety of insulin degludec to insulin glargine in patients with type 2 diabetes at high risk of CV events. In 2015, insulin degludec was FDA-approved based on efficacy and safety data from the BEGIN clinical program and interim data from the DEVOTE trial; however, the DEVOTE data will not be shared publically until the trial publication in the second half of 2016 in order to maintain study integrity (Clinicaltrials.gov [NCT01959529], 2016; Novo Nordisk press release, 2015).
- The safety and efficacy of LY insulin glargine (BASAGLAR) compared to insulin glargine (LANTUS) were evaluated in 2 pivotal studies enrolling 534 and 744 patients with type 1 (ELEMENT 1 trial) and type 2 (ELEMENT 2 trial) diabetes mellitus, respectively. Both trials were multicenter, parallel group, randomized controlled trials; ELEMENT 1 was open-label and ELEMENT 2 was double-blinded. 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. Oral antidiabetic 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. A non-inferiority margin for the 95% CI upper limit was pre-specified at 0.4%. If this was met, a non-inferiority margin of 0.3% was also tested. Key secondary endpoints included hypoglycemia rates and mean weight change. In both ELEMENT 1 and ELEMENT 2, LY insulin glargine and insulin glargine had similar and significant (P<0.001) within-group decreases in HbA1c values from baseline. LY insulin glargine met non-inferiority criteria compared to insulin glargine for change in HbA1c from baseline to 24 weeks in both trials (ELEMENT 1: -0.35% vs. -0.46%, respectively; least squares mean difference, 0.108%; 95% CI, -0.002 to 0.219; P>0.05; ELEMENT 2: -1.29% vs. -1.34%, respectively; least squares mean difference, 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), adjusted for 1 year, 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]).

- 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 analogs head-to-head, several trials have demonstrated non-inferiority between the products in the same outcomes when used in the management of type 1 diabetes and as add-on therapy in patients with type 2 diabetes (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 insulin glargine and metformin versus insulin detemir and metformin, insulin glargine lowered HbA1c more than insulin detemir (Meneghini et al, 2013[b]). In clinical trials and using indirect comparisons, long-acting insulin agents appear to be similarly effective in achieving and maintaining glycemic control:
- A 2011 Cochrane review (included 4 trials; n = 2250 patients) found 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).
- 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 insulin glargine U-300 (TOUJEO) 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).
- A direct comparative trial evaluating two types of premixed biphasic insulin demonstrated similar results in terms of reducing HbA1c (Domeki et al, 2014). Another trial comparing biphasic insulin to basal plus prandial insulin in type 2 diabetes mellitus demonstrated that basal plus prandial insulin therapy is slightly more effective than premixed insulin with less hypoglycemia (Riddle et al, 2014[a]).
- Insulin therapies have been compared to GLP-1 agonists. The study results are mixed. A study comparing glycemic control with insulin glargine versus exenatide demonstrated that better glycemic control was sustained with exenatide (Diamant et al, 2012). Other studies have demonstrated that GLP-1 agonists are statistically noninferior to insulin glargine for the change in HbA1c (Inagaki et al, 2012, Weissman et al, 2014). Also, a study comparing the addition of albiglutide to insulin glargine was found to be noninferior to the addition of insulin lispro to insulin glargine (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).
- Refer to the Conclusions section for treatment guideline recommendations.

SAFETY SUMMARY

- 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.

- 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.
  - 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:
  - Hypoglycemia is the most commonly observed adverse reaction. 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 adverse events 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 Interactions:
  - β-blockers, clonidine, guanethidine, and reserpine may all mask hypoglycemic reactions.
  - Thiazolidinediones can cause dose-related fluid retention, particularly when used in combination with insulin.
  - Refer to prescribing information for all drugs that can increase or reduce the glucose-lowering ability of insulin.
- Risk Evaluation and Mitigation Strategy (REMS)
  - The FDA requires a communication plan to inform health care professionals about the serious risk of acute bronchospasm associated with AFREZZA.
  - The FDA includes risk mitigation strategies for hypoglycemia in the prescribing information for the insulin glargine formulations (LANTUS, LANTUS SoloStar, and TOUJEO). Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended. The long-acting effect of insulin glargine may delay recovery from hypoglycemia. Also, to minimize the risk of hypoglycemia with these products, do not administer them intravenously, intramuscularly, or in an insulin pump or dilute or mix them with other insulin products or solutions.

DOSING AND ADMINISTRATION

Table 3a. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Rapid-Acting Insulins				
AFREZZA (insulin human)	Single-use cartridges: 4 units (0.35 mg insulin), 8 units (0.7 mg insulin), 12 units (1 mg insulin)	Starting mealtime dose: Insulin naïve individuals: 4 units of AFREZZA at each meal. Individuals using subcutaneous prandial insulin: determine the appropriate AFREZZA dose for each meal by converting from the injected dose using the dose conversion table (see Table 3b). Individuals using subcutaneous pre-mixed insulin: estimate the mealtime injected dose by dividing half of the total daily injected pre-mixed insulin dose equally among the three meals of the day. Convert each estimated mealtime dose to an appropriate AFREZZA dose using the dose conversion table (see Table 3b). Administer half of the total daily injected pre-mixed dose as an injected basal insulin dose.	Dosage adjustment may be needed when switching from another insulin to AFREZZA or due to drug interactions. AFREZZA should only be administered via oral inhalation using the AFREZZA Inhaler. See prescribing information for further dosing information in other situations.	Administer at the beginning of a meal. AFREZZA is administered using a single inhalation per cartridge. For doses exceeding 12 units, inhalations from multiple cartridges are required. Keep the inhaler level with the white mouthpiece on top and purple base on bottom after a cartridge have been inserted into the inhaler to prevent loss of drug effect.
APIDRA (insulin glulisine)	100 units/mL: Cartridge (OptiClik® delivery device): 3 mL Pen (SoloStar® prefilled): 3 mL Vial: 10 mL	Dose and frequency are individualized per patient needs. Use in a regimen with intermediate- or long-acting insulin.	Administer within 15 minutes before a meal or within 20 minutes after starting a meal. Must not be mixed or diluted when used in an external insulin infusion pump.	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. APIDRA-specific information should be followed for in-use time, frequency of changing infusion sets, or other details specific to APIDRA usage.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
HUMALOG (insulin lispro)	100 units/mL: Cartridge: 3 mL KwikPen (prefilled): 3 mL Vial: 3 mL, 10 mL 200 units/mL: KwikPen (prefilled): 3 mL	Dose and frequency are individualized per patient needs. Use in a regimen with intermediate- or long-acting insulin.	Administer within 15 minutes before a meal or immediately after a meal. HUMALOG U-100 by subcutaneous injection may be mixed with NPH only. Must not be mixed or diluted when used in an external insulin infusion pump. Do not mix HUMALOG U-200 with any other insulin. Do not perform dose conversion when using either strength of the KwikPen.	Injection sites should be rotated within the same region (abdomen, thigh, buttocks or upper arm) from one injection to the next to reduce the risk of lipodystrophy. Do not administer HUMALOG U-200 by continuous subcutaneous or intravenous infusion.
NOVOLOG (insulin aspart)	100 units/mL: Cartridge (PenFill): 3 mL FlexPen: 3 mL FlexTouch: 3 mL Vial: 10 mL	Dose and frequency are individualized per patient needs. Use in a regimen with intermediate- or long-acting insulin.	Should be injected immediately (within 5-10 minutes) before a meal. Must not be mixed or diluted when used in an external insulin infusion pump.	Injection sites should be rotated within the same region (abdomen, thigh, buttocks, or upper arm) from one injection to the next to reduce the risk of lipodystrophy.
Short-Acting Insulins				
HUMULIN R (insulin, regular, human recombinant)	100 units/mL: Vial: 3 mL, 10 mL 500 units/mL: Vial: 20 mL	When given SQ, generally given three or more times daily before meals. U-500: Generally given two to three times daily before meals. Dose and frequency are individualized per patient needs. Often used concomitantly with intermediate- or long-acting insulin.	Injection should be followed by a meal within approximately 30 minutes of administration. U-500 should only be given SQ and should not be mixed with other insulins.	Injection sites should be rotated within the same region (abdomen, thigh, gluteal region or upper arm) from one injection to the next to reduce the risk of lipodystrophy.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
NOVOLIN R (insulin, regular, human recombinant)	100 units/mL: Vial: 10 mL	Dose and frequency are individualized per patient needs. Often used in combination with intermediate- or long-acting insulin.	Injection should be followed by a meal within approximately 30 minutes of administration.	Injection sites should be rotated within the same region (abdomen, thigh, buttocks, or upper arm) from one injection to the next to reduce the risk of lipodystrophy.
Intermediate-Acting Insulins				
HUMULIN N, (insulin, NPH, human recombinant isophane)	100 units/mL: KwikPen (prefilled): 3 mL Vial: 3 mL, 10 mL	Generally given in one to two injections per day. Dose and frequency are individualized per patient needs.	Administer 30 to 60 minutes before a meal or bedtime.	Injection sites should be rotated within the same region (abdomen, thigh, buttocks, or upper arm) from one injection to the next to reduce the risk of lipodystrophy.
NOVOLIN N (insulin, NPH, human recombinant isophane)	100 units/mL: Vial: 3 mL, 10 mL	Generally given in one to two injections per day. Dose and frequency are individualized per patient needs.	Administer 30 to 60 minutes before a meal or bedtime.	Injection sites should be rotated within the same region (abdomen, thigh, buttocks, or upper arm) from one injection to the next to reduce the risk of lipodystrophy.
Long-Acting Insulins				
BASAGLAR (LY insulin glargine)	100 units/mL: KwikPen (prefilled): 3 mL	Administer between 1 and 80 units per injection SQ once daily into the thigh, upper arm, or abdomen. Dose is individualized based on patient needs. Type 1 diabetes: Starting dose in insulin-naïve patients is approximately one-third of the total daily insulin dose. Short- or rapid-acting, pre-meal insulin should be used to satisfy the remainder of the daily insulin requirements. Type 2 diabetes: Starting dose in insulin-naïve patients is 0.2 units/kg or up to 10 units once daily.	May be administered at any time of day, but at same time every day. Do not administer intravenously or use in insulin pumps.	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.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
LANTUS (insulin glargine)	100 units/mL: Cartridge (for use with OptiClik): 3 mL SoloStar (disposable device): 3 mL Vial: 10 mL	Recommended starting dose in insulin-naïve type 2 diabetes patients: 0.2 units/kg or up to 10 units SQ once daily. Dose is individualized based on patient needs.	May be administered at any time of day, but at same time every day. Do not administer intravenously or use in insulin pumps. See full prescribing information when converting to once daily LANTUS from other insulin therapies.	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.
LEVEMIR (insulin detemir)	100 units/mL: FlexPen: 3 mL FlexTouch: 3 mL Vial: 10 mL	Administer SQ once or twice daily. Dose is individualized based on patient needs.	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. Do not use in insulin pumps.	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.
TOUJEO (insulin glargine U-300)	300 units/mL: Pen (SoloStar prefilled): 1.5 mL	Administer SQ once daily. Dose is individualized based on patient needs. The dose of TOUJEO ranges from 1 to 80 units per one injection. Type 1 diabetes: Starting dose in insulin-naive patients is approximately one-third to one-half the total daily insulin dose. The remainder of the total daily insulin dose should be given as a short-acting insulin and divided between each daily meal. Type 2 diabetes: Starting dose in insulin-naïve	Administer at the same time each day. When changing patients to TOUJEO, monitor glucose frequently in the first weeks of therapy. To minimize the risk of hypoglycemia, titrate the dose of TOUJEO no more frequently than every 3 to 4 days. Do not administer TOUJEO intravenously, intramuscularly, or in an insulin pump.	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. Do not mix with any other insulin products or solutions.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		patients is 0.2 units per kilogram of body weight once daily.		
TRESIBA (insulin degludec)	100 units/mL: FlexTouch: 3 mL 200 units/mL: FlexTouch: 3 mL	Administer SQ once daily. Dose is individualized based on patient needs. Type 1 diabetes: Starting dose in insulin-naïve patients is approximately one-third to one-half of the total daily insulin dose. The remainder of the total daily insulin dose should be given as a short-acting insulin and divided between each daily meal. Type 2 diabetes: Starting dose in insulin-naïve patients is 10 units once daily. Patients already on insulin therapy: Start at the same unit dose as the total daily long- or intermediate-acting insulin unit dose.	May be administered at any time of day. The recommended number of days between dose increases is 3 to 4 days. Do not administer intravenously, intramuscularly, or in an insulin infusion pump.	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. Do not dilute or mix with any other insulin products or solutions.
Combination Insulins, Rapid-Acting and Intermediate-Acting				
HUMALOG Mix 50/50, HUMALOG Mix 75/25 (insulin lispro protamine/ insulin lispro)	100 units/mL: Vial: 10 mL KwikPen (prefilled): 3 mL	Dose and frequency are individualized per patient needs.	Administer within 15 minutes before meals. Do not use in insulin pumps.	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.
NOVOLOG Mix 70/30 (insulin aspart protamine/ insulin aspart)	100 units/mL: FlexPen: 3 mL Vial: 10 mL	Typically dosed on a twice daily basis. Dose and frequency are individualized per patient needs.	Administer within 15 minutes before meals for type 1 diabetes. Administer within 15 minutes before or after meals for type 2 diabetes. Do not use in insulin pumps.	Injection sites should be rotated within the same region (abdomen, thigh, buttocks or upper arm) from one injection to the next to reduce the risk of lipodystrophy.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Combination Insulins, Short-Acting and Intermediate-Acting				
HUMULIN 70/30 (NPH, human insulin isophane/ regular human insulin)	100 units/mL: KwikPen (prefilled): 3 mL Vial: 3 mL, 10 mL	Generally given in two injections per day. Dose and frequency are individualized per patient needs.	Administer 30 to 60 minutes before a meal.	Injection sites should be rotated within the same region (abdomen, thigh, buttocks, or upper arm) from one injection to the next to reduce the risk of lipodystrophy.
NOVOLIN 70/30 (NPH, human insulin isophane/ regular human insulin)	100 units/mL: Vial: 10 mL	Generally given in two injections per day. Dose and frequency are individualized per patient needs.	Administer 30 to 60 minutes before a meal.	Injection sites should be rotated within the same region (abdomen, thigh, buttocks, or upper arm) from one injection to the next to reduce the risk of lipodystrophy.

NPH=neutral protamine Hagedorn, SQ=subcutaneous

Table 3b. Mealtime AFREZZA Dose Conversion Table

Injected Mealtime Insulin Dose	AFREZZA Dose	# of 4-unit cartridges needed	# of 8 unit cartridges needed	# of 12 unit cartridges needed
Up to 4 units	4 units	1		
5 to 8 units	8 units		1	
9 to 12 units	12 units	1*	1*	1
13 to 16 units	16 units		2	
17 to 20 units	20 units		1	1
21 to 24 units	24 units			2

*A 4-unit and 8-unit may be combined; alternatively, a single 12-unit may be used.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Rapid-Acting Insulins					
AFREZZA (insulin human)	No overall differences in safety or effectiveness were observed between patients over 65 and younger patients.	Safety and efficacy have not been established.	Safety and efficacy have not been established.	Safety and efficacy have not been established.	Pregnancy Category C* It is highly likely that the insulin and carrier in AFREZZA is excreted in human milk. A decision should be made whether to discontinue nursing or discontinue use of the drug.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
APIDRA (insulin glulisine)	Use caution with initial dosing and changes in dosing to avoid hypoglycemic reactions.	Safety and efficacy in children < 4 years with type 1 diabetes have not been established. Safety and efficacy in children with type 2 diabetes have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	Pregnancy category C* Unknown; use with caution. Adjustment of insulin dose may be needed while breastfeeding.
HUMALOG (insulin lispro)	Use caution with initial dosing and changes in dosing to avoid hypoglycemic reactions.	Safety and efficacy in children < 3 years with type 1 diabetes have not been established. Safety and efficacy in children with type 2 diabetes have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	Pregnancy category B* Unknown; use with caution. Adjustment of insulin dose may be needed while breastfeeding.
NOVOLOG (insulin aspart)	Use caution with initial dosing and changes in dosing to avoid hypoglycemic reactions.	Safety and efficacy in children < 2 years with type 1 diabetes have not been established. Safety and efficacy in children with type 2 diabetes have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	Pregnancy category B* Unknown; use with caution. Adjustment of insulin dose may be needed while breastfeeding.
Short-Acting Insulins					
HUMULIN R (insulin, regular, human recombinant)	Use caution with initial dosing and changes in dosing to avoid hypoglycemic reactions.	Approved for use in children. U-500: Safety and efficacy in children have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	Pregnancy category B* Unknown; use with caution. Adjustment of insulin dose may be needed while breastfeeding.
NOVOLIN R (insulin, regular, human recombinant)	Use caution with initial dosing and changes in dosing to avoid hypoglycemic reactions.	Safety and efficacy in children < 2 years with type 1 diabetes have not been established. Safety and efficacy in children with type 2 diabetes have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	Pregnancy category B* Unknown; use with caution. Adjustment of insulin dose may be needed while breastfeeding.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Intermediate-Acting Insulins					
HUMULIN N, NOVOLIN N (insulin, NPH, human recombinant isophane)	Use caution with initial dosing and changes in dosing to avoid hypoglycemic reactions.	Safety and efficacy in children have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	Pregnancy category B* Unknown; use with caution. Adjustment of insulin dose may be needed while breastfeeding.
Long-Acting Insulins					
BASAGLAR (LY insulin glargine)	Use caution with initial dosing and changes in dosing to avoid hypoglycemic reactions.	Safety and efficacy in children < 6 years with type 1 diabetes have not been established. Safety and efficacy in children with type 2 diabetes has not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	Pregnancy category C* Unknown; use with caution. Adjustment of insulin dose may be needed while breastfeeding.
LANTUS (insulin glargine)	Use caution with initial dosing and changes in dosing to avoid hypoglycemic reactions.	Safety and efficacy in children < 6 years with type 1 diabetes have not been established. Safety and efficacy in children with type 2 diabetes have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	Pregnancy category C* Unknown; use with caution. Adjustment of insulin dose may be needed while breastfeeding.
LEVEMIR (insulin detemir)	Use caution with initial dosing and changes in dosing to avoid hypoglycemic reactions.	Safety and efficacy in children < 2 years with type 1 diabetes have not been established. Safety and efficacy in children with type 2 diabetes have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	Pregnancy category B* Unknown; use with caution. Adjustment of insulin dose may be needed while breastfeeding.
TOUJEO (insulin glargine U-300)	Use caution with initial dosing and changes in dosing to avoid hypoglycemic reactions.	Safety and efficacy have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	There are no clinical studies of the use of TOUJEO in pregnant women. Female patients should be advised to tell their physicians if they intend to become, or if they become pregnant while taking TOUJEO.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
					Unknown; use with caution. Adjustment of insulin dose may be needed while breastfeeding.
TRESIBA (insulin degludec)	Use caution with initial dosing and changes in dosing to avoid hypoglycemic reactions.	Safety and efficacy have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	Pregnancy category C* Unknown; use with caution. Adjustment of insulin dose may be needed while breastfeeding.
Combination Insulins, Rapid-Acting and Intermediate-Acting					
HUMALOG Mix 50/50, HUMALOG Mix 75/25 (insulin lispro protamine/ insulin lispro)	Use caution with initial dosing and changes in dosing to avoid hypoglycemic reactions.	Safety and efficacy in children have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	Pregnancy category B* Unknown; use with caution. Adjustment of insulin dose may be needed while breastfeeding.
NOVOLOG Mix 70/30 (insulin aspart protamine/ insulin aspart)					
Combination Insulins, Short-Acting and Intermediate-Acting					
HUMULIN 70/30, NOVOLIN 70/30 (NPH, human insulin isophane/ regular human insulin)	Use caution with initial dosing and changes in dosing to avoid hypoglycemic reactions.	No information available.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	Pregnancy category B* Unknown; use with caution. Adjustment of insulin dose may be needed while breastfeeding.

* Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

(Clinical Pharmacology, 2016)

CONCLUSION

- The insulin products are approved for use in the management of both type 1 and 2 diabetes. 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 subcutaneous injection, which allows for prolonged absorption and less pain compared to intramuscular 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 adverse reactions 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 suggests 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 does 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 patients with type 1 diabetes. Current guidelines recommend that most people with type 1 diabetes be treated with multiple daily injections (three to four injections per day of basal and prandial insulin) or continuous subcutaneous insulin infusion. In addition, the guidelines suggest that most people with type 1 diabetes should use insulin analogs to reduce hypoglycemia risk. Rapid-acting inhaled insulin used before meals in type 1 diabetes patients leads to inferior HbA1c lowering when compared with insulin aspart, but with less hypoglycemia across all HbA1c target categories (ADA, 2016; Handelsman et al, 2015).
- According to current clinical guidelines regarding the management of type 2 diabetes, 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. Furthermore, due to the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients and should not be delayed in those who are not achieving glycemic goals with noninsulin therapies (ADA, 2016; Garber et al, 2016; Handelsman et al, 2015; Inzucchi et al, 2015).
- Guidelines suggests 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, 2016; Garber et al, 2016; Handelsman et al, 2015; Inzucchi et al, 2015).
- In general, no one specific insulin product among the various classifications is recommended or preferred over another. Insulin therapy must be individualized as the products within the different classifications play specific roles in achieving adequate glycemic control.

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Therapeutic Class Overview
Sodium-Glucose Cotransporter 2 Inhibitors

INTRODUCTION

- Diabetes mellitus affects more than 29 million people in the United States (Centers for Disease Control [CDC], 2016).
- Type 2 diabetes mellitus (T2DM) is the most common form of diabetes and is characterized by elevated fasting and postprandial glucose concentrations (American Diabetes Association [ADA], 2017[a]). It is a chronic illness that requires continuing medical care and ongoing patient self-management education and support to prevent acute complications and to reduce the risk of long-term complications (ADA, 2017[b]).
- Complications of T2DM include hypertension, heart disease, stroke, vision loss, kidney disease, and neuropathy. It is the leading cause of kidney failure and the seventh leading cause of death in the U.S. (CDC, 2016).
- In addition to dietary and lifestyle management, T2DM can be treated with insulin, one or more oral medications, or a combination of both. Many patients with T2DM will require combination therapy (Garber et al, 2017).
- Classes of oral medications for the management of blood glucose levels in patients with T2DM focus on increasing insulin secretion, increasing insulin responsiveness, or both, decreasing the rate of carbohydrate absorption, decreasing rate of hepatic glucose production, decreasing rate of glucagon secretion, and blocking glucose reabsorption by the kidney (Garber et al, 2017; Inzucchi et al, 2015).
- Pharmacologic options for type 2 diabetes include sulfonylureas, biguanides, thiazolidinediones (TZDs), meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogs, amylinomimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, combination products, and insulin.
- The SGLT2 inhibitors class consists of three agents, canagliflozin, dapagliflozin, and empagliflozin, and their combination products.
- Medispan class: sodium-glucose cotransporter 2 inhibitors

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
Dapagliflozin products			
FARXIGA™ (dapagliflozin)	AstraZeneca / Bristol Myers Squibb	01/08/2014	-
XIGDUO XR™ (dapagliflozin/ metformin hydrochloride extended release)	AstraZeneca Pharmaceuticals	10/29/2014	-
Canagliflozin products			
INVOKANA™ (canagliflozin)	Janssen Pharmaceuticals	03/29/2013	-
INVOKAMET® (canagliflozin/metformin hydrochloride)	Janssen Pharmaceuticals	08/08/2014	-
INVOKAMET® XR (canagliflozin/metformin extended release)	Janssen Pharmaceuticals	09/20/2016	-
Empagliflozin products			
JARDIANCE® (empagliflozin)	Boehringer Ingelheim Pharmaceuticals / Eli Lilly & Co.	08/01/2014	-
GLYXAMBI® (empagliflozin/linagliptin)	Boehringer Ingelheim Pharmaceuticals / Eli Lilly & Co.	01/30/2015	-
SYNJARDY® (empagliflozin/metformin)	Boehringer Ingelheim Pharmaceuticals / Eli Lilly & Co.	08/26/2015	-

Drug	Manufacturer	FDA Approval Date	Generic Availability
SYNJARDY® XR (empagliflozin/metformin extended release)	Boehringer Ingelheim Pharmaceuticals / Eli Lilly & Co.	12/09/2016	-

(Drugs@FDA, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indications	Single Entity Products			Combination Products			
	FARXIGA (dapagliflozin)	INVOKANA (canagliflozin)	JARDIANCE (empagliflozin)	GLYXAMBI (empagliflozin/ linagliptin)	INVOKAMET, INVOKAMET XR (canagliflozin/ metformin)	SYNJARDY, SYNJARDY XR (empagliflozin/ metformin)	XIGDUO XR (dapagliflozin/ metformin XR)
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM	✓	✓	✓				
To reduce the risk of cardiovascular (CV) death in adult patients with T2DM and established CV disease			✓				
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both canagliflozin/dapagliflozin/empagliflozin and metformin is appropriate.					✓	✓*	✓
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both empagliflozin and linagliptin is appropriate				✓*			

*Products containing empagliflozin include the clinical trial information on EMPA-REG OUTCOME study as well as the following statement in the indications section: The effectiveness of GLYXAMBI/SYNJARDY/SYNJARDY XR on reducing the risk of CV death in adults with type 2 diabetes mellitus and CV disease has not been established.

Limitations of use: Canagliflozin, dapagliflozin, and empagliflozin are not recommended in patients with type 1 diabetes mellitus (T1DM) or for the treatment of diabetic ketoacidosis. GLYXAMBI has not been studied in patients with a history of pancreatitis.

(Prescribing information: FARXIGA, 2016; GLYXAMBI, 2016; INVOKANA, 2016; INVOKAMET, 2016; INVOKAMET XR, 2016; JARDIANCE, 2016; SYNJARDY, 2016; SYNJARDY XR, 2016; XIGDUO XR, 2016)

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

- The safety and efficacy of the SGLT2 inhibitors were evaluated in patients that were drug-naïve or in patients whose glucose was inadequately controlled with other oral agents and/or insulin. SGLT2 inhibitors have demonstrated efficacy in lowering glycosylated hemoglobin (HbA1c) levels by ~0.6% to 1%. They have been studied as monotherapy and in combination with other antidiabetic agents. Most trials evaluated the addition of an SGLT2 inhibitor to one or more classes of antidiabetic agents.

- The SGLT2 inhibitors have consistently shown significant beneficial effects on HbA1c, fasting plasma glucose (FPB), weight gain, post-prandial glucose (PPG), and blood pressure when used as monotherapy or in combination therapy:
    - As monotherapy (Bailey et al, 2012; Inagaki et al, 2014; Ferrannini et al, 2010; Ferrannini et al, 2013; Stenlöf et al, 2013)
    - With metformin (Haring et al, 2014[a]; Henry et al, 2012; Bailey et al, 2010; Leiter et al, 2015; Rosenstock et al, 2013; Rosenstock et al, 2016; Ross et al, 2015)
    - With a sulfonylurea (Fulcher et al, 2015; Strojek et al, 2011; Strojek et al, 2014; Wilding et al, 2013)
    - With metformin and a sulfonylurea (Haring et al, 2014[b]; Matthaei et al, 2015)
    - TZDs (Kovacs et al, 2014; Rosenstock et al, 2012; Forst et al, 2012)
    - DPP-4 inhibitor (Roden et al, 2013; Jabbour et al, 2014; Lavalle-Gonzalez et al, 2013; Rosenstock et al, 2015[a]; Schernthaner et al, 2013)
    - Insulin (Rosenstock et al, 2014; Rosenstock et al, 2015[b]; Wilding et al, 2012; Neal et al, 2015).
- The combination of SGLT2 inhibitors with metformin lower HbA1c compared to placebo. These studies use the coadministration of the two components instead of fixed-dose combination tablets for INVOKAMET, SYNJARDY, and XIGDUO XR. The bioequivalency of INVOKAMET XR and SYNJARDY XR to the immediate release combination products in healthy subjects was used to support the FDA approval of these extended release combination products.
- GLYXAMBI (empagliflozin/linagliptin) is the first FDA-approved SGLT2-inhibitor/DPP-4 inhibitor combination product. A 52-week, phase 3, double-blind, parallel-group, randomized-controlled trial in patients with T2DM demonstrated reductions in HbA1c with GLYXAMBI that were superior to those of empagliflozin or linagliptin alone as add-on to metformin (DeFronzo et al, 2015).
- The SGLT2 inhibitors have also shown noninferiority in decreasing HbA1c in direct comparisons when compared to sulfonylureas:
    - Dapagliflozin vs glipizide, both in combination with metformin (Nauck et al, 2011)
    - Canagliflozin vs glimepiride (Cefalu et al, 2013)
    - Empagliflozin vs glimepiride (Ridderstrale et al, 2014).
- As of yet, there are no direct comparative trials comparing the efficacy of canagliflozin, dapagliflozin, and empagliflozin.
- Additional studies have demonstrated the safety and efficacy of SGLT2 inhibitors in special populations:
    - Patients with type 2 diabetes and chronic kidney disease (Barnett et al, 2014; Kohan et al, 2014; Yale et al, 2014; Yale et al, 2013)
    - Patients with type 2 diabetes and CV disease (Leiter et al, 2014)
    - Elderly patients (Bode et al, 1995; Bode et al, 2015; Sinclair et al, 2014; Sinclair et al, 2016).
    - A pooled analysis of six phase 3, double-blind, placebo-controlled, randomized clinical trials compared the efficacy and safety of canagliflozin in patients < 75 years and ≥ 75 years of age. Canagliflozin 100 mg and 300 mg were associated with placebo-subtracted mean reductions in HbA1c in patients < 75 years (-0.69% and -0.85%, respectively) and ≥ 75 years (-0.65% and -0.55%, respectively). Dose-related reductions in FPG, body weight, and blood pressure were also seen with canagliflozin 100 mg and 300 mg in patients in both age groups. Overall adverse event incidences were 67.1% with canagliflozin 100 mg, 68.6% with canagliflozin 300 mg, and 65.9% with non-canagliflozin (pooled group of comparators in all studies) in patients < 75 years, and 72.4%, 79.1%, and 72.3%, respectively, in patients ≥ 75 years, with a similar safety profile in both groups (Sinclair et al, 2016).
- Various long-term studies have been conducted that provide data on the safety and efficacy after at least one year of treatment with the SGLT2 inhibitors (Araki et al, 2015; Bailey et al, 2015; Bode et al, 2015; Del Prato et al, 2015; Kovacs et al, 2015; Nauck et al, 2014).
- Other post-hoc analyses of pooled data from randomized controlled trials have further evaluated the effects of SGLT2 inhibitors on parameters such as blood pressure, weight gain, and adverse events (Davies et al, 2015; Ptaszynska et al, 2014; Weir et al, 2014).

- Furthermore, various meta-analyses have been conducted that have demonstrated the efficacy of the SGLT2 inhibitors (Liakos et al, 2014; Orme et al, 2014; Sun et al, 2014; Yang et al, 2014).
- The Agency for Healthcare Research and Quality (AHRQ) updated the review of the diabetes medications for adults with T2DM (Bolen et al, 2016). An additional eight new studies were identified. DPP-4 inhibitors were noted to have more evidence demonstrating that the reductions in HbA1c were less than observed with metformin. Monotherapy with metformin, TZDs, and sulfonylureas reduce HbA1c to a similar degree. Body weight was maintained or reduced by metformin, DPP-4 inhibitors, GLP-1 agonists, and SGLT2 inhibitors. Weight gain was associated with sulfonylureas, TZDs, and insulin with between group differences of 1 to 5 kg. Systolic blood pressure was reduced by 3 to 5 mm Hg by SGLT2 inhibitors and GLP-1 agonists compared to metformin. Risk of total and severe hypoglycemia was increased with sulfonylureas compared to monotherapy with metformin or TZDs. Some adverse events were higher with specific classes of drugs including gastrointestinal (GI) events (metformin and GLP-1 agonists) and risk of genital mycotic infection (SGLT2 inhibitors). Moderate strength evidence supports that sulfonylurea monotherapy was associated with a 50 to 70 percent higher relative risk (absolute risk 0.1 to 2.9% in RCT; number needed to treat range 20 to 1000) of CV mortality compared with metformin monotherapy.
- EMPA-REG OUTCOME was the first study to demonstrate a positive benefit on CV outcomes due to glucose lowering with empagliflozin as add-on to standard of care in T2DM patients with high CV risk (Zinman et al, 2015). Empagliflozin significantly reduced the risk of the combined endpoint (CV death, nonfatal myocardial infarction [MI], or nonfatal stroke) by 14% vs. placebo ($P < 0.001$ for non-inferiority; $P = 0.04$ for superiority). Whether this benefit is a class effect remains unclear; long-term studies on CV outcomes for canagliflozin and dapagliflozin are currently ongoing, with results expected in 2018 and 2019, respectively.
    - A recently published follow-up to the EMPA-REG Outcome study examined the pre-specified secondary objective of the effect of empagliflozin on microvascular outcomes, and in particular, progression of kidney disease in patients with T2DM at high risk for CV events. In this new analysis, incident or worsening nephropathy occurred in 525 of 4124 patients taking empagliflozin and 388 of 2061 in the placebo group (12.7% vs. 18.8%; HR: 0.61; 95% CI, 0.53 to 0.70; $P < 0.001$). This renal end point consisted of a combination of progression to macroalbuminuria, a doubling of serum creatinine, the start of renal-replacement therapy, or renal death. A relative risk reduction of 38% was seen with the endpoint of progression to macroalbuminuria, which occurred in 459 of 4091 patients taking empagliflozin compared with 330 of 2033 patients on placebo (11.2% vs.16.2%; HR: 0.62; 95% CI, 0.54 to 0.72; $P < 0.001$) (Wanner et al, 2016).

Guidelines:

- Several consensus guidelines recommend metformin as the optimal first-line drug, unless there are prevalent contraindications or intolerance to treatment. SGLT2 inhibitors may be prescribed as a part of subsequent dual or triple therapy, if the target is not achieved after three months at maximum tolerated doses. All guidelines emphasize individualized therapy based upon a patient's specific factors such as comorbidities, weight, risk of hypoglycemia, and duration of diabetes (ADA, 2017; Copeland et al, 2013; Inzucchi et al, 2015). Metformin is considered the drug of choice for children with T2DM (Copeland et al, 2013).
- ADA/European Association for the Study of Diabetes (EASD) - Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach recommend metformin as initial monotherapy for T2DM also (Inzucchi et al, 2015).
    - Monotherapy: Metformin remains the optimal drug for monotherapy due to its low cost, proven safety record, weight neutrality, and possible benefits on CV outcomes.
        - In patients intolerant of, or with contraindications for, metformin, an initial drug from other classes discussed under "Dual therapy" should be considered.
    - Dual therapy: If the HbA1c target is not achieved after ~3 months with metformin monotherapy, adding one of the six treatment options below may be considered (listed order is not meant to denote any specific preference). Other drugs (e.g., alpha-glucosidase inhibitors, colesevelam, bromocriptine, and pramlintide) may be tried in specific situations but are generally not favored

due to modest efficacy, the frequency of administration, and/or side effects. For all patients, initiating therapy with a dual combination should be considered when HbA1c is ≥ 9% (75 mmol/mol) in order to achieve the HbA1c target more expeditiously.
    - SFU (rapid-acting secretagogues [meglitinides] may be used instead of SFUs in patients with irregular meal schedules or those who develop late postprandial hypoglycemia on an SFU).
    - TZD
    - DPP-4 inhibitor
    - SGLT2 inhibitor
    - GLP-1 receptor agonist
    - Basal insulin
  - Triple therapy: Triple therapy may be considered if the HbA1c goal is not achieved after 3 months with dual therapy. Options for triple therapy include (order is not meant to denote any specific preference):
    - Metformin + SFU + (TZD or DPP-4 inhibitor or SGLT2 inhibitor or GLP-1 receptor agonist or insulin)
    - Metformin + TZD + (SFU or DPP-4 inhibitor or SGLT2 inhibitor or GLP-1 receptor agonist or insulin)
    - Metformin + DPP-4 inhibitor + (SFU or TZD or SGLT2 inhibitor or insulin)
    - Metformin + SGLT2 inhibitor + (SFU or TZD or DPP-4 inhibitor or insulin)
    - Metformin + GLP-1 receptor agonist + (SFU or TZD or insulin)
    - Metformin + basal insulin + (TZD or DPP-4 inhibitor or SGLT2 inhibitor or GLP-1 receptor agonist)
  - Combination injectable therapy: If the HbA1c goal is not achieved after 3 months with triple therapy and the patient is (1) on oral combination, moving to injectables is recommended; (2) on GLP-1 receptor agonist therapy, adding basal insulin is recommended; (3) on optimally treated basal insulin, adding a GLP-1 receptor agonist or mealtime insulin is recommended. In refractory patients, adding a TZD or SGLT2 inhibitor may be considered.
    - Initial therapy at this stage should be considered when BG is ≥ 300 to 350 mg/dL (≥ 16.7 to 19.4 mmol/L) and/or HbA1c ≥ 10 to 12% (≥ 86 to 108 mmol/mol), especially if the patient is symptomatic or if catabolic features (weight loss, ketosis) are present, in which case basal insulin + mealtime insulin is the preferred initial regimen.

- American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) - Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm were recently updated from 2016 (Garber et al, 2017). The choice of diabetes therapies must be individualized based on attributes specific to both patients and the medications themselves. Medication selection should consider antihyperglycemic efficacy, mechanism of action, risk of inducing hypoglycemia, risk of weight gain, other adverse events, tolerability, ease of use, likely adherence, cost, and safety in heart, kidney, or liver disease. Minimizing the risks of hypoglycemia and weight gain are priorities. These guidelines recommend the following therapies:
  - Lifestyle therapy, including a medically assisted weight loss program, is recommended for all patients.
  - Should patients not achieve their goal HbA1c in three months, it is recommended that they escalate and add on therapy (medication options listed in order of recommended choice):

  For HbA1c of < 7.5%:
  - Monotherapy: Metformin, a GLP-1 receptor agonist, SGLT2 inhibitor, DPP-4 inhibitor, or an alpha-glucosidase inhibitor. TZD or SFU/glinide should be used with caution.

  For HbA1c of ≥ 7.5%:
  - Dual therapy: Metformin or another first-line agent + a second agent (e.g., GLP-1 receptor agonist, SGLT2 inhibitor, DPP-4 inhibitor, colesevelam, bromocriptine quick release (QR) or an alpha-glucosidase inhibitor). TZD, basal insulin, or SFU/glinide should be used with caution.

- Triple therapy: Metformin or another first-line agent + a second-line agent + a third agent (e.g., GLP-1 receptor agonist, SGLT2 inhibitor, DPP-4 inhibitor, colesevelam, bromocriptine QR, or an alpha-glucosidase inhibitor). TZD, basal insulin, or SFU/glinide should be used with caution.
- If triple therapy fails to achieve the HbA1c goal in three months, then adding or intensifying insulin therapy should be considered.

For HbA1c of > 9%:

- In patients without symptoms, dual therapy or triple therapy should be considered.
- In patients with symptoms, insulin ± other agents should be considered.
- For patients with or without symptoms, adding or intensifying insulin should be considered.

SGLT2 inhibitors specific information:

- SGLT2 inhibitors have a glucosuric effect that results in decreased HbA1c, weight, and SBP.
- Empagliflozin is the only SGLT2 inhibitor associated with significantly lower rates of all-cause and CV death and lower risk of hospitalization for heart failure. Empagliflozin received FDA-approval for the indication of reduction of cardiac mortality.
- Safety concerns with treatment include increased risks of mycotic genital infections, slightly increased low-density lipoprotein cholesterol (LDL-C) levels, limited efficacy in patients with an eGFR < 45 mL/min/1.73 m^2, potential hypotension due to increased diuresis, and incidences of bone fractures in patients taking canagliflozin and dapagliflozin. Post-marketing reports of diabetic ketoacidosis (DKA) have been reported in T1DM and T2DM with less than expected hyperglycemia (euglycemic DKA).

SAFETY SUMMARY

- Contraindications:
  - History of serious hypersensitivity reaction to canagliflozin, dapagliflozin, or empagliflozin.
  - Severe renal impairment (eGFR < 30 mL/min/1.73 m^2), end-stage renal disease, or dialysis.
  - Metformin-containing products have the following contraindications:
    - Severe renal impairment (INVOKAMET, INVOKAMET XR, SYNJARDY, SYNJARDY XR: eGFR < 45 mL/min/1.73 m^2; XIGDUO XR: eGFR < 60 mL/min/1.73 m^2), end-stage renal disease, or dialysis.
    - Known hypersensitivity to metformin hydrochloride
    - Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.
  - Linagliptin-containing products have the following contraindications:
    - History of hypersensitivity reactions to linagliptin, such as anaphylaxis, angioedema, exfoliative skin conditions, urticarial, or bronchial hyperreactivity.
- Boxed Warnings:
  - Metformin-containing products carry a Boxed Warning for lactic acidosis. Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as concomitant use of certain drugs, age > 65 years, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and abdominal pain. Laboratory abnormalities include increase lactate/pyruvate ratio, anion gap acidosis, metformin plasma levels generally > 5 mcg/mL, and elevated blood lactate. If acidosis is suspected, discontinue treatment and hospitalize the patient immediately.
- Warnings and Precautions
  - Several FDA drug safety communications have been issued for canagliflozin over the past year.
    - The FDA published a drug safety communication in June 2016 stating that the existing warning about the risk of acute kidney injury for the canagliflozin (INVOKANA, INVOKAMET, INVOKAMET XR) and dapagliflozin (FARXIGA, XIGDUO XR) has been strengthened. Based on recent confirmed cases of acute kidney injury, the warning in the drug label has been revised to include more specific parameters regarding the monitoring

of renal function and discontinuation in cases of renal impairment (FDA Drug Safety Communication, 2016).

- The FDA issued a new drug safety communication in May 2016 with interim safety results from an ongoing clinical trial that found an increase in leg and foot amputations, mostly affecting the toes, in patients treated with canagliflozin. The FDA is currently investigating this new safety issue and will provide an update when there is more information available (FDA Drug Safety Communication, May 2016).
- The FDA issued drug safety communication regarding the risk of fracture and bone density in 2016.
    - Bone fracture –The FDA evaluated the incidence of bone fractures based on a pooled analysis of nine clinical trials (n = 10,194) with patients ages 55 to 80 who had a mean duration of exposure to canagliflozin of 85 weeks. The incidence rates of bone fractures were greater with canagliflozin 100 mg and 300 mg vs. placebo or an active comparator (1.4 and 1.5 vs. 1.1 per 100 patient-years of exposure, respectively). Fractures were observed as early as 12 weeks after treatment initiation and were more likely to be low trauma (e.g., fall from no more than standing height), and affect the upper extremities (Watts et al, 2016).
    - Decreased bone mineral density – Based on an FDA-required post-marketing trial, canagliflozin caused greater loss of bone mineral density at the hip and lower spine than placebo over two years in elderly individuals (55 to 80 years of age) with poorly controlled T2DM. Placebo-corrected declines in bone mineral density at the total hip were 0.9% and 1.2%, respectively for canagliflozin 100 mg and 300 mg, and were 0.1% at the femoral neck for both canagliflozin doses. Placebo-adjusted bone mineral density decline at the distal forearm was 0.4% with canagliflozin 300 mg and 0% with canagliflozin 100 mg (Bilezikian et al, 2016; FDA Drug Safety Communication, 2015).

Table 3. Warnings and Precautions

Warnings and Precautions	Single-Entity Products			Combination Products			
	FARXIGA (dapagliflozin)	INVOKANA (canagliflozin)	JARDIANCE (empagliflozin)	GLYXAMBI (empagliflozin/ linagliptin)	INVOKAMET, INVOKAMET XR (canagliflozin/ metformin)	SYNJARDY, SYNJARDY XR (empagliflozin/ metformin)	XIGDUO XR (dapagliflozin/ metformin ER)
Hypotension: Before initiating therapy, assess volume status and correct hypovolemia in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics.	✔	✔	✔	✔	✔	✔	✔
Ketoacidosis: Assess patients who present with signs/symptoms of metabolic acidosis regardless of blood glucose level.	✔	✔	✔	✔	✔	✔	✔
Acute kidney injury and impairment in renal function: Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat. Monitor renal function during	✔	✔	✔	✔	✔	✔	✔

therapy.							
Impairment in renal function: Monitor renal function during therapy. More frequent monitoring is recommended in patients with eGFR < 60 mL/min/1.73 m^2. Avoid use of dapagliflozin when eGFR < 60 mL/min/1.73 m^2.	✔	✔	✔	✔	✔	✔	✔
Hypoglycemia: Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination.	✔	✔	✔	✔	✔	✔	✔
Macrovascular outcomes: No clinical studies have established conclusive evidence of macrovascular risk reduction.	✔	✔		✔	✔	✔	✔
Hyperkalemia: Monitor potassium levels in patients with impaired renal function and in patients predisposed to hyperkalemia.		✔			✔		
Hypersensitivity reactions: Monitor for anaphylaxis and angioedema. Discontinue use and treat and monitor until signs and symptoms resolve.		✔		✔	✔		
Genital mycotic infections: Monitor and treat if indicated.	✔	✔	✔	✔	✔	✔	✔
Increased LDL-C: Monitor LDL-C and treat per standard of care.	✔	✔	✔	✔	✔	✔	✔
Bladder cancer: An imbalance in bladder cancers was observed in clinical trials. Dapagliflozin should not be used in patients with active bladder cancer and should be used with caution in patients with a prior history of bladder cancer.	✔						✔
Urosepsis and Pyelonephritis: Evaluate for signs/symptoms of UTI and treat promptly, if indicated.	✔	✔	✔	✔	✔	✔	✔
Bone fracture: An increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed. Consider factors that contribute to fracture risk before initiating canagliflozin		✔			✔		
Vitamin B_{12} deficiency: Metformin may lower vitamin B_{12} levels. Monitor hematologic parameters annually.					✔	✔	✔
Pancreatitis: There have been post marketing reports of acute pancreatitis, including fatal pancreatitis. Discontinue if suspected.				✔			
Arthralgia: Severe and debilitating arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue if appropriate.				✔			
Bullous pemphigoid: Patients taking DPP-4 inhibitors have required hospitalization due to bullous pemphigoid. Patients should report development of blisters or erosions. Discontinue if suspected.				✔			
Radiologic studies with intravascular iodinated contrast materials: metformin can lead to acute					✔	✔	✔

alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Metformin-containing agents should be withheld at the time of or prior to the procedure (and withheld for 48 hours subsequent to the procedure). They should be reinstituted only after renal function is normal or mildly impaired.							

- Adverse effects:
  - The most common adverse effects seen with the SGLT2 inhibitors are genital mycotic infections and urinary tract infections.
  - Most common adverse reactions associated with metformin (5% or greater incidence) are diarrhea, nausea, vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache.
- Drug Interactions:

  All SGLT2 Inhibitors:
  - Positive urine glucose test: Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.
  - Interference with 1,5-anhydroglucitol (1,5-AG) assay: Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

  Canagliflozin:
  - Co-administration of canagliflozin with inducers of uridine diphosphate glucuronosyltransferase (UGT) enzymes such as rifampin, phenytoin, phenobarbital, and ritonavir may result in decreased INVOKANA area under the concentration curve (AUC); consider increasing canagliflozin dosage to 300 mg once daily in patients tolerating 100 mg once daily who have an eGFR of 60 mL/min/1.73 m^2 or more and require additional glycemic control. Consider another antihyperglycemic agent in patients with eGFR of 45 or less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer.
  - Co-administration of canagliflozin 300 mg with digoxin have been reported to increase the AUC and mean peak drug concentration of digoxin (20% and 36%, respectively).

  Dapagliflozin:
  - When dapagliflozin is used with insulin or an insulin secretagogue (e.g., sulfonylurea) a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycemia.

  Empagliflozin:
  - Diuretics: Coadministration of diuretics with increased urine volume and frequency of voids. This may increase the potential for volume depletion.

  Linagliptin-containing agents:
  - Efficacy of linagliptin may be reduced when used in combination with a strong inducer of CYP3A4 or P-gp. Consider alternative treatments.

  Metformin-containing agents:
  - Cationic drugs such as cimetidine may reduce metformin elimination and may increase the risk for lactic acidosis. Other drugs which may increase exposure to metformin include ranolazine, vandetanib, and dolutegravir.
  - Alcohol may potentiate the effect of metformin on lactate metabolism. Advise against excessive alcohol intake.
  - Carbonic anhydrase Inhibitors: Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis and may increase the risk of lactic acidosis.
  - Drugs affecting glycemic control: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids,

phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid. When such drugs are administered, monitor for loss of blood glucose control. When such drugs are withdrawn from a patient receiving a metformin-containing drug, monitor for hypoglycemia.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Single entity products				
FARXIGA (dapagliflozin)	Tablet: 5 mg, 10 mg	Starting dose is 5 mg once daily in the morning. Dose can be increased to 10 mg once daily in patients tolerating FARXIGA who require additional glycemic control.	Assess renal function before initiating FARXIGA. Do not initiate FARXIGA if eGFR is < 60 mL/min/1.73 m^2.	Take with or without food.
INVOKANA (canagliflozin)	Tablet: 100 mg, 300 mg	The recommended starting dose is 100 mg once daily. Dose can be increased to 300 mg once daily in patients who have an eGFR ≥ 60 mL/min/1.73 m^2 and require additional glycemic control.	Limit dose to 100 mg once daily in patients who have an eGFR 45 to < 60 mL/min/1.73 m^2. Discontinue therapy if eGFR falls below 45 mL/min/1.73 m^2.	Take before the first meal of the day.
JARDIANCE (empagliflozin)	Tablet: 10 mg, 25 mg	10 mg once daily in the morning. The dose may be increased to 25 mg in patients tolerating JARDIANCE.	Do not initiate if eGFR is < 45 mL/min/1.73 m^2. Discontinue therapy if eGFR falls below 45 mL/min/1.73 m^2.	Take with or without food.
Combination products				
INVOKAMET (canagliflozin/ metformin)	Tablets: 50/500 mg 50/1000 mg 150/500 mg 150/1000 mg	Recommended starting dose is 50 mg canagliflozin/500 mg metformin twice daily. Individual based on the patient's current regimen. Take twice daily with meals, with gradual dose escalation to reduce the GI side effects due to metformin.	Do not exceed a daily dose of metformin 2,000 mg and canagliflozin 300 mg. Assess renal function before initiating INVOKAMET. Limit canagliflozin to 50 mg twice daily in patients with eGFR of 45 to < 60 mL/min/1.73 m^2. Do not initiate INVOKAMET if eGFR is < 45 mL/min/1.73 m^2.	May need to discontinue at time of, or prior to, iodinated contrast imaging procedure in patients with an eGFR between 45 and 60 mL/min/1.73 m^2; in patients with a history of liver disease, alcoholism or heart failure; in patients who will be administered intra-arterial iodinated contrast.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
INVOKAMET XR (canagliflozin/ metformin ER)	Tablets: 50/500 mg 50/1000 mg 150/500 mg 150/1000 mg	Take 2 tablets once daily with the morning meal. In patients currently not treated with either canagliflozin or metformin, initiate therapy with two INVOKAMET XR tablets, each containing canagliflozin 50 mg and metformin 500 mg. In patients already treated with canagliflozin and metformin, switch to two INVOKAMET XR tablets containing the same total daily dose of canagliflozin and the same, or nearest appropriate, total daily dose of metformin.	Do not exceed a daily dose of metformin 2,000 mg and canagliflozin 300 mg. Assess renal function before initiating INVOKAMET XR and periodically thereafter. Limit canagliflozin to 50 mg twice daily in patients with eGFR of 45 to < 60 mL/min/1.73 m^2. Do not initiate INVOKAMET XR if eGFR is < 45 mL/min/1.73 m^2.	May need to discontinue at time of, or prior to, iodinated contrast imaging procedure in patients with an eGFR between 45 and 60 mL/min/1.73 m^2; in patients with a history of liver disease, alcoholism or heart failure; in patients who will be administered intra-arterial iodinated contrast. Swallow whole. Do not crush, cut, or chew.
XIGDUO XR (dapagliflozin/ metformin ER)	Tablets: 5/500 mg 5/1000 mg 10/500 mg 10/1000 mg	Individualize the starting dose based on the patient's current regimen. Take once daily in the morning with meals, with gradual dose escalation to reduce the GI side effects due to metformin.	Do not exceed a daily dose of metformin 2,000 mg and dapagliflozin 10 mg. In patients with volume depletion, correcting this condition prior to initiation of XIGDUO XR is recommended. Do not initiate if eGFR is < 60 mL/min/1.73 m^2.	Must be swallowed whole and never crushed, cut, or chewed. Take with food. May need to discontinue at time of, or prior to, iodinated contrast imaging procedure.
GLYXAMBI (empagliflozin/ linagliptin)	Tablets: 10/5 mg, 25/5 mg	Recommended starting dose is 10 mg empagliflozin/5 mg linagliptin once daily in the morning. May increase dose to 25 mg empagliflozin/5 mg linagliptin once daily.	Do not initiate or continue if eGFR < 45 mL/min/1.73 m^2.	Take with or without food.
SYNJARDY (empagliflozin/ metformin)	Tablets: 5/500 mg, 5/1000 mg, 12.5/500 mg, 12.5/1000 mg	Individualize the starting dose based on the patient's current regimen. Take twice daily with meals, with gradual dose escalation to reduce the GI	Do not exceed a daily dose of 25 mg empagliflozin/2000 mg metformin. Do not initiate if eGFR is < 45 mL/min/1.73	Take with meals. May need to discontinue at time of, or prior to, iodinated contrast imaging procedure in patients with an eGFR

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		side effects due to metformin.	m^2.	between 45 and 60 mL/min/1.73 m^2; in patients with a history of liver disease, alcoholism or heart failure; in patients who will be administered intra-arterial iodinated contrast.
SYNJARDY XR (empagliflozin/ metformin ER)	Tablets: 5/1000 mg, 10/1000 mg, 12.5/1000 mg, 25/1000 mg	Individualize the starting dose based on the patient's current regimen. Take once daily with a meal in the morning, with gradual dose escalation to reduce the GI side effects due to metformin.	Do not exceed a daily dose of 25 mg empagliflozin/2000 mg metformin. Do not initiate if eGFR is < 45 mL/min/1.73 m^2.	Take with a meal. Swallow whole, do not split, crush, dissolve, or chew. May need to discontinue at time of, or prior to, iodinated contrast imaging procedure in patients with an eGFR between 45 and 60 mL/min/1.73 m^2; in patients with a history of liver disease, alcoholism or heart failure; in patients who will be administered intra-arterial iodinated contrast.

eGFR=estimated glomerular filtration rate

SPECIAL POPULATIONS

Table 5. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Single entity products					
FARXIGA (dapagliflozin)	No dosage change is recommended based on age.	Safety and effectiveness in pediatric patients < 18 years of age have not been established.	Treatment should not be initiated in patients with eGFR < 60 mL/min/1.73 m^2). Use of FARXIGA is not recommended in patients with eGFR falls persistently between 30 to < 60 mL/min/1.73 m^2.	No dose adjustment is recommended for patients with mild, moderate, or severe hepatic impairment. However, the benefits and risks for the use of dapagliflozin in patients with severe hepatic impairment should be	Pregnancy category C* (no data; potential benefits should justify the potential risk to fetus) Discontinue FARXIGA or discontinue nursing.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
				individually assessed since the safety and efficacy of dapagliflozin have not been specifically studied in this population.	
INVOKANA (canagliflozin)	Patients aged ≥ 65 years had a higher incidence of adverse reactions related to reduced intravascular volume. Smaller reductions in HbA1c were seen patients aged ≥ 65 years.	Safety and effectiveness in pediatric patients < 18 years of age have not been established.	Treatment should not be initiated in patients with eGFR < 45 mL/min/1.73 m^2). Use of INVOKANA is not recommended in patients with eGFR is persistently < 45 mL/min/1.73 m^2.	Not recommended with severe hepatic impairment.	Females should be advised of the potential risk to fetus, especially during second and third trimesters. Not recommended when breastfeeding.
JARDIANCE (empagliflozin)	No Jardiance dosage change is recommended based on age. Decreased efficacy is expected in elderly patients with renal impairment. The risk of UTIs and volume-depletion adverse reactions increased in patients ≥ 75 years old.	Safety and effectiveness in pediatric patients < 18 years of age have not been established.	JARDIANCE should not be initiated in patients with an eGFR < 45 mL/min/ 1.73 m^2. Discontinue if eGFR is persistently < 45 mL/min/1.73 m^2.	No dosing adjustment needed.	Consider appropriate alternative therapies, especially during the second and third trimesters. Unknown if excreted in human milk. Not recommended when breastfeeding.
Combination products					
INVOKAMET, INVOKAMET XR (canagliflozin/ metformin)	There is a higher incidence of AEs related to reduced intravascular volume. Assess renal function more frequently.	Safety and effectiveness in pediatric patients < 18 years of age have not been established.	Higher incidence of AEs related to reduced intravascular volume and renal function. Contraindicated in patients with moderate to severe renal impairment (eGFR < 45 mL/min/1.73 m^2), end stage renal	Not recommended in patients with hepatic impairment.	Females should be advised of the potential risk to fetus, especially during second and third trimesters. There is no information regarding its presence in

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
			disease, or patients on dialysis.		breast milk, effects on breastfed infant, or effects on milk production. Not recommended while breastfeeding.
GLYXAMBI (empagliflozin/ linagliptin)	Empagliflozin is associated with osmotic diuresis, which could affect hydration in patients aged ≥ 75 years. No dose change is recommended.	Safety and effectiveness in pediatric patients < 18 years of age have not been established.	GLYXAMBI should not be initiated in patients with an eGFR < 45 mL/min/ 1.73 m^2. Discontinue if eGFR is < 45 mL/min/1.73 m^2.	No dosing adjustment needed.	Empagliflozin is not recommended during the second and third trimesters. Not recommended while breastfeeding.
SYNJARDY, SYNJARDY XR (empagliflozin/ metformin)	There is a higher incidence of adverse reactions related to reduced renal function (e.g., UTIs and volume depletion) in patients aged ≥ 75 years. Renal function should be assessed more frequently in elderly patients. No dose change for empagliflozin is recommended.	Safety and effectiveness in pediatric patients < 18 years of age have not been established.	Contraindicated in patients with eGFR < 45 mL/min/1.73 m^2.	Not recommended with hepatic impairment.	Females should be advised of the potential risk to fetus, especially during second and third trimesters. Not recommended when breastfeeding. Advise premenopausal females of the potential for an unintended pregnancy.
XIGDUO XR (dapagliflozin/ metformin)	No dosage change is recommended based on age.	Safety and effectiveness in pediatric patients < 18 years of age have not been established.	Contraindicated in patients with moderate to severe renal impairment (eGFR < 60 mL/min/1.73 m^2) No dose adjustment	Not recommended with hepatic impairment.	Pregnancy category C* (no data; potential benefits should justify the potential risk to fetus)

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
			is required in patients with mild renal impairment.		Discontinue nursing or XIGDUO XR.

eGFR=estimated glomerular filtration rate
*Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus. 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

- Canagliflozin, dapagliflozin, and empagliflozin are inhibitors of sodium-glucose co-transporter 2 (SGLT2). SGLT2 is responsible for the majority of reabsorption of glucose filtered by the kidney. By inhibiting SGLT2, these agents reduce reabsorption of filtered glucose, lower the renal threshold for glucose, and thereby increase urinary glucose excretion.
- Similar to other currently available oral antidiabetic agents, SGLT2 inhibitors are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). SGLT2 inhibitors have demonstrated efficacy in lowering HbA1c levels by ~0.6% to 1%. They have been studied as monotherapy and in combination with metformin and other antidiabetic agents.
- The SGLT2 inhibitor/metformin combinations include INVOKAMET/INVOKAMET XR (canagliflozin/metformin), SYNJARDY/SYNJARDY XR (empagliflozin/metformin), and XIGDUO XR (dapagliflozin/metformin).
- GLYXAMBI (empagliflozin/linagliptin) is the first Food and Drug Administration (FDA)-approved SGLT2-inhibitor/dipeptidyl peptidase-4 inhibitor combination product. A 52-week, phase 3, double-blind, parallel-group, randomized-controlled trial in patients with T2DM demonstrated reductions in HbA1c with empagliflozin/linagliptin that were superior to those of empagliflozin or linagliptin alone as add-on to metformin (DeFronzo et al, 2015).
- In clinical trials, they have been evaluated in patients that were drug-naïve or in patients whose glucose was inadequately controlled with other oral agents and/or insulin. They have demonstrated effectiveness when used as monotherapy and in combination with other antidiabetic agents. Most trials evaluated the addition of an SGLT2 inhibitor to one or more classes of antidiabetic agents.
- The SGLT2 inhibitors have consistently shown significant beneficial effects on HbA1c, fasting plasma glucose, weight gain, post-prandial glucose, and blood pressure when used as monotherapy or in combination therapy.
- SGLT2 inhibitors have additional beneficial effects such as weight reduction and decreases in blood pressure. These beneficial changes are hypothesized to result from either a loss of calories associated with induction of urinary glucose excretion or a reduction in fluid volume through the osmotic diuretic effect. These agents are not associated with hypoglycemia; however, hypoglycemia risk may increase when combined with insulin or an insulin secretagogue.
- All three single-entity SGLT2 inhibitors are dosed once daily. Dapagliflozin is not recommended in patients with an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2. Empagliflozin and canagliflozin are not recommended in patients with an eGFR < 45 mL/min/1.73 m^2. Volume depletion issues should be corrected prior to initiation of SGLT2 therapy.
- The SGLT2 inhibitors share a similar safety profile, including increased cholesterol levels, increased serum creatinine and a concomitant decrease in eGFR, volume depletion, and genital mycotic infections. A warning for bone fractures was added for canagliflozin-containing products recently. Warnings for diabetic ketoacidosis, urosepsis, and pyelonephritis were also added to the SGLT2 inhibitor labeling after increased incidences were reported post-marketing.
- Consensus guidelines generally recommend metformin as the optimal first-line drug, unless there are prevalent contraindications or intolerance to treatment. SGLT2 inhibitors may be prescribed as a part of subsequent dual or triple therapy, if the target is not achieved after three months at maximum tolerated

doses. All guidelines emphasize individualized therapy based upon a patient's specific factors such as comorbidities, weight, risk of hypoglycemia, and duration of diabetes (Garber et al, 2017; ADA 2017; Inzucchi et al, 2015).

- Evidence that glucose lowering reduces the rates of CV events and death has not been convincingly shown until the publication of results from the EMPA-REG OUTCOME trial, which was a long-term, placebo-controlled study involving 7020 patients with T2DM at high risk for CV events. When added to standard of care, empagliflozin significantly reduced the risk of the combined endpoint (CV death, nonfatal myocardial infarction, or nonfatal stroke) by 14% vs. placebo ($P < 0.001$ for non-inferiority; $P = 0.04$ for superiority). In addition, there was a 38% reduction in CV death, 35% reduction in hospitalization for heart failure, and 32% reduction in death from any cause associated with its use; however, there were no significant between-group differences in the rates of MI or stroke. The underlying mechanism of empagliflozin and its effect on CV outcomes are not clearly understood (Zinman et al, 2015). Recently updated guidelines acknowledge the established CV benefit with empagliflozin (ADA, 2017; Garber et al, 2017).
- The SGLT2 inhibitors may provide another treatment option for glycemic control in patients unable to tolerate first-line treatment with metformin or other oral antidiabetic therapies due to adverse effects (AEs) or risk for hypoglycemia. Positive CV outcomes have been demonstrated with empagliflozin, which suggest that it may play a significant role in T2DM patients at high risk for CV events. Although the long term effects of SGLT2 inhibition are not known at this time, clinical studies demonstrate that the benefits outweigh the risks.

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Therapeutic Class Overview
Ophthalmic Immunomodulators

INTRODUCTION

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

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
RESTASIS® (cyclosporine ophthalmic emulsion)	Allergan	December 23, 2002	-
XIIDRA® (lifitegrast ophthalmic solution)	Shire	July 11, 2016	-

(Drugs@FDA, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

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

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

(RESTASIS prescribing information, 2013; XIIDRA prescribing information, 2016)

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

- The pivotal trials for cyclosporine ophthalmic emulsion were two randomized, placebo-controlled trials that included 877 patients and an open-label, extension trial that included 412 patients (Barber et al, 2005; Sall et al, 2000). All patients were diagnosed with moderate-to-severe KCS and decreased tear production based on the Schirmer tear test. The combined results of the two placebo-controlled trials demonstrated that cyclosporine ophthalmic emulsion 0.05% and 0.1% were associated with significant improvements from baseline in corneal staining, Schirmer tear test scores, Ocular Surface Disease Index (OSDI) scores, Subjective Facial Expression Rating Scale scores, and various dry eye related symptoms (Sall et al, 2000). Specifically compared to placebo, at four months, improvements in

corneal staining were significant in both cyclosporine ophthalmic emulsion groups compared to placebo (P≤0.044), and at six months, only the cyclosporine ophthalmic emulsion 0.05% group demonstrated significance over placebo (P=0.008). Additionally, at six months, improvements in Schirmer tear test scores were significantly greater for both cyclosporine ophthalmic emulsion groups compared to placebo (P≤0.05 for both) and from baseline scores (P values not reported). Improvements in OSDI and Subjective Facial Expression Rating Scale scores were significant compared to baseline for all treatment groups (P<0.001), but there were no significant differences among these groups (P values not reported). Improvements in blurred vision were significantly greater in the cyclosporine ophthalmic emulsion 0.05% group than placebo at all follow-up visits (P≤0.014), and significant improvements were achieved at all time points within all treatment groups when compared to baseline for relief of dry eye symptoms including dryness (P<0.001), sandy/gritty feeling (P<0.001), and itching (P≤0.038). A Chinese, double-blind study used similar subjective ratings for dry eye symptoms and found that cyclosporine ophthalmic emulsion 0.05% improved measures over eight weeks (Chen et al, 2010).

- An open-label, extension trial was also conducted to determine the long term safety of cyclosporine ophthalmic emulsion (Barber et al, 2005). After three consecutive 12-month periods, results demonstrated that cyclosporine ophthalmic emulsion was safe and well tolerated. Over three years, adverse events were found in 65.3% (269/412) of patients with ocular burning reported most commonly (12.1%). This trial also demonstrated sustained efficacy of cyclosporine ophthalmic emulsion over an extended period of time.
- A trial comparing cyclosporine ophthalmic emulsion to punctal plugs or a combination of both demonstrated that both treatments improved the symptoms of dry eye, but punctal plugs achieved results more rapidly than cyclosporine ophthalmic emulsion (Roberts et al, 2007).
- A systematic review of 18 RCTs examined the efficacy and safety of topical cyclosporine for treatment of dry eye disease. All cyclosporine formulations proved safe for the treatment of dry eye disease. Symptoms improved in 100% (9/9 RCTs), tear function improved in 72% (13/18 RCTs) and ocular surface damage was ameliorated in 53% (9/17 RCTs) (Saccheti et al, 2014).
    - Statistical comparison of cyclosporine efficacy through a meta-analysis of data was not possible due to a lack of standardized criteria and comparable outcomes among studies.
- The safety and efficacy of lifitegrast ophthalmic solution for the treatment of dry eye disease were assessed in a total of 1,181 patients (1,067 of which received lifitegrast 5%) in four 12-week, randomized, multicenter, double-masked, vehicle-controlled studies (Semba et al, 2012; Sheppard et al, 2014; Tauber et al, 2015; XIIDRA prescribing information 2016). The use of artificial tears was not allowed during the studies. The clinical trials evaluated various endpoints related to signs and symptoms of dry eye disease. However, the FDA approval relied on an assessment of symptoms based on change from baseline in patient reported eye dryness score (EDS; 0 to 100 visual analogue [VAS] scale) and an assessment of signs based on the inferior corneal staining score (ICSS; 0 to 4 scale).
- A larger reduction in EDS favoring lifitegrast was observed in all studies at day 42 and day 84.
    - EDS was used as a primary symptom endpoint in 2 of the 4 studies (OPUS-2 and OPUS-3); the other 2 evaluated EDS as a secondary endpoint.
    - In OPUS-1, the primary symptom endpoint was the visual-related function subscale score of the Ocular Surface Disease Index (VR-OSDI) questionnaire. No difference between lifitegrast and placebo was seen in the mean change from baseline to day 84 (P=0.7894) (Sheppard et al, 2014).
- At day 84, a larger reduction in ICSS favoring lifitegrast was observed in 3 of the 4 studies (no statistically significant difference between lifitegrast and placebo was found in the OPUS-2 study).
- In a one-year safety study (N=331: 220 lifitegrast; 111 placebo), there were no serious ocular treatment-emergent adverse events (TEAEs). Overall, 53.6% of participants receiving lifitegrast experienced ≥1 ocular TEAE versus 34.2% in the placebo group; most TEAEs were mild to moderate in severity, with burning, instillation site reaction, reduced visual acuity, dry eye, and dysgeusia reported most commonly (Donnenfeld et al, 2016).
- Clinical guidelines consider cyclosporine ophthalmic emulsion to be an appropriate therapy for patients with moderate dry eye syndrome, and also in the treatment of severe atopic KCS or for those patients with atopic KCS who have failed conventional therapy (AAO Dry Eye Syndrome, 2013). However, depending on patient preference and physician experience, any of the recognized treatment options for dry eye syndrome may be used to treat the disease regardless of the severity rating. The guidelines have not yet been updated to include lifitegrast.

SAFETY SUMMARY

- Cyclosporine ophthalmic emulsion
    - Cyclosporine ophthalmic emulsion is contraindicated in patients with known or suspected hypersensitivity to any ingredient in the formulation of the product.
    - Warnings include the risk of eye injury and contamination when administering the medication if the vial tip touches the eye or other surfaces and use with contact lenses. Cyclosporine ophthalmic emulsion should not

be administered while wearing contact lenses. If contact lenses are worn, remove contact lenses prior to the administration of the emulsion. Reinsert lenses 15 minutes following administration of cyclosporine ophthalmic emulsion.
  - Ocular burning is the most frequently reported adverse event. Other adverse events reported include ocular pain, conjunctival hyperemia, visual disturbance (blurring), and other local ocular effects.
- Lifitegrast ophthalmic solution
  - There are no contraindications.
  - The most commonly reported adverse events reported in 5 to 25% of patients were instillation site irritation, dysgeusia, and reduced visual acuity.
  - Other adverse events reported in 1 to 5% of patients included blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus, and sinusitis.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
RESTASIS (cyclosporine ophthalmic emulsion)	Ophthalmic emulsion: 0.05% (30 single-use vials each containing 0.4 mL)	To increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca: Ophthalmic emulsion: instill 1 drop in each eye twice daily approximately 12 hours apart	Cyclosporine ophthalmic emulsion can be used concomitantly with artificial tears; however, patients should allow for a 15 minute interval between the products. Discard vial immediately after use.
XIIDRA (lifitegrast ophthalmic solution)	Ophthalmic solution: 5% (60 single-use polyethylene containers each containing 0.2 mL)	Instill one drop of Xiidra twice daily (approximately 12 hours apart) into each eye using a single-use container.	Contact lenses should be removed prior to the administration of lifitegrast and may be reinserted 15 minutes following administration. Discard the single-use container immediately after using in each eye.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
RESTASIS (cyclosporine ophthalmic emulsion)	No overall difference in safety or effectiveness has been observed between elderly and younger patients.	Safety and efficacy in children <16 years of age have not been established.	No dosage adjustment required.	No dosage adjustment required.	Pregnancy category C* Yes, excreted in breast milk with systemic administration (% unknown); use with caution.
XIIDRA (lifitegrast ophthalmic solution)	No overall differences in safety or effectiveness have been observed between elderly	Safety and efficacy in pediatric patients <17 years of age have not	No dosage adjustment required.	No dosage adjustment required.	There are no available data on lifitegrast use in pregnant women to inform any drug associated risks.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	and younger adult patients.	been established.			There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low.

* 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

- RESTASIS (cyclosporine ophthalmic emulsion) is the first ophthalmic emulsion FDA-approved to increase tear production in patients with keratoconjunctivitis sicca (KCS). Although the exact mechanism of action of this agent is unknown, it is assumed that it acts as a partial immunomodulator.
- XIIDRA (lifitegrast ophthalmic solution) is the second prescription treatment to receive FDA-approval for treatment of dry eye disease. Lifitegrast is a novel small molecule integrin antagonist that inhibits T cell-mediated inflammation by blocking the binding of two important cell surface proteins (lymphocyte function-associated antigen 1 [LFA-1] and intercellular adhesion molecule 1 [ICAM-1]), thus lessening overall inflammatory responses. However, the exact mechanism of action of lifitegrast in dry eye disease is unknown.
- In clinical trials, cyclosporine ophthalmic emulsion demonstrated significant increases in tear production and decreases in dry eye symptoms compared to placebo and demonstrated safety for up to three years (Sall et al, 2000; Barber et al, 2005; Roberts et al, 2007).
- Lifitegrast also demonstrated significant improvements in the signs and symptoms of dry eye disease compared with placebo in clinical trials. Lifitegrast was well tolerated with no unexpected adverse events in a one-year safety exposure study (Donnenfeld et al, 2016; Semba et al, 2012; Sheppard et al, 2014; Tauber et al, 2015; XIIDRA prescribing information 2016).
- Clinical guidelines consider cyclosporine ophthalmic emulsion to be an appropriate therapy for patients with moderate to severe dry eye syndrome (AAO Dry Eye Syndrome, 2013; AOA Ocular Surface Disorders, 2010). Lifitegrast has not yet been incorporated into the guidelines.
- There are no comparative trials of cyclosporine ophthalmic emulsion and lifitegrast ophthalmic solution.

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