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RICHARD WHITLEY, MS
Director

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NOTICE OF PUBLIC MEETING – PHARMACY AND THERAPEUTICS COMMITTEE

AGENDA

Date of Publication:	**May 30, 2018**
Date and Time of Meeting:	**June 28, 2018 at 1:00 PM**
Name of Organization:	**The State of Nevada, Department of Health and Human Services (DHHS), Division of Health Care Financing and Policy (DHCFP)**
Place of Meeting:	**North Nevada Location:** **Division of Public & Behavioral Health** **4150 Technology Way, Room 303** **Carson City, Nevada 89706** **South Nevada Location:** **Springs Preserve** **333 S Valley View Blvd.** **Las Vegas, Nevada 89107** **Please check with staff upon arrival to verify room location**
Webinar Registration:	https://optum.webex.com/optum/onstage/g.php?MTID=e560752b8f9dc86cbac9ec27d34f429cc **OR** www.webex.com, select "Join," enter Meeting Number 645 934 684, your name and email and then select "Join." A Password should not be necessary, but if asked, enter "uCdjKY$3"

OR

Audio Only: **(763) 957-6300**

Event Number: **645 934 684**

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

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

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

AGENDA

1. Call to Order and Roll Call

2. Public Comment

3. Administrative

a. **For Possible Action**: Review and Approve Meeting Minutes from March 22, 2018

b. Status Update by the DHCFP

1. Public Comment

4. Proposed New Drug Classes

a. Monoclonal Antibodies for the Treatment of Respiratory Conditions

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

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

5. Established Drug Classes

a. Cardiovascular Agents – Antihypertensive Agents – Direct Renin Inhibitors

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

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

a. Analgesics – Opiate Agonists – Abuse Deterrent

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

b. Analgesics – Opiate Agonists

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

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

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

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

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

e. Hormones and Hormone Modifiers – Antidiabetic Agents – Incretin Mimetics

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

f. Respiratory Agents – Respiratory Anti-inflammatory Agents – Nasal Corticosteroids

1. Public Comment
2. Drug Class Review Presentation – OptumRx

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

g. Respiratory Agents – Respiratory Anti-inflammatory – Agents Respiratory Corticosteroids

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

h. Respiratory Agents – Respiratory Antimuscarinic Combinations.

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

i. Gastrointestinal Agents – Antiemetics – Miscellaneous

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

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

j. Ophthalmic Agents – Antiglaucoma Agents

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

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

If requested in writing, a draft copy of the changes will be mailed to you. Requests and/or written comments on the proposed changes may be sent to the Colleen McLachlan at the

Division of Health Care Financing and Policy, 1100 E. William Street, Suite 101, Carson City, Nevada 89701.

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

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

Preferred Products	PA Criteria	Non-Preferred Products
PEG-INTRON® and REDIPEN		
Anti-hepatitis Agents		
Polymerase Inhibitors/Combination Products		
EPCLUSA® HARVONI® MAVYRET® (NEW) SOVALDI® ZEPATIER®	**PA required: (see below)** http://dhcfp.nv.gov/uploadedFiles/dhcfpnvgov/content/Resources/AdminSupport/Manuals/MSMCh1200Packet6-11-15(1).pdf https://www.medicaid.nv.gov/Downloads/provider/Pharmacy_Announcement_Viekira_2015-0721.pdf	DAKLINZA® OLYSIO® TECHNIVIE® VIEKIRA® PAK VOSEVI® (NEW)
Ribavirins		
RIBAVIRIN		RIBASPHERE RIBAPAK® MODERIBA® REBETOL®
Anti-Herpetic Agents		
ACYCLOVIR FAMVIR® VALCYCLOVIR		
Influenza Agents		
AMANTADINE TAMIFLU® RIMANTADINE RELENZA®		OSELTAMIVIR CAP RAPIVAB
Cephalosporins		
Second-Generation Cephalosporins		
CEFACLOR CAPS and SUSP CEFACLOR ER CEFUROXIME TABS and SUSP CEFPROZIL SUSP		CEFTIN® CECLOR® CECLOR CD® CEFZIL
Third-Generation Cephalosporins		
CEFDINIR CAPS / SUSP CEFPODOXIME TABS and SUSP		CEDAX® CAPS and SUSP CEFDITOREN OMNICEF® SPECTRACEF® SUPRAX® VANTIN®
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® MOXIFLOXACIN BAXDELA®
Autonomic Agents		
Sympathomimetics		
Self-Injectable Epinephrine		
EPINEPHRINE AUTO INJ EPINEPHRINE®	* PA required	ADRENACLICK® QL AUVI-Q® *
Biologic Response Modifiers		
Immunomodulators		
Targeted Immunomodulators		
ACTEMRA® (NEW) CIMZIA® COSENTYX® ENBREL® HUMIRA® INFLECTRA® (NEW) KINERET® ORENCIA® OTEZLA® SIMPONI® XELJANZ®	Prior authorization is required for all drugs in this class https://www.medicaid.nv.gov/Downloads/provider/FA-61.pdf	DUPIXENT® (NEW) ENTYVIO® ILARIS® KEVZARA® REMICADE® RENFLEXIS® SILIQ® STELARA® TALTZ® TREMFYA®
Multiple Sclerosis Agents		
Injectable		
AVONEX® AVONEX® ADMIN PACK BETASERON® COPAXONE® QL EXTAVIA® OCREVUS®	*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
REBIF® QL TYSABRI®		
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 ‡ NONPREFERRED FOR OVER 10 YEARS OLD	ACCURETIC® EPANED® ‡ FOSINOPRIL MAVIK® MOEXIPRIL QUINAPRIL QUINARETIC® QBRELIS® TRANDOLAPRIL UNIVASC®
Beta-Blockers		
ACEBUTOLOL ATENOLOL ATENOLOL/CHLORTH BETAXOLOL BISOPROLOL BISOPROLOL/HCTZ BYSTOLIC®*	*Restricted to ICD-10 codes J40-J48	SOTYLIZE®

Preferred Products	PA Criteria	Non-Preferred Products
CARVEDILOL LABETALOL METOPROLOL (Reg 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		
ORENITRAM® SILDENAFIL TRACLEER®		ADCIRCA® ADEMPAS® LETAIRIS® OPSUMIT®

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

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

Preferred Products	PA Criteria	Non-Preferred Products
Topical Antivirals		
ABREVA® XERESE® CREAM ZOVIRAX®, OINTMENT		ACYCLOVIR OINT DENAVIR®
Topical Scabicides		
NIX® PERMETHRIN RID® SKLICE® ULESFIA®	* PA required	EURAX® LINDANE MALATHION NATROBA® * OVIDE® SPINOSAD
Topical Anti-inflammatory Agents		
Immunomodulators: Topical		
ELIDEL® QL EUCRISA® (NEW) 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		AKYNZEO®

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

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

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

Preferred Products	PA Criteria	Non-Preferred Products
ONGLYZA® TRADJENTA®		OSENI®
Incretin Mimetics		
BYDUREON® * BYETTA® * TANZEUM® TRULICITY® VICTOZA® *	* PA required	ADLYXIN® SOLIQUA® XULTOPHY®
Insulins (Vials, Pens and Inhaled)		
APIDRA® HUMALOG® HUMULIN® LANTUS® LEVEMIR ® NOVOLIN® NOVOLOG® TRESIBA FLEX INJ		AFREZZA® BASAGLAR® 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 SYNJARDY® SYNJARDY® XR XIGDUO XR®
Sulfonylureas		
AMARYL® CHLORPROPAMIDE DIABETA® GLIMEPIRIDE (Amaryl®) GLIPIZIDE (Glucotrol®) GLUCOTROL® GLUCOVANCE® GLIPIZIDE EXT-REL (Glucotrol XL®) GLIPIZIDE/METFORMIN (Metaglip®) GLYBURIDE MICRONIZED (Glynase®)		

	Preferred Products	PA Criteria	Non-Preferred Products
	GLYBURIDE/METFORMIN (Glucovance®) GLUCOTROL XL® GLYBURIDE (Diabeta®) GLYNASE® METAGLIP® TOLAZAMIDE TOLBUTAMIDE		
Thiazolidinediones			
	ACTOPLUS MET XR® ACTOS® ACTOPLUS MET® AVANDAMET® AVANDARYL® AVANDIA® DUETACT®		
Pituitary Hormones			
Growth hormone modifiers			
	GENOTROPIN® NORDITROPIN®	**PA required for entire class** https://www.medicaid.nv.gov/Downloads/provider/FA-67.pdf	HUMATROPE® NUTROPIN AQ® OMNITROPE® NUTROPIN® SAIZEN® SEROSTIM® SOMAVERT® TEV-TROPIN® ZORBTIVE®
Progestins for Cachexia			
	MEGESTROL ACETATE, SUSP		MEGACE ES®
Musculoskeletal Agents			
Antigout Agents			
	ALLOPURINOL COLCHICINE TAB/CAP PROBENECID PROBENECID/COLCHICINE ULORIC®		COLCRYS® TAB MITIGARE® CAP ZURAMPIC® ZYLOPRIM®
Bone Resorption Inhibitors			
Bisphosphonates			
	ALENDRONATE TABS FOSAMAX PLUS D®		ACTONEL® ALENDRONATE SOLUTION ATELVIA® BINOSTO® BONIVA®

	Preferred Products	PA Criteria	Non-Preferred Products
			DIDRONEL® ETIDRONATE IBANDRONATE SKELID®
Nasal Calcitonins			
	MIACALCIN®		FORTICAL® CALCITONIN-SALMON
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® BRIVIACT® CARBAMAZEPINE CARBAMAZEPINE XR CARBATROL ER® CELONTIN® DEPAKENE® DEPAKOTE ER® DEPAKOTE® DIVALPROEX SODIUM	PA required for members under 18 years old	APTIOM® OXTELLAR XR® POTIGA® QUDEXY XR® TROKENDI XR® SPRITAM®

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

Preferred Products	PA Criteria	Non-Preferred Products
KLONOPIN® TRANXENE T-TAB® VALIUM®		
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® ELETRIPTAN 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		ALPHAGAN® BETAGAN® BETOPTIC ® COSOPT® COSOPT PF® OCUPRESS®

Preferred Products	PA Criteria	Non-Preferred Products
COMBIGAN® DORZOLAM DORZOLAM / TIMOLOL LEVOBUNOLOL METIPRANOLOL SIMBRINZA® TIMOLOL DROPS/ GEL SOLN		OPTIPRANOLOL® TIMOPTIC® TIMOPTIC XE® TRUSOPT®
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® OLOPATADINE (drop/sol) (NEW) OPTIVAR® PATADAY® PATANOL®
Ophthalmic Anti-infectives		
Ophthalmic Macrolides		
ERYTHROMYCIN OINTMENT		
Ophthalmic Quinolones		
BESIVANCE® CIPROFLOXACIN LEVOFLOXACIN MOXEZA® VIGAMOX®		CILOXAN® MOXIFLOXACIN OFLOXACIN® ZYMAXID®
Ophthalmic Anti-infective/Anti-inflammatory Combinations		
NEO/POLY/DEX PRED-G SULF/PRED NA SOL OP TOBRADEX OIN TOBRADEX SUS ZYLET SUS		BLEPHAMIDE MAXITROL NEO/POLY/BAC OIN /HC NEO/POLY/HC SUS OP TOBRA/DEXAME SUS TOBRADEX SUS TOBRADEX ST SUS

Preferred Products	PA Criteria	Non-Preferred Products
Ophthalmic Anti-inflammatory Agents		
Ophthalmic Corticosteroids		
ALREX® DEXAMETHASONE DUREZOL® FLUOROMETHOLONE LOTEMAX® PREDNISOLONE		FLAREX® FML® FML FORTE® MAXIDEX® OMNIPRED® PRED FORTE® PRED MILD® VEXOL®
Ophthalmic Nonsteroidal Anti-inflammatory Drugs (NSAIDs)		
DICLOFENAC FLURBIPROFEN ILEVRO® KETOROLAC NEVANAC®		ACULAR® ACULAR LS® ACUVAIL® BROMDAY® BROMFENAC® PROLENSA®
Ophthalmics for Dry Eye Disease		
RESTASIS®		XIIDRA®
Otic Agents		
Otic Anti-infectives		
Otic Quinolones		
CIPRODEX® CIPRO HC® OTIC SUSP OFLOXACIN		CIPROFLOXACIN SOL 0.2% CETRAXAL® OTOVEL® SOLN
Psychotropic Agents		
ADHD Agents		
ADDERALL XR® ADZENYS® AMPHETAMINE SALT COMBO IR DEXMETHYLPHENIDATE DEXTROAMPHETAMINE SA TAB DEXTROAMPHETAMINE TAB DEXTROSTAT® DYANAVEL® FOCALIN XR® GUANFACINE ER	**PA required for entire class** **Children's Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-69.pdf	ADDERALL® AMPHETAMINE SALT COMBO XR APTENSIO XR® ATOMOXETINE CONCERTA® COTEMPLA XR®-ODT DAYTRANA® DESOXYN® DEXEDRINE® DEXTROAMPHETAMINE SOLUTION EVEKEO® FOCALIN® INTUNIV® KAPVAY® METADATE ER®

Preferred Products	PA Criteria	Non-Preferred Products
METADATE CD® METHYLIN® METHYLIN ER® METHYLPHENIDATE METHYLPHENIDATE ER (All forms generic extended release) METHYLPHENIDATE SOL PROCENTRA® QUILLICHEW® QUILLIVANT® XR SUSP RITALIN LA® STRATTERA® VYVANSE®	**Adult Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-68.pdf	MYDAYIS® RITALIN® ZENZEDI®
Antidepressants		
Other		
BUPROPION BUPROPION SR BUPROPION XL DULOXETINE * MIRTAZAPINE MIRTAZAPINE RAPID TABS PRISTIQ® TRAZODONE VENLAFAXINE (ALL FORMS)	PA required for members under 18 years old * PA required *No PA required if ICD-10 - M79.1; M60.0-M60.9, M61.1.*	APLENZIN® BRINTELLIX® 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®	**PA required for Ages under 18 years old**	ABILIFY® CLOZARIL® FAZACLO®

Preferred Products	PA Criteria	Non-Preferred Products
LATUDA® NUPLAZID®* OLANZAPINE QUETIAPINE QUETIAPINE XR REXULTI® RISPERIDONE SAPHRIS® VRAYLAR® ZIPRASIDONE	**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)	GEODON® INVEGA® PALIPERIDONE RISPERDAL® SEROQUEL® SEROQUEL XR® ZYPREXA®
Anxiolytics, Sedatives, and Hypnotics		
ESTAZOLAM FLURAZEPAM ROZEREM® TEMAZEPAM TRIAZOLAM ZALEPLON ZOLPIDEM	No PA required if approved diagnosis code transmitted on claim (All agents in this class)	AMBIEN® AMBIEN CR® BELSOMRA® DORAL® ESZOPICLONE EDLUAR® HETLIOZ® INTERMEZZO® LUNESTA® SILENOR® SOMNOTE®
	PA required for members under 18 years old	SONATA® ZOLPIDEM CR ZOLPIMIST®
Psychostimulants		
Narcolepsy Agents		
Provigil® *	* (No PA required for ICD-10 code G47.4)	MODAFINIL NUVIGIL® XYREM®
Respiratory Agents		
Nasal Antihistamines		
DYMISTA® PATANASE®		ASTEPRO® AZELASTINE OLOPATADINE
Respiratory Anti-inflammatory Agents		
Leukotriene Receptor Antagonists		
MONTELUKAST		ACCOLATE®

	Preferred Products	PA Criteria	Non-Preferred Products
	ZAFIRLUKAST ZYFLO® ZYFLO CR®		SINGULAIR® ZILEUTON ER
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® ARMONAIR® (NEW) BUDESONIDE NEBS*
Nasal Corticosteroids			
	FLUTICASONE NASONEX®		BECONASE AQ® FLONASE® 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	LEVALBUTEROL* HFA PROAIR® HFA PROAIR RESPICLICK® VENTOLIN HFA® XOPENEX® Solution* QL

Preferred Products	PA Criteria	Non-Preferred Products
Respiratory Corticosteriod/Long-Acting Beta-Agonist Combinations		
ADVAIR DISKUS® ADVAIR HFA® DULERA® SYMBICORT®		AIRDUO® BREO ELLIPTA® FLUTICASONE PROPIONATE/SALMETEROL
Respiratory Long-Acting Antimuscarinic/Long-Acting Beta-Agonist Combinations		
ANORO ELLIPTA® BEVESPI® (NEW) STIOLTO RESPIMAT®		UTIBRON NEOHALER ®
Toxicology Agents		
Antidotes		
Opiate Antagonists		
EVZIO ® NALOXONE NARCAN® NASAL SPRAY		
Substance Abuse Agents		
Mixed Opiate Agonists/Antagonists		
BUNAVAIL® SUBOXONE® ZUBSOLV®	PA required for class	BUPRENORPHINE / NALOXONE

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.]

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

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

(c) Anticonvulsant medications;

(d) Antirejection medications for organ transplants;

(e) Antidiabetic medications;

(f) Antihemophilic medications; and

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

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

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

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

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

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

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

Definition of "Therapeutic Alternative"

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

BRIAN SANDOVAL
Governor

RICHARD WHITLEY, MS
Director

MARTA JENSEN
Administrator

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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http://dhcfp.nv.gov

Pharmacy and Therapeutics Committee

Date and Time of Meeting: **Thursday, December 7, 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 St
Ste. 3A
Carson City, NV 89701

South Nevada Location:
Silver State Health Insurance Exchange
150 N. Stephanie St
Ste. 100
Henderson, NV 89074

Attendees

Board Members (Present)
Shamim Nagy, MD, Chair
Michael Hautekeet, RPh
Mark Decerbo, Pharm.D.
Adam Zold, Pharm.D.
Joseph Adashek, MD
Chris Highley, DO
Evelyn Chu, Pharm.D.
Kate Ward, Pharm.D.

Board Members (Absent)
(None)

DHCFP:
Duane Young, Chief, DHCFP
Holly Long, Social Services Program Specialist
Gabe Lither, DAG

DXC:
Beth Henry, Account Operations Executive

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

Public (Las Vegas):
Charissa Anne, J&J
John Madigal, J&J
Jane Stephen, Allergan
Vicky Viss, Synergy
Janette Thompson, Synergy
Rupa Shah, Purdue
Cathy Gross, Purdue
Paul Krisfylus, Gilead
Marc Rueckert, Pfizer
Elizabeth Simons, Abbvie
Melissa Walsh, Novartis
Laurence Ikeda, Pfizer
Sheila Sanchez, Walgreens
Sangeeta Auawana, Abbvie
Ryan Bitton, HPN
Karen Jackson, Trividia
James Osborne, GSK
Dan Tubridy, BI
Bruce Smith, GSK
Nana Numapau, BI
Vito Mazzacone, BI
Cynthia Albert, Merck
Phil Walsh, Sunovian
Nick Nguyen, Sunovian
Wilson Liu, Sunovian
Tom Perkins, DSI
Allen Quan, DSI
Jennifer Lauper, BMS
Betty Chan, Gilead
James Kotuski, Gilead
William Crawford, DSI
Nick Lourenco, DSI
Patrick Mory, Horizon
Mike Sans, DSI
Matt Mendigurson, DSI
Sandy Sierawski, Pfizer
Rich Blair, Pfizer

Public (Carson City):
(None)

Public (Teleconference):

Don Harada, Ferring
Brenda Nunnally, AstraZeneca
Kelvin Yamashita, Sanofi
Chris Stanfield, Supernus
Raffi Rodrigo
Stephanie Ferrell, DXC
Tanya Phares, SilverSummit
Shawna DeRousse, UHC
Noreen Dentscheff, SilverSummit
Gary Okano, BMS
Johnna Young, HPE
A Fodor, DSI
Tom Beranek, Centene

AGENDA

1. Call to Order and Roll Call

Dr. Nagy called the meeting to order at 1:00 PM and calls for roll call.

Chris Highley

Mike Hautekeet

Kate Ward

Holly Long

Joseph Adashek

Evelyn Chu

Shamim Nagy

Gabe Lither

Adam Zold

Mark Decerbo

Duane Young

Kevin Whittington

Carl Jeffery

2. Public Comment

3. Administrative

Shamim Nagy, Chair: Any public comment? No comments. Any discussion from the meeting minutes from the September 28, 2017 meeting?

Joseph Adashek: I move that we accept the minutes.

Adam Zold: Second

Voting: Ayes across the board, the motion carries.

Shamim Nagy, Chair: Status update from Mr. Young.

Duane Young: As of November 16, 2017, the division became in compliance with mental health parody and addiction equity act of 2008. The public hearing was held to bring our changes in compliance on December 21, 2017. There will be a special public hearing being held to bring us in compliance with the legislative mandate within the budget that we cover medical nutrition therapy, for registered dietitian provider type, adult podiatry services and gender reassignment services.

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

a. Gastrointestinal Agents - Functional Gastrointestinal Disorder Drugs

Shamim Nagy, Chair: Thank you. Public comment? None. Getting into established drug class review being reviewed due to the release of new drugs. Gastrointestinal agents, functional gastrointestinal disorder drugs. Public comment?

Jeanette Thompson: Good afternoon, my name is Jeanette Thompson, I am the medical science liaison for Synergy Pharmaceuticals. I would like to talk about our very first product called Trulance. [Covers approved indication, disease background, and other treatment options. Covers mechanism of action and chemical structure, safety and efficacy trials, contraindications, indications and dosing. Asks the board to consider adding Trulance to the preferred drug list].

Rupa Shaw: My name is Rupa Shaw and I am a clinical pharmacist and medical science liaison with Purdue Pharma. I'm here to provide public comment for Symproic. [Covers indication, contraindications, the recommended dose and strength and administration. Discusses OIC as defined by a change when initiating opioid therapy in bowel habits, decrease frequency, stress during bowel movement, incomplete evacuation and straining during a bowel movement. The prevalence of OIC in patients taking an opioid ranges between 40 and 50%. Covers the mechanism of action including blocking the mu opioid receptor, leading to the decrease of the constipating effects of opioids. CNS penetration is minimal. Monitoring of patients on Symproic is covered. Studies are discussed demonstrating benefits and clinical outcomes. Gives overview of adverse events].

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

Mark Ernst: My name is Mark Ernst, I am a practicing physician's assistant here in Nevada. I have been practicing since 2000 in the area of pain management. I have been asked to say a few words about my clinical experience. What I have seen over the years is laxative use is not very helpful for post op issues and for pain medications with opioid induced constipation. I started using one of the medications, Movantik and have seen a decrease in constipation issues and pain complaints. I'm dealing with pain every day with patients, I don't need to add additional GI problems and may add to sending them out to be evaluated. When they come back we place them on this kind of medication and they seem to do just fine. From my perspective, I just want to have these options available. About half of my patients have this problem. The use of this medication has approved their outcomes with less GI issues and have less complaints when they come back. I have been very pleased with it and it is a great option to have when dispensing opioids.

Adam Zold: You say you use Movantik mainly?

Mark Ernst: I have used some others like Linzess or some others to help with constipation like over the counter. The OTC is not the best. When someone is constipated, adding bulk compounds just seems to make things worse with bloating, I like to stop it before it gets worse.

Adam Zold: Have any of your patients benefited more from others?

Mark Ernst: I have had success with Linzess, but every time I use Movantik, people that have used it tell me it works. I had one patient having a bowel movement every 14 days, started this and now has one every 5 days. I have patients that don't take it every day because it works so well.

Joseph Adashek: How many doctors are in your practice?

Mark Ernst: We have one MD.

Joseph Adashek: I was just wondering if everyone felt the same way, but you have a small practice.

Mark Ernst: The prior practice was four MD's and four mid-levels, it was pretty standard.

Shamim Nagy, Chair: Any other public comment? No. Optum presentation for preferred?

Carl Jeffery: There are two new agents that have been covered already. I have a quick chart showing the three different disease states these cover, chronic idiopathic constipation, opioid induced constipation and irritable bowel syndrome with constipation. We also have IBS-D, diarrhea predominant, Viberzi and Xifaxin are indicated for that, but we are excluding these for our discussion. Symproic is indicated for OIC for adults with cancer and non-cancer pain receiving opioids. Trulance is the other with the indication for CIC. Symproic has a change of spontaneous bowel movement, about half of the study recipients had a spontaneous bowel movement greater than three times per week vs. about a third for those on placebo. Trulance is kind of similar with the CIC, we are seeing about 20% are responding to the medication vs about 12% on placebo. These medications are effective for about one in five patients that get them. Guidelines have not been updated yet to include these agents. Optum recommends these products be considered clinically and therapeutically equivalent.

Shamim Nagy, Chair: Any discussion?

Joseph Adashek: Is Movantik the only one for opioid induced constipation?

Carl Jeffery: We have Amitiza preferred and is indicated for opioid induced constipation.

Joseph Adashek: Is there a difference between the two medications? Any studies comparing one to the other?

Carl Jeffery: Not that I am aware of, those head-to-head studies are pretty hard to come by. Off the top of my head I am not aware of anything.

Adam Zold: I move they are clinically and therapeutically equivalent.

Joseph Adashek: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: Optum recommends the two new products, Trulance and Symproic be listed as non-preferred because we think Amitiza and Linzess we preferred have the indications covered. We would leave the rest of the class the same.

Shamim Nagy, Chair: Any discussion?

Adam Zold: Do you have any usage data on the Movantik?

Kevin Whittington: Movantik for a quarter 186 claims, by comparison Linzess had 372 claims and Amitiza had 149.

Joseph Adashek: Were all those claims for Movantik, they had to have a prior authorization?

Carl Jeffery: Right, Amitiza, Movantik and Relistor all have prior authorization criteria from the DUR Board.

Joseph Adashek: So it is pretty equal or similar for Movantik to get permission as the others. Are the other ones on the preferred drug list, do you need a PA for those two?

Carl Jeffery: Amitiza and Linzess are preferred and Amitiza requires PA, but not Linzess. It is in the works but has not been processed yet.

Joseph Adashek: I would move that we add Movantik to preferred list to the recommendations.

Adam Zold: Second.

Voting: Ayes: 4; Nay: 4 - the motion does not pass.

Chris Highley: I would like to make a comment on this class. I have a lot of experience, for what is worth the patients that have tried Movantik for OIC tend to go back to the old school methods for the treatment of constipation with over the counters. Linzess is very effective, but I have not tried the new agents that were presented today.

Joseph Adashek: I move that we accept the recommendations by Optum.

Evelyn Chu: Second.

Voting: Ayes across the board - the motion carries.

b. Ophthalmic Agents - Ophthalmic Antihistamines

Shamim Nagy, Chair: The next is ophthalmic agents, ophthalmic antihistamines. Is there any public comment? No public comment.

Carl Jeffery: This is an easy one, there is a new generic for the olopatadine, a generic for Pataday and Patanol. It is an AB rated generic. There was a new product in the write-up in your binder,

ceterizine liquid, but it was not approved yet, but we will talk about that in the future. With the addition of the generic, Optum recommends the board consider these clinically and therapeutically equivalent.

Evelyn Chu: I move we accept the list as clinically and therapeutically equivalent.

Joseph Adashek: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: Optum recommends the generics be added as non-preferred and keep the rest of the class the same.

Joseph Adashek: I move we accept the recommendations.

Adam Zold: Second.

Voting: Ayes across the board, the motion carries.

c. Respiratory Agents - Respiratory Anti-inflammatory Agents - Respiratory Corticosteroids

Shamim Nagy, Chair: The next class is respiratory agents, respiratory corticosteroids. Any public comment? No public comment.

Carl Jeffery: We have a new product, Armonair which is a combination of fluticasone propionate which is the same ingredient as Flovent. It went off patent so they had an opportunity to put it in another product. It is a unique delivery mechanism, but it is indicated like the other product, prophylaxis of asthma. This one is indicated only for ages 12 and up where the Flovent is approved down to 4 and over. It is still one inhalation twice daily. They had to do all their own studies. It was demonstrated effective in two 12 week confirmatory trials and a 26 week dose ranging trial and a safety trial. It was shown to be effective in all those for 12 and over. No real big changes with this one, I don't know that it has a big advantage over other agents in the class. Optum recommends the board consider these clinically and therapeutically equivalent.

Evelyn Chu: I move we accept the list as clinically and therapeutically equivalent.

Adam Zold: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: Optum recommends the new product Armonair be added as non-preferred because it doesn't appear to offer any benefit over the Flovent that is currently preferred.

Joseph Adashek: I move we accept Optum's recommendations.

Adam Zold: Second.

Voting: Ayes across the board, the motion carries.

d. Dermatological Agents - Topical Anti-inflammatory Agents - Immunomodulators: Topical

Shamim Nagy, Chair: The next class is dermatological agents, topical anti-inflammatory agents, immunomodulators topical. Do we have any public comment?

Rich Blair: My name is Rich Blair, I am a licensed pharmacist and field director for Pfizer. I am here to talk about Eucrisa, a non-steroid ointment for the treatment for mild to moderate atopic dermatitis and ask you to consider for formulary. [Covered overview of disease, symptoms and prevalence. Covers Eucrisa background including mechanism of action, application of product and chemical structure. Provides information on indication and studies for approval. Details safety concerns and adverse reactions. Provides information on long-term safety information and contraindications].

Shamim Nagy, Chair: Any other public comment?

Rosemary Hume: Good afternoon, my name is Rosemary Hume, I am a partner at St. Rose Pediatrics. I have been practicing for 26 years. I am excited about Eucrisa because it is the first non-steroidal option parents have had in over 10 years. I have had experience with this and the patients that have used it down to age two. Parents are thrilled that they can use a non-steroid especially to their young babies face. I urge the committee to add this medication to their formulary. Any questions?

Shamim Nagy, Chair: Any other public comment?

Carl Jeffery: We just heard about the new medication in this class, Eucrisa. I have on the screen the indications. It is for mild to moderate atopic dermatitis in patients as young as 2 years old. The other products on the market, Elidel and Protopic are indicated for second line therapy usually after a trial of a steroid or some other alternative therapy. The Eucrisa is not really understood how the mechanism works. It was shown effective in two trials. About a third of the patients responded to this medication, showing a greater than a 2-grade improvement vs. about a quarter of the population that responded to the vehicle controlled. Optum recommends the board consider these clinically and therapeutically equivalent.

Joseph Adashek: I move that we accept the recommendation that they are clinically and therapeutically equivalent

Evelyn Chu: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: Optum recommends Eucrisa, the new medication be considered non-preferred and keep the rest of the class the same with Elidel and Protopic as preferred.

Adam Zold: I have had probably five or six patients on Eucrisa over the past few months. They all seem to love it and have responded well and have better outcomes. Like Dr Hume said, they

don't have to worry about where they put it or have their skin thin out. I would like to make a motion to add it as preferred.

Joseph Adashek: Second.

Chris Highley: Just a quick question on where you can apply this. Protopic and Elidel, are they able to be applied to the face? Is there a restriction on where these can be applied?

Carl Jeffery: I don't know that off the top of my head, I will throw it out to the community or board.

Chris Highley: The presenter said Eucrisa can be applied to the face, I can't recall if the others can be applied to the face.

Mark Decerbo: In this regard, it might help to have a discussion before voting, but I am not aware of any restriction of applying the T-cell activators to the face. I think it was more to steroids which our PDL does not include.

Voting: Ayes: 7 Nay: 1 - The motion carries.

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

Shamim Nagy, Chair: The next class, Anti-infective agents, antivirals, anti-hepatitis agents. Do we have any public comment?

Betty Chan: Hi my name is Betty Chan, I am the medical scientist speaking on behalf of Gilead Sciences today. Gilead has four marketed products, Sovaldi, Harvoni, Epclusa and Vosevi. Sovaldi is only used with combination with interferon. Harvoni is indicated for genotypes 1, 4, 5, 6 including people who are post liver transplant including patients who are decomp and adolescents. We also have Epclusa which is the pan-genotypic regimen with highest SVR rates and robust treatment data. Our newest approval was Vosevi, indicated for DAA experience patients and retreatment. I'm not here to advocate for choosing one agent over another. All the DAA single tablet regimens have established high SVR rates, high efficacy, and minimal tolerability issues, highly safe and also there is low resistance. They have made a significant impact on the lives of HCV patients. There are variations between the agents, mainly in the indications, drug-drug interaction and special population such as patients with a liver transplant. There is not one product that can cover all patient types. What Gilead is advocating is to allow physicians to make the determination for which agent is most appropriate for their patient. Nevada has always had open access provided the patients meet the criteria. We are asking the committee to maintain open access and allow the physicians to choose the most appropriate agent. Thank you and I will answer any questions.

Shamim Nagy, Chair: Any other public comment?

Dr Sangeeta Auawan: Good afternoon, I am Dr. Sangeeta Auawan from AbbVie medical affairs. Mavyret was recently approved as a once daily ribavirin free ritonavir free pan-genotypic regimen

for the treatment with chronic hep C. Mavyret is indicated for all genotypes and with or without compensated cirrhosis. It is also indicated in chronic hep C genotype 1 patients that have previously failed a regimen containing a NS5A or an NS3 inhibitor, but not both. It is estimated that Mavyret can treat up to 95% of patients with chronic Hep C. The vast majority of patients awaiting treatment are naive and non-cirrhotic and would be eligible for 8 weeks of treatment. Mavyret's clinical development program included over 2300 patients over 9 clinical trials. I am going to summarize the efficacy rates. 99% SVR was seen with patients without cirrhosis for all genotypes treated for 8 weeks in the pooled analysis. 99% SVR was seen in 146 patients with compensated cirrhosis across genotypes 1,2,4,5 and 6 regardless of treatment experienced when treated for 12 weeks. For genotype 3 patients with compensated cirrhosis, we saw a SVR rates of 100% and 96% for treatments of 12 weeks and treatment experienced for 16 weeks. 100% SVR were seen in patients with chronic kidney disease. CKD stages 4 and 5 including patients on dialysis across all genotypes, regardless of prior treatment experience when treated for 12 weeks. No dose adjustments are needed for hep C patients who are renally impaired or who are coinfected with HIV. With regards to safety, Mavyret carries a boxed warning regarding the risk of hepatitis B reactivation and it is important to test all patients for evidence of all prior Heb B exposure. If a patient is co-infected, monitoring is required post treatment for hepatitis B reactivation. Mavyret has two contraindications, one for severe hepatic impairment, who are Child-Pugh C and patient taking atazanavir or rifampin. The most common adverse events greater than 10% include headache and fatigue. I appreciate the committee's time and request the board add to the formulary for the following reasons, it is the only once daily pan-genotypic ribavirin free regimens that has been approved by the FDA to treat patients with chronic hep C across all genotypes including those with and without cirrhosis and those who are treatment experienced, have HIV and chronic kidney disease. Up to 95% of patients can be treated with Mavyret and the vast majority can be treated for 8 weeks.

Shamim Nagy, Chair: Any other discussion? We need a motion for therapeutic and clinical equivalency.

Joseph Adashek: I move that we agree with the recommendation that they are clinically and therapeutically equivalent.

Evelyn Chu: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: Optum recommends the two new products, Mavyret be added preferred because it has the indication for first line therapy and Vosevi for non-preferred because it is only indicated after treatment failure.

Mark Decerbo: I move to accept the PDL as presented.

Adam Zold: Second.

Voting: Ayes across the board, the motion carries.

f. Respiratory Agents - Respiratory Long-Acting Antimuscarinic/Long-Acting Beta-Agonist Combinations

Shamim Nagy, Chair: The next topic is respiratory agents, long-acting antimuscarinic and long-acting beta agonist combinations. Do we have any public comment?

James Osborn: Good afternoon, I'm James Osborn, a health outcomes liaison with GlaxoSmithKline. I will keep it brief since we are on the preferred side. I just want to bring a few changes, a few head to head studies that have become available with Anoro vs. Stiolto as well as Utibron vs. Anoro, non-inferiority studies. Anoro did show not only non-inferiority, but superiority to Stiolto product, it was an open label study, we were not able to get placebo Respimat devices, but we did blind the technician. Then the study by Utibron, both products showed similar improvements in lung function, but Utibron was unable to demonstrate non-inferiority. I would be happy to take any questions about those studies

Shamim Nagy, Chair: Any questions or other comment?

Nick Nguyen: Hi my name is Nick Nguyen, I am the director of Health Economics and Research with Sunovian. Thanks for the opportunity to present information on Utibron. Utibron is a dual combination bronchodilator and it is a LAMA and LABA, indicated twice daily for long-acting maintenance treatment of COPD. Utibron contains a LABA so it carries a class wide warning of asthma related death. It is not indicated for acute bronchospasm or asthma. Patients in the Utibron clinical study demonstrate sustained lung function. In the pooled analysis in the two 12 week trials, the Utibron demonstrated clinically meaningful improvement in health related quality of life as measured by the SGRQ and a reduction in daily rescue medication use. These findings are consistent with the 2017 GOLD report that recommends LAMA/LABA for patients with moderate COPD, to be treated sooner or LABA/ICS who require maintenance bronchodilation. Utibron has demonstrated both clinical and safety profile and in addition is the delivery device, is a neohaler and twice daily. It provides visual and audio cues, it is a single dose dry powder inhaler and the capsules are transparent. Patients can see if any powder is left providing visual confirmation that the powder has been dispersed. If there is powder left, they can repeat the inhalation. As long as it is empty, the patient has received the full dose. Utibron is also cost effective based on economic models with patients with moderate to severe COPD. In closing and based on GOLD guidelines, the clinical outcomes shows Utibron provides a cost effective treatment. The head to head non-inferiority trial was mentioned earlier, I just wanted to note that it was correctly reported as reported. The two endpoints were similar suggesting that both Utibron and Anoro are similar in effectiveness. The non-inferiority was based on a very stringent margin that was a priority of 20ml vs. 50ml non-inferiority margin, which was about half of the 100ml that is usually deemed clinically meaningful for the FEV1, so I just wanted to point that out that the study was very similar in the results. So based on the GOLD guidelines and also on Sunovian I respectfully ask that Utibron be added to the preferred drug list for Medicaid beneficiaries. I will take any question.

Gabe Lither: This committee is not to consider cost in any their decision. I appreciate you not bringing up cost in your discussions.

Shamim Nagy, Chair: Any other public comment?

Carl Jeffery: We have another new agent in this class. The screen shows the indications including the Bevespi which is similar to others, the long term maintenance of COPD. It is a combination of glycopyrrolate and formoterol, both medication in other agents. The normal dose is two inhalation twice daily. There were two 24 week double-blind placebo controlled studies showing it was effective. Optum recommends the board consider these clinically and therapeutically equivalent.

Adam Zold: I motion they are clinically and therapeutically equivalent.

Joseph Adashek: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: Optum recommends Bevespi be considered preferred and the rest the class remain the same.

Mark Decerbo: With Bevespi and Utibron both glycopyrrolate and both twice daily, is there any insight behind Optum's recommendation in that regard?

Carl Jeffery: I think there are some good studies behind the Bevespi.

Joseph Adashek: I move that we accept Optum's recommendation.

Evelyn Chu: Second.

Voting: Ayes across the board, the motion carries.

g. Analgesics - Opiate Agonists - Abuse Deterrent

Shamim Nagy, Chair: The next class is analgesics, opiate agonists, abuse deterrent. Do we have any public comment?

RS: My name is Rupa Shaw, a pharmacist with Purdue representing Hysingla ER. If you have any questions, I would be happy to take them.

Allen Quan: Good afternoon, my name is Allen Quan, I am a pharmacist and MSL with DSI. I am here to speak on Morphabond. Morphabond ER is an orally administered extended release abuse deterrent formulation of the schedule 2 controlled substance morphine sulfate. It is indicated for the management of pain severe enough to require around the clock treatment where alternative therapies are inadequate to provide sufficient management of pain. [Covers indications from package insert, abuse deterrent properties for intranasal and IV routes, two barriers for abuse deterrence. Still subject to abuse and misuse. Five box warnings. Refers to the full prescribing information]. In summary, the opioid epidemic is a complex problem with no single solution. Morphabond ER is formulated with inactive ingredients that make the tablet more difficult to adulterate, misuse and abuse while maintaining the extended release characteristics even if the tablet is subjected to physical manipulation and or chemical extraction. Morphabond ER is

expected to reduce abuse by both intranasal and IV routes of administration, however abuse by intranasal, IV and oral routes is still possible. That concludes my testimony. Any questions?

Shamim Nagy, Chair: Any other public comment?

James Bosinger: My name is James Bosinger, I specialize in pain management in Las Vegas. I would like to talk about Morphabond ER. We are all aware of all the talk about the opioid epidemic. Certainly there will still be abuse of products out there. I'm in support of the Morphabond ER for the short time it has been out. I think it is important that we have more options to treat our patients with chronic pain. Morphabond is with some of the other abuse deterrent products and they all have their place. The one thing unique about Morphabond is the physical barriers. We know that if a patient is going to abuse or tamper with it they are more than likely going to crush it. This formula is difficult to crush, but not impossible. Even if it is crushed and someone tries to inject it, it has been shown to reduce its ability to draw up in a syringe. I think this is certainly a positive feature of this medication. Secondly, even if it was inhaled or snorted, it is shown to maintain its extended release properties. Therefore if a patient was to attempt to tamper with this medication, because abuse is still possible, the drug likability scores are negligible, no different than if the medication is taken orally. There are a number of properties to reduce the abuse. I would like to ask we are able to have safer medications available and some with abuse deterrent properties and I think we need to have those options.

Shamim Nagy, Chair: Any other public comment.

Larry Ikeda: My name is Larry Ikeda, I am a physician with Pfizer pharmaceuticals. I am a field director. I wanted to remind the committee of two things. First, just because a product has abuse deterrent technology doesn't mean the FDA has approved that for labeling to be abuse deterrent, there are further studies required to be submitted to the FDA in order for the product to be approved to be labeled as abuse deterrent. The second is the most common types of abuse are oral and intranasal, IV abuse is rather rare for prescription opioids. I just wanted to remind the committee of those facts.

Shamim Nagy, Chair: Any other public comment? None.

Carl Jeffery: We heard about the new product, Morphabond ER. It was approved based on studies for MS Contin. We heard about the abuse deterrent properties, increased resistance to cutting, crushing and breaking. It was shown in the package insert that they gave it to people who have a history of drug abuse, it shows less drug liking, they would rather have a non-abuse deterrent product. This goes across the board with other products labeled with abuse deterrent properties. Optum recommends the board consider these clinically and therapeutically equivalent. Just a reminder, several meetings ago, we broke out the abuse deterrent opioids vs. the regular extended release opioids. We only include products that have been approved by the FDA as abuse deterrent. There are some other medications that say they have abuse deterrent properties, but have not been given permission to advertise that from the FDA. I think this class will be getting bigger as more studies come out.

Mike Hautekeet: Are we going to vote on the abuse deterrence factor or the therapeutic aspect? Which one are we going to vote?

Carl Jeffery: I think that is a good consideration, I would encourage the board to consider both aspects of the products. This is the list of products that the Nevada Medicaid patients are more likely to get. Do you want prescribers to write one medication over another, that is really where we are guiding the prescribing of the products? If there is one that clearly has better abuse deterrent properties and shown to be clinically effective, maybe that would have some benefit.

Mark Decerbo: In this climate, an increase utilization in abuse deterrent products isn't necessarily due to what we do here with the different categories. Is there any data that Optum has from us splitting these out as a separate class, have we seen a shift of our Medicaid prescribing going from the standard agonists to the abuse deterrent?

Carl Jeffery: The data would be good, that is something worth looking at. We have not looked at that trend from the different classes. We have the utilization, we don't have it trended over the last year. I think that is worth looking into at a future meeting.

Shamim Nagy, Chair: Any other discussion? We need a motion for equivalence.

Mark Decerbo: I move we accept the list as presented as clinically and therapeutically equivalent.

Joseph Adashek: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: Optum recommends Morphabond be considered non-preferred because we have Embeda that has been shown to be abuse deterrent and is also a morphine product with encapsulated naloxone to reduce abuse. It is a different mechanism for reducing abuse. The rest of the class would remain the same, Embeda and Hysingla would remain preferred and Morphabond, OxyContin and Xtampza would be non-preferred.

Evelyn Chu: Does the Embeda have a one-to-one conversion with morphine or is it a different conversion?

Carl Jeffery: I don't know that off the top of my head.

Larry Ikeda: Yes, it is a one-to-one equivalent. It is an extended release, however the extended release properties of Embeda are more similar to the extended release of Kadian, where the half-life is 29 hours, so it is a true once a day morphine formulation.

Shamim Nagy, Chair: Any other questions?

Mark Decerbo: I would be curious in the future to see that data. I'm fine with the current recommendation, but in the future I could be swayed depending on utilization. If we have 50% on MS Contin being switched to the abuse deterrent formulation, that would be a different calculus in my mind.

Adam Zold: On the Morphabond, since it does not have naltrexone, does anyone else have any opinions we should have both on the preferred list? We have one with naltrexone and one without to give more options like Dr. Bossinger had suggested.

Joseph Adashek: I don't have a lot of preference on these products from my practice. I would have to refer to someone with a little more expertise in this area.

Mark Decerbo: Personally, I'm fine with how the PDL is now, but as I mentioned before, if it looks like a significant number is on a recurring regular basis or are switching from the standard MS Contin, that would change my mind for the need for how aggressive we need to be with the PDL.

Shamim Nagy, Chair: So we are going to be every three months, separate reporting for that? How are we going to accommodate that?

Carl Jeffery: We can bring back to the next meeting for a point of discussion, if there are no recommendations, we can bring it back for possible action for the committee to take action. I also wanted to point out that these fall under the requirements for the quantity limits that we put in place for all opioids and is applied across the board regardless if they are abuse deterrent or regular and that is 60mg morphine equivalents per day up to 7 day allowance and 13 fills per rolling 12 months. That applies to any opioid that is currently available. All of these will require prior authorization and there are some requirements to meet like if they are on the lowest effective dose, if there is a pain contract on file, if they keeping their office visits, all of those requirements have to be met before they can get these agents on a routine basis.

Shamim Nagy, Chair: If there is no further discussion, we need approval of the list as presented.

Adam Zold: I want to make a motion, being on the retail side of pharmacy, I see a lot of opioid problems come in the door every day and I would like to see more open access even with the stipulations from Medicaid which do help and we are appreciative of those, I would like to make a motion to move Morphabond to preferred with the other two. Any discussion?

Joseph Adashek: I will second the motion?

Mark Decerbo: I don't know about this, in concept I don't have a problem with the motion, but without numbers, it's hard to know. I think back to some of the other therapeutic classes different from here where we remove things from the PDL and we look at the utilization and there have been two patients for the year. The numbers behind the recommendation matter. If I saw something like 90% of all the new opioid prescriptions for our Medicaid population are the abuse deterrent, that would change my approach to it, but without the numbers it is a guessing game for me.

Carl Jeffery: Would the current utilization help for the abuse deterrent? We don't have the non-abuse deterrent.

Kevin Whittington: The Morphabond doesn't have any utilization at this point or at least when we pulled the data. Embeda had 74 claims, Hysingla 93, OxyContin 289 and Xtampza had 8 claims.

Shamim Nagy, Chair: We have a motion and a second, we will vote.

Voting: Ayes: 4 Nay: 4 - the motion does not carry.

Joseph Adashek: If we make a motion the other way and it is still tied, what happens then?

Gabe Lither: The default is something comes on as non-preferred. If nothing were to happen, it would still be non-preferred.

Joseph Adashek: I make the motion that we accept the recommendation by Optum.

Evelyn Chu: I second the motion.

Voting: Aye: 7 Nay: 1. The motion carries.

Adam Zold: Is that something we will be going over at the next meeting?

Carl Jeffery: Yes, I think we can bring it back for the next meeting with some numbers and maybe by then a new medication will be in this class too. I know there are some manufactures that are working on getting approval.

5. Established Drug Classes

a. Dermatological Agents - Topical Analgesics

Shamim Nagy, Chair: The next is established drug classes, dermatological agents, topical analgesics. Do we have any public comment?

Carl Jeffery: I think this is a funny class, it is a hodgepodge of medications, but it is all the topical analgesics. We have a generic for diclofenac gel. I don't have any clinical slides, but I'm not going to get into the therapeutics. We have topical NSAIDs and topical lidocaine, we also added capsaicin, I know it works well for some patients. I know there are some differences in this class, but they are all for the treatment of topical pain. Optum recommends the board consider these clinically and therapeutically equivalent.

Adam Zold: I motion these are clinically and therapeutically equivalent.

Mark Decerbo: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: Optum recommends that we are going to mix the class up a little bit. There is a generic for Emla, lidocaine and prilocaine cream, it is only indicated for port access or IV administration, we have had a few requests come over. Moving the brand Flector and Pennsaid to preferred and adding capsaicin as preferred and the generic diclofenac as non-preferred.

Evelyn Chu: I move we accept the drug list as presented.

Joseph Adashek: Second.

Voting: Ayes across the board, the motion carries.

b. Biologic Response Modifiers - Immunomodulators - Targeted Immunomodulators

Shamim Nagy, Chair: The next class is biologic response modifiers, immunomodulators, targeted immunomodulators. Do we have any public comment? No public comment.

Carl Jeffery: We do have a new product in this class, I will give a quick overview. Dupixent, it is a limited indication for atopic dermatitis. It has a loading dose of 600mg SQ and then 300mg SQ every other week. It was demonstrated effective for adults with atopic dermatitis. The reason this class came back was at the last meeting we had a discussion about requiring a single preferred agent before getting a non-preferred. That was really the reason it is coming back for discussion. The language we have used before is a requirement of only a single agent before getting a non-preferred agents. Optum recommends the class be considered clinically and therapeutically equivalent.

Joseph Adashek: I move we accept the recommendation.

Mark Decerbo: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: Since this class came back up, we had an opportunity to look at the numbers again. The new medication, Dupixent is such a limited indication, we thought we would make it non-preferred. But we will move Actemra and Inflectra to preferred to give a few more options.

Kate Ward: The decision between Inflectra and Remicade, when the prescription is for Remicade, will it be able to be auto-substituted?

Carl Jeffery: My understanding, is it is not AB rated, so it cannot be automatically substituted, they are BX rated, so you need a new order. As far as Medicaid, they would cross over, so if they have a prescription for Remicade and they have a prior authorization already for Inflectra, they would cross over and be approved.

Adam Zold: I make a motion to accept Optum's recommendation.

Evelyn Chu: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: The next discussion if the board wants to only require failure of a single agent before getting a non-preferred.

Mark Decerbo: Can you give use some background, are there some other classes where we have gone away from the two failure requirement, or is there anything in statute?

Carl Jeffery: There is nothing in statute that prohibits this action, there is a statute that limits some classes where we are required to only require a single agent failure and those are anti-diabetics, antipsychotics and anticonvulsants. There is a requirement already in statute. The board has added this to MS medications. I know the board has made this action before. I think what it comes down

to is that these are pretty fragile patients anyway and once you find a medication that works, I think it is challenging make a patient try two agents especially for someone with severe plaque psoriasis. This gives the choice to the doctor.

Shamim Nagy, Chair: Are you going to make a specific class of medications?

Carl Jeffery: No, we wouldn't make any changes to the class, they would just have to try one preferred agent before getting a non-preferred instead of having to try two preferred medications.

Mark Decerbo: Separate request, for institutional knowledge, at future meetings, could we get something brief of which ones require a single failure or by statute would give us some history.

Adam Zold: I make the motion that only a single failure of a preferred be required before getting a non-preferred.

Evelyn Chu: Second.

Voting: Ayes across the board, the motion carries.

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

Shamim Nagy, Chair: The next is a report of new drugs to market.

Carl Jeffery: I went through and pulled out some medications that the board might be interested in. There are some new medications that were recently approved. Abilify with the tracking chip, it was approved and it was some big news. I don't think it is on the market yet, but should be released soon. I think there is some promising or scary technology. My understanding is that there is a patch they wear and it talks to your phone and tracks when the patient takes the medication. There is a chip in the pill that talks to the phone through the patch. I don't know how it will be packaged if it will contain a patch. Some of the others, we have an updated Bydureon, it is a pen. The one currently needs to be reconstituted. There are some new SGLT2 with all the combination and another GLP1 that is on the way out that is similar to Byetta. Another medication for major depressive disorder, esketamine. There has been some articles about ketamine used for depression, I'm guessing they are related. Estimated release in 2018. Some of the generics that may impact the board is Daytrana, Proventil HFA and ProAir HFA will be going generic. The old Byetta version went generic, and these are probably tied up in patent litigation, Rozerem and Latuda are all scheduled for 2018. All things to see next year.

7. Closing Discussion

Shamim Nagy, Chair: Closing comments, do we have any public comment? No. Date for the next meeting?

Carl Jeffery: March 22, 2018. We have the LCB booked for next year.

Duane Young: We have the Legislative Council Building in Carson City and the State Legislative Building here in Las Vegas.

Shamim Nagy, Chair: The meeting is adjourned.

Meeting adjourned at 2:56 PM.

Therapeutic Class Overview

Antiasthmatic – Monoclonal Antibodies

INTRODUCTION

- Asthma is a chronic lung disease that inflames and narrows the airways, making it difficult to breathe. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing (*National Heart, Lung, and Blood Institute [NHLBI] 2014*).
- The exact cause(s) of asthma are unknown. A combination of factors such as genetics, certain respiratory infections during childhood, and contact with airborne allergens can contribute to its development (*NHLBI 2014*).
- The goal of asthma management – asthma control – can be described in the following domains (*NHLBI 2007*):
  - Reduction of impairment
    - Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the daytime, at night, or after exertion)
    - Require infrequent use (≤2 days a week) of short-acting beta-agonist (SABA) for quick relief of symptoms
    - Maintain (near) normal pulmonary function
    - Maintain normal activity levels (including exercise and other physical activity and attendance at work or school)
    - Meet patients' and families' expectations of and satisfaction with asthma care.
  - Reduction of risk
    - Prevent recurrent exacerbations of asthma and minimize the need for emergency department (ED) visits or hospitalizations
    - Prevent progressive loss of lung function; for children, prevent reduced lung growth
    - Provide optimal pharmacotherapy with minimal or no adverse effects.
- Current pharmacologic options for asthma management are categorized as: (1) long-term control medications to achieve and maintain control of persistent asthma, and (2) quick-relief medications used to treat acute symptoms and exacerbations.
  - Long-term control medications include:
    - Corticosteroids (inhaled corticosteroids [ICS] for long-term control; short courses of oral corticosteroids to gain prompt control of disease, long-term oral corticosteroids for severe persistent asthma)
    - Cromolyn sodium and nedocromil
    - Immunomodulators (e.g., omalizumab)
    - Leukotriene modulators
    - Long-acting β-agonists (LABAs)
    - Methylxanthines (i.e., theophylline)
  - Quick-relief medications include:
    - Anticholinergics (i.e., ipratropium bromide), as an alternative bronchodilator for those not tolerating a SABA
    - SABAs (therapy of choice for relief of acute symptoms and prevention of exercise-induced bronchospasm)
    - Systemic corticosteroids (not short-acting, but used for moderate and severe exacerbations) (*NHLBI 2007*)
- Approximately 5 to 10% of asthma patients have severe disease. Severe asthma includes various clinical phenotypes of poorly controlled asthma characterized by frequent use of high-dose ICS and/or oral corticosteroids (*Chung et al 2014*).
- While there are currently no widely accepted definitions of specific asthma phenotypes, several strategies have been proposed to categorize severe asthma phenotypes based on characteristics such as patient age, disease onset, corticosteroid resistance, chronic airflow obstruction, or type of cellular infiltrate in the airway lumen or lung tissue (*Walford et al 2014*).
- Chronic idiopathic urticaria (CIU), also called chronic urticaria or spontaneous urticaria, is defined by the presence of hives on most days of the week for a period of 6 weeks or longer, with or without angioedema. The hives are circumscribed, raised, erythematous plaques, often with central pallor, and variable in size. No external allergic cause or contributing disease process can be identified in 80 to 90% of adults and children with CIU (*Khan 2017, Saini 2017*).
- CIU affects up to 1% of the general population in the United States, and the prevalence is believed to be similar in other countries. The condition is more common in adults than children and typically begins in the third to fifth decades of life.

CIU is a self-limited disorder in most patients although the condition generally has a prolonged duration of 1 to 5 years (*Saini 2017*).

- Non-sedating H_1-antihistamines are the cornerstone of therapy for CIU. Limited courses of oral glucocorticoids are often used in combination with antihistamines for refractory symptoms. Other pharmacologic options for patients who do not respond to H_1-antihistamines include the use of H_2-antihistamines, leukotriene modifiers, cyclosporine, sulfasalazine, and dapsone (*Khan 2017, Maurer et al 2013*).
- Eosinophilic granulomatosis with polyangiitis (EGPA), previously called Churg-Strauss syndrome, is a systemic necrotizing vasculitis that affects small-to-medium-sized vessels. It is typically associated with eosinophilia and severe asthma (*Groh et al 2015, Schwartz et al 2016).*
- EGPA is a rare condition with a prevalence of approximately 13 cases per 1 million persons and an annual incidence of approximately 7 new cases per 1 million persons. It has a higher incidence in patients with asthma (*Groh et al 2015*).
- Systemic glucocorticoids are the mainstay of treatment for EGPA. For refractory EGPA, the addition of cyclophosphamide, azathioprine, methotrexate, rituximab, or intravenous immunoglobulins (IVIG) can be considered *(Groh et al 2015).* In more than 85% of patients with EGPA, remission can be achieved with glucocorticoids with or without an immunosuppressant; however, relapses occur in more than 33% of patients (*Pagnoux 2016*).
- This monograph describes the use of Cinqair (reslizumab), Fasenra (benralizumab), Nucala (mepolizumab), and Xolair (omalizumab).
  - Cinqair, Fasenra, and Nucala are humanized monoclonal antibody interleukin-5 (IL-5) antagonists, each approved as an add-on maintenance treatment for patients with severe asthma with an eosinophilic phenotype. The mechanism of action of Fasenra is slightly different, in that it binds to the IL-5 receptor on immune effector cells, whereas Cinqair and Nucala bind to the IL-5 cytokine. Eosinophils play a key role in the pathobiology of airway disorders by contributing to inflammation through release of leukotrienes and pro-inflammatory cytokines. Increases in eosinophils are often correlated with greater asthma severity. IL-5, a cytokine critical to eosinophil differentiation and survival, has been isolated as a potential target in eosinophilic asthma.
  - Nucala is also approved for the treatment of adult patients with EGPA.
  - Xolair is a recombinant DNA-derived monoclonal antibody that selectively binds to human immunoglobulin E (IgE). Xolair, which reduces the allergic response mediators, is useful in a subset of patients with allergic asthma. In addition, Xolair has been shown to improve symptoms in patients with CIU.
- Medispan class: Antiasthmatic – Monoclonal Antibodies

Table 1. Medications Included Within Class Review

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

(*Drugs@FDA 2017, Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations 2017*)

INDICATIONS

- Xolair is indicated for:
  - Patients 6 years of age and older with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with an ICS. Xolair has been shown to decrease the incidence of asthma exacerbations in these patients.
  - The treatment of adults and adolescents 12 years of age and older with CIU who remain symptomatic despite H_1-antihistamine treatment.

Limitations of use include the following:
  - Xolair is not indicated for the relief of acute bronchospasm or status asthmaticus.
  - Xolair is not indicated for treatment of other allergic conditions or other forms of urticaria.

- Fasenra is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.

Limitations of use include the following:
- Fasenra is not indicated for treatment of other eosinophilic conditions.
- Fasenra is not indicated for the relief of acute bronchospasm or status asthmaticus.

- Nucala is indicated for:
  - The add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.
  - The treatment of adult patients with EGPA.

Limitations of use include the following:
- Nucala is not indicated for the relief of acute bronchospasm or status asthmaticus.

- Cinqair is indicated for the add-on maintenance treatment of patients with severe asthma aged 18 years and older with an eosinophilic phenotype.

Limitations of use include the following:
- Cinqair is not indicated for treatment of other eosinophilic conditions.
- Cinqair is not indicated for the relief of acute bronchospasm or status asthmaticus.

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

CLINICAL EFFICACY SUMMARY

OMALIZUMAB

Asthma

- The original Food and Drug Administration (FDA) approval of omalizumab was based on the results of 3 randomized, double-blind, placebo-controlled, multicenter trials conducted in patients at least 12 years of age with moderate to severe asthma for at least 1 year and a positive skin test reaction to a perennial aeroallergen. All patients were required to have a baseline IgE between 30 and 700 international unit (IU)/mL and body weight not more than 150 kg. Patients were treated according to a dosing table to administer at least 0.016 mg/kg/IU (IgE/mL) of omalizumab or placebo over each 4-week period.
  - Each study was comprised of a run-in period to achieve a stable conversion to a common ICS, followed by randomization to omalizumab or placebo. Patients received omalizumab for 16 weeks with an unchanged ICS dose unless an acute exacerbation necessitated an increase. Patients then entered an ICS reduction phase of 12 (*Busse et al 2001, Solèr et al 2001*) and 16 weeks (*Holgate et al 2004*) during which ICS dose reduction was attempted in a step-wise manner.
  - In the 28-week study by Busse et al (N=525), during the steroid stable phase, patients treated with omalizumab had fewer mean exacerbations/subject (0.28 vs 0.54; P=0.006) and decreased mean duration of exacerbations (7.8 vs 12.7 days; P<0.001) compared with placebo-treated patients. Similarly, during the steroid reduction phase, omalizumab was associated with fewer exacerbations/subject (0.39 vs 0.66; P=0.003), and a shorter mean duration of exacerbations (9.4 vs 12.6 days; P=0.021) (*Busse et al 2001*).
  - In the 28-week study by Solèr et al (N=546), asthma exacerbations/patient, the primary endpoint, decreased more in the omalizumab group compared to placebo during both the stable steroid (0.28 vs 0.66; P<0.001) and steroid reduction phases (0.36 vs 0.75; P<0.001) (*Solèr et al 2001*).
  - In the 32-week study by Holgate et al (N=246), the percentage reduction in ICS dose, the primary endpoint, was greater among patients treated with omalizumab than among patients treated with placebo (median, 60 vs 50%; P=0.003). The percentages of patients with at least 1 asthma exacerbation were similar between omalizumab and placebo groups during both the stable steroid and steroid reduction phases (P value not reported). The absence of an observed treatment effect may be related to differences in the patient population compared with the first 2 studies, study sample size, or other factors (*Holgate et al 2004*).

- A meta-analysis of 3 of the previously mentioned trials (*Busse et al 2001, Solèr et al 2001, Holgate et al 2004*) and their extension studies assessed the efficacy of omalizumab in a subgroup of 254 patients at high risk of serious asthma-related mortality and morbidity. Patients were defined as high-risk due to asthma histories that included the following: intubation history, emergency room visit within the last year, overnight hospitalization, or intensive care unit treatment. The primary outcome was an annualized rate of acute exacerbation episodes based on data from the initial 16-week stable steroid phase for high-risk patients. Two kinds of acute exacerbation episodes were considered as endpoints: significant acute exacerbation episodes and all acute exacerbation episodes (i.e., all episodes recorded by the investigator). Significant acute exacerbation episodes were defined as those requiring a doubling of baseline ICS dose (*Busse et al 2001, Solèr et al 2001*) or use of systemic steroids (all 3 studies). During the stable steroid phase, mean significant acute exacerbation episode rates were 1.56 and 0.69/patient-year, respectively, a reduction of 56% with omalizumab (P=0.007). Similar reductions in exacerbations in favor of omalizumab were observed for the whole study period and for all acute exacerbation episodes. The authors concluded that 113 significant acute exacerbation episodes were prevented for every 100 patients treated with omalizumab for 1 year (*Holgate et al 2001*).
- A Cochrane Review conducted in 2014 evaluated the efficacy of omalizumab in patients with allergic asthma. Treatment with omalizumab was associated with a significant reduction in the odds of a patient having an asthma exacerbation (odds ratio [OR], 0.55; 95% confidence interval [CI], 0.42 to 0.6; 10 studies, 3,261 participants). This represents an absolute reduction from 26% for participants suffering an exacerbation on placebo to 16% on omalizumab, over 16 to 60 weeks. Additionally, in patients with moderate to severe asthma and in those who were receiving background ICS therapy, treatment with omalizumab resulted in a significant reduction in the odds of having an asthma exacerbation (OR, 0.50; 95% CI, 0.42 to 0.6; 7 studies, 1,889 participants). A significant benefit was noted for subcutaneous (SC) omalizumab vs placebo with regard to reducing hospitalizations (OR, 0.16, 95% CI, 0.06 to 0.42; 4 studies, 1,824 participants), representing an absolute reduction in risk from 3% with placebo to 0.5% with omalizumab over 28 to 60 weeks. The authors concluded that omalizumab was effective in reducing asthma exacerbations and hospitalizations as an adjunctive therapy to ICS and significantly more effective than placebo in increasing the numbers of participants who were able to reduce or withdraw their ICS. Omalizumab was generally well tolerated, although there were more injection site reactions with omalizumab. However, the clinical value of the reduction in steroid consumption has to be considered in light of the high cost of omalizumab (*Normansell et al 2014*).
- A systematic review of 8 randomized, placebo-controlled trials (N=3,429) evaluated the efficacy and safety of SC omalizumab as add-on therapy to corticosteroids in children and adults with moderate to severe allergic asthma. At the end of the steroid reduction phase, patients taking omalizumab were more likely to be able to withdraw corticosteroids completely compared with placebo (relative risk, 1.8; 95% CI, 1.42 to 2.28; P=0.00001). Omalizumab patients showed a decreased risk for asthma exacerbations at the end of the stable (relative risk, 0.57; 95% CI, 0.48 to 0.66; P=0.0001) and adjustable-steroid phases (relative risk, 0.55; 95% CI, 0.47 to 0.64; P=0.0001); post-hoc analysis suggests this effect was independent of duration of treatment, age, severity of asthma, and risk of bias. The frequency of serious adverse effects was similar between omalizumab (3.8%) and placebo (5.3%). However, injection site reactions were more frequent in the omalizumab patients (19.9 vs 13.2%). Omalizumab was not associated with an increased risk of hypersensitivity reactions, cardiovascular effects, or malignant neoplasms (*Rodrigo et al 2011*).
- In July 2016, the FDA expanded the indication of omalizumab to patients 6 to 11 years of age with moderate to severe persistent asthma. The approval was based primarily on a 52-week, randomized, double-blind, placebo-controlled, multicenter trial. The study evaluated the safety and efficacy of omalizumab as add-on therapy in 628 pediatric patients ages 6 to <12 years with moderate to severe asthma inadequately controlled despite the use of an ICS (*Lanier et al 2009*).
  - Over the 24-week fixed-steroid phase, omalizumab reduced the rate of clinically significant asthma exacerbations (worsening symptoms requiring doubling of baseline ICS dose and/or systemic steroids) by 31% vs placebo (0.45 vs 0.64; rate ratio, 0.69; P=0.007). Over a period of 52 weeks, the exacerbation rate was reduced by 43% (P<0.001). Other efficacy variables such as nocturnal symptom scores, beta-agonist use, and forced expiratory volume in 1 second (FEV_1) were not significantly different in omalizumab-treated patients compared to placebo.
- A 2017 systematic review of 3 randomized, placebo-controlled trials and 5 observational studies evaluated the safety and efficacy of omalizumab in children and adolescents. Omalizumab reduced exacerbations compared with placebo or baseline in all studies that included this outcome. The randomized controlled trials did not identify significant differences in FEV_1; however, 3 of the 4 observational studies that included this outcome did find significant FEV_1 improvement with omalizumab. Generally, ICS and rescue medication use were reduced with omalizumab in the studies. The authors

concluded that the evidence strongly supports omalizumab safety and efficacy in patients 6 to 11 years *(Corren et al 2017)*.

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

Chronic Idiopathic Urticaria

- The safety and efficacy of omalizumab for the treatment of CIU was assessed in 2 placebo-controlled, multiple-dose clinical studies. Patients received omalizumab 75, 150, or 300 mg or placebo by SC injection every 4 weeks in addition to their baseline level of H_1 antihistamine therapy for 24 or 12 weeks, followed by a 16-week washout observation period. In both studies, patients who received omalizumab 150 mg or 300 mg had greater decreases from baseline in weekly itch severity scores and weekly hive count scores than placebo at week 12. The 75 mg dose did not demonstrate consistent evidence of efficacy and is not approved for use (*Kaplan et al 2013, Maurer et al 2013*).
- Another randomized, double-blind, placebo-controlled study evaluated omalizumab as add-on therapy for 24 weeks in patients with CIU who remained symptomatic despite H_1 antihistamine therapy. Similar to previous studies, patients treated with omalizumab had significantly greater reductions in weekly itch severity score from baseline to week 12 compared to placebo (P≤0.001) (*Saini et al 2014*).
- A meta-analysis of randomized clinical trials evaluating omalizumab for the treatment of CIU was published in 2016. The analysis included 7 randomized, placebo-controlled studies with 1,312 patients with CIU. Patients treated with omalizumab (75 to 600 mg every 4 weeks) had significantly reduced weekly itch and weekly wheal scores compared with the placebo group. The effects of omalizumab were dose dependent, with the strongest reduction in weekly itch and weekly wheal scores observed with 300 mg. Rates of complete response were significantly higher in the omalizumab group (P<0.00001) and dose dependent, with the highest rates in the 300 mg group. Rates of patients with adverse events were similar in the omalizumab and placebo groups (*Zhao et al 2016*).
- A Phase 4 randomized clinical trial evaluated the effect of omalizumab in 205 patients with antihistamine-resistant CIU/chronic spontaneous urticaria. After an initial 24-week period of open-label treatment with omalizumab 300 mg every 4 weeks, patients randomized to continue omalizumab for another 24 weeks of double-blind therapy experienced a significantly lower rate of clinical worsening compared with patients randomized to double-blind placebo (21.0% vs 60.4%, P<0.0001). No new safety signals were detected over the 48-week omalizumab treatment period *(Maurer et al 2017)*.

BENRALIZUMAB

Asthma

- The safety and efficacy of benralizumab were evaluated in a 52-week dose-ranging exacerbation trial, 3 confirmatory trials, and a 12-week lung function trial (*Bleecker et al 2016, Castro et al 2014, Ferguson et al 2017, Fitzgerald et al 2016, Nair et al 2017*).
  - In a randomized, controlled, double-blind, dose-ranging Phase 2b study, 324 adults with uncontrolled eosinophilic asthma were randomly assigned to placebo (n=80), benralizumab 2 mg (n=81), benralizumab 20 mg (n=81), or benralizumab 100 mg (n=82) and 285 adults with non-eosinophilic asthma were randomized to benralizumab 100 mg (n=142) or placebo (n=143) (*Castro et al 2014*). Treatments were given as 2 SC injections every 4 weeks for the first 3 doses, then every 8 weeks, for 1 year. Among adults with eosinophilic asthma, benralizumab 100 mg reduced exacerbation rates as compared to placebo (0.34 vs 0.57; rate reduction, 41%; 80% CI, 11 to 60, P=0.096). A significant reduction in exacerbation rates was not seen with benralizumab 2 mg or 20 mg as compared to placebo in these patients. In patients with a baseline blood eosinophil count of at least 300 cells/µL, exacerbation rates were lower than in the placebo group for the benralizumab 20 mg (0.30 vs 0.68; rate reduction, 57%; 80% CI, 33 to 72; P=0.015) and 100 mg (0.38 vs 0.68; rate reduction, 43%; 80% CI, 18 to 60; P=0.049) groups.
  - SIROCCO was a randomized, multicenter, double-blind, placebo-controlled, 48-week, Phase 3 trial (N=1205) involving patients with severe asthma with eosinophilia uncontrolled with high-dose ICS and LABAs (*Bleecker et al 2016*). Enrolled patients were randomly assigned to placebo (n=407), benralizumab 30 mg every 4 weeks (n=400), or benralizumab 30 mg every 8 weeks (n=398). Compared with placebo, benralizumab reduced the annual asthma exacerbation rate over 48 weeks when administered every 4 weeks (rate ratio, 0.55; 95% CI, 0.42 to 0.71; P<0.0001) or every 8 weeks (rate ratio, 0.49; 95% CI, 0.37 to 0.64; P<0.0001). Both doses of benralizumab also significantly improved pre-bronchodilator FEV_1 in patients at week 48 vs placebo. Asthma symptoms were improved with benralizumab every 8 weeks, but not every 4 weeks, as compared to placebo.
  - CALIMA was a randomized, multicenter, double-blind, placebo-controlled, 56-week, Phase 3 trial that assessed benralizumab as add-on therapy (to high-dose ICS and LABA) for patients with severe, uncontrolled asthma and elevated blood eosinophil counts (*Fitzgerald et al 2016*). A total of 1306 patients were randomly assigned to benralizumab 30 mg every 4 weeks (n=425), benralizumab 30 mg every 8 weeks (n=441) or placebo (n=440). When compared to placebo, significant reductions in annual exacerbation rates were seen with benralizumab every 4 weeks (rate ratio, 0.64; 95% CI, 0.49 to 0.85; P=0.0018) and every 8 weeks (rate ratio, 0.72; 95% CI, 0.54 to 0.95; P=0.0188). Benralizumab was also associated with significantly improved pre-bronchodilator FEV_1 and total asthma symptom scores vs placebo.
  - BISE was a randomized, multicenter, double-blind, placebo-controlled, 12-week, Phase 3 trial that evaluated benralizumab therapy for patients with mild to moderate persistent asthma (*Ferguson et al 2017*). Patients (N=211) had been receiving either low- to medium-dose ICS or low-dose ICS plus LABA therapy and were randomized to benralizumab 30 mg every 4 weeks (n=106) or placebo (n=105). Benralizumab resulted in an 80 mL (95% CI, 0 to 150, P=0.04) greater improvement in pre-bronchodilator FEV_1 after 12 weeks as compared to placebo. Despite this improvement, this lung function result does not warrant the use of benralizumab in mild to moderate asthma because it did not reach the minimum clinically important improvement of 10%.
  - ZONDA was a randomized, multicenter, double-blind, placebo-controlled, 28-week trial that primarily assessed whether or not benralizumab was effective as an oral glucocorticoid-sparing therapy in patients on oral steroids to manage severe asthma associated with eosinophilia (*Nair et al 2017*). Of the enrolled patients, 220 were randomly assigned to benralizumab 30 mg every 4 weeks (n=72), benralizumab 30 mg every 8 weeks (n=73), or placebo (n=75). Results revealed that the 2 benralizumab dosing regimens significantly reduced the median final oral glucocorticoid doses from baseline by 75% vs a 25% reduction seen with placebo (P<0.001 for both comparisons). Additionally, benralizumab administered every 4 weeks resulted in an annual exacerbation rate that was 55% lower than that seen with placebo (marginal rate, 0.83 vs 1.83; P=0.003) and benralizumab administered every 8 weeks resulted in a 70% lower rate than that seen with placebo (marginal rate, 0.54 to 1.83; P<0.001).

MEPOLIZUMAB

Asthma

- The safety and efficacy of mepolizumab were evaluated in 3 double-blind, placebo-controlled, multicenter, randomized controlled trials in adolescent and adult patients with severe refractory asthma and signs of eosinophilic inflammation. Generally, patients were eligible for enrollment in the trials if they had eosinophils ≥150 cells/µL in the peripheral blood at screening or ≥300 cells/µL at some time during the previous year. Patients also were required to be on a high-dose ICS as well as another controller medication *(Pavord et al 2012, Ortega et al 2014, Bel et al 2014)*.
  - DREAM was a dose-ranging, 52-week, Phase 2b/3 study (N=621) that compared annual asthma exacerbation frequency and improvements in clinical symptoms between patients receiving 75 mg, 250 mg, and 750 mg intravenous (IV) mepolizumab and placebo. Mepolizumab decreased clinically significant exacerbation rates across all doses compared to placebo, at a rate of 2.40 per patient per year in the placebo group, 1.24 in the 75 mg mepolizumab group (P<0.0001), 1.46 in the 250 mg mepolizumab group (P=0.0005), and 1.15 in the 750 mg mepolizumab group (P<0.0001). No significant improvements were found for secondary clinical symptom measures, which included change in pre-bronchodilator FEV_1 from baseline, or change in Asthma Control Questionnaire (ACQ) scores *(Pavord et al 2012)*.
  - MENSA was a 32-week Phase 3 trial (N=576) that compared annual asthma exacerbation frequency and improvements in clinical symptoms between patients receiving SC and IV mepolizumab vs placebo. Patients were selected on the basis of frequent exacerbations, treatment with high doses of ICS, and a defined blood eosinophil count. Both SC and IV mepolizumab significantly decreased clinically significant exacerbation rates compared to placebo, at a rate of 1.74 per patient per year in the placebo group, 0.93 per patient per year in the IV mepolizumab group (P<0.001), and 0.83 per patient per year in the SC mepolizumab group (P<0.001). In both the SC and IV mepolizumab-treated groups, the ACQ scores met thresholds for minimal clinically important change and were significantly improved compared to placebo (P<0.001) *(Ortega et al 2014)*.
  - SIRIUS was a 24-week Phase 3 trial (N=135) that compared oral corticosteroid requirements between patients receiving SC mepolizumab and placebo. The likelihood of a reduction in the daily oral glucocorticoid dose was 2.39 times higher in the mepolizumab group (95% CI, 1.25 to 4.56; P=0.008). The median reduction in daily oral corticosteroid dose was 50% (95% CI, 20 to 75) in the mepolizumab-treated group compared to 0% (95% CI, -20 to 33.3) in the placebo group (P=0.007) *(Bel et al 2014)*.
- A post-hoc analysis of data from DREAM and MENSA was conducted to assess the relationship between baseline blood eosinophil counts and efficacy of mepolizumab. Of 1,192 patients, 846 received mepolizumab and 346 received placebo. The overall rate of mean exacerbations per person per year was reduced from 1.91 with placebo to 1.01 with mepolizumab (47% reduction; rate ratio, 0.53; 95% CI, 0.44 to 0.62; P<0.0001). The exacerbation rate reduction with mepolizumab vs placebo increased progressively from 52% (rate ratio, 0.48; 95% CI, 0.39 to 0.58) in patients with a baseline blood eosinophil count of ≥150 cells/µL to 70% (rate ratio, 0.30; 95% CI, 0.23 to 0.40) in patients with a baseline count of ≥500 cells/µL. At a baseline count <150 cells/µL, predicted efficacy of mepolizumab was reduced. The authors concluded that the use of a baseline blood eosinophil count will help to select patients who are likely to achieve important asthma outcomes with mepolizumab (*Ortega et al 2016*).
- COSMOS was a 52-week, open-label extension study in patients who received mepolizumab or placebo in MENSA or SIRIUS. Patients received SC mepolizumab regardless of prior treatment allocation and continued to receive appropriate standard-of-care asthma therapy throughout. In total, 558 (86%; previous mepolizumab: 358; previous placebo: 200) and 94 (14%; previous mepolizumab: 58; previous placebo: 36) patients experienced on-treatment adverse events and serious adverse events, respectively. No fatal adverse events or instances of mepolizumab-related anaphylaxis were reported. Mepolizumab treatment was shown to exert a durable response, with patients who previously received mepolizumab in MENSA or SIRIUS maintaining reductions in exacerbation rate and oral corticosteroid dosing throughout COSMOS. Patients who previously received placebo in MENSA or SIRIUS demonstrated improvements in these endpoints following treatment with mepolizumab (*Lugogo et al 2016*).
- A systematic review and meta-analysis compared hospitalization or hospitalization and/or emergency room visit rates in patients with severe eosinophilic asthma treated with mepolizumab or placebo in addition to standard of care for at least 24 weeks. Four studies (N=1,388) were eligible for inclusion. Mepolizumab significantly reduced the rate of exacerbations requiring hospitalization (relative rate, 0.49; 95% CI, 0.30 to 0.80; P=0.004) and hospitalization/emergency room visit (relative rate, 0.49; 95% CI, 0.33 to 0.73; P<0.001) vs placebo. Significant

reductions of 45% and 38% were also observed for the proportion of patients experiencing 1 or more hospitalization and hospitalization and/or emergency room visit, respectively (*Yancey et al 2017*).

Eosinophilic Granulomatosis with Polyangiitis

- A 52-week, randomized, placebo-controlled, double-blind, parallel-group, multicenter, Phase 3 trial assessed the efficacy and safety of mepolizumab as add-on therapy (to glucocorticoid treatment, with or without immunosuppressive therapy) for patients with relapsing or refractory EGPA (*Wechsler et al 2017*). A total of 136 patients were randomly assigned to mepolizumab 300 mg every 4 weeks (n=68) or placebo (n=68). Results demonstrated the following for the mepolizumab and placebo groups, respectively:
  - Percentage of patients with ≥24 weeks of accrued remission: 28% vs 3% (OR, 5.91; 95% CI, 2.68 to 13.03; P<0.001).
  - Percentage of patients in remission at both week 36 and week 48: 32% vs 3% (OR, 16.74; 95% CI, 3.61 to 77.56; P<0.001).
  - Annualized relapse rate: 1.14 vs 2.27 (rate ratio, 0.50; 95% CI, 0.36 to 0.70; P<0.001).
  - Percentage of patients able to reduce their daily dose of concomitant prednisone or prednisolone to 4 mg or less (average of weeks 48 to 52): 44% vs 7% (OR, 0.20; 95% CI, 0.09 to 0.41; P<0.001).

RESLIZUMAB

Asthma

- The safety and efficacy of reslizumab were evaluated in 4 double-blind, placebo-controlled, multicenter, randomized controlled trials. In all 4 studies, patients were required to be on at least a medium-dose ICS with or without additional controller medications (*Bjermer et al 2016, Castro et al 2015, Corren et al* 2016).
  - Studies 3082 and 3083 were 52-week studies (N=953) in patients with asthma who were required to have a blood eosinophil count ≥400 cells/μL, and at least 1 asthma exacerbation requiring systemic corticosteroid use over the past 12 months. These studies compared the asthma exacerbation rate and improvements in clinical symptoms between patients receiving reslizumab 3 mg/kg IV administered once every 4 weeks and placebo. In both studies, patients receiving reslizumab had a significant reduction in the frequency of asthma exacerbations (Study 3082: rate ratio, 0.50; 95% CI, 0.37 to 0.67; Study 3083: rate ratio, 0.41; 95% CI, 0.28 to 0.59; both P<0.0001) compared with those receiving placebo. In both trials, an improvement in FEV_1 was evident for reslizumab vs placebo by the first on-treatment assessment at week 4, which was sustained through week 52. Reslizumab treatment also resulted in significant improvements compared with placebo in AQLQ total score, ACQ-7 score, and Asthma Symptom Utility Index (ASUI) score (*Castro et al 2015*).
  - Study 3081 was a 16-week study (N=315) in patients who were required to have a blood eosinophil count ≥400 cells/μL. The study compared the change from baseline in FEV_1 and improvements in clinical symptoms between reslizumab 3 mg/kg vs placebo. Reslizumab 3 mg/kg significantly improved FEV_1 (difference vs placebo: 160 mL; 95% CI, 60 to 259; P=0.0018). Reslizumab also statistically significantly improved ACQ and AQLQ; however, the minimally important difference was only reached for AQLQ (*Bjermer et al 2016*).
    - Study 3084 was a 16-week study in 496 patients unselected for baseline blood eosinophil levels (approximately 80% of patients had a screening blood eosinophil count <400 cells/μL). Patients were not allowed to be on maintenance oral corticosteroids. The study compared the change from baseline in FEV_1 and improvements in clinical symptoms between reslizumab 3 mg/kg vs placebo. In the subgroup of patients with baseline eosinophils <400 cells/μL, patients treated with reslizumab showed no significant improvement in FEV_1 compared with placebo. In the subgroup with eosinophils ≥400 cells/μL, however, treatment with reslizumab was associated with much larger improvements in FEV_1, ACQ, and rescue SABA use compared with placebo (*Corren et al 2016*).
- A 2017 meta-analysis of 5 randomized controlled trials comparing reslizumab to placebo (N=1,366) revealed improvements in exacerbations, FEV_1, and ACQ score with reslizumab. Asthma exacerbations occurred less frequently in reslizumab patients vs placebo (OR, 0.46; 95% CI, 0.35 to 0.59; P<0.00001). FEV_1 also improved with reslizumab compared to placebo (mean difference, 0.16; 95% CI, 0.10 to 0.23; P<0.00001). Finally, ACQ score improved with reslizumab compared to placebo (mean difference, -0.26; 95% CI, -0.36 to -0.16; P<0.00001). All studies included in the meta-analysis were of limited duration of 15 or 16 weeks (*Li et al 2017*).

COMPARATIVE REVIEWS

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

CLINICAL GUIDELINES

Asthma

- According to guidelines from the NHLBI/National Asthma Education and Prevention Program, pharmacologic therapy is based on a stepwise approach in which medications are increased until asthma is controlled and then decreased when possible to minimize side effects of treatments. The level of asthma control is based on (*NHLBI 2007*):
  - Reported symptoms over the past 2 to 4 weeks
  - Current level of lung function (FEV_1 and FEV_1/forced vital capacity [FVC] values)
  - Number of exacerbations requiring oral corticosteroids per year.
- The NHLBI guidelines state that omalizumab is used as adjunctive therapy in patients 12 years and older who have allergies and severe persistent asthma that is not adequately controlled with the combination of high-dose ICS and LABA therapy (*NHLBI 2007*).
- In 2017, the Global Initiative for Asthma (GINA) published updated guidelines for asthma management and prevention. For patients with severe asthma uncontrolled on Step 4 treatment (e.g., 2 or more controllers plus as-needed reliever medication), phenotyping into categories such as severe allergic, aspirin-exacerbated or eosinophilic asthma is suggested. Anti-IgE treatment with omalizumab is recommended as the preferred option for the management of patients at Step 5 of treatment. Similarly, add-on anti-IL-5 therapy (i.e., mepolizumab, reslizumab) is recommended for patients aged ≥12 years with severe eosinophilic asthma that is uncontrolled on Step 4 treatment (*GINA 2017*).

Chronic Idiopathic Urticaria

- Guidelines developed by the American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma & Immunology, and the Joint Council of Allergy, Asthma & Immunology recommend a stepwise treatment approach for CIU. Treatment with omalizumab is recommended in patients inadequately controlled with antihistamines and a leukotriene receptor antagonist (*Bernstein et al 2014*).
- Updated joint guidelines by the European Academy of Allergy and Clinical Immunology, the Global Allergy and Asthma European Network, the European Dermatology Forum, and the World Allergy Organization recommend treatment with omalizumab, cyclosporine, or a leukotriene receptor antagonist in patients with symptoms despite treatment with a 4-fold dose of modern second generation antihistamines (*Zuberbier et al 2013*).
- Recent guidelines published by the British Society for Allergy and Clinical Immunology similarly recommend omalizumab as a potential second-line agent in patients inadequately controlled on a 4-fold dose of a non-sedating antihistamine (*Powell et al 2015*).

Eosinophilic Granulomatosis with Polyangiitis

- Both the EGPA (Churg-Strauss) Consensus Task Force recommendations and the American Society for Apheresis guideline recommend glucocorticoids alone for patients without life- and/or organ-threatening EGPA. For patients with life- and/or organ-threatening EGPA, both glucocorticoids and an immunosuppressant are recommended, as well as maintenance therapy with azathioprine or methotrexate. IVIG can be considered for refractory EGPA or for treatment during pregnancy (*Groh et al 2015, Schwartz et al 2016*).
  - These guidelines have not been updated to include the place in therapy for mepolizumab; however, the EGPA Consensus Task Force recommendations notes that mepolizumab hold promise for this condition based on the pilot studies available at the time of guideline development (*Groh et al 2015*).

SAFETY SUMMARY

Cinqair:

- Contraindication: History of hypersensitivity to Cinqair or excipients in the formulation.
- Boxed warning: Anaphylaxis has been observed with Cinqair infusion in 0.3% of patients in placebo-controlled clinical studies. Anaphylaxis was reported as early as the second dose of Cinqair. Patients should be observed for an appropriate period of time after Cinqair administration by a healthcare professional prepared to manage anaphylaxis.
- Key warning and precaution:
  - In placebo-controlled clinical studies, 6/1028 (0.6%) patients receiving 3 mg/kg Cinqair had ≥1 malignant neoplasm reported compared to 2/730 (0.3%) patients in the placebo group. The observed malignancies in Cinqair-treated patients were diverse in nature and without clustering of any particular tissue type.
- The most common adverse reaction (≥2%) includes oropharyngeal pain.

Fasenra:

- Contraindication: History of hypersensitivity to Fasenra or excipients in the formulation.
- Key warnings and precautions:
  - Hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of Fasenra. Fasenra should be discontinued in the event of a hypersensitivity reaction.
  - Systemic or inhaled corticosteroids should not be discontinued abruptly upon initiation of therapy with Fasenra. Corticosteroids should be decreased gradually, if appropriate.
  - Pre-existing helminth infections should be treated before therapy with Fasenra. If patients become infected while receiving Fasenra and do not respond to anti-helminth treatment, Fasenra should be discontinued until the parasitic infection resolves.
- The most common adverse reactions (≥5%) include headache and pharyngitis.

Nucala:

- Contraindication: History of hypersensitivity to Nucala or excipients in the formulation.
- Key warnings and precautions:
  - Hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of Nucala.

- Herpes zoster infections have occurred in patients receiving Nucala. In controlled clinical trials, 2 serious adverse reactions of herpes zoster occurred in patients treated with Nucala compared with none in patients treated with placebo.
- The most common adverse reactions (≥5%) include headache, injection site reaction, back pain, and fatigue.

Xolair:

- Contraindication: Severe hypersensitivity reaction to Xolair or any ingredient of Xolair.
- Boxed warning: Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported. Observe patients closely for an appropriate period of time after Xolair administration. Health care providers administering Xolair should be prepared to manage anaphylaxis that can be life-threatening.
  - Patients with a prior history of anaphylactic reactions to other causes may be at an increased risk for anaphylaxis. The frequency of anaphylaxis is reported to be between 0.1 to 0.2% and may occur immediately or up to a year post-treatment.
- Key warnings and precautions:
  - Malignant neoplasms were observed in a higher rate of Xolair-treated patients (0.5%) than control patients (0.2%) in clinical trials. A subsequent 5-year observational cohort study found similar rates of primary malignancies in Xolair- and non-Xolair-treated patients. However, study limitations preclude definitively ruling out a malignancy risk with Xolair (*Long et al 2014*).
  - Rarely, patients on therapy with Xolair may present with serious systemic eosinophilia, which may present with features of vasculitis consistent with Churg-Strauss syndrome. These events usually have been associated with the reduction of oral corticosteroid therapy.
  - Some patients have reported signs and symptoms similar to serum sickness, including arthritis/arthralgia, rash, fever, and lymphadenopathy.
- Adverse reactions in asthma studies: In patients ≥12 years of age, the most commonly observed adverse reactions in clinical studies (≥1% in Xolair-treated patients and more frequently than reported with placebo) were arthralgia, pain (general), leg pain, fatigue, dizziness, fracture, arm pain, pruritus, dermatitis, and earache. In clinical studies with pediatric patients 6 to <12 years of age, the most common adverse reactions were nasopharyngitis, headache, pyrexia, upper abdominal pain, streptococcal pharyngitis, otitis media, viral gastroenteritis, arthropod bites, and epistaxis.
- Adverse reactions in CIU studies: Adverse reactions from 3 placebo-controlled, multiple-dose CIU studies that occurred in ≥2% of patients receiving Xolair and more frequently than in those receiving placebo included arthralgia, cough, headache, nasopharyngitis, nausea, sinusitis, upper respiratory tract infection, and viral upper respiratory tract infection.
- Cardiovascular and cerebrovascular events in asthma studies: In a 5-year observational cohort study, a higher incidence of overall cardiovascular and cerebrovascular serious adverse events was observed in Xolair-treated patients compared to non-Xolair-treated patients. To further evaluate the risk, a pooled analysis of 25 randomized, controlled, clinical trials was conducted. An increased risk of cardiovascular and cerebrovascular serious adverse events was not noted, but the low number of events, the young patient population, and the short duration of follow-up prevent a definite conclusion about the absence of a risk (*FDA 2014*).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Route	Usual Recommended Frequency	Comments
Cinqair (reslizumab)	IV	Every 4 weeks	• Administered by IV infusion over 20 to 50 minutes. • Safety and effectiveness in pediatric patients (aged 17 years and younger) have not been established.
Fasenra (benralizumab)	SC	Every 4 weeks for first 3 doses, followed by every 8 weeks	• Safety and efficacy in pediatric patients younger than 12 years have not been established.

Drug	Route	Usual Recommended Frequency	Comments
Nucala (mepolizumab)	SC	Asthma: every 4 weeks EGPA: every 4 weeks	• Safety and efficacy in pediatric patients younger than 12 years with asthma have not been established. • Safety and efficacy in pediatric patients other than those with asthma have not been established.
Xolair (omalizumab)	SC	Allergic asthma: Every 2 or 4 weeks CIU: Every 4 weeks	Allergic asthma: • The dose and frequency is determined by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). • Safety and efficacy in pediatric patients with asthma below 6 years of age have not been established. CIU: • Dosing in CIU is not dependent on serum IgE level or body weight. • Safety and efficacy in pediatric patients with CIU below 12 years of age have not been established.

See the current prescribing information for full details.

CONCLUSION

- Xolair is a humanized monoclonal antibody that is FDA-approved for patients 6 years of age and older with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with an ICS. Xolair has been shown to decrease the incidence of asthma exacerbations in these patients.
- Although clinical trial results have been mixed and several trials had an open-label design, there is some evidence to indicate that Xolair may decrease asthma-related emergency visits and hospitalizations, as well as decreasing the dose of ICS and rescue medication and increasing symptom-free days (*Buhl et al 2002, Busse et al 2011, Holgate et al 2004, Lanier et al 2003, Solèr et al 2011*).
- Xolair is administered SC in a physician's office every 2 to 4 weeks in a dose that is determined by body weight and the levels of serum IgE. Xolair carries a boxed warning due to the risk of anaphylaxis, and thus must be administered under medical supervision.
- Although Xolair therapy is generally safe, analysis of a 5-year, observational cohort, epidemiological study (EXCELS) showed an increased number of cardiovascular and cerebrovascular adverse events in patients receiving Xolair compared to placebo (*Iribarren et al 2017*). However, a pooled analysis of 25 randomized, double-blind, placebo-controlled clinical trials did not find notable imbalances in the rates of cardiovascular and cerebrovascular serious adverse events (*FDA 2014*).
- Asthma guidelines generally recommend Xolair therapy in patients with severe allergic asthma that is inadequately controlled with a combination of high-dose ICS and LABA (*GINA 2017, NHLBI 2007*). Based on the limited place in therapy and the need for administration under medical supervision, Xolair is appropriate for a small percentage of patients with asthma.
- Xolair received FDA-approval for the treatment of adults and adolescents (12 years of age and above) with CIU who remain symptomatic despite H_1-antihistamine treatment. Two randomized, placebo-controlled trials demonstrated its efficacy in reducing weekly itch severity scores and weekly hive count scores significantly greater than placebo at week 12. Xolair was well-tolerated, with a safety profile similar to that observed in asthma patients. In patients with CIU, Xolair is dosed at 150 or 300 mg SC every 4 weeks in a physician's office. Guidelines for the treatment of CIU generally recommend treatment with Xolair in patients who are inadequately controlled with a 4-fold dose of modern second

generation antihistamines and, in some cases, a leukotriene receptor antagonist (*Bernstein et al 2014, Zuberbier et al 2013, Powell et al 2015*).

- Cinqair, Fasenra , and Nucala are IL-5 antagonists approved as add-on treatment options for patients with severe eosinophilic asthma, with demonstrated effectiveness in reducing asthma exacerbations (*Bel et al 2014, Bjermer et al 2016, Castro et al 2015, Corren et al 2016, Pavord et al 2012, Ortega et al 2014, Bleecker et al 2016, Fitzgerald et al 2016*). The mechanism of action of Fasenra is slightly different, in that it binds to the IL-5 receptor on immune effector cells, whereas Cinqair and Nucala bind to the IL-5 cytokine. All of these agents provide a more targeted treatment option for patients with severe, refractory asthma and should be considered in those with an eosinophilic phenotype uncontrolled on conventional asthma therapy (*GINA 2017*).
- Nucala is the only IL-5 antagonist approved for the treatment of adult patients with EGPA.
- There are no head-to-head trials comparing Cinqair, Fasenra, and Nucala. However, a systematic review of the IL-5 antagonists conducted in patients with asthma poorly controlled by ICS revealed that all of the IL-5 antagonists reduced asthma exacerbations by approximately 50% and improved FEV_1 by 0.08 L to 0.11 L. Overall, there was not an increase in serious adverse events with any IL-5 antagonist; however, more patients discontinued benralizumab (36/1599) than placebo (9/998) due to adverse events *(Farne et al 2017)*.
- Compared to Nucala and Fasenra, Cinqair does have several limitations, including: an indication for patients aged 18 years and older (12 years and older for Nucala and Fasenra), IV administration (SC for Nucala and Fasenra), and a boxed warning for anaphylaxis.

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Therapeutic Class Overview
Renin Inhibitors and Combinations

INTRODUCTION

- Approximately 92.1 million American adults have at least one type of cardiovascular disease according to the 2017 American Heart Association Heart Disease and Stroke Statistics update. From 2004 to 2014, mortality associated with cardiovascular disease declined 25.3% (Benjamin et al, 2017).
- An estimated 85.7 million Americans or 34% of US adults aged ≥20 years have high blood pressure (BP). Hypertension is an independent risk factor for cardiovascular disease and increases the mortality risks of cardiovascular disease and other diseases (Benjamin et al, 2017).
- Lowering of BP has been shown to reduce the risk of fatal and nonfatal cardiovascular events including stroke and myocardial infarctions (MI) improving cardiovascular health and reducing cardiovascular risk also includes lipid control, diabetes management, smoking cessation, exercise, weight management, and limited sodium intake (Benjamin et al, 2017).
- Aliskiren (TEKTURNA®) is the only single entity direct renin inhibitor available in the United States (U.S.) and is Food and Drug Administration (FDA)-approved for the treatment of hypertension, either as monotherapy or in combination with other antihypertensive agents.
- Currently, only one combination renin inhibitor product is available in the US. This product combines the direct renin inhibitor, aliskiren, with a thiazide diuretic (TEKTURNA-HCT®) and is approved for hypertension.
- Studies have demonstrated that the combination of two inhibitors of the renin angiotensin system (RAS), including aliskiren, an angiotensin converting enzyme inhibitor (ACE-I) or an angiotensin II receptor blocker (ARB), provide no renal or cardiovascular benefits, and significant adverse events, particularly in patients with diabetes and/or renal insufficiency. All agents in this class have safety warnings against combined use (Fried et al, 2013; ONTARGET Investigators, 2008; Parving et al, 2012; Pfeffer et al, 2003b; Sakata et al, 2015). Due to the results of these trials, Novartis AG also announced the market withdrawal of VALTURNA® (aliskiren/valsartan) effective in July 2012 (FDA Drug Safety Communication, 2012). More recently, two other combination products have been withdrawn from the market: TEKAMLO® (aliskiren/amlodipine) and AMTURNIDE® (aliskiren/amlodipine/hydrochlorothiazide).
- This review will focus on the direct renin inhibitors and combination agents which are FDA-approved to treat hypertension.
- Medispan class: Direct Renin Inhibitors; Direct Renin Inhibitors & Thiazide/Thiazide-like combinations

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
Single Entity Agent			
TEKTURNA (aliskiren)	Novartis	03/05/2007	-
Combination Agent			
TEKTURNA HCT (aliskiren/hydrochlorothiazide)	Novartis	01/18/2008	-

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	TEKTURNA (aliskiren)	TEKTURNA HCT (aliskiren/HCTZ)
Treatment of hypertension	✔	-
Treatment of hypertension as initial therapy in patients likely to need multiple drugs to achieve blood pressure goals	-	✔
Treatment of hypertension in patients not adequately controlled with monotherapy	-	✔

Indication	TEKTURNA (aliskiren)	TEKTURNA HCT (aliskiren/HCTZ)
Treatment of hypertension as a substitute for the titrated components	-	✔

Abbrv: HCTZ=hydrochlorothiazide

(Prescribing information: TEKTURNA, 2016; TEKTURNA HCT, 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

- Aliskiren has been shown to lower BP to a greater degree than placebo and this effect is dose-dependent (Oh et al, 2007; Kushiro et al, 2006; Musini et al, 2017; Villa et al, 2012; Fortin et al, 2011).
- There are limited studies comparing aliskiren to other antihypertensive agents, including the ACE-Is and ARBs. These studies have generally demonstrated similar efficacy when administered in comparable doses and frequencies (Strasser et al, 2007; Duprez et al, 2010; Andersen et al, 2008; Zhu et al, 2012; Gradman et al, 2005; Krone et al, 2011; Stanton et al, 2003). In general, the incidence of side effects was also similar between treatment groups. One study reported better efficacy with aliskiren compared to ramipril, and a higher incidence of cough with ramipril (5.5%) compared to aliskiren (2.1%) (Andersen et al, 2008). A second study showed that after eight weeks of treatment, aliskiren was noninferior to ramipril in regard to antihypertensive effects on mean sitting diastolic blood pressure (DBP) (Zhu et al, 2012).
- One study compared aliskiren monotherapy to hydrochlorothiazide monotherapy and demonstrated significantly lower systolic (SBP) and DBP at weeks 6 and 12 with aliskiren in addition to better overall response rates; however, the significant difference in SBP was not maintained at week 52 (Schmieder et al, 2009a; Schmieder et al, 2009b).
- In separate studies, the combination of aliskiren/hydrochlorothiazide was shown to be significantly more effective than hydrochlorothiazide and aliskiren monotherapy at reducing SBP after 8 and 12 weeks, respectively (P<0.0001 compared to monotherapy in both studies). Similarly, greater improvements in DBP were also achieved with aliskiren/hydrochlorothiazide in both studies compared to treatment with monotherapy (P<0.0001 compared to monotherapy in both studies) (Basile et al, 2011; Black et al, 2010).
- In a randomized study, patients receiving treatment with aliskiren/hydrochlorothiazide or amlodipine monotherapy experienced a reduction in SBP from baseline to week 8, but no differences were observed between treatments (-28.6 vs -28.1 mm Hg for aliskiren/hydrochlorothiazide and amlodipine, respectively; P=0.8) (Ferdinand et al, 2011).
- A comparative effectiveness review evaluated ACE-Is, ARBs and aliskiren (Sanders et al, 2011). Two studies comparing ACE-Is with aliskiren demonstrated a greater reduction in BP with aliskiren compared to ramipril. One study compared aliskiren and losartan which showed no significant difference in BP reduction.
- The ASTRONAUT trial evaluated the effect of aliskiren in combination with standard therapy in heart failure (HF) patients hospitalized for worsening disease. Aliskiren did not result in a reduction in the primary endpoint of cardiovascular mortality or HF re-hospitalization at six months, or at 12 months (the secondary endpoint) (Gheorghiade et al, 2013). However, an ASTRONAUT substudy examined diabetic patient outcomes in the ASTRONAUT trial, and although there was no difference between diabetic and non-diabetic patient outcomes for the primary endpoint at 6 months, there was a statistically significant difference at 12 months, with less non-diabetic patients experiencing cardiovascular mortality or HF re-hospitalization. Results should be interpreted with caution as this was a sub-analysis of a statistically significant secondary outcome. Results insinuate that a larger trial excluding diabetic patients may provide more answers regarding treatment of patients with HF hospitalized for worsening disease (Maggioni et al, 2013).
- The termination of the ALTITUDE trial was due to an increased incidence of non-fatal stroke, renal complications, hyperkalemia, and hypotension in the aliskiren treatment arm when added to standard care in patients with type 2 diabetes and concomitant renal impairment. Novartis AG ceased promotion of aliskiren-containing products for use in combination with an ACE-I or ARB (Parving et al, 2012).
- Following the premature termination of the ALTITUDE study, the APOLLO study was also terminated. The APOLLO study included 11,000 elderly patients and was designed to examine the effects of aliskiren on cardiovascular events such as heart attack or stroke. Some patients were diabetic and taking ACE-Is or ARBs in combination with aliskiren,

which is included as a contraindication in current labeling. However, it is not completely clear if this is why the APOLLO study was terminated (Teo et al, 2014).

- According to the results from the ATMOSPHERE trial, aliskiren did not meet non-inferiority compared to enalapril for the composite outcome of death due to cardiovascular causes or hospitalization for heart failure in patients with chronic heart failure (McMurray et al, 2016). The combination of enalapril with aliskiren led to more hypotension, elevated serum creatinine, and elevated potassium levels compared to enalapril therapy without any benefits in the composite outcome.

SAFETY SUMMARY

- Avoid use of aliskiren-containing medications with ARBs or ACE-Is, particularly in patients with diabetes and/or moderate renal impairment (glomerular filtration rate [GFR] <60 mL/min).
- All agents in this class carry a boxed warning regarding use in pregnancy. When pregnancy is detected, discontinue aliskiren-containing products as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. Thiazides may cause fetal or neonatal jaundice, thrombocytopenia, and other adverse reactions.
- Symptomatic hypotension may occur after initiation of aliskiren in patients with an activated RAS, such as those who are volume- and/or salt-depleted. Correct those conditions prior to treatment. A transient hypotensive response does not contraindicate further treatment once blood pressure has been stabilized.
- Other warnings include risk of angioedema, worsening of renal function, and hyperkalemia.
- Concurrent use of aliskiren and cyclosporine or itraconazole results in a significant increase in blood concentrations of aliskiren. Concurrent use is not recommended.
- Hydrochlorothiazide is contraindicated in patients with known anuria or hypersensitivity to sulfonamide derived drugs like hydrochlorothiazide or to any of the components.
- Electrolyte imbalances may occur in patients on a combination containing hydrochlorothiazide.
- Common adverse events include dizziness and headache.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
TEKTURNA (aliskiren)	Tablet: 150 mg 300 mg	Treatment of HTN to lower BP: Initial, 150 mg daily; may increase daily dose to 300 mg daily if BP not adequately controlled	Establish a routine for the administration of aliskiren in relation to meal time. High fat meals reduce absorption.
TEKTURNA HCT (aliskiren/HCTZ)	Tablet: 150 mg/12.5 mg 150 mg/25 mg 300 mg/12.5 mg 300 mg/25 mg	Treatment of HTN to lower BP: Initial, 150 mg/12.5 mg daily; maximum, 300 mg/25 mg daily	Establish a routine for the administration of aliskiren in relation to meal time. High fat meals reduce absorption. Order of increasing mean effect are 150/12.5 mg, 150/25 mg or 300/12.5 mg, and 300/25 mg.

Abbrv: BP=blood pressure, HCTZ=hydrochlorothiazide, HTN=hypertension

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
TEKTURNA (aliskiren)	No dosage adjustment required in the elderly population; greater sensitivity of some elderly cannot be ruled out.	Safety and efficacy have not been established in pediatric patients <18 years.	Safety and effectiveness in patients with eGFR <30 mL/min have not been established.	No dosage adjustment required.	Can cause fetal harm; discontinue drug. It is unknown whether the drug is excreted in breast milk; breastfeeding is not recommended.
TEKTURNA HCT (aliskiren/ HCTZ)	No dosage adjustment required in the elderly population; greater sensitivity of some elderly cannot be ruled out	Safety and efficacy have not been established in pediatric patients <18 years.	Safety and effectiveness of patients with severe renal impairment with CrCL <30 mL/min have not been established.	Up-titrate slowly due to the HCTZ component; minor alterations in fluid and electrolyte balance may precipitate hepatic coma.	Can cause fetal harm; discontinue drug. Thiazides are excreted in human milk; It is unknown whether aliskiren is excreted in human milk; breastfeeding is not recommended.

Abbrv: CrCL = creatinine clearance; eGFR = estimated glomerular filtration rate; HCTZ = hydrochlorothiazide

CONCLUSION

- Aliskiren is the only single-entity direct renin inhibitor marketed in the United States. Aliskiren is FDA-approved for the treatment of hypertension. The only currently available renin inhibitor combination (TEKTURNA-HCT®) is also FDA-approved for the treatment of hypertension. Previously available combination products including AMTURNIDE®, TEKAMLO®, and VALTURNA® have all been removed from the market.
- Aliskiren-containing products are contraindicated for use in combination with an ACE-I or ARB in patients with diabetes and/or those with moderate renal impairment. Aliskiren and thiazide diuretics are not recommended for use during pregnancy.
- Clinical trials have demonstrated that aliskiren 150 mg to 300 mg once daily is significantly more effective than placebo in lowering both SBP and DBP in men and women with mild-to-moderate essential hypertension (Musini et al, 2017; Kushiro et al, 2006; Oh et al, 2007).
- Limited lower quality comparative studies of aliskiren with other antihypertensive agents have generally demonstrated similar efficacy when administered in comparable doses (Strasser et al, 2007; Duprez et al, 2010; Andersen et al, 2008; Zhu et al, 2012; Gradman et al, 2005; Krone et al, 2011; Stanton et al, 2003). In general, the incidence of side effects was also comparable. Aliskiren alone or in combination with enalapril does not display any benefits in patients with chronic heart failure compared to enalapril therapy.
- Most hypertension guidelines do not address the use of aliskiren, specifically outside of labeled recommendations (Go et al, 2014; James et al, 2013; Weber et al, 2014). The 2013 European Society of Hypertension/European Society of Cardiology Guidelines (ESH/ESC) hypertension guidelines state that the use of aliskiren in the treatment of hypertension is justified based on available evidence. Available evidence shows that aliskiren monotherapy lowers

SBP and DBP, and a greater hypertensive effect is achieved when given in combination with a thiazide. Prolonged administration of combination therapy has a favorable effect on asymptomatic organ damage, or prognostic biomarkers for heart failure, such as BNP. Although, no trial data is available for the effect of aliskiren on cardiovascular and renal morbidity and fatal events in hypertension (Mancia et al, 2013).

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Therapeutic Class Overview
Opioids, Long Acting

INTRODUCTION

- Pain originates from somatic or visceral structures. Somatic pain is localized and typically results from injury or disease of the skin, musculoskeletal structures, and joints. Visceral pain arises from internal organ dysfunction or from functional pathology. Pain can be acute or chronic. Acute pain often results from injury or inflammation and may have a survival role and assist in the healing process by minimizing reinjury. In contrast, chronic pain, often defined as pain persisting for over three to six months, may be considered a disease in that it serves no useful purpose (*Cohen et al 2012*).
  - Chronic pain is estimated to affect 100 million Americans and the total annual incremental cost of health care in 2010 due to pain ranges from $560 billion to $635 billion in the United States (U.S.). This includes medical costs and costs related to disability days and lost wages and productivity (*American Academy of Pain Medicine [AAPM] 2014*).
- Pain may be classified as nociceptive pain and neuropathic pain.
  - Nociceptive pain, including cancer pain, results from an injury or disease affecting somatic structures such as skin, muscle, tendons and ligaments, bone, and joints. It is typically treated with nonopioid analgesics or opioids.
  - Neuropathic pain results from disease or injury to the peripheral or central nervous systems and is less responsive to opioids. It is often treated with adjuvant drugs such as antidepressants and antiepileptics (*Cohen et al 2012*).
- Several pharmacologic and nonpharmacologic options are currently available for the management of pain. Treatment options include pharmacologic treatment, physical medicine, behavioral medicine, neuromodulation, interventional, and surgical approaches. Pharmacologic therapy should not be the sole focus of pain treatment; however, it is the most widely utilized option (*Cohen et al 2012*).
  - Major pharmacologic categories used in the management of pain include non-opioid analgesics, tramadol, opioid analgesics, alpha-2 (α_2) adrenergic agonists, antidepressants, anticonvulsants, muscle relaxants, N-methyl-d-aspartate receptor antagonists, and topical analgesics. Opioids are available in both short-acting and long-acting or sustained release formulations (*Cohen et al 2012*).
  - Combining different types of treatments, including multiple types of analgesics, may provide an additive analgesic effect without increasing adverse effects (*Cohen et al 2012, The Medical Letter 2013*).
- It is important that patients receive appropriate pain treatment with careful consideration of the benefits and risks of treatment options. The use of opioid analgesics presents serious risks, including overdose and opioid use disorder. From 1999 to 2014, there were more than 165,000 deaths due to opioid analgesic overdoses in the U.S. (*Dowell et al 2016*).
- The long-acting opioids have gained increasing attention regarding overuse, abuse, and diversion. Some manufacturers have addressed concerns about abuse and misuse by developing new formulations designed to help discourage the improper use of opioid medications.
  - In January 2013, the Food and Drug Administration (FDA) released draft guidance for industry regarding abuse deterrent opioids. This document was finalized in April 2015. The guidance explains the FDA's current direction regarding studies conducted to demonstrate that a given formulation has abuse deterrent properties. The guidance also makes recommendations about how those studies should be performed and evaluated (*FDA Industry Guidance 2015*). The 2015 guidance does not address generic opioids. Subsequently in March 2016, the FDA issued draft guidance to support industry in the development of generic versions of abuse-deterrent opioids (*FDA Industry Guidance 2016*).
  - In 2013, reformulated OxyContin (oxycodone) became the first long-acting opioid to be approved with labeling describing the product's abuse deterrent properties consistent with the FDA's guidance for industry (*Hale et al 2016*).
  - Since the approval of reformulated OxyContin, several other long-acting opioids have been approved with abuse deterrent labeling, including, Arymo ER (morphine), Embeda (morphine and naltrexone), Hysingla ER (hydrocodone), Morphabond (morphine), Targiniq ER (oxycodone and naloxone), Troxyca ER (oxycodone and naltrexone), Vantrela ER (hydrocodone), and Xtampza ER (oxycodone); however, Targiniq ER, Troxyca ER, and Vantrela ER have yet to launch (*Drugs@FDA 2017, Hale et al 2016*).
- A number of federal agencies have recently implemented measures to combat drug abuse and misuse. The Centers for Medicare & Medicaid Services (CMS) has issued guidance in an effort to improve drug utilization review controls in Part D prescription plans. The Drug Enforcement Agency (DEA) issued a nationwide alert regarding fentanyl products laced with heroin, causing significant drug incidents and overdoses nationwide. The U.S. Office of Disease Prevention and

Health Promotion announced a new interactive training tool, “Pathways to Safer Opioid Use,” which teaches healthcare providers how to implement opioid-related recommendations from the adverse events action plan. Additionally, the National Institute on Drug Abuse (NIDA), a component of the National Institutes of Health (NIH), has a number of studies and initiatives to educate providers and patients about opioid addiction and treatment. On July 13, the National Academies of Science, Engineering, and Medicine (NASAM) also released a consensus report, commissioned by the FDA, which outlined the state of the science regarding prescription opioid abuse and misuse, as well as the evolving role that opioids play in pain management. (*CMS 2017, DEA 2016, Office of Disease Prevention and Health Promotion 2015, NASAM 2017, NIDA 2015*).

- In March 2016, the Centers for Disease Control and Prevention (CDC) issued a guideline for prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care. The guideline addresses when to initiate or continue opioids for chronic pain; opioid selection, dosage, duration, follow-up, and discontinuation; and assessing risks and addressing harms of opioid use. The guideline encourages prescribers to follow best practices for responsible opioid prescribing due to the risks of opioid use (*Dowell et al 2016*).
- Methadone is FDA-approved for detoxification and maintenance treatment of opioid addiction.
  - Methadone products when used for the treatment of opioid addiction in detoxification or maintenance programs, shall be dispensed only by opioid treatment programs (and agencies, practitioners or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority. Certified treatment programs shall dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (42 CFR 8.12) (*Prescribing information: Dolophine 2017, methadone oral solution 2016, Methadose 2016*).
- Included in this review are the long-acting opioids which are primarily utilized in the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time. Long-acting opioids are available in a variety of different dosage forms, and currently several agents are available generically (*Drugs@FDA 2017*). Targiniq ER, Troxyca ER, and Vantrela ER are not included in this review as they have not been launched yet.
  - All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of transdermal buprenorphine, a partial opioid agonist, which is a Schedule III controlled substance (*Drugs@FDA 2017*).
- Since some agents are available under multiple brand names, many tables in this review are arranged by generic name.
- Medispan class: Opioid Agonists

Table 1. Medications Included Within Class Review

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

Drug	Generic Availability
Embeda[†] (morphine sulfate/ naltrexone)	-
Xartemis XR (oxycodone hydrochloride/ acetaminophen)	-

*Generic products of the pre-reformulated Opana ER are available. The branded versions of Opana ER (pre- and post-reformulation) are no longer available on the market.

[†]Approved as an abuse deterrent (AD) formulation which is consistent with the FDA's 2015 guidance for industry, *Abuse-Deterrent Opioids – Evaluation and Labeling.*

[‡]OxyContin had various patents extending out to 2027. Patent litigation on OxyContin reached an agreement between manufacturers. In late 2014, a number of generic products launched.

[§]In February 2015, a new formulation of Zohydro ER was FDA-approved with AD properties; however, it has not been deemed to meet the FDA requirements for labeling as an AD opioid.

[¶]Avinza branded products were discontinued by Pfizer in July 2015.

(*Drugs@FDA 2017, FDA Industry Guidance 2015, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Single Entity Agents										Combination Products	
	buprenorphine	fentanyl	hydrocodone	hydromorphone	levorphanol	methadone	morphine	oxycodone	oxymorphone	tapentadol	morphine sulfate/ naltrexone	oxycodone/ acetaminophen
Pain Management												
Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in adults.	✔		✔	✔		✔ *	✔	✔	✔	✔	✔	
Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in opioid-tolerant pediatric patients ≥ 11 years of age who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent.								✔ †				
Management of moderate to severe pain in patients where an opioid analgesic is appropriate.					✔							
Management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.		✔ ‡		✔ ‡								
For the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate.												✔
Management of neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate										✔		
Opioid Addiction												
Detoxification treatment of opioid addiction (heroin or other morphine-like drugs)						✔						
Maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with social and medical services						✔						
Limitations of Use												
Limitations of Use: Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release (ER) opioid formulations, reserve this agent for use in	✔	✔	✔	✔		✔	✔	✔	✔	✔	✔	✔

Indication	Single Entity Agents										Combination Products	
	buprenorphine	fentanyl	hydrocodone	hydromorphone	levorphanol	methadone	morphine	oxycodone	oxymorphone	tapentadol	morphine sulfate/ naltrexone	oxycodone/ acetaminophen
patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.												
Limitations of Use: Not indicated as an as-needed (prn) analgesic.	✔		✔	✔		✔	✔	✔	✔	✔	✔	

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

(Prescribing information: Arymo ER 2017, Butrans 2016, Dolophine 2017, Duragesic 2016, Embeda 2016, Exalgo 2016, Hysingla ER 2016, Kadian 2016, levorphanol 2015, methadone oral solution 2016, Methadose 2016, Morphabond 2017, MS Contin 2016, Nucynta ER 2016, Opana ER 2016, OxyContin 2016, Xartemis XR 2017, Xtampza ER 2016, Zohydro ER 2016)

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

CLINICAL EFFICACY SUMMARY

- As a class, the long-acting opioids are a well-established therapy for the treatment of moderate to severe pain. In general, opioids are used for the treatment of non-cancer and cancer pain; however, data establishing their effectiveness in the treatment of neuropathic pain are available. Head-to-head trials of long-acting opioids do exist and for the most part the effectiveness of the individual agents, in terms of pain relief, appears to be similar. Small differences between the agents exist in side effect profiles, and associated improvements in quality of life or sleep domains (*Agarwal et al 2007, Allan et al 2001, Allan et al 2005, Bao et al 2016, Bekkering et al 2011, Bruera et al 2004, Buynak et al 2010, Caldwell et al 2002, Caraceni et al 2011, Chou et al 2015, Clark et al 2004, Conaghan et al 2011, Felden et al 2011, Finkel et al 2005, Finnerup et al 2015, Gimbel et al 2003, Gordon et al [a], 2010, Gordon et al [b], 2010, Karlsson et al 2009, Hale et al 2007, Hale et al 2010, Katz et al 2010, King et al 2011, Kivitz et al 2006, Langford et al 2006, Ma et al 2008, Melilli et al 2014, Mercadante et al 2010, Mesgarpour et al 2014, Morley et al 2003, Musclow et al 2012, Nicholson et al 2017, Park et al 2011, Pigni et al 2011, Quigley et al 2002, Rauck et al 2014, Schwartz et al 2011, Slatkin et al 2010, Sloan et al 2005, Watson et al 2003, Whittle et al 2011, Wiffen et al 2013, Wild et al 2010*).

- Recent systematic reviews and meta-analyses recommend opioids as a potential treatment option for various forms of non-cancer and cancer-related pain. No single opioid is recommended over the others (*Chou et al 2015, Finnerup et al 2015, Mesgarpour et al 2014*).
  - The Agency for Healthcare Research and Quality (AHRQ) conducted a systematic review (N=39 studies, 40 publications) of the effectiveness and risks of long-term (>3 months) opioid therapy for chronic pain and included both randomized and observational studies. Findings indicated that three randomized, head-to-head trials of various long-acting opioids found no differences in one-year outcomes related to pain or function. One good-quality case-control study found current opioid use to be associated with increased risk for hip, humerus, or wrist fracture versus non-use (adjusted odds ratio [OR], 1.27; 95% confidence interval [CI], 1.21 to 1.33). The risk was highest with one prescription (OR, 2.7; 95% CI, 2.34 to 3.13) and decreased with higher numbers of prescriptions, with no increased risk with more than 20 cumulative prescriptions. One fair-quality cohort study found that a cumulative opioid supply of at least 180 days over a 3.5-year period was associated with an increased risk for myocardial infarction versus no long-term opioid therapy (adjusted incidence rate ratio, 2.66; 95% CI, 2.3 to 3.08) (*Chou et al 2015*).
  - The Special Interest Group on Neuropathic Pain of the International Association for the Study of Pain conducted a systematic review and meta-analysis of randomized, double-blinded studies of oral and topical therapy for neuropathic pain and required a number needed to treat (NNT) for 50% pain relief as the primary measure. For tapentadol ER, the review identified one negative study and one positive enrichment study with a potential bias and a high NNT of 10.2 (95% CI, 5.3 to 185.5) in 67% of the patients responding to the open phase. Thirteen trials were identified with strong opioids, in which oxycodone (10 to 120 mg/day) and morphine (90 to 240 mg/day) were used mainly in peripheral neuropathic pain. The final quality of evidence was moderate. Ten trials were positive with a combined NNT of 4.3 (95% CI, 3.4 to 5.8) and a number needed to harm of 11.7 (95% CI, 8.4 to 19.3). Maximum effectiveness seemed to be associated with 180 mg morphine or equivalent (*Finnerup et al 2015*).
  - Another systematic review evaluated long-acting opioids in the treatment of moderate to severe cancer pain. The review included only double-blinded, randomized controlled trials for efficacy assessments; open-label and controlled observational studies were allowed for safety assessments. A total of five RCTs and four observational studies met criteria for inclusion. Similar pain intensity improvements were demonstrated for oxycodone ER, oxycodone/naloxone ER, hydromorphone ER, and oxycodone ER. However, the average equivalent dose of oxycodone ER was significantly different from hydromorphone ER. The Morphine ER and hydromorphone ER groups had similar improvements in average cancer pain in the past 24 hours and “current pain in the morning;” however, the “worst pain in the past 24 hours” and “current pain in the evening” were significantly lower in the hydromorphone ER group. The quality of life scores were comparable between oxycodone ER and oxycodone/naloxone ER as well as morphine ER and hydromorphone ER in two trials. The rate of discontinuation due to lack of efficacy was similar among patients treated with morphine ER, hydromorphone ER, oxycodone ER or oxycodone/naloxone ER and ranged from 1.1% (oxycodone/naloxone ER) to 6.5% (hydromorphone ER). The risk of experiencing serious adverse events was comparable in patients treated with morphine ER or hydromorphone ER, morphine ER or fentanyl ER, and morphine ER or oxycodone ER. Overall, the reviewers concluded that there was no difference in efficacy and risk of harms among ER opioids in the treatment of cancer-related pain based on current evidence (*Mesgarpour et al 2014*).

- Arymo ER and Morphabond were approved based on bioequivalence to MS Contin. In lieu of conducting new nonclinical studies and clinical studies of the safety and efficacy, the manufacturers relied on previous findings of efficacy and safety for MS Contin (*FDA Summary Review: Arymo ER 2017, Morphabond 2017*).

CLINICAL GUIDELINES

- Clinical guidelines do not state a preference for the use of one long-acting opioid over another for the use in moderate to severe pain (*Attal et al 2010, Bril et al 2011, Dubinsky et al 2004, Chou et al 2009, Hochberg et al 2012, Paice et al 2016*). However, opioid rotation is recommended if a patient experiences adverse effects from one agent (*Chou et al 2009*). In addition, methadone safety guidelines from the 2014 American Pain Society recommend buprenorphine as an alternative to methadone for the treatment of opioid addiction in patients with risk factors or known QTc prolongation (*Chou et al 2014*).

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

- Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible (category A, evidence 3).
- Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder (category A, evidence 2).

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

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

- In February 2017, the American College of Physicians published clinical practice guidelines for noninvasive treatments of acute, subacute, and chronic low back pain. The guidelines state that clinicians should only consider opioids as an option in patients who have failed other treatments (e.g., non-pharmacological treatment, nonsteroidal anti-inflammatory drugs [NSAIDs], tramadol, duloxetine) and only if the potential benefits outweigh the risks for individual patients and after a discussion of known risks and realistic benefits with patients (*Qaseem et al 2017*).
  - There is moderate-quality evidence that show strong opioids (tapentadol, morphine, hydromorphone, and oxymorphone) are associated with a small short-term improvement in pain scores (about 1 point on a pain scale of 0 to 10) and function compared with placebo. There is moderate-quality evidence that show no differences among different long-acting opioids for pain or function, and low-quality evidence shows no clear differences in pain relief between long- and short-acting opioids.

- In February 2017, the American Society of Interventional Pain Physicians (ASIPP) also published new practice guidelines for responsible, safe, and effective prescription opioids for chronic non-cancer pain. Similar to other guidelines, they do not recommend one opioid agent over the others. They do provide the following recommendations and conclusions for long-term opioid therapy (*Manchikanti et al 2017*):
  - Initiate opioid therapy with low dose, short-acting drugs, with appropriate monitoring (Evidence: Level II; Strength of Recommendation: Moderate).
  - Consider up to 40 MME as low dose, 41 to 90 MME as a moderate dose, and greater than 91 MME as high dose (Evidence: Level II; Strength of Recommendation: Moderate).
  - Avoid long-acting opioids for the initiation of opioid therapy (Evidence: Level I; Strength of Recommendation:
  - Strong).
  - Recommend methadone only for use after failure of other opioid therapy and only by clinicians with specific training in its risks and uses, within FDA recommended doses (Evidence: Level I; Strength of Recommendation: Strong).
  - Understand and educate patients of the effectiveness and adverse consequences (Evidence: Level I; Strength of Recommendation: Strong).
  - Similar effectiveness for long-acting and short-acting opioids with increased adverse consequences of long-acting opioids (Evidence: Level I-II; Strength of recommendation: Moderate to strong).
  - Recommend long-acting or high dose opioids only in specific circumstances with severe intractable pain (Evidence: Level I; Strength of Recommendation: Strong).

SAFETY SUMMARY

- On July 9, 2012, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) program for all ER and long-acting opioids included in this review, with the exception of levorphanol. This program has been updated to include new formulations and medications. The REMS program is part of the national prescription drug abuse plan announced in

2011 to combat prescription drug misuse and abuse. Program components include prescriber education and training, patient education, and a communication plan for prescribers.

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

DOSING AND ADMINISTRATION

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

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Arymo ER, Avinza†, Kadian*, Morphabond, MS Contin (morphine sulfate)	ER capsules and tablets	Oral	Arymo ER, MS Contin: Every 8 to 12 hours Avinza: Once daily Morphabond: Every 12 hours Kadian: Once daily	• Renal dose adjustment is required. • Hepatic dose adjustment is required.
Butrans (buprenorphine)	Transdermal system	Topical	Administration every 7 days	• Not evaluated in patients with severe hepatic impairment and should be administered with caution.
Dolophine, Methadose (methadone)	Oral solution, dispersible tablet, tablets	Oral	Every 8 to 12 hours (for management of pain)	• Due to the large variability in half-life (eg, 8 to 59 hours), dose adjustments may vary greatly. Dose increases may be no more frequent than every three to five days; however some may require up to 12 days. • Due to the metabolism of methadone, patients with liver impairment may be at risk of accumulating methadone after multiple dosing.
Duragesic (fentanyl)	Transdermal system	Topical	Administration every 72 hours (Some patients may not achieve adequate analgesia using this dosing interval and may require systems be applied at 48 hours)	• Avoid use in patients with severe renal impairment. • Avoid use in patients with severe hepatic impairment.
Exalgo (hydromorphone)	ER tablets	Oral	Once daily	• Moderate renal impairment: start 50% of the usual dose. • Severe renal impairment: start 25% of the usual dose. • Moderate hepatic impairment: start 25% of the usual dose.
Hysingla ER Zohydro ER (hydrocodone bitartrate)	ER capsules and tablets	Oral	Hysingla ER: Once daily Zohydro ER: Every 12 hours	• For severe impairment, reduce the HYSINGLA dose to 1/2 the usual initial dose and start ZOHYDRO at the lowest dose of 10 mg every 12 hours. • HYSINGLA: In moderate to severe impairment (including end stage renal disease), reduce the initial dose to 1/2 the usual initial dose.
Levorphanol	Tablets	Oral	Every 6 to 8 hours	
Nucynta ER (tapentadol)	ER tablets	Oral	Twice daily	• Not recommended in patients with severe renal impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				• Not recommended in patients with severe hepatic impairment.
Opana ER (oxymorphone)‡	ER tablets	Oral		• Contraindicated in moderate and severe hepatic impairment.
OxyContin; Xtampza ER (oxycodone)	ER capsules and tablets	Oral	Every 12 hours	• In hepatic impairment, initiate dose at 1/3 to 1/2 the recommended initial dose.
Combination Products				
Embeda (morphine sulfate/ naltrexone)	ER capsules	Oral	Once daily	• Renal dose adjustment may be required in severe renal impairment. • Hepatic dose adjustment may be required in severe hepatic impairment.
Xartemis XR (oxycodone/ acetaminophen)	ER tablets	Oral	Every 12 hours	

*Available only as brand name Kadian
†All Avinza branded products have been removed from the market.
§Available only as brand name OxyContin.
‡Generic products of the pre-reformulated Opana ER are available. The branded versions of Opana ER (pre- and post-reformulation) are no longer available on the market.

CONCLUSION

- Opioids have been the mainstay of pain treatment for a number of years, and there is well documented evidence of their effectiveness. Oral morphine is the standard for comparison for all other opioid agents currently available. There are several long-acting opioid agents available which are FDA-approved for the treatment of moderate to severe pain in patients requiring around-the-clock analgesia (*Cohen et al 2012*).
  - Xartemis XR is the only long-acting agent in class indicated for severe acute pain.
  - Levorphanol is indicated for moderate to severe pain where an opioid analgesic is appropriate; however, the FDA-approved indication does not stipulate that patients require around-the-clock, daily dosing for use.
  - Nucynta ER is the only long-acting agent in class also indicated for neuropathic pain which requires daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
  - OxyContin has recently been FDA-approved as an option in pediatric patients, aged ≥ 11 years, for daily, around-the-clock, long term opioid treatment and for which alternative treatment options are inadequate. Unlike adults, pediatric patients must have responded to a minimum opioid daily dose of ≥ 20 mg oxycodone for 5 consecutive days prior to initiating treatment with OxyContin. Although study efficacy and safety data are not rigorous, OxyContin has been prescribed off-label for years within the pediatric population (*FDA Summary: OxyContin 2015*).
- All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of transdermal buprenorphine which is a Schedule III controlled substance.
- Since 2013, a number of abuse deterrent formulations have come to the market. Although various manufacturers have introduced formulations with properties to deter misuse potential; there are only a few agents that have completed studies supporting the potential to deter abuse and misuse. The only long-acting opioids that meet all requirements and are currently available include OxyContin (oxycodone hydrochloride extended release), Embeda (morphine sulfate/naltrexone), Hysingla ER (hydrocodone bitartrate extended release), and Xtampza ER (oxycodone extended release) (*FDA Industry Guidance 2015*).
- Almost all long-acting opioids are part of the REMS program. In general, all of the long-acting opioids are similar in terms of adverse events, warnings, and contraindications. Methadone-containing products warn of the potential for QTc

prolongation and risks associated with an interaction with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) is cited within Duragesic, Hysingla ER, OxyContin, and Zohydro ER labeling. The main differences among the individual agents and formulations are due to dosing requirements and generic availability.
    - Several generic long-acting opioids exist, including hydromorphone; oxymorphone; levorphanol; fentanyl transdermal systems; methadone tablets, solution, and concentrate; morphine sulfate ER tablets and capsules; and oxycodone.
- Head-to-head trials demonstrate similar efficacy among the agents in the class. Systematic reviews and treatment guidelines from several professional organizations support and recommend opioids as a potential treatment option for various forms of non-cancer and cancer-related pain. No single opioid is recommended over the others (*Chou et al 2015, Finnerup et al 2015, Mesgarpour et al 2014*). Methadone safety guidelines from the 2014 American Pain Society recommend buprenorphine as an alternative to methadone for the treatment of opioid addiction in patients with risk factors or known QTc prolongation (*Chou et al 2014*).Other current clinical guidelines do not state a preference for the use of one long-acting opioid over another for the use in moderate to severe pain (*Attal et al 2010, Bril et al 2011, Dubinsky et al 2004, Chou et al 2009, Hochberg et al 2012, Manchikanti et al 2012, Qaseem et al 2017*). However, opioid rotation is recommended if a patient experiences adverse effects from one agent (*Chou et al 2009*). A guideline from the CDC has recently been published that addresses the use of chronic pain outside of active cancer treatment, palliative care, and end-of-life care; this guideline emphasizes the use of nonpharmacologic and nonopioid therapies when possible, and notes that clinicians should consider opioid therapy only if the expected benefits for both pain and function are anticipated to outweigh risks to the patient (*Dowell et al 2016*).

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Therapeutic Class Overview
Sodium-Glucose Cotransporter 2 Inhibitors

INTRODUCTION

- Diabetes mellitus affects more than 30 million people in the United States *(Centers for Disease Control and Prevention [CDC] 2017)*.
- 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. *(National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK] 2017, CDC 2017)*.
- 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 T2DM include sulfonylureas (SFUs), 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 inhibitor 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	Generic Availability
Dapagliflozin products	
Farxiga (dapagliflozin)	-
Xigduo XR (dapagliflozin/metformin hydrochloride extended-release)	-
Qtern (dapagliflozin/saxagliptin)	-
Canagliflozin products	
Invokana (canagliflozin)	-
Invokamet (canagliflozin/metformin hydrochloride)	-
Invokamet XR (canagliflozin/metformin extended-release)	-
Empagliflozin products	
Jardiance (empagliflozin)	-
Glyxambi (empagliflozin/linagliptin)	-
Synjardy (empagliflozin/metformin)	-
Synjardy XR (empagliflozin/metformin extended-release)	-

(*Drugs@FDA 2017, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 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)	Qtern (dapagliflozin/ saxagliptin)	Invokamet, Invokamet XR† (canagliflozin/ metformin)	Synjardy, Synjardy XR† (empagliflozin/ metformin)	Xigduo XR† (dapagliflozin/ metformin ER)
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				✓*				
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM who have inadequate control with dapagliflozin or who are already treated with dapagliflozin and saxagliptin					✓			

† These combination products contain metformin extended-release (ER).

* 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 T2DM 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 (DKA). Glyxambi has not been studied in patients with a history of pancreatitis. Qtern should only be used in patients who tolerate 10 mg dapagliflozin.

(*Prescribing information: Farxiga 2017, Glyxambi 2017, Invokana 2017, Invokamet 2017, Invokamet XR 2017, Jardiance 2016, Qtern 2017, Synjardy 2016, Synjardy XR 2016, Xigduo XR 2017*)

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

CLINICAL EFFICACY SUMMARY

- The 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 ~0.5% to 1% *(Inzucchi et al 2015)*. 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 (FPG), weight gain, post-prandial glucose (PPG), and blood pressure when used as monotherapy or in combination therapy:
  - As monotherapy *(Bailey et al 2012, Ferrannini et al 2010, Ferrannini et al 2013, Inagaki et al 2014, Stenlöf et al 2013)*
  - With metformin *(Bailey et al 2010, Haring et al 2014, Henry et al 2012, Leiter et al 2015, Rosenstock et al 2013, Rosenstock et al 2016, Ross et al 2015)*
  - With an SFU *(Fulcher et al 2015, Strojek et al 2011, Strojek et al 2014, Wilding et al 2013)*
  - With metformin and an SFU *(Haring et al 2013, Matthaei et al 2015)*
  - As add-on therapy to TZDs *(Forst et al 2014, Kovacs et al 2014, Rosenstock et al 2012)*
  - As add-on therapy or compared to DPP-4 inhibitors *(Jabbour et al 2014, Lavalle-Gonzalez et al 2013, Roden et al 2013, Rosenstock et al 2015[a], Schernthaner et al 2013)*
  - As add-on therapy to insulin *(Neal et al 2015, Rosenstock et al 2014, Rosenstock et al 2015[b], Wilding et al 2012)*
- 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 Food and Drug Administration (FDA) approval of these extended-release combination products.
- Glyxambi (empagliflozin/linagliptin) was the first FDA-approved SGLT2-inhibitor/DPP-4 inhibitor combination product. A 52-week, phase 3, double-blind, parallel-group, randomized controlled trial (RCT) 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)*. Qtern (dapagliflozin/saxagliptin) was approved in February 2017; efficacy and safety were observed as add-on therapy with saxagliptin in patients on dapagliflozin plus metformin at 24 weeks *(Matthaei et al 2015)* and at 52 weeks *(Matthaei et al 2016)*; with dapagliflozin added to saxagliptin plus metformin at 24 weeks *(Mathieu et al 2015)* and 52 weeks *(Mathieu et al 2016)*; and with saxagliptin plus dapagliflozin addition vs. the single addition of saxagliptin or dapagliflozin to metformin at 24 weeks *(Rosenstock et al 2015[a])*.
- The SGLT2 inhibitors have also shown noninferiority in decreasing HbA1c in direct comparisons when compared to SFUs:
  - 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)*
- Additional studies have demonstrated the safety and efficacy of SGLT2 inhibitors in special populations:
  - Patients with T2DM and chronic kidney disease *(Barnett et al 2014, Kohan et al 2014, Yale et al 2014, Yale et al 2013)*
  - Patients with T2DM 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, RCTs 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 RCTs 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 individual efficacy of the SGLT2 inhibitors *(Liakos et al 2014, Orme et al 2014, Sun et al 2014, Yang et al 2014)*.

Comparative efficacy

- While there are no head-to-head studies comparing the efficacy and safety of the SGLT2 inhibitors, a 2016 systematic review and network meta-analysis found that canagliflozin 300 mg reduced HbA1c, FPG, and systolic blood pressure, while increasing low-density lipoprotein cholesterol (LDL-C) to a greater extent compared with other inhibitors (dapagliflozin and empagliflozin) at any dose *(Zaccardi et al 2016)*.
- Another systematic review and network meta-analysis found similar results *(Shyangdan et al 2016)*. When used as monotherapy, a greater proportion of patients achieved a HbA1c <7% on canagliflozin 300 mg than on canagliflozin 100 mg and dapagliflozin 10 mg, but there were no significant differences compared with either dose of empagliflozin. Canagliflozin 300 mg reduced HbA1c more than other SGLT-2 inhibitors, with the mean difference ranging from 0.20% to 0.64%. There were no significant differences between the SGLT2 inhibitors with respect to weight reduction.
- The Agency for Healthcare Research and Quality (AHRQ) updated its review of the diabetes medications for adults with T2DM to include the results from an additional eight studies *(Bolen et al 2016)*. Findings related to the SGLT2 inhibitors included some of the following:
  - Body weight was maintained or reduced by metformin, DPP-4 inhibitors, GLP-1 agonists, and SGLT2 inhibitors.
  - Systolic blood pressure was reduced by 3 to 5 mm Hg by SGLT2 inhibitors and GLP-1 agonists compared to metformin.
  - 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).

Cardiovascular outcomes studies

- 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). In addition, there was a 38% reduction in CV death, 35% reduction in hospitalization for heart failure (HHF), 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. Recently updated guidelines acknowledge the established CV benefit with empagliflozin *(ADA 2017, Garber et al 2017)*.
  - 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%; hazard ratio [HR]: 0.61; 95% confidence interval [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)*.
- The CANVAS Program was comprised of 2 trials, the Canagliflozin Cardiovascular Assessment Study (CANVAS) and CANVAS-Renal (CANVAS-R), that included a total of 10,142 patients with T2DM and high CV risk *(Neal et al 2017)*. The studies were designed to assess the CV safety and efficacy of canagliflozin, as well as to evaluate the balance between potential benefits of the drug and its associated risks (eg, genitourinary infection, DKA, fracture). Significantly fewer participants in the canagliflozin group had a primary outcome event (the composite of death from CV causes, nonfatal MI, or nonfatal stroke) vs. placebo: 26.9 vs. 31.5 participants with an event per 1000 patient-years (HR, 0.86; 95% CI, 0.75 to 0.97; $p < 0.001$ for noninferiority; $p = 0.02$ for superiority).
- A Phase 3, multicenter trial to evaluate the effect of dapagliflozin on the incidence of CV events, known as DECLARE-TIMI58, is currently underway with results expected by 2019 *(ClinicalTrials.gov)*.
- The Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors (CVD REAL) study is the first large real-world study of > 300,000 patients with T2DM, both with and without established cardiovascular disease (CVD) that evaluated outcomes of HHF and all-cause death in patients with T2DM treated with SGLT2 inhibitors vs. other glucose-lowering drugs. Data were collected from patients living in 6 countries (United States, Germany, Sweden, Norway, Denmark, and the United Kingdom) *(Kosiborod et al 2017)*. Overall, treatment with SGLT2 inhibitors

vs. other agents was associated with a 39% relative risk reduction in HHF, a 51% reduction in all-cause death, and a 46% reduction in the HHF or death composite.

CLINICAL GUIDELINES

Overview

- 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[b], 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 *(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 (eg, 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 blood glucose 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 *(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 (eg, 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 (eg, 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 inhibitor-specific information:

- SGLT2 inhibitors have a glucosuric effect that results in decreased HbA1c, weight, and systolic blood pressure.
- Empagliflozin is the only SGLT2 inhibitor associated with significantly lower rates of all-cause and CV death and lower risk of HHF. 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 LDL-C levels, limited efficacy in patients with an estimated glomerular filtration rate (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 DKA have been reported in T1DM and T2DM with less than expected hyperglycemia (euglycemic DKA).

- ADA Standards of Medical Care in Diabetes – 2017 *(ADA 2017[b])*
  - A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include efficacy, hypoglycemia risk, impact on weight, potential side effects, cost, and patient preferences. Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacologic agent for the treatment of T2DM.
  - SGLT2 inhibitors provide insulin-independent glucose lowering by blocking glucose reabsorption in the proximal renal tubule by inhibiting SGLT2. These agents provide modest weight loss and blood pressure reduction in T2DM. None of the available 3 agents are FDA-approved for the treatment of patients with T1DM.
  - The FDA issued a warning about the risk of ketoacidosis occurring in the absence of significant hyperglycemia (euglycemic DKA) in patients with type 1 and type 2 diabetes treated with SGLT2 inhibitors. Symptoms of ketoacidosis include dyspnea, nausea, vomiting, and abdominal pain. Patients should be instructed to stop taking SGLT2 inhibitors and seek medical attention immediately if they have symptoms or signs of ketoacidosis.
  - In patients with long-standing suboptimally controlled T2DM and established atherosclerotic CV disease, empagliflozin or liraglutide should be considered as they have been shown to reduce CV and all-cause mortality when added to standard care.

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 DKA, with or without coma. DKA 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.
- Saxagliptin-containing products have the following contraindications:
  - History of a serious hypersensitivity reaction to dapagliflozin or to saxagliptin, including anaphylaxis, angioedema or exfoliative skin conditions.
  - Moderate to severe renal impairment (eGFR < 45 mL/min/1.73 m^2), end-stage renal disease, or dialysis.

- Boxed Warnings:
  - Canagliflozin-containing products carry a Boxed Warning for lower limb amputation. An approximately 2-fold increased risk of lower limb amputations associated with canagliflozin use was observed in the CANVAS and CANVAS-R trials in patients with T2DM who had established CVD or were at risk for CVD. Amputations of the toe and midfoot were most frequent; however, amputations involving the leg were also observed. Some patients had multiple amputations, some involving both limbs. Before initiating, consider factors that may increase the risk of amputation. Monitor patients receiving canagliflozin for infections or ulcers of the lower limbs, and discontinue if these occur.
  - 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 increased 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 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[b])*.
    - The drug safety communication issued in May 2016 with interim safety results from the CANVAS and CANVAS-R studies has since culminated in a formal boxed warning on all canagliflozin-containing agents for the risk of lower limb amputation *(FDA Drug Safety Communication 2016[a] and 2017)*.
    - The FDA issued a drug safety communication regarding the risk of fracture and bone density in 2016.
      - 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 (eg, fall from no more than standing height), and affect the upper extremities *(Watts et al 2016)*.
      - 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)	Qtern (dapagliflozin/ saxagliptin)	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	✔				✔			✔

Warnings and Precautions	Single-Entity Products			Combination Products				
	Farxiga (dapagliflozin)	Invokana (canagliflozin)	Jardiance (empagliflozin)	Glyxambi (empagliflozin/ linagliptin)	Qtern (dapagliflozin/ saxagliptin)	Invokamet, Invokamet XR (canagliflozin/ metformin)	Synjardy, Synjardy XR (empagliflozin/ metformin)	Xigduo XR (dapagliflozin/ metformin ER)
caution in patients with a prior history of bladder cancer.								
Lower limb amputation: An approximately 2-fold increased risk of lower limb amputations was observed with canagliflozin in patients with T2DM who had either established CVD or were at risk for CVD.		✔				✔		
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.				✔	✔			
Heart failure: In a CV outcomes trial enrolling participants with established atherosclerotic cardiovascular disease (ASCVD) or multiple risk factors for ASCVD (SAVOR trial), more patients randomized to saxagliptin (289/8280, 3.5%) were hospitalized for heart failure compared to patients randomized to placebo (228/8212, 2.8%). In a time-to-first-event analysis the risk of HHF was higher in the saxagliptin group (estimated HR: 1.27; 95% CI, 1.07 to 1.51). Subjects with a prior history of heart failure and					✔			

Warnings and Precautions	Single-Entity Products			Combination Products				
	Farxiga (dapagliflozin)	Invokana (canagliflozin)	Jardiance (empagliflozin)	Glyxambi (empagliflozin/ linagliptin)	Qtern (dapagliflozin/ saxagliptin)	Invokamet, Invokamet XR (canagliflozin/ metformin)	Synjardy, Synjardy XR (empagliflozin/ metformin)	Xigduo XR (dapagliflozin/ metformin ER)
subjects with renal impairment had a higher risk for HHF, irrespective of treatment assignment; monitor, observe, and advise patients of this risk and consider discontinuation in any patients that develop signs of heart failure.								
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 canagliflozin 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 to 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 (eg, SFU), a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycemia.

  Empagliflozin:

- Diuretics: Co-administration of diuretics with increased urine volume and frequency of voids may increase the potential for volume depletion.

Linagliptin-containing products:

- Efficacy of linagliptin may be reduced when used in combination with a strong inducer of cytochrome P450 (CYP) 3A4 or P-glycoprotein. Consider alternative treatments.

Saxagliptin-containing products:

- Ketoconazole significantly increased saxagliptin exposure. Similar significant increases in plasma concentrations of saxagliptin are anticipated with other strong CYP3A4/5 inhibitors; do not co-administer Qtern with strong CYP3A4/5 inhibitors.

Metformin-containing products:

- 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.
- Topiramate or other carbonic anhydrase inhibitors (eg, 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.
- 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	Available Formulations	Route	Usual Recommended Frequency	Comments
Single entity products				
Farxiga (dapagliflozin)	Tablets	Oral	Daily	Initiation is not recommended if eGFR is < 60 mL/min/1.73 m^2. Not recommended in patients with an eGFR persistently between 30 and < 60 mL/min/1.73 m^2.
Invokana (canagliflozin)	Tablets	Oral	Daily	Limit dose to 100 mg once daily in patients who have an eGFR of 45 to < 60 mL/min/1.73 m^2. Not recommended if eGFR persistently falls below 45 mL/min/1.73 m^2. Not recommended in cases of severe hepatic impairment.
Jardiance (empagliflozin)	Tablets	Oral	Daily	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.
Combination products				
Invokamet (canagliflozin/ metformin)	Tablets	Oral	Two times daily	Limit canagliflozin to 50 mg twice daily in patients with eGFR of 45 to < 60 mL/min/1.73 m^2. Contraindicated in patients with moderate to severe renal impairment (eGFR < 45

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				mL/min/1.73 m^2), end stage renal disease, or patients on dialysis. Not recommended in patients with hepatic impairment.
Invokamet XR (canagliflozin/ metformin ER)	Tablets	Oral	Daily	Limit canagliflozin to 50 mg twice daily in patients with eGFR of 45 to < 60 mL/min/1.73 m^2. Contraindicated in patients with moderate to severe renal impairment (eGFR < 45 mL/min/1.73 m^2), end stage renal disease, or patients on dialysis. Not recommended in patients with hepatic impairment.
Xigduo XR (dapagliflozin/ metformin ER)	Tablets	Oral	Daily	Contraindicated in patients with moderate to severe renal impairment (eGFR < 60 mL/min/1.73 m^2). Not recommended in hepatic impairment.
Qtern (dapagliflozin/ saxagliptin)	Tablets	Oral	Daily	Do not initiate if eGFR is < 60 mL/min/1.73 m^2. Discontinue if eGFR falls persistently below 60 mL/min/1.73 m^2.
Glyxambi (empagliflozin/ linagliptin)	Tablets	Oral	Daily	Do not initiate or continue if eGFR < 45 mL/min/1.73 m^2. Discontinue if eGFR is < 45 mL/min/1.73 m^2.
Synjardy (empagliflozin/ metformin)	Tablets	Oral	Two times daily	Contraindicated in patients with eGFR < 45 mL/min/1.73 m^2. Advise premenopausal females of the potential for an unintended pregnancy.
Synjardy XR (empagliflozin/ metformin ER)	Tablets	Oral	Daily	Contraindicated in patients with eGFR < 45 mL/min/1.73 m^2. Advise premenopausal females of the potential for an unintended pregnancy.

See the current prescribing information for full details

CONCLUSION

- Canagliflozin, dapagliflozin, and empagliflozin are inhibitors of SGLT2, the co-transporter 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 T2DM. SGLT2 inhibitors have demonstrated efficacy in lowering HbA1c levels by ~0.5% 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) and Qtern (dapagliflozin/saxagliptin) are SGLT2 inhibitor/DPP-4 inhibitor combination products.
- In clinical trials, the SGLT2 inhibitors 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, FPG, weight gain, PPG, 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 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 LDL-C levels, increased serum creatinine and a concomitant decrease in eGFR, volume depletion, and genital mycotic infections. Warnings for bone fractures and most recently, lower limb amputation were added for canagliflozin-containing products. Warnings for DKA, urosepsis, and pyelonephritis were also added to the labeling of SGLT2 inhibitors 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.
- Evidence that glucose lowering reduces the rates of CV events and death had 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 MI, or nonfatal stroke) by 14% vs. placebo ($p < 0.001$ for non-inferiority; $p = 0.04$ for superiority). In the CANVAS trials, significantly fewer participants in the canagliflozin group had a primary outcome event (the composite of death from CV causes, nonfatal MI, or nonfatal stroke) vs. placebo: 26.9 vs. 31.5 participants with an event per 1000 patient-years (HR: 0.86; 95% CI, 0.75 to 0.97; $p < 0.001$ for noninferiority; $p = 0.02$ for superiority).
- 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 or risk for hypoglycemia. Positive CV outcomes have been demonstrated with empagliflozin and now most recently with canagliflozin, which suggest that SGLT2 inhibitors may play a significant role in T2DM patients at high risk for CV events; however, the results of an ongoing CV outcomes study with dapagliflozin are still pending. 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
Insulin and Combination Agents

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 2018).*
- The classification of diabetes includes four clinical classes: 1) Type 1 diabetes (T1DM) which results from beta-cell (β-cell) destruction, usually leading to absolute insulin deficiency; 2) Type 2 diabetes (T2DM) which results from a progressive insulin secretory defect on the background of insulin resistance; 3) Other specific types of diabetes due to other causes, e.g., genetic defects in β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced (such as in the treatment of HIV/AIDS or after organ transplantation; and 4) Gestational diabetes mellitus (diabetes diagnosed during pregnancy that is not clearly overt diabetes) *(ADA 2018).*
- In 2015, an estimated 30.3 million people, or 9.4%, of the United States (US) population had diabetes mellitus, with 7.2 million estimated to be undiagnosed *(Centers for Disease Control and Prevention [CDC] 2017).*
- The insulin products are approved for use in the management of both T1DM and T2DM. Other pharmacologic options for T2DM include sulfonylureas, biguanides, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, amylinomimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and combination products.
- Insulin is used as replacement therapy in patients with diabetes, replacing deficient endogenous insulin and temporarily restoring the ability of the body to properly utilize carbohydrates, fats, and proteins. Insulin is secreted by the β-cells in the pancreas and lowers blood glucose by facilitating peripheral glucose uptake into cells and by inhibiting gluconeogenesis in the liver. In addition to its glycemic effects, insulin has anabolic properties, enhancing protein synthesis, inhibiting lipolysis in adipocytes, and stimulating lipogenesis *(Powers 2015)*.
- The first insulin products were derived from animal sources, primarily pork and beef; however, they are no longer available in the US. These older products have been replaced with human insulin and insulin analogs. Human insulin is biosynthesized utilizing recombinant deoxyribonucleic acid (DNA) with strains of *Escherichia coli* or *Saccharomyces cerevisiae* (baker's yeast) and is structurally identical to endogenous insulin. Insulin analogs are also derived from recombinant DNA technology. They are structurally different from human insulin but have comparable glucose-lowering effects. The insulin analogs differ in the addition, deletion, or substitution of amino acids on the B chain *(Powers 2015)*. Insulin analogs available today include insulin aspart, insulin degludec, insulin detemir, insulin glargine, insulin glulisine, and insulin lispro. The primary differences between commercially available insulin products revolve around pharmacodynamic and pharmacokinetic properties, particularly onset and duration of action. Individual insulin products are often classified into categories based on their onset and duration of action.
  - Bolus insulin products, also known as rapid- or short-acting insulin, include insulin aspart, insulin glulisine, insulin lispro, and certain human insulins. Unique formulations within this category include a rapid-acting, human insulin inhalation powder, and a higher strength of rapid-acting insulin lispro that provides 200 units (U) per milliliter (U-200). In September 2017, Fiasp (insulin aspart) was approved *(Novo Nordisk news release 2017).* Fiasp is a new formulation of Novolog that contains niacinamide. Niacinamide helps to increase the speed of initial insulin absorption, resulting in an onset of appearance in the blood in an estimated 2.5 minutes. Additionally, in December 2017, Admelog (insulin lispro) was the first short-acting insulin approved as a "follow-on" product through the Food and Drug Administration's (FDA) abbreviated 505(b)(2) pathway *(FDA news release 2017).*
  - Basal insulin products, also known as intermediate- or long-acting insulin, include neutral protamine Hagedorn (NPH) isophane, insulin degludec, insulin detemir, and insulin glargine. Unique products within this category include a formulation of insulin glargine that provides 300 U of insulin glargine per milliliter and enables patients to utilize a higher dose in one injection. Additionally, Basaglar (insulin glargine) was approved under the FDA 505(b)(2) pathway. *(Fierce Biotech FDA press release 2015, Drugs@FDA 2018).*

- Insulin therapy is usually administered by subcutaneous (SC) injection, which allows for prolonged absorption and less pain compared to intramuscular (IM) injection. Currently there are no generic insulin products available. Of note, insulin products are available by prescription, as well as over-the-counter (OTC) (short- and intermediate-acting products only).
- This review will focus on the insulin preparations and combination insulin/GLP-1 agonist products outlined in Table 1 for their respective FDA-approved indications. FDA-approved products that do not have upcoming launch plans, such as Ryzodeg 70/30 (insulin degludec/insulin aspart), have been excluded from this review *(Novo Nordisk press release 2015*).
- Medispan Class: Antidiabetics, Insulin

Table 1. Medications Included Within Class Review

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

(Drugs@FDA 2018)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications – Insulins

Product	Adjunct to diet and exercise to improve glycemic control in adults and children with T1DM and T2DM	Control of hyperglycemia in patients with diabetes mellitus	Improve glycemic control in adults with diabetes mellitus	Improve glycemic control in adults and children with diabetes mellitus
Rapid-Acting Insulins				
Admelog				✔
Afrezza			✔ §	
Apidra				✔
Fiasp			✔	
Humalog				✔
Novolog				✔
Short-Acting Insulins				
Humulin R	✔ *			
Novolin R				✔
Intermediate-Acting Insulins				
Humulin N				✔
Novolin N				✔
Long-Acting Insulins†				
Basaglar				✔ ‡
Lantus				✔ ‡
Levemir				✔
Toujeo			✔	
Tresiba				✔ ‖
Combination Insulins, Rapid-Acting and Intermediate-Acting				
Humalog Mix 50/50 Humalog Mix 75/25		✔		
Novolog Mix 70/30			✔	
Combination Insulins, Short-Acting and Intermediate-Acting				
Humulin 70/30			✔	
Novolin 70/30			✔	

* Humulin R U-500 is useful for the treatment of insulin-resistant patients with diabetes requiring daily doses of more than 200 units. 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 T2DM.
§ Limitations of use: Must use with a long-acting insulin in patients with T1DM. Not recommended for treating diabetic ketoacidosis. Not recommended in patients who smoke.
‖ Indicated for patients 1 year of age and older with diabetes mellitus; not recommended for pediatric patients requiring < 5 units of TRESIBA.

(Prescribing information: Admelog 2017, Afrezza 2017, Apidra 2015, Basaglar 2017, Fiasp 2017, Humalog 2017, Humalog Mix 50/50 2017, Humalog Mix 75/25 2017, Humulin 70/30 2017, Humulin N 2017, Humulin R U-100 2017, Humulin R U-500 2017, Lantus 2017, Levemir 2015, Novolin 70/30 2016, Novolin N 2016, Novolin R 2016, Novolog 2017, Novolog Mix 70/30 2017, Toujeo 2015, Tresiba 2016)

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

Indication	**Soliqua** (insulin glargine/ lixisenatide)	**Xultophy** (insulin degludec/ liraglutide)
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM inadequately controlled on:		
Basal insulin (< 60 U daily) or lixisenatide	✔	--
Basal insulin (< 50 U daily) or liraglutide (≤ 1.8 mg daily)	--	✔
Limitations of Use		
Not recommended as first-line therapy for patients inadequately controlled on diet and exercise.	--	✔
Has not been studied in patients with a history of unexplained pancreatitis. Other antidiabetic therapies should be considered in patients with a history of pancreatitis.	✔	✔
Not recommended for use in combination with any other product containing another GLP-1 receptor agonist.	✔	✔
Not for treatment of T1DM or diabetic ketoacidosis.	✔	✔
Not recommended for use in patients with gastroparesis.	✔	--
Has not been studied in combination with prandial insulin.	✔	✔

(*Prescribing information: Soliqua 2017, Xultophy 2016*)

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

CLINICAL EFFICACY SUMMARY

Rapid- and Short-Acting Insulins

- Clinical trials conducted with the newer insulin analogs have shown that they are at least as effective as the older insulin formulations. A large meta-analysis revealed that both insulin aspart and insulin lispro produced comparable lowering of glycosylated hemoglobin (HbA1c) in patients with T2DM compared to regular insulin *(Plank et al 2005).* In patients with T1DM, insulin lispro and insulin aspart produced small, but significant differences in lowering HbA1c compared to regular insulin. Clinical trials comparing insulin glulisine to regular insulin demonstrated similar results, with at least comparable decreases in HbA1c and a few trials reporting a significantly greater decrease in HbA1c when compared to regular insulin in patients with T1DM and T2DM *(Dailey et al 2004, Fullerton et al 2016, Garg et al 2005, Rayman et al 2007).*
- The rapid-acting analogs have demonstrated a more favorable post-prandial glycemic profile compared to regular insulin in patients with T1DM or T2DM *(Anderson et al 1997a, Chen et al 2006, Dailey et al 2004, Raskin et al 2000, Vignati et al 1997).* Most trials reported comparable rates of hypoglycemia between rapid-acting insulin analogs and regular insulin *(Anderson et al 1997b, Bretzel et al 2004, Chen et al 2006, Colquitt et al 2003, Dailey et al 2004, Fairchild et al 2000, Garg et al 2005, Home et al 2006, McSorley et al 2002, Mortensen et al 2006, Plank et al 2005, Raskin et al 2000, Vignati et al 1997).* One large trial of patients with T1DM reported a 12% lower incidence of hypoglycemia with insulin lispro compared to regular insulin ($p < 0.001$) *(Anderson et al 1997a).* In another trial, a significantly lower frequency of nocturnal hypoglycemia was reported in patients with T2DM patients with insulin glulisine compared to regular insulin (9.1% vs 14.5%; $p = 0.029$) *(Rayman et al 2007).*
- Afrezza was evaluated in both T1DM and T2DM patients; in a 24-week open-label (OL), active-controlled (AC), non-inferiority trial, patients with T1DM on basal insulin were randomized to receive prandial Afrezza or insulin aspart. Afrezza met the prespecified non-inferiority margin of 0.4% reduction of HbA1c from baseline, but reductions were

significantly less with Afrezza compared to insulin aspart and fewer Afrezza patients achieved a HbA1c target of < 7% *(Bode et al 2015).* T2DM patients inadequately controlled on oral antidiabetic agents (OADs) were randomized to receive Afrezza or placebo in a double-blind (DB) trial. At week 24, treatment with Afrezza provided a statistically significantly greater mean reduction in HbA1c than placebo *(Rosenstock et al 2015[a]).*

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

Long-Acting Insulins

- While not consistently demonstrated, data suggest that long-acting insulin analogs are superior to isophane (NPH) insulin in decreasing HbA1c, as well as the incidence of hypoglycemia in patients with T1DM and T2DM as demonstrated by the results of several active-comparator trials and meta-analyses *(Bartley et al 2008, Bazzano et al 2008, Buse et al 2009, Chase et al 2008, De Leeuw et al 2005, Fritsche et al 2003, Garber et al 2007, Haak et al 2005, Heller et al 2009, Hermansen et al 2004, Hermansen et al 2006, Home et al 2004, Horvath et al 2007, Kølendorf et al 2006, Lee et al 2012, Montañana et al 2008, Pan et al 2007, Pieber et al 2005, Philis-Tsimikas et al 2006, Raslová et al 2007, Ratner et al 2000, Riddle et al 2003, Robertson et al 2007, Rosenstock et al 2005, Russell-Jones et al 2004, Siegmund et al 2007, Standl et al 2004, Tan et al 2004, Tricco et al 2014, Vague et al 2003, Yenigun et al 2009, Yki-Järvinen et al 2000, Yki-Järvinen et al 2006).*
- The safety and efficacy of the long-acting analog Toujeo (insulin glargine U-300) have been compared to that of Lantus (insulin glargine U-100) in OL, randomized, active-controlled, parallel studies of up to 26 weeks in patients with T1DM and T2DM. The reductions in HbA1c and fasting plasma glucose with Toujeo were found to be similar to that of Lantus *(Bolli et al 2015, Home et al 2015, Riddle et al 2014[b], Yki-Järvinen et al 2014).*
- Tresiba (insulin degludec) was evaluated in more than 5,600 T1DM and T2DM patients throughout 9 pivotal studies and 5 extension studies (BEGIN clinical program).
  - In 8 of the pivotal trials, Tresiba was non-inferior to Lantus (insulin glargine U-100) or Levemir (insulin detemir) in lowering HbA1c from baseline, with similar rates of hypoglycemia; in 5 trials, the rate of nocturnal hypoglycemia was significantly lower with Tresiba compared to Lantus or Levemir *(Davies et al 2014, Garber et al 2012, Gough et al 2013, Heller et al 2012, Mathieu et al 2013, Meneghini et al 2013[a], Onishi et al 2013, Zinman et al 2012).* It is noteworthy that 2 of the 8 Tresiba trials resulted in a nominally lower reduction in HbA1c for Tresiba compared to the active comparator basal insulin agents *(Davies et al 2014, Heller et al 2012).* The HbA1c and hypoglycemia trends were also observed in the published extension trials *(Bode et al 2013, Davies et al 2016, Hollander et al 2015, Rodbard et al 2013).* In the ninth pivotal trial, Tresiba lowered HbA1c significantly more than oral sitagliptin 100 mg once daily in patients with T2DM who were receiving 1 or 2 concomitant background OAD agents (treatment difference, -0.43; 95% CI, -0.61 to -0.24; p < 0.001), but there were significantly more episodes of overall confirmed hypoglycemia (p < 0.0001) *(Philis-Tsimikas et al 2013).*

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

- The efficacy of Tresiba vs. Lantus in reducing the rate of symptomatic hypoglycemic episodes in patients with T1DM and T2DM was examined in the SWITCH 1 and SWITCH 2 trials, respectively. These 65-week, DB, crossover trials enrolled patients with hypoglycemia risk factors to receive Tresiba or Lantus. In both trials, Tresiba was found to cause fewer symptomatic hypoglycemic episodes (SWITCH 1: estimated rate ratio [ERR], 0.89; $p < 0.001$; SWITCH 2: ERR, 0.70; $p < 0.001$) and nocturnal hypoglycemic episodes (SWITCH 1: ERR, 0.64; $p < 0.001$; SWITCH 2: ERR, 0.58; $p < 0.001$) during the maintenance period than Lantus *(Lane et al 2017, Wysham et al 2017)*.
- Additionally, Tresiba was evaluated for safety and efficacy in pediatric patients (ages 1 to 17) (N = 350) with T1DM in a 26-week, randomized, OL trial. Tresiba was non-inferior to Lantus with a difference in HbA1c reduction from baseline of 0.15% (95% CI, -0.03 to 0.33%) between the groups (pre-specified non-inferiority margin, 0.4%) *(Tresiba prescribing information 2016).*
- The safety and efficacy of Basaglar (insulin glargine U-100) compared to Lantus (insulin glargine U-100) were evaluated in 2 pivotal studies enrolling 534 and 744 patients with T1DM (ELEMENT 1 trial) and T2DM (ELEMENT 2 trial), respectively. Both trials were multicenter, parallel group, randomized controlled trials (RCTs); ELEMENT 1 was OL and ELEMENT 2 was DB. Both trials were conducted over 24 weeks; however, ELEMENT 1 also included a 28-week comparative safety extension period. Mealtime insulin lispro was administered 3 times daily in both groups within the ELEMENT 1 trial. OAD medication was permitted in conjunction with insulin treatment within the ELEMENT 2 trial. The primary efficacy endpoint tested the non-inferiority of agents by the reduction in HbA1c from baseline to 24 weeks. In both ELEMENT 1 and ELEMENT 2, Basaglar and Lantus had similar and significant ($p < 0.001$) within-group decreases in HbA1c values from baseline. Basaglar met non-inferiority criteria compared to Lantus for change in HbA1c from baseline to 24 weeks in both trials (ELEMENT 1: -0.35% vs -0.46%, respectively; least squares mean difference [LSMD], 0.108%; 95% CI, -0.002 to 0.219; $p > 0.05$; ELEMENT 2: -1.29% vs -1.34%, respectively; LSMD, 0.052%; 95% CI, -0.07 to 0.175; $p > 0.05$). There were no statistically significant differences between treatment groups for the rate of each category of hypoglycemia (total, nocturnal, severe) at 24 or 52 weeks in ELEMENT 1 and at 24 weeks in ELEMENT 2 ($p > 0.05$ for all treatment comparisons). No significant differences between treatment groups were seen for change from baseline in body weight (ELEMENT 1, week 24 and 52: both $p > 0.05$; ELEMENT 2, week 24: $p > 0.05$) *(Blevins et al 2015, Rosenstock et al 2015[b]).*
- At this time, there is a lack of substantial head-to-head data demonstrating the superiority of one long-acting insulin analog over another. When comparing the long-acting insulin analogs head-to-head, several trials have demonstrated non-inferiority among the products when used in the management of T1DM and as add-on therapy in patients with T2DM *(Heller et al 2009, Hollander et al 2008, Pieber et al 2007, Raskin et al 2009, Rosenstock et al 2008, Swinnen et al 2010).*
  - In one head-to-head trial of Lantus and metformin vs Levemir and metformin, Lantus had greater HbA1c lowering, but Levemir demonstrated less weight gain and hypoglycemia *(Meneghini et al 2013[b]).*
  - A 2011 Cochrane review (included 4 trials; N = 2250) concluded that Lantus and Levemir are equally effective in achieving and maintaining glycemic control (HbA1c). The review also found no differences in overall, nocturnal, and severe hypoglycemic events *(Swinnen et al 2011).*
  - To further inform the differences between basal insulin agents, a network meta-analysis (included 41 trials, of which 25 trials included patients on basal-oral therapy; N = 15,746) evaluated the safety and efficacy of Toujeo (insulin glargine U-300) vs other basal insulin therapies in the treatment of T2DM. The authors found that the change in

HbA1c was comparable between Toujeo and Levemir (difference, -0.08; 95% credible interval [CrI], -0.4 to 0.24) and Tresiba (difference, -0.12; CrI, -0.42 to 0.2). Additionally, there were no differences in nocturnal or documented symptomatic hypoglycemic events *(Freemantle et al 2016).*

Combination Insulins

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

Other Evidence

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

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

- A 2017 systematic review and meta-analysis evaluated the efficacy and safety of insulin degludec/liraglutide vs insulin glargine/lixisenatide treatment in T2DM (*Cai 2017*). The analysis included 8 trials. The absolute HbA1c change relative to baseline with insulin glargine/lixisenatide was -1.50% and -1.89% with insulin degludec/liraglutide; comparisons between the groups revealed no significant differences. Additionally, there was no significant difference between the groups with regard to body weight changes.

Soliqua (insulin glargine/lixisenatide)

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

glargine/lixisenatide and insulin glargine; however, fewer lixisenatide-treated patients experienced documented symptomatic hypoglycemic events compared to insulin glargine/lixisenatide (6.4% vs 25.6%, respectively) *(Aroda et al 2016, Rosenstock et al 2016, FDA summary review [Soliqua] 2016).*

Xultophy (insulin degludec/liraglutide)

- The efficacy and safety of insulin degludec/liraglutide were evaluated over 26 weeks in 9 Phase 3, parallel-group, AC, RCTs, titled the DUAL trials *(Xultophy dossier 2016).* Currently, results from DUAL I through VII are available, and DUAL VIII and IX trials are ongoing; therefore, these trials will not be discussed. The DUAL I, IV, VI, and VII trials were conducted in patients uncontrolled while administered OADs, and since insulin degludec/liraglutide is not FDA-approved for use in patients previously uncontrolled on OADs, these trials have been excluded from this review:
  - T2DM patients uncontrolled on basal insulin and OADs:
    - The DUAL II trial was a 2-treatment arm, DB study in 413 T2DM patients that compared insulin degludec/liraglutide (n = 207) to insulin degludec (n = 206). Prior to randomization, uncontrolled patients were receiving basal insulin (20 to 40 U) and metformin ± OADs. The maximum dose of insulin degludec allowed in the trial was 50 U, and the maximum allowed dose of liraglutide was 1.8 mg. HbA1c reduction from baseline after 26 weeks of treatment, the primary endpoint, was 1.9% for insulin degludec/liraglutide and 0.9% for insulin degludec. The estimated treatment difference (ETD) for HbA1c statistically favored combination injectable therapy over monotherapy (ETD, −1.1%; 95% CI, −1.3 to −0.8; p < 0.0001) *(Buse et al 2014).*
    - The DUAL V trial was a 2-treatment arm, OL, non-inferiority study in 557 T2DM patients that compared insulin degludec/liraglutide (n = 278) to insulin glargine (n = 279) and metformin. Prior to randomization, uncontrolled patients were receiving insulin glargine (20 to 50 U) and metformin. The trial maximum dose of insulin degludec/liraglutide was 50 U of insulin degludec and 1.8 mg of liraglutide; there was no maximum dose for insulin glargine. For the primary endpoint, an upper bound of the 95% CI < 0.3% was required for non-inferiority, which was achieved. The HbA1c reduction from baseline after 26 weeks of treatment was -1.8% for insulin degludec/liraglutide and -1.1% for insulin glargine. The ETD for HbA1c statistically favored combination injectable therapy over monotherapy (ETD, −0.59%; 95% CI, −0.74 to −0.45; p < 0.001 for non-inferiority) *(Lingvay et al 2016).*
  - T2DM patients uncontrolled on GLP-1 receptor agonists:
    - The DUAL III trial was a 2-treatment arm, OL study in 438 T2DM patients that compared insulin degludec/liraglutide (n = 292) to the currently administered maximum dose of GLP-1 receptor agonist (n = 146) and metformin ± OAD therapy. Prior to randomization, patients were receiving maximum doses of liraglutide once daily or exenatide twice daily, according to the local labeling, and metformin ± OADs. The trial maximum dose of insulin degludec/liraglutide was 50 U of insulin degludec and 1.8 mg of liraglutide. HbA1c reduction from baseline after 26 weeks of treatment, the primary endpoint, was 1.4% for insulin degludec/liraglutide and 0.3% for unchanged doses of GLP-1 receptor agonists. The ETD for HbA1c statistically favored combination injectable therapy over monotherapy (ETD, −0.94%; 95% CI, −1.1 to −0.8; p < 0.001) *(Linjawi et al 2017).*
  - Weight and hypoglycemic events: Treatment with insulin degludec/liraglutide was associated with mean weight losses of up to 2.7 kg and weight gain of 2 kg from baseline across the aforementioned trials. Hypoglycemia rates with insulin degludec/liraglutide were comparable to insulin degludec. However, compared to GLP-1 receptor agonists, the estimated rate ratio (ERR) was 25.36 (95% CI, 10.63 to 60.51; p < 0.001), demonstrating a statistically significantly higher rate of hypoglycemic episodes in the insulin degludec/liraglutide group vs the GLP-1 receptor agonist group. Conversely, the ERR favored insulin degludec/liraglutide over insulin glargine with a statistically significantly higher rate of hypoglycemic episodes in the insulin glargine group (ERR, 0.43; 95% CI, 0.3 to 0.61; p < 0.001) *(Buse et al 2014, Lingvay et al 2016, Linjawi et al 2017, Xultophy dossier 2016).*

Cardiovascular (CV) outcomes

- A number of key CV studies have been conducted with insulin glargine, insulin degludec, liraglutide, and lixisenatide; of these, only liraglutide has demonstrated CV-positive outcomes. Studies with adequate power have not been conducted with the long-acting insulin and GLP-1 receptor agonist combination products.
  - The ORIGIN trial was a randomized trial without blinding conducted in 12,612 patients with CV risk factors plus impaired fasting glucose, impaired glucose tolerance, or T2DM. Patients were randomized to receive insulin glargine or standard of care therapy, which included continuing their pre-existing glycemic control regimen. CV risk factors at baseline included previous MI, stroke, angina, or revascularization. After a median 6.2 year follow-up, no significant difference in the co-primary outcomes of nonfatal MI, nonfatal stroke, or death from CV causes, and these events plus

revascularization or hospitalization for heart failure (HF), were observed. The rates of incident CV outcomes were similar in the insulin glargine and standard care groups: 2.94 and 2.85 per 100 person-years, respectively, for the first co-primary outcome (HR, 1.02; 95% CI, 0.94 to 1.11; p = 0.63) and 5.52 and 5.28 per 100 person-years, respectively, for the second co-primary outcome (HR, 1.04; 95% CI, 0.97 to 1.11; p = 0.27) *(Gerstein et al 2012).*

- ELIXA, a multi-center (MC), DB, randomized, placebo-controlled (PC) trial (N = 6068) was conducted to evaluate the long-term effects of lixisenatide vs placebo on CV outcomes in patients with T2DM who had a recent acute coronary syndrome event within 180 days of screening. The primary endpoint was a composite of the first occurrence of any of the following: death from CV causes, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina. The median follow-up was 25 months. It was found that the primary endpoint event occurred in 13.4% of patients in the lixisenatide group and 13.2% in the placebo group (HR, 1.02; 95% CI, 0.89 to 1.17), which demonstrated non-inferiority of lixisenatide to placebo (p < 0.001), but did not demonstrate superiority (p = 0.81). The rates of the individual CV components of the primary endpoint were similar between the lixisenatide and placebo groups *(Pfeffer et al 2015)*.
- LEADER, a MC, DB, randomized, PC trial (N = 9340) was conducted to evaluate the long-term effects of liraglutide vs placebo on CV outcomes in patients with T2DM and high CV risk. The median follow-up was 3.8 years. It was found that the primary composite outcome (CV death, nonfatal MI, or nonfatal stroke) occurred in fewer patients in the liraglutide group (13%) vs the placebo group (14.9%) (HR, 0.87; 95% CI, 0.78 to 0.97; p < 0.001 for noninferiority; p = 0.01 for superiority). Mortality from CV causes was lower in the liraglutide group (4.7%) vs the placebo group (6%) (HR, 0.78; 95% CI, 0.66 to 0.93; p = 0.007). Additionally, the rate of death from any cause was lower in the liraglutide group (8.2%) vs the placebo group (9.6%) (HR, 0.85; 95% CI, 0.74 to 0.97; p = 0.02).The rates of nonfatal MI, nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group *(Marso et al 2016).*

CLINICAL GUIDELINES

- Insulin is the mainstay of therapy for patients with T1DM. Current guidelines recommend that most people with T1DM be treated with multiple daily injections (3 to 4 injections per day of basal and prandial insulin) or continuous subcutaneous insulin infusion. In addition, the guidelines suggest that most people with T1DM should use insulin analogs to reduce hypoglycemia risk. Rapid-acting inhaled insulin used before meals in T1DM patients leads to inferior HbA1c lowering when compared with insulin aspart, but with less hypoglycemia across all HbA1c target categories *(ADA 2018, Handelsman et al 2015).*
- According to current clinical guidelines regarding the management of T2DM, consideration should be given to initiating insulin therapy (with or without other agents) at the outset of treatment in newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or HbA1c. Furthermore, due to the progressive nature of T2DM, 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 2018, Garber et al 2018, Handelsman et al 2015, Inzucchi et al 2015).*
- Guidelines suggest that an insulin treatment program be designed specifically for an individual patient, to match the supply of insulin to his or her dietary/exercise habits and prevailing glucose trends, as revealed through self-monitoring. Anticipated glucose-lowering effects should be balanced with the convenience of the regimen in the context of an individual's specific therapy goals *(ADA 2018, Garber et al 2018, Handelsman et al 2015, Inzucchi et al 2015).*
  - The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACA) T2DM management algorithm identifies lifestyle therapies such as weight loss, comprehensive management of lipids and blood pressure, safety, and simplicity as crucial factors of a T2DM regimen. The guideline suggests basal (long-acting) insulin for patients unable to achieve their glycemic goals with multiple glycemic control agents, or for those who are symptomatic with an entry HbA1c > 9.0%. Basal insulin titration should occur every 2 to 3 days as needed. If an intensified regimen is needed, prandial control with the addition of a GLP-1 agonist, SGLT2 inhibitor, or prandial (rapid-acting) insulin prior to meals should be considered *(Garber et al 2018).*
    - The guideline also states that newer basal insulin formulations (glargine U-300, and degludec U-100 and U-200) have more prolonged and stable pharmacokinetic and pharmacodynamic characteristics than glargine U-100 and detemir. RCTs have reported equivalent glycemic control and lower rates of severe or confirmed hypoglycemia, particularly nocturnal hypoglycemia, compared to glargine U-100 and detemir insulin; however, no recommendation for specific insulin products is given.
  - The ADA Standards of Medical Care in Diabetes offers similar emphasis on lifestyle modifications and CV disease risk management. The ADA guideline states that insulin therapy (with or without additional agents) should be initiated

in patients with newly diagnosed T2DM who are symptomatic and/or have a HbA1c ≥ 10% and/or blood glucose ≥ 300 mg/dL. For patients with T2DM who are not achieving glycemic goals, drug intensification, including consideration of insulin therapy, should not be delayed. No recommendation for specific insulin products is given; insulin products should be chosen based on safety, convenience, and patient cost considerations *(ADA 2018).*

- According to the AACE/ACE guideline, patients whose basal insulin regimens fail to provide glucose control may benefit from the addition of a GLP-1 receptor agonist, SGLT2 inhibitor, or DPP-4 inhibitor. (*Garber et al 2018*). The combination of basal insulin with a GLP-1 receptor agonist may offer greater efficacy than the oral agents.

SAFETY SUMMARY

Insulins

- Contraindications:
  - Insulins are contraindicated during episodes of hypoglycemia and with hypersensitivity to any ingredient of the product.
  - In addition, Afrezza is also contraindicated in patients with chronic lung disease, such as asthma or chronic obstructive pulmonary disease (COPD), because of the risk of acute bronchospasm.
- Boxed Warnings:
  - Afrezza has a Boxed Warning for the risk of acute bronchospasm in patients with chronic lung disease. Before initiating Afrezza, a detailed medical history, physical examination, and spirometry should be performed to identify potential lung disease in all patients.
- Warnings/Precautions:
  - Insulin pens must never be shared between patients, even if the needle is changed. Patients using insulin vials must never reuse or share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.
  - Frequent glucose monitoring and insulin dose reduction may be required in patients with renal or hepatic impairment.
  - All insulins can cause hypokalemia, which if untreated, may result in respiratory paralysis, ventricular arrhythmia, and death.
  - Long-term use of insulin can cause lipodystrophy at the site of repeated insulin injections.
  - Accidental mix-ups between basal insulin products and other insulins, particularly rapid-acting insulins, have been reported. To avoid medication errors, patients should be instructed to always check the insulin label before each injection.
  - Administration of Humulin R U-500 in syringes other that U-500 insulin syringes has resulted in dosing errors. Patients should be prescribed U-500 syringes for use with Humulin R U-500 vials. The prescribed dose should always be expressed in units of insulin.
  - Afrezza has additional respiratory-related warnings and precautions associated with its use including acute bronchospasm in patients with chronic lung disease, decline in pulmonary function, and lung cancer.
- Adverse Events (AEs):
  - Hypoglycemia is the most commonly observed AE. Hypoglycemia can impair concentration ability and reaction time which may place an individual and others at risk in situations where these abilities are important. Severe hypoglycemia can cause seizures, may be life-threatening, or cause death. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia.
  - Weight gain, sodium retention and edema, and injection site reactions can occur.
  - Additional AEs observed with the inhaled insulin, Afrezza, include cough, throat pain or irritation, headache, diarrhea, productive cough, fatigue, nausea, decreased pulmonary function test, bronchitis, and urinary tract infection.
- Drug Interactons:
  - β-blockers, clonidine, guanethidine, and reserpine may mask hypoglycemic reactions.
  - Thiazolidinediones can cause dose-related fluid retention, particularly when used in combination with insulin.
  - Refer to the prescribing information for all drugs that can increase or reduce the glucose-lowering ability of insulin.
- Risk Evaluation and Mitigation Strategy (REMS)
  - The FDA requires a communication plan to inform health care professionals about the serious risk of acute bronchospasm associated with Afrezza.

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

- Contraindications:

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

- Warnings/Precautions:
  - Warnings and precautions are consistent with each individual agent and include pancreatitis, serious hypersensitivity reactions/allergic reactions, hypoglycemia or hyperglycemia, the potential for overdose due to medication errors, acute kidney injury, hypokalemia, the potential for fluid retention and heart failure with use of thiazolidinediones, and the lack of clinical studies showing macrovascular risk reduction. Prefilled pens should never be shared between patients (even if the needle is changed) due to the risk of transmission of blood-borne pathogens.
  - Additional warnings and precautions for Soliqua include immunogenicity risks associated with the development of antibodies to insulin glargine and lixisenatide resulting in a loss of glycemic control.
- AEs:
  - The most common AEs reported with these agents include nausea, nasopharyngitis, diarrhea, headache, and upper respiratory tract infection.
  - Additional common AEs include hypoglycemia and allergic reactions with Soliqua and increased lipase with Xultophy.
- Drug Interactions:
  - The GLP-1 receptor agonist components may cause delayed gastric emptying of oral medications. Certain medications may require administration 1 hour before (ie, antibiotics, acetaminophen, oral contraceptives, or other medications dependent on threshold concentrations for efficacy) or 11 hours after (ie, oral contraceptives) administration of the GLP-1 receptor agonist.
  - Monitor use closely when administered concomitantly with other medications that may affect glucose metabolism.
  - Antiadrenergic medications (ie, beta blockers, clonidine, guanethidine, and reserpine) may mask the signs and symptoms of hypoglycemia.
- REMS programs:
  - As with other liraglutide-containing products, there is a REMS program for Xultophy, which includes a communication plan for alerting healthcare professionals about the risk of acute pancreatitis (including necrotizing pancreatitis) and the potential risk of MTC *(REMS@FDA 2018).*
- Lixisenatide and liraglutide slow gastric emptying. Patients with gastroparesis were excluded from trials; therefore, agents are generally not recommended in cases of severe gastroparesis.

DOSING AND ADMINISTRATION

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

Table 4. Dosing and Administration

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

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
				dysfunction have not been established.
Apidra (insulin glulisine)	100 U/mL: SoloStar pen, vial	SC	Administer within 15 minutes before a meal or within 20 minutes after starting a meal. Dose and frequency are individualized per patient needs. Use in a regimen with intermediate- or long-acting insulin.	Safety and efficacy in children < 4 years with T1DM or in children with T2DM have not been established.
Fiasp (insulin aspart)	100 U/mL: FlexTouch, vial	SC, IV	Administer at the start of a meal or within 20 minutes after starting a meal. Use in a regimen with intermediate- or long-acting insulin.	Safety and efficacy have not been established in children.
Humalog (insulin lispro)	100 U/mL: Cartridge, KwikPen, Junior KwikPen, vial 200 U/mL: KwikPen	SC, IV (U-100 only)	Administer within 15 minutes before a meal or immediately after a meal. Use in a regimen with intermediate- or long-acting insulin.	Safety and efficacy in children < 3 years with T1DM and in children with T2DM have not been established.
Novolog (insulin aspart)	100 U/mL: Cartridge (PenFill), FlexPen, Vial	SC, IV	Novolog: Should be injected immediately (within 5 to 10 minutes) before a meal. Use in a regimen with intermediate- or long-acting insulin.	Safety and efficacy in children < 2 years with T1DM and in children with T2DM have not been established.
Short-Acting Insulins				
Humulin R (insulin, regular, human recombinant)	100 U/mL: Vial 500 U/mL KwikPen, vial	SC, IV (U-100 only)	When given SC, generally given 3 or more times daily before meals (within 30 minutes). U-500: Generally given 2 to 3 times daily before meals. Often used concomitantly with intermediate- or long-acting insulin.	U-500: safety and efficacy in children have not been established. Dose conversion should not be performed when using the U-500 KwikPen or a U-500 insulin syringe. Only a U-500 insulin syringe should be used with the Humulin U-500 vial.

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
Novolin R Novolin R ReliOn (insulin, regular, human recombinant)	100 U/mL: Vial	SC, IV	Administration should be followed by a meal within 30 minutes of administration. Often used in combination with intermediate- or long-acting insulin.	Safety and efficacy in children < 2 years with T1DM or in children with T2DM have not been established. Use in pumps is not recommended due to risk of precipitation.
Intermediate-Acting Insulins				
Humulin N (insulin, NPH, human recombinant isophane)	100 U/mL: KwikPen, vial	SC	Generally given in 1 to 2 injections per day 30 to 60 minutes before a meal or bedtime.	Safety and efficacy in children have not been established.
Novolin N Novolin N ReliOn (insulin, NPH, human recombinant isophane)	100 U/mL: Vial	SC	Generally given in 1 to 2 injections per day 30 to 60 minutes before a meal or bedtime.	
Long-Acting Insulins				
Basaglar (insulin glargine)	100 U/mL: KwikPen	SC	Daily May be administered at any time of day, but at same time every day.	Safety and efficacy in children < 6 years with T1DM and in children with T2DM have not been established.
Lantus (insulin glargine)	100 U/mL: SoloStar pen, vial	SC	Daily May be administered at any time of day, but at same time every day.	Safety and efficacy in children < 6 years with T1DM and in children with T2DM have not been established.
Levemir (insulin detemir)	100 U/mL: FlexTouch pen, vial	SC	Daily to twice daily 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.	Safety and efficacy in children < 2 years with T1DM and in children with T2DM have not been established.
Toujeo (insulin glargine U-300)	300 U/mL: SoloStar pen	SC	Daily Administer at the same time each day.	Safety and efficacy in children have not been established. To minimize the risk of hypoglycemia, the dose of Toujeo should be titrated no more frequently than every 3 to 4 days.
Tresiba (insulin degludec)	100 U/mL: FlexTouch pen	SC	Daily	Safety and efficacy in children < 1 year have not been

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
	200 U/mL: FlexTouch pen		May be administered at any time of day.	established (use in children ≥ 1 year with T2DM is supported by evidence from adult T2DM studies). The recommended number of days between dose increases is 3 to 4 days.
Combination Insulins, Rapid-Acting and Intermediate-Acting				
Humalog Mix 50/50 Humalog Mix 75/25 (insulin lispro protamine/insulin lispro)	100 U/mL: KwikPen, vial	SC	Administer within 15 minutes before meals.	Safety and efficacy in children have not been established.
Novolog Mix 70/30 (insulin aspart protamine/insulin aspart)	100 U/mL: FlexPen, vial	SC	Twice daily T1DM: administer within 15 minutes before meals T2DM: administer within 15 minutes before or after meal	
Combination Insulins, Short-Acting and Intermediate-Acting				
Humulin 70/30 (NPH, human insulin isophane/regular human insulin)	100 U/mL: KwikPen, vial	SC	Twice daily 30 to 45 minutes before a meal	Safety and efficacy in children have not been established.
Novolin 70/30 Novolin 70/30 ReliOn (NPH, human insulin isophane/regular human insulin)	100 U/mL: Vial	SC	Twice daily 30 to 60 minutes before a meal	
Combination Products, Long-Acting Insulin and GLP-1 Receptor Agonist				
Soliqua 100/33 (insulin glargine/lixisenatide)	Injection (prefilled pen)	SC	Once daily	For patients who require daily doses below 15 U or over 60 U, an alternative antidiabetic agent should be prescribed. Not recommended for use in end-stage renal disease (ESRD). Frequent BG monitoring and dose adjustment may be necessary in hepatic impairment.
Xultophy 100/3.6 (insulin degludec/liraglutide)	Injection (prefilled pen)	SC	Once daily	For patients who require daily doses below 16 U or over 50 U, an alternative antidiabetic agent should be prescribed.

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
				Has not been studied in patients with renal or hepatic impairment.

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

(Clinical Pharmacology, 2018)

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

CONCLUSION

Insulins

- The insulin products are approved for use in the management of both T1DM and T2DM. The primary differences between commercially available insulin products revolve around pharmacodynamic and pharmacokinetic properties, particularly onset and duration of action.
- Individual insulin products are classified by their onset and duration of actions and may fall into one of four categories: rapid-, short-, intermediate-, or long-acting insulins. Insulin therapy is usually administered by 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 suggest that long-acting insulin analogs are superior to NPH in decreasing HbA1c and are associated with a lower incidence of hypoglycemic events. Furthermore, head-to-head data 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 T1DM. Current guidelines recommend that most people with T1DM be treated with multiple daily injections (3 to 4 injections per day of basal and prandial insulin) or continuous subcutaneous insulin infusion. In addition, the guidelines suggest that most people with T1DM should use insulin analogs to reduce hypoglycemia risk. Rapid-acting inhaled insulin used before meals in T1DM patients leads to inferior HbA1c lowering when compared with insulin aspart, but with less hypoglycemia across all HbA1c target categories *(ADA 2018, Handelsman et al 2015).*
- According to current clinical guidelines regarding the management of T2DM, consideration should be given to initiating insulin therapy (with or without other agents) at the outset of treatment in newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or HbA1c. Furthermore, due to the progressive nature of T2DM, 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 2018, Garber et al 2018, Handelsman et al 2015, Inzucchi et al 2015).*
- Guidelines suggest that an insulin treatment program be designed specifically for an individual patient, to match the supply of insulin to his or her dietary/exercise habits and prevailing glucose trends, as revealed through self-monitoring. Anticipated glucose-lowering effects should be balanced with the convenience of the regimen in the context of an individual's specific therapy goals *(ADA, 2018, Garber et al 2018, 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.

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

- Insulin glargine/lixisenatide (Soliqua) and insulin degludec/liraglutide (Xultophy) are long-acting insulin and incretin-based antidiabetic combination therapies that are FDA-approved as adjunctive therapy to diet and exercise in adult

T2DM patients who are uncontrolled on a basal insulin or lixisenatide and liraglutide, respectively. The indication for both agents has dose limitations: Xultophy is indicated for patients uncontrolled on < 50 U daily of a basal insulin or ≤ 1.8 mg daily of liraglutide, and Soliqua is indicated for patients uncontrolled on < 60 U daily of a basal insulin. Neither agent is FDA-approved for use in T2DM patients who are uncontrolled on OADs.

- The medications are administered through a fixed ratio pen. Soliqua may be administered in doses of 15 to 60 U of insulin glargine and 5 to 20 mcg of lixisenatide, while Xultophy may be administered in doses of 10 to 50 U of insulin degludec and 0.36 to 1.3 mcg of liraglutide SC once daily depending on prior treatment and dosages. Individualized dosing is recommended based on metabolic needs, blood glucose monitoring, glycemic control, type of diabetes, and prior insulin use of the patient.
- These agents have been studied in combination with metformin, sulfonylureas, pioglitazone, and meglitinides. In studies, Soliqua demonstrated HbA1c reductions ranging from 0.3 to 0.5% vs insulin glargine and 0.8% vs lixisenatide. Xultophy demonstrated estimated treatment differences in HbA1c reductions of 1% vs insulin degludec monotherapy, 0.6% vs insulin glargine monotherapy, and 0.9% vs a GLP-1 receptor agonist (eg, liraglutide or exenatide twice daily). Across trials, Xultophy and Soliqua were associated with both weight losses and gains. Hypoglycemia rates are mostly similar to those observed within the basal insulin monotherapy arms; however, the GLP-1 receptor agonists were associated with less hypoglycemic events *(Aroda et al 2016, Buse et al 2014, FDA summary review [Soliqua] 2016, Lingvay et al 2016, Linjawi et al 2017, Rosenstock et al 2016).* Several CV outcomes trials have been conducted in patients with T2DM who were administered basal insulin monotherapy or GLP-1 receptor agonist monotherapy. Of these trials, the only trial which demonstrated a reduced CV risk was the LEADER trial, which compared liraglutide to placebo *(Gerstein et al 2012, Marso et al 2016, Marso et al 2017, Pfeffer et al 2015).*
- Overall, the safety profiles of these agents are similar. A few differences are that Xultophy has a boxed warning regarding the risk of thyroid C-cell tumors and is contraindicated in patients with a history of MTC or MEN 2. There is also a REMS program for Xultophy, which includes a communication plan for alerting healthcare professionals about the risk of acute pancreatitis and the potential risk of MTC. Other key warnings for these products include increased risks of pancreatitis, hypoglycemia or hyperglycemia, the potential for overdose due to medication errors, acute kidney injury, hypokalemia, and the potential for fluid retention and heart failure with use of thiazolidinediones. Soliqua has an additional warning and precaution regarding immunogenicity risks associated with the development of antibodies which may result in the loss of glycemic control. Common AEs include gastrointestinal effects (eg, nausea, diarrhea, etc), nasopharyngitis, headache, and upper respiratory tract infection.

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Therapeutic Class Overview
Incretin Mimetics & Amylinomimetics

INTRODUCTION

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

Table 1. Medications Included Within Class Review

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

*On July 26, 2017, the manufacturer announced plans to discontinue the manufacturing and sale of Tanzeum by July 2018 due to business reasons (*Tanzeum Discontinuation FAQ 2017*).

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

INDICATIONS

Table 2. FDA Approved Indications

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

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

(Prescribing information: *Adlyxin 2016*, *Bydureon 2017, Bydureon BCise 2017, Byetta 2015, Ozempic 2017, Symlin 2016, Tanzeum 2017, Trulicity 2017, Victoza 2017*)

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

CLINICAL EFFICACY SUMMARY

Albiglutide

- The approval of albiglutide was based on 8 pivotal trials involving over 5000 patients as a part of the HARMONY phase 3 program (*Tanzeum FDA Medical Review 2014*, *Tanzeum Prescribing Information 2017*). The majority of the trials were multicenter (MC), randomized, double-blind (DB), placebo-controlled (PC) or active control (AC) studies in adult patients with inadequately controlled T2DM (HbA1c 7% to 10%); however, 3 trials were open-label (OL). The primary outcome in each trial was change in HbA1c from baseline at 26 to 104 weeks.
  - HARMONY 1 demonstrated that albiglutide 30 mg once weekly was superior to placebo in patients taking concurrent pioglitazone with or without metformin at 52 weeks, with a mean reduction in HbA1c of 0.8% (*Reusch et al 2014*).
  - HARMONY 2 compared both albiglutide 30 mg and 50 mg once weekly to placebo in patients treated with diet and exercise alone and found that both were superior to placebo at 52 weeks. The least squares mean difference from placebo in HbA1c was -0.84% with the 30 mg dose and -1.04% with the 50 mg dose (*Nauck et al 2016*).
  - HARMONY 3 demonstrated that albiglutide 30 mg to 50 mg once weekly was superior to placebo, sitagliptin 100 mg once daily, and glimepiride 2 to 4 mg daily in patients taking concurrent metformin at 2 years, with a mean reduction in HbA1c of 0.6% (*Ahrén et al 2014*).
  - HARMONY 4 was an OL trial comparing albiglutide (30 mg to 50 mg once weekly) to protocol-titrated insulin glargine in patients taking concurrent metformin with or without an SFU. In this study, albiglutide demonstrated noninferiority to insulin glargine in HbA1c improvement at 52 weeks (*Weissman et al 2014*).
  - HARMONY 5 compared albiglutide (30 mg to 50 mg once weekly) to placebo and pioglitazone (30 mg to 45 mg per day) in patients taking concurrent metformin and glimepiride. At week 52, albiglutide did not meet the pre-specified noninferiority margin compared to pioglitazone; however, it was superior to placebo and had a mean reduction in HbA1c of 0.6% (*Home et al 2015*).
  - HARMONY 6, another OL trial, demonstrated that albiglutide 30 mg to 50 mg once weekly was noninferior to insulin lispro 3 times daily in patients taking concurrent pioglitazone with or without metformin at 26 weeks, with a mean reduction in HbA1c of 0.8% (*Rosenstock et al 2014a*).
  - HARMONY 7 was an OL study comparing albiglutide 50 mg once weekly to liraglutide 1.8 mg daily in patients taking concomitant metformin, TZD, SFU, or a combination of the medications. At week 32, the mean model adjusted change in HbA1c was -0.78% with albiglutide and -0.99% with liraglutide. Albiglutide failed to meet noninferiority (p = 0.085) (*Pratley et al 2014*).

- HARMONY 8 demonstrated that albiglutide 30 mg to 50 mg was superior to sitagliptin 25 to 100 mg in patients with impaired renal function on concurrent agents or lifestyle treatment at 26 weeks, with a mean reduction in HbA1c of 0.8% compared to a reduction of 0.5% with sitagliptin (*Leiter et al 2014*).

Dulaglutide

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

Exenatide

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

- Exenatide once weekly was also compared to daily insulin glargine in diabetic patients inadequately controlled with OADs. Following 26 weeks of therapy, exenatide was found to be statistically noninferior to insulin glargine for the change in HbA1c from baseline to endpoint (*Inagaki et al 2012*).

Exenatide ER

- Approval of exenatide ER in the management of T2DM was based on the clinical evidence for safety and efficacy derived from the DURATION trials (1 through 5). Exenatide ER was added to existing antidiabetic regimens in 4 of the 5 trials (1, 2, 3, and 5). In contrast, DURATION-4 compared exenatide ER, metformin, pioglitazone, and sitagliptin all as monotherapy (*Bergenstal et al 2010, Blevins et al 2011, Diamant et al 2010, Drucker et al 2008, Russell-Jones et al 2012*).
  - Overall, exenatide ER as add-on therapy to existing antidiabetic regimens significantly decreased HbA1c compared to exenatide ($p < 0.005$), sitagliptin ($p < 0.0001$), pioglitazone ($p = 0.0165$), and insulin therapy ($p = 0.017$), with no increased risk of hypoglycemia. In terms of decreases in body weight, exenatide ER was superior compared to sitagliptin ($p = 0.0002$) and pioglitazone ($p < 0.0001$), and similar compared to exenatide ($p = 0.89$) (*Bergenstal et al 2010, Blevins et al 2011, Drucker et al 2008*).
  - As expected, GI-related adverse events (AEs) were reported more commonly with the incretin-based therapies. When compared to exenatide, exenatide ER was associated with lower incidences of nausea (14.0% vs 35.0%) and vomiting (4.7% vs 8.9%), and higher incidences of diarrhea (9.3% vs 4.1%) and injection site-related AEs (13% vs 10%) (*Blevins et al 2011*).
  - In the DURATION-4 trial, the decrease in HbA1c achieved with exenatide ER monotherapy was superior compared to sitagliptin ($p < 0.001$) and similar compared to metformin ($p = 0.62$) and pioglitazone ($p = 0.328$). Exenatide ER and metformin were similar in terms of associated decreases in body weight, with exenatide ER achieving superiority compared to sitagliptin and pioglitazone. Overall, exenatide ER was associated with more GI-related AEs, with the exception of diarrhea which occurred at the highest frequency in patients receiving metformin (*Diamant et al 2010*).
- In a post-hoc analysis of 4 clinical trials, patients were treated with weekly exenatide for 52 weeks. Patients had significant lowering of HbA1c, blood pressure and low density lipoprotein (LDL) levels without an increase in weight or hypoglycemia (*Bergenstal et al 2013*).
- The DURATION-6 trial compared HbA1c reductions between liraglutide once daily and exenatide once weekly in patients with T2DM previously treated with lifestyle modifications and oral agents. Both therapies resulted in improvements in glycemic control; however, greater reductions were noted with liraglutide (*Buse et al 2013*).
- Bydureon BCise is a new formulation of Bydureon that is administered via an autoinjector device. It was approved based on the results of two 28-week, OL, AC trials. In the DURATION-NEO-1 trial, Bydureon BCise 2 mg once weekly achieved a statistically significant HbA1c reduction vs Byetta 10 mcg twice daily ($p < 0.05$) in patients with T2DM inadequately controlled with diet and exercise alone or with a stable regimen of metformin, an SFU, a TZD, or a combination of any 2 of these agents. In the DURATION-NEO-2 trial, Bydureon BCise 2 mg once weekly achieved a statistically significant HbA1c reduction vs placebo ($p < 0.05$) in patients with T2DM on metformin. The difference vs sitagliptin was -0.28% (95% CI, -0.62% to -0.02%) (*Bydureon BCise Prescribing Information 2017, Gadde et al 2017, Wysham et al 2017)*.

Liraglutide

- Approval of liraglutide in the management of T2DM was based on the clinical evidence for safety and efficacy derived from the LEAD trials (1 through 6). The LEAD trials evaluated liraglutide monotherapy (LEAD-3); add-on therapy to an SFU (LEAD-1), metformin (LEAD-2), metformin plus a TZD (LEAD-4), metformin plus an SFU (LEAD-5); and monotherapy head-to-head with exenatide (LEAD-6).
  - In LEAD-1, liraglutide was compared to placebo or rosiglitazone as add-on therapy to an SFU. After 26 weeks, liraglutide (0.6, 1.2, and 1.8 mg per day) significantly decreased HbA1c compared to placebo ($p < 0.0001$ for all), with only higher doses achieving superiority compared to rosiglitazone ($p < 0.001$ for both) (*Marre et al 2009*).
  - In LEAD-2, liraglutide was compared to placebo and an SFU as add-on therapy to metformin. Liraglutide significantly decreased HbA1c compared to placebo; however, similar decreases were observed with liraglutide compared to the SFU. Liraglutide was associated with significant decreases in body weight compared to placebo ($p < 0.01$) and the SFU ($p < 0.001$) (*Nauck et al 2009*). Results of an 18-month OL extension trial were consistent with the DB study (*Nauck et al 2013*).
  - In LEAD-3, liraglutide was compared to an SFU as monotherapy, and liraglutide was superior in decreasing HbA1c ($p = 0.0014$ and $p < 0.0001$ for liraglutide 1.2 mg and 1.8 mg, respectively). In addition, increases in body weight were reported with the SFU, while liraglutide significantly decreased body weight ($p = 0.027$) (*Garber et al 2009*). In a 1-

year extension trial, patients continuing liraglutide for a total of 2 years maintained significant improvements in HbA1c compared to the SFU (*Garber et al 2011*).
  - In LEAD-4 and LEAD-5, liraglutide was compared to placebo as add-on therapy to metformin plus an SFU and to a TZD. LEAD-5 also had an OL arm of insulin therapy. Results achieved with liraglutide in terms of decreases in HbA1c, body weight, and FPG compared to placebo were similar to those observed in the other LEAD trials (*Russell-Jones et al 2009; Zinman et al 2009*). When compared to insulin therapy, decreases in HbA1c ($p = 0.0015$) and body weight ($p < 0.001$) and improvements in β-cell function ($p = 0.0019$) were significantly greater with liraglutide. It was noted that decreases in PPG were not different between the 2 treatments, and the likelihood of patients achieving FPG goals were also similar (*Russell-Jones et al 2009*).
  - LEAD-6 was a head-to-head trial comparing liraglutide to exenatide as add-on therapy to existing antidiabetic treatment regimens. Liraglutide significantly decreased HbA1c compared to exenatide (1.12% vs 0.79%; $p < 0.0001$), and a significantly greater proportion of patients receiving liraglutide achieved HbA1c goals of < 7%. Significant decreases in FPG were also achieved with liraglutide ($p < 0.0001$); however, exenatide significantly decreased PPG after breakfast and dinner ($p < 0.0001$ and $p = 0.0005$) (*Buse et al 2009*). A 14-week, extension trial revealed that patients who were switched from exenatide to liraglutide achieved additional glycemic control and cardiometabolic benefits (*Buse et al 2010*).

Lixisenatide

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

HbA1c reduction from baseline to week 24. However, lixisenatide provided less HbA1c reduction than exenatide and the difference was statistically significant; the least squares mean difference vs exenatide was 0.17% (p = 0.0175) (*Adlyxin Prescribing Information 2016, Rosenstock et al 2013*).
  - A meta-analysis (MA) of 76-week data from 5 trials in the GetGoal clinical trial program (GetGoal-M, GetGoal-F1, GetGoal-S, GetGoal-P, and GetGoal-L) supported the sustained efficacy and tolerability of lixisenatide (*Broglio et al 2017*).

Semaglutide

- The approval of semaglutide was based on several phase 3 trials as part of the SUSTAIN clinical trial program. Semaglutide was evaluated as monotherapy, in combination with OADs, and in combination with basal insulin. Its efficacy was compared with placebo, sitagliptin, exenatide ER, insulin glargine, and dulaglutide. The primary endpoint, the difference in change in HbA1c from baseline to trial end between the semaglutide and comparator groups, was assessed at varying time points ranging between 30 and 56 weeks.
  - SUSTAIN 1 was a 30-week, PC trial which found that semaglutide 0.5 mg and 1 mg weekly significantly improved HbA1c vs placebo (p < 0.0001) (*Sorli et al 2017)*.
  - SUSTAIN 2 was a 56-week, OL trial that compared semaglutide 0.5 mg and 1 mg weekly to sitagliptin 100 mg daily in patients on metformin and/or TZDs. Compared with sitagliptin, treatment with semaglutide resulted in statistically significant reductions in HbA1c from baseline to week 56. The mean change from baseline was -1.3% for semaglutide 0.5 mg, -1.5% for semaglutide 1 mg, and -0.7% for sitagliptin. The difference vs sitagliptin was -0.6% (p < 0.0001) for semaglutide 0.5 mg and -0.8% (p < 0.0001) for semaglutide 1 mg (*Ahrén et al 2017, Ozempic Prescribing Information 2017*).
  - SUSTAIN 3 was a 56-week, OL trial that compared semaglutide 1 mg to exenatide ER 2 mg once weekly. At week 56, mean change from baseline in HbA1c was -1.4% in the semaglutide group vs -0.9% in the exenatide ER group (difference: -0.5%, p < 0.0001) (*Ahmann et al 2018, Ozempic Prescribing Information 2017*).
  - SUSTAIN 4 was a 30-week OL, AC trial in patients on metformin with or without an SFU that compared semaglutide 0.5 mg and 1 mg to insulin glargine initiated at 10 units once daily. Compared with insulin glargine, treatment with semaglutide resulted in statistically significant reductions in HbA1c from baseline to week 30. The mean change from baseline was -1.2% for semaglutide 0.5 mg, -1.5% for semaglutide 1 mg, and -0.9% for insulin glargine. The difference vs insulin glargine was -0.3% (p < 0.0001) for semaglutide 0.5 mg and -0.6% (p < 0.0001) for semaglutide 1 mg (*Aroda et al 2017*, *Ozempic Prescribing Information 2017*).
  - SUSTAIN 5 was a 30-week, DB, PC trial in patients inadequately controlled with basal insulin, with or without metformin, which found that semaglutide 0.5 mg and 1 mg significantly reduced HbA1c vs placebo (p < 0.0001) (*Ozempic Prescribing Information 2017).*
  - SUSTAIN 7 was a 40-week, OL trial that compared semaglutide to dulaglutide once weekly in patients on metformin monotherapy. From a mean baseline HbA1c of 8.2%, semaglutide 0.5 mg achieved a statistically significant reduction of 1.5% vs a reduction of 1.1% with dulaglutide 0.75 mg at week 40, while semaglutide 1.0 mg achieved a statistically significant reduction of 1.8% vs a reduction of 1.4% with dulaglutide 1.5 mg (both p < 0.0001 for noninferiority and superiority) *(Pratley et al 2018).*

Cardiovascular (CV) outcomes

- Several RCTs designed to assess the impact of incretin-based therapy on CV outcomes are in progress, including trials for albiglutide (HARMONY Outcomes, results expected in March 2018) and dulaglutide (REWIND, results expected in July 2018) (*ClinicalTrials.gov [NCT01394952, NCT02465515] 2018)*.
- A MC, DB, PC, RCT (EXSCEL trial; N = 14,752) was conducted to evaluate the long-term effects of exenatide ER vs placebo, as added to usual care, on CV outcomes in patients with T2DM with or without previous CV disease. A total of 73.1% of patients had previous CV disease, and the median follow-up was 3.2 years. A primary composite outcome event (CV death, non-fatal MI, or non-fatal stroke) occurred in 11.4% of patients in the exenatide ER group vs 12.2% in the placebo group (hazard ratio [HR], 0.91; 95% confidence interval [CI], 0.83 to 1.00). Thus, exenatide ER was found to be noninferior to placebo with respect to safety (p < 0.001), but not superior to placebo with respect to efficacy (p = 0.06). The risk of death from any cause was 6.9% vs 7.9% in the exenatide ER and placebo groups, respectively (HR, 0.86; 95% CI, 0.77 to 0.97); the difference was not statistically significant on the basis of the hierarchical testing plan. The rates of death from CV causes, nonfatal MI, nonfatal stroke, and hospitalization for heart failure did not differ significantly between groups (*Holman et al 2017*).
- A MC, DB, PC, RCT (LEADER trial; N = 9340) was conducted to evaluate the long-term effects of liraglutide vs placebo on CV outcomes in patients with T2DM and high CV risk. The median follow-up was 3.8 years. It was found that the primary composite outcome (CV death, non-fatal MI, or non-fatal stroke) occurred in fewer patients in the liraglutide

group (13.0%) vs the placebo group (14.9%) (HR, 0.87; 95% CI, 0.78 to 0.97; p < 0.001 for noninferiority; p = 0.01 for superiority). Fewer patients died from CV causes in the liraglutide group (4.7%) vs the placebo group (6.0%) (HR, 0.78; 95% CI, 0.66 to 0.93; p = 0.007). The rate of death from any cause was lower in the liraglutide group (8.2%) vs the placebo group (9.6%) (HR, 0.85; 95% CI, 0.74 to 0.97; p = 0.02). The rates of nonfatal MI, nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group (*Marso et al 2016a*).
    - A prespecified secondary analysis found that the composite renal outcome (new-onset persistent macroalbumineria, persistent doubling of serum creatinine level, end-stage renal disease, and death due to renal disease) occurred in fewer patients in the liraglutide group vs the placebo group (5.7% vs 7.2%; HR, 0.78; 95% CI, 0.67 to 0.92; p = 0.003) (*Mann et al 2017*).
- A MC, DB, PC, RCT (ELIXA trial; N = 6068) evaluated the long-term effects of lixisenatide vs placebo on CV outcomes in patients with T2DM who had a recent acute coronary syndrome (ACS) event within 180 days of screening. The median follow-up was 25 months. It was found that the primary endpoint event (a composite of the first occurrence of any of the following: death from CV causes, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina) occurred in 13.4% of patients in the lixisenatide group and 13.2% in the placebo group (HR, 1.02; 95% CI, 0.89 to 1.17), which demonstrated noninferiority of lixisenatide to placebo (p < 0.001), but did not demonstrate superiority (p = 0.81). The rates of the individual CV components of the primary endpoint were similar between the lixisenatide and placebo groups (*Pfeffer et al 2015*).
- *Marso et al 2016b* conducted a MC, DB, PC, RCT (SUSTAIN 6 trial; N = 3297) to assess the noninferiority of semaglutide as compared to placebo in terms of CV safety in patients with T2DM, 83.0% of whom had CV disease. Patients were randomized to semaglutide 0.5 mg or 1.0 mg once weekly or placebo. The median observation time was 2.1 years. The primary composite outcome was the first occurrence of CV death, nonfatal MI, or nonfatal stroke. The noninferiority margin was 1.8 for the upper boundary of the 95% CI of the HR. A larger study is planned to validate the results (*Skydsgaard 2016*).
    - The primary composite outcome occurred in 6.6% of the semaglutide group vs 8.9% of the placebo group (HR: 0.74 [95%CI, 0.58 to 0.95]; p < 0.001 for noninferiority). Although a p value of 0.02 for superiority was calculated; testing for superiority was not prespecified. Nonfatal stroke occurred in 1.6% in the semaglutide group vs 2.7% in the placebo group (HR: 0.61 [95% CI, 0.38 to 0.99]; p = 0.04). Rates of nonfatal MI, CV death, and all-cause death were not statistically significantly different between groups.
    - Rates of new or worsening nephropathy were lower in the semaglutide group, but rates of retinopathy complications were significantly higher (3.0% for semaglutide vs 1.8% for placebo, HR: 1.76 [95% CI, 1.11 to 2.78]; p = 0.02).

Meta-analyses

- Meta-analyses and Cochrane Reviews evaluating GLP-1 receptor agonists have found that they lead to decreases in HbA1c of ~1%, with greater decreases in body weight and systolic blood pressure compared to placebo and other antidiabetic agents (*Wang et al 2013, Shyangdan et al 2011, Sun et al 2015*).
- A systematic review and mixed-treatment comparison analysis of GLP-1 receptor agonists found that there were no differences in efficacy within the short-acting (exenatide or lixisenatide) or long-acting (albiglutide, dulaglutide, exenatide ER, liraglutide) groups. However, dulaglutide, liraglutide, and exenatide ER were superior to exenatide and lixisenatide at lowering HbA1c and FPG. There were no clinically meaningful differences between agents in weight loss or hypoglycemia. Albiglutide had the lowest risk of nausea and diarrhea, while exenatide ER had the lowest risk of vomiting (*Htike et al 2016*).
- Meta-analyses have revealed that incretin-based therapies are not associated with an increased risk of pancreatitis and appear to reduce all-cause mortality, CV mortality, and the incidence of MI compared to placebo or other antidiabetic agents. However, treatment with GLP-1 receptor agonists was associated with a significant increase in the incidence of cholelithiasis (*Monami et al 2017a*, *Monami et al 2017b)*.
- A meta-analysis found that overall, GLP-1 receptor agonists did not appear to be associated with an increase in the incidence of retinopathy, and there was a reduction in the incidence of nephropathy vs comparators (*Dicembrini et al 2017*).

Pramlintide

- The safety and efficacy of pramlintide in patients with T1DM have been established in PC, RCTs when administered in addition to existing insulin regimens. In a 52-week, DB, MC, PC study, pramlintide significantly reduced HbA1c from baseline compared to placebo (-0.39% vs -0.12%; p = 0.0071) and was also associated with a significant weight loss compared to placebo (p < 0.001) (*Whitehouse et al 2002*). In a second 52-week study, patients experienced a significant reduction in HbA1c when receiving pramlintide 60 mcg 3 times daily (-0.41 vs -0.18%; p = 0.012) and pramlintide 60

mcg 4 times daily (-0.39 vs -0.18%; p = 0.013) at 26 weeks. Treatment with pramlintide 3 or 4 times daily continued to maintain reductions in HbA1c at 52 weeks compared to treatment with placebo (p = 0.011 and p = 0.001 for the 3- and 4 times daily dosing, respectively) (*Ratner et al 2004*).

- A systematic review and meta-analysis of 10 randomized, PC studies (N = 3297) evaluating the effect of pramlintide as adjunctive therapy to insulin in patients with T1DM found that, compared to placebo, pramlintide resulted in significant reductions in HbA1c (p < 0.001), total daily insulin dose (p = 0.024), mean mealtime insulin dose (p < 0.001), body weight (p < 0.001), and PPG (p = 0.002) (*Qiao et al 2017*).
- A systematic review and meta-analysis of 8 PC, RCTs assessed the effect of pramlintide in patients with T2DM and in obese patients without diabetes. Four T2DM studies (N = 930; 16 to 52 weeks duration) and 4 obesity studies (N = 686; 6 to 24 weeks duration) were included. Of the T2DM studies, 3 studies used meal-time placebo as the comparator while 1 study used rapid-acting insulin as the comparator. When endpoint data from all T2DM studies were combined, pramlintide was associated with a small but significant reduction in HbA1c (mean difference: -0.33% [95% CI, -0.51 to -0.14]; p = 0.0004). In the meta-analysis of the T2DM studies, patients on pramlintide were 1.52 times more likely to reach the HbA1c goal ≤ 7% than patients in the control group; however, this difference was not significant (p = 0.18). Pramlintide was associated with a significant change in body weight in patients with T2DM compared to the control group (-2.57 kg [95% CI, -3.44 to -1.70]; p < 0.00001) (*Singh-Franco et al 2011*).

CLINICAL GUIDELINES

- According to current clinical guidelines, metformin remains the cornerstone of most T2DM treatment regimens. The incretin mimetics are recommended as a potential second-line treatment option to be added to metformin in patients not achieving glycemic goals. Clinical guidelines note a lower rate of hypoglycemia, established efficacy and safety profile when used in combination with metformin, demonstrated effectiveness in reducing PPG, and the potential for weight loss as advantages associated with the incretin mimetics compared to other antidiabetic agents. No one incretin mimetic is recommended or preferred over another in the general treatment algorithm. The ADA guidelines recommend that lifestyle management and metformin should be initiated in patients with T2DM and established atherosclerotic CV disease; subsequent addition of an agent proven to reduce MACE and CV mortality (currently empagliflozin and liraglutide) is given a grade A recommendation, while consideration of canagliflozin to reduce MACE is given a grade C recommendation. Current clinical guidelines do not support the use of amylinomimetics in the management of T2DM. Among T1DM patients, the addition of pramlintide to first-line insulin therapy may be considered to enhance glycemic control and to assist with weight management (*ADA 2018; Garber et al 2018, Inzucchi et al 2015*).

SAFETY SUMMARY

- GLP-1 receptor agonists are contraindicated in patients with hypersensitivity to any component of the products. With the exception of exenatide and lixisenatide, they are also contraindicated in those with a personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome, type 2 (MEN 2).
- All GLP-1 receptor agonists, except exenatide and lixisenatide, carry a boxed warning for risk of thyroid C-cell tumors. Other safety risks include pancreatitis (including fatal and non-fatal hemorrhagic or necrotizing pancreatitis), serious hypersensitivity reactions, immunogenicity, serious hypoglycemia when used in combination with SFUs or insulin, and renal impairment. Liraglutide also has a warning for acute gallbladder disease. Semaglutide carries a warning for diabetic retinopathy complications due to the results of the SUSTAIN 6 trial, which found a higher rate of events in patients treated with semaglutide vs placebo; the absolute risk was larger among patients with a history of diabetic retinopathy at baseline compared to those without. Common AEs with these drugs include: nausea, diarrhea, vomiting, headache, and injection site reactions.
- Pramlintide is contraindicated in patients with hypersensitivity to any component of the drug and in those with hypoglycemia unawareness and confirmed gastroparesis. It has a boxed warning for increased risk of hypoglycemia, particularly in patients with T1DM. Common AEs include nausea, headache, anorexia, and vomiting; the incidence of nausea tends to be higher at the beginning of treatment and decreases with time in most patients. Gradual titration of the dose minimizes the incidence and severity of nausea
- Albiglutide, exenatide, and pramlintide are Pregnancy Category C. Dulaglutide, exenatide ER, liraglutide, semaglutide, and lixisenatide are uncategorized in accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR).
  - There are no adequate and well-controlled studies in pregnant women. These drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether these drugs are excreted in human milk.

- Due to the long washout period for albiglutide, discontinuation of the drug at least 1 month before a planned pregnancy should be considered.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Adlyxin (lixisenatide)	Injection	SC	Once daily	Inject in the abdomen, thigh, or upper arm. Administer within 1 hour before the first meal of the day, preferably the same meal each day.
Bydureon (exenatide ER)	Injection	SC	Once weekly	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food. Administer immediately after the powder is suspended.
Bydureon BCise (exenatide ER)	Injection	SC	Once weekly	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food. Administer immediately after the autoinjector is prepared.
Byetta (exenatide)	Injection	SC	Twice daily	Inject in the thigh, abdomen, or upper arm. Inject within 60 minutes prior to the morning and evening meals (or before the 2 main meals of the day, approximately 6 hours or more apart).
Ozempic (semaglutide)	Injection	SC	Once weekly	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food.
Symlin (pramlintide)	Injection	SC	Prior to major meals	Inject in the thigh or abdomen. Administer immediately prior to each major meal. Reduce mealtime insulin doses by 50%. Adjust insulin doses to optimize glycemic control once the target dose of pramlintide is achieved and nausea (if experienced) has subsided. The dose should be decreased if significant nausea persists.
Tanzeum (albiglutide)	Injection	SC	Once weekly	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food. Wait 15 minutes for the 30-mg pen and 30 minutes for the 50-mg pen after the lyophilized powder and diluent are mixed to ensure reconstitution.
Trulicity (dulaglutide)	Injection	SC	Once weekly	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food.
Victoza (liraglutide)	Injection	SC	Once daily	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food.

CONCLUSION

- The GLP-1 receptor agonists exenatide, exenatide ER, albiglutide, dulaglutide, liraglutide, lixisenatide, and semaglutide are incretin-based antidiabetic therapies that are FDA-approved as adjunctive therapy to diet and exercise in adult patients with T2DM. Additionally, liraglutide is indicated to reduce the risk of major adverse CV events in patients with established CV disease. Pramlintide is the only agent within the amylinomimetic medication class and is FDA-approved as adjunctive therapy in patients with T1DM or T2DM who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.
- The incretin mimetics are available as SC injections to be administered in the abdomen, thigh, or upper arm. Exenatide is administered twice daily (60 minutes prior to meals); liraglutide is administered once daily (independent of meals); and lixisenatide is administered once daily (1 hour prior to the first meal of the day). Exenatide ER, albiglutide, dulaglutide, and semaglutide are administered once weekly. Pramlintide is available as a SC injection to be administered immediately prior to each major meal.
- The incretin mimetics have been studied extensively in combination with, and in comparison to, a variety of antidiabetic therapies. The agents are significantly more effective than placebo in reducing HbA1c, FPG, PPG, and body weight. Efficacy data comparing treatment to an SFU, TZD, DPP-4 inhibitor or insulin is mixed, with the GLP-1 agonists achieving significantly greater or comparable benefits in glycemic outcomes.
- Several CV outcomes trials evaluating GLP-1 receptor agonists in patients with T2DM and high CV risk have been published. The LEADER trial demonstrated a statistically significant CV risk reduction with liraglutide vs placebo (*Marso et al 2016a*), whereas the ELIXA trial did not demonstrate a statistically significant difference between lixisenatide vs placebo (*Pfeffer et al 2015*) and the EXSCEL trial did not demonstrate a statistically significant difference between exenatide ER vs placebo (*Holman et al 2017*). Although the risk of MACE was lower with semaglutide vs. placebo in the SUSTAIN 6 trial, a superiority analysis was not prespecified (*Marso et al 2016b*). A larger CV outcome study is planned.
- Overall, the AE profiles of the GLP-1 receptor agonists are similar. With the exception of lixisenatide and exenatide, all of the agents have a boxed warning regarding the risk of thyroid C-cell tumors. Other warnings include increased risks of pancreatitis (including fatal and non-fatal hemorrhagic or necrotizing pancreatitis), serious hypersensitivity reactions, immunogenicity, serious hypoglycemia when used in combination with SFUs or insulin, and renal impairment. Liraglutide also has a warning for acute gallbladder disease, while semaglutide has a warning for diabetic retinopathy complications.
- According to current clinical guidelines, metformin remains the cornerstone of most T2DM treatment regimens. The incretin mimetics are recommended as a potential second-line treatment option to be added to metformin in patients not achieving glycemic goals. Clinical guidelines note a lower rate of hypoglycemia, established efficacy and safety profile when used in combination with metformin, demonstrated effectiveness in reducing PPG, and the potential for weight loss as advantages associated with the incretin mimetics compared to other antidiabetic agents. No one incretin mimetic is recommended or preferred over another in the general treatment algorithm; however, the ADA guidelines recommend that liraglutide and the SGLT2 inhibitors, empagliflozin and canagliflozin, should be considered in patients with long-standing suboptimally controlled T2DM and established atherosclerotic CV disease. Current clinical guidelines do not support the use of amylinomimetics in the management of T2DM. For T1DM, the addition of pramlintide to first-line insulin therapy may be considered to enhance glycemic control and to assist with weight management (*ADA 2018; Garber et al 2018, Inzucchi et al 2015*).

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Therapeutic Class Overview
Intranasal Corticosteroids

INTRODUCTION

- Intranasal corticosteroids are primarily used to treat perennial allergic rhinitis (PAR) and seasonal allergic rhinitis (SAR) and may be useful in the treatment of some forms of nonallergic rhinitis (Wallace et al, 2008).
- Symptoms associated with allergic rhinitis include nasal congestion, rhinorrhea, sneezing and/or nasal itching. These symptoms result from a complex allergen-driven mucosal inflammation caused by resident and infiltrating inflammatory cells and a number of vasoactive and proinflammatory mediators (Dykewicz et al, 2017; Wallace et al, 2008).
- Treatment should consist of patient education, allergen avoidance activities and pharmacological therapies. Patients should be educated on how to avoid known triggers, such as aeroallergens, dust mites, molds and irritants whenever possible. In addition to environmental control measures, pharmacological therapies may be used to control symptoms.
- Intranasal corticosteroids down-regulate the inflammatory response by binding to the intracellular glucocorticoid receptors of inflammatory cells and causing a conformational change, thereby controlling the rate of protein synthesis and suppressing the transcription of cytokine and chemokine genes (Clinical Pharmacology®, 2017).
- Most intranasal corticosteroids are approved by the Food and Drug Administration (FDA) for the treatment of PAR and SAR. Mometasone (Nasonex) carries an additional indication for the prophylaxis of SAR. Nasacort Allergy 24hr (triamcinolone acetate), Flonase Allergy Relief (fluticasone propionate), Flonase Sensimist Allergy Relief (fluticasone furoate), and Rhinocort Allergy (budesonide) are all FDA-approved for over-the-counter use (Drugs@FDA, 2017).
- Nasal polyposis is an inflammatory condition of the nasal and sinus mucosa and usually presents as persistent nasal obstruction (Wallace et al, 2008). 2 currently available intranasal corticosteroids, beclomethasone (BECONASE AQ®) and mometasone (Nasonex) are also FDA-approved for the management of nasal polyps. In September 2017, fluticasone propionate (Xhance) was approved for management of nasal polyps in (Xhance prescribing information, 2017; Optinose press release, 2017).
- Beclomethasone (Beconase AQ) and fluticasone propionate are approved for the management of nonallergic rhinitis (eg, infectious rhinitis, hormonal rhinitis and vasomotor nonallergic rhinitis with eosinophilia syndrome). Unlike allergic rhinitis, nonallergic rhinitis is characterized by periodic or perennial symptoms that are not a result of immunoglobulin E-dependent events (Wallace et al, 2008).
- Beclomethasone (Qnasl) and ciclesonide (Zetonna) are the only 2 intranasal corticosteroid products formulated as a “dry” nasal aerosol; all other products within the class are formulated as aqueous suspensions.
- Recently, Veramyst (fluticasone furoate) was withdrawn from the market after over-the-counter Flonase Sensimist Allergy Relief (fluticasone furoate) was launched (GlaxoSmithKline press release, 2017; Snyder-Bulik, 2017). In January 2016, branded prescription Rhinocort Aqua was discontinued for the US market and over-the-counter Rhinocort Allergy spray was launched instead (AstraZeneca oral communication, 2017). Additionally, the prescription intranasal triamcinolone is unavailable per the FDA Orange Book, but the over-the-counter Nasacort Allergy 24hr spray is available (Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017).
- Continuous administration of intranasal corticosteroids is more efficacious than as-needed dosing, and the onset of therapeutic effect occurs between 3 and twelve hours (Dykewicz et al, 2017; Wallace et al, 2008).
- As a result of both the route of administration and the relatively low systemic bioavailability of these agents, intranasal corticosteroids are generally not associated with any clinically significant systemic adverse events. Moreover, drug interactions are limited when administered at recommended doses. The most common adverse events include nasal irritation and mild epistaxis.
- The agents included in this review are listed in Table 1 by brand name. Since there are some branded agents that contain the same generic component, the remaining tables in the review are organized by generic name.
- Medispan Class: Nasal Steroids

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Beconase AQ (beclomethasone dipropionate monohydrate)	-
Flonase Allergy Relief† (fluticasone propionate)	✔

Drug	Generic Availability
Flonase Sesimist Allergy Relief† (fluticasone furoate)	-
flunisolide*	✔
fluticasone propionate*	✔
Nasacort Allergy 24hr† (triamcinolone acetonide)	✔
Nasonex (mometasone furoate monohydrate)	✔
Omnaris (ciclesonide)	-
Qnasl (beclomethasone dipropionate)	-
Rhinocort Allergy†‡ (budesonide)	✔
triamcinolone	✔
Xhance (fluticasone propionate)	-
Zetonna (ciclesonide)	-

*Brand prescription Flonase (fluticasone propionate), Nasalide (flunisolide), and Nasacort AQ (triamcinolone) are no longer marketed; however, generics for these products are available.
†Over-the-counter product
‡As of January 2016, AstraZeneca no longer produced for the US market branded prescription Rhinocort Aqua (budesonide). McNeil Healthcare officially launched prescription strength over-the-counter Rhinocort Aqua (budesonide) nasal spray, marketed as Rhinocort Allergy spray (AstraZeneca, oral communication, 2017).

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Beclomethasone	Budesonide (OTC)	Ciclesonide	Flunisolide	Fluticasone furoate	Fluticasone furoate (OTC)	Fluticasone propionate	Fluticasone propionate (OTC)	Mometasone	Triamcinolone	Triamcinolone (OTC)
Indications for Prescription Products											
Treatment/relief of symptoms of SAR and PAR	✔ (age ≥6)*		✔ (age ≥12)†		✔ (age ≥2)						
Treatment of nasal symptoms of SAR	✔ (age ≥4)‡		✔ (age ≥6)§	✔ (age ≥6)					✔ (age ≥2)	✔ (age ≥2)	
Treatment of nasal symptoms of PAR	✔ (age ≥4)‡		✔ (age ≥12)§	✔ (age ≥6)					✔ (age ≥2)	✔ (age ≥2)	
Treatment/relief of nasal congestion associated with SAR									✔ (age ≥2)		
Prophylaxis of nasal symptoms of SAR									✔ (age ≥12)		
Relief of symptoms of nonallergic (vasomotor) rhinitis	✔ (age ≥6)*										
Management of nasal symptoms of perennial nonallergic rhinitis							✔ (age ≥4)				
Treatment of nasal polyps							✔ (age ≥18)#		✔ (age ≥18)		
Prevention of recurrence of nasal polyps following surgical removal	✔ (age ≥6)*										
OTC Uses											

Indication	Beclomethasone	Budesonide (OTC)	Ciclesonide	Flunisolide	Fluticasone furoate	Fluticasone furoate (OTC)	Fluticasone propionate	Fluticasone propionate (OTC)	Mometasone	Triamcinolone	Triamcinolone (OTC)
Temporary relief of symptoms of hay fever or other upper respiratory allergies: nasal congestion, runny nose, sneezing, and itchy nose		✔ (age ≥6)									✔ (age ≥2)
Temporary relief of symptoms of hay fever or other upper respiratory allergies: nasal congestion, runny nose, sneezing, itchy nose, and itchy, watery eyes						✔ (age ≥2)‖		✔ (age ≥4)			

OTC = over-the-counter
*Beconase AQ
†Zetonna
‡Qnasl
§Omnaris
#Xhance
‖Itchy, watery eyes use is for patients ≥12 years of age

(*Prescribing information: Beconase AQ, 2015; Flonase Allergy Relief, 2017; Flonase Sensimist, 2017; flunisolide, 2016; fluticasone propionate, 2016; Nasacort Allergy 24HR, 2016; Nasonex, 2013; Omnaris, 2013; Qnasl, 2017; Rhinocort Allergy, 2017; triamcinolone, 2013; Xhance, 2017; Zetonna, 2014*)

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

CLINICAL EFFICACY SUMMARY

- Daily administration of intranasal corticosteroids is associated with statistically significant improvements in allergy-related total nasal symptom score (TNSS) and health related quality of life scores. Numerous head-to-head clinical trials comparing the available intranasal corticosteroids have generally demonstrated no significant clinical differences among the available intranasal corticosteroids with regard to efficacy. Some studies have reported differences in sensory perceptions and patient preference with 1 agent compared to another. Patients administering the agents noted differences in odor, aftertaste, and severity of irritation, though these differences were not associated with differences in efficacy between the agents (Aasand et al, 1982; Al-Mohaimeid, 1993; Andersson et al, 1995; Bachert et al, 2002; Bachert et al, 2004; Berger et al, 2003; Day et al, 1998; Drouin et al 1996; Graft et al, 1996; Gross et al, 2002; Haye et al, 1993; Hebert et al, 1996; Khanna et al, 2005; LaForce et al, 1994; Langrick, 1984; Lumry et al, 2003; Mak et al, 2013; Mandl et al, 1997; McAllen et al, 1980; McArthur, 1994; Meltzer et al, 2005; Meltzer et al, 2008; Meltzer et al, 2010; Naclerio et al, 2003; Ratner et al, 1992; Sahay et al, 1980; Shah et al, 2003; Sipila et al, 1983; Small et al, 1997; Stern et al, 1997; Stokes et al, 2004; Svendsen et al, 1989; Van As et al, 1993; Vanzieleghem et al, 1987; Varshney et al, 2012; Welsh et al, 1987; Winder et al, 1993, Y1zaki et al, 2016).
- Head-to-head trials evaluating the efficacy and safety of beclomethasone, fluticasone propionate and flunisolide demonstrate that these agents are comparable to other agents within the class. However, additional results of these studies reinforce that all of the intranasal corticosteroids should be considered equally efficacious (Aasand et al, 1984; Bachert et al, 2004; Berger et al, 2003; Drouin et al, 1996; Mak et al, 2013; McAllen et al, 1980; Meltzer et al, 2010; Meltzer et al, 2008; Ratner et al, 1992; Sahay et al, 1980; Sipila et al, 1983; Small et al, 1997; Stokes et al, 2004; Van As et al, 1993).
- To date, the newly approved intranasal corticosteroid aerosol formulations have been demonstrated to be significantly more effective compared to placebo. In a 6-week study of patients with PAR, aerosolized beclomethasone significantly improved reflective TNSS compared to placebo (-2.46 vs -1.63; P<0.001). Furthermore, beclomethasone was associated with a statistically significant improvement in quality of life score compared to placebo (P=0.001) (Meltzer et al, 2012). A 2-week study of beclomethasone nasal aerosol 80 µg daily in pediatric patients 6 to 11 years of age with SAR also demonstrated improvement in reflective TNSS compared to placebo (-1.9 vs -1.2; P<0.001) (Storms et al, 2013). A 12-week study of beclomethasone nasal aerosol 80 µg daily in pediatric patients 4 to 11 years of age with perennial allergic rhinitis demonstrated improvement in both reflective and instantaneous TNSS compared to placebo (mean treatment difference -0.53 [P=0.009] and -0.52 [P=0.008], respectively) (Berger et al, 2015).
- The aerosolized ciclesonide formulation has also been shown to significantly improve symptoms of allergic rhinitis compared to placebo. In a study by Ratner et al, ciclesonide administered at a daily dose of 80 µg or 160 µg reduced reflective TNSS by 15.1 and 16%, respectively, compared to 3.7% in the placebo group (P<0.001 for both). In addition, significant improvements were observed with both doses of ciclesonide compared to placebo with regard to ocular symptom scores and quality of life (P<0.001 for both). Similar improvements in outcomes were reported in additional studies of up to 26 weeks duration (Berger et al, 2012; LaForce et al, 2009; Mohar et al, 2012; Ratner et al, 2010; Ratner et al, 2012).
- A systematic review of 40 studies evaluated the use of topical corticosteroids in the treatment or prevention of recurrence of nasal polyps. Topical corticosteroids were effective compared to placebo in the improvement in overall symptoms, nasal obstruction, and a reduction in the size of polyps. Additionally, topical corticosteroids prevented the regrowth of polyps following surgery. No differences in adverse events between topical corticosteroids and placebo were observed (Kalish et al, 2012).
- The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review of pharmacological therapies for the treatment of SAR. A total of 59 randomized controlled trials met inclusion criteria to compare agents of 6 classes for relative efficacy. Agents included oral and nasal antihistamines and decongestants, intranasal corticosteroids, leukotriene modifiers, cromolyn, ipratropium, and normal saline. Overall, there was insufficient evidence to draw a conclusion about relative efficacy among most of the agents used for the treatment of SAR. For a few comparisons, sufficient evidence was available to draw a conclusion. Oral selective antihistamines and montelukast were equivalent for efficacy in reducing nasal and eye symptoms. Montelukast was superior to oral selective antihistamines for controlling asthma symptoms. Based on evidence, intranasal antihistamines and intranasal corticosteroids had equivalent efficacy for nasal and eye symptoms. Similarly, montelukast was comparable to intranasal corticosteroids for nasal symptoms. The combination of intranasal antihistamines and intranasal corticosteroids demonstrated equivalent efficacy in nasal and eye symptom resolution compared to either monotherapy. No information

was available about the use of these agents for the treatment of SAR in pregnant women. For children, conclusions about relative efficacy were not determined due to insufficient evidence (Glacy et al, 2013).

- A meta-analysis evaluated nasal corticosteroids, sublingual allergen immunotherapy (SLIT), second generation H1-antihistamines, combination azelastine hydrochloride with fluticasone propionate nasal spray, and montelukast for the treatment of SAR. By indirect comparison, nasal corticosteroids and grass pollen SLIT tablets had a greater relative clinical impact on symptom scores compared to azelastine hydrochloride combined with fluticasone propionate nasal spray, second generation H1-antihistamines, and montelukast (Devillier et al, 2014). In a similar indirect, meta-analysis, SLIT (timothy grass and ragweed) and mometasone furoate improved TNSS to a greater extent than montelukast and desloratadine in the treatment of both SAR and PAR (Durham et al, 2016).
- A meta-analysis compared the effects of intranasal corticosteroids for treatment of chronic rhinosinusitis. A total of 9 randomized controlled trials were included. There was no evidence that 1 intranasal spray was more effective than another for disease severity or disease-specific quality of life. Epistaxis was more common with higher doses compared to lower doses (Chong et al, 2016).

CLINICAL GUIDELINES

- Intranasal corticosteroids are considered first-line agents for the treatment of allergic rhinitis, especially for patients with moderate to severe symptoms. Consensus guidelines do not recommend the use of 1 intranasal corticosteroid product over another. Intranasal corticosteroids combined with intranasal antihistamines are considered to be more effective than either alone in the treatment of allergic rhinitis. Addition of oral antihistamines is not effective (Bousquet et al, 2016; Brozek et al, 2017; Dykewicz et al, 2017; Seidman et al, 2015; Wallace et al, 2008).

SAFETY SUMMARY

- The intranasal corticosteroids are contraindicated in patients with hypersensitivity to any of the ingredients.
- Intranasal corticosteroids should not be used in patients with recent nasal septal ulcers, nasal surgery or trauma, as they may impair wound healing. Intranasal corticosteroids should be used cautiously, if at all, in patients with untreated infections.
- Systemic corticosteroid effects such as hypercorticism and adrenal suppression may occur when intranasal steroids are used at higher-than-recommended doses or in susceptible individuals at recommended doses. Patients using corticosteroids may be more susceptible to infection; specific effects of the dose, route and duration of use are not known. Intranasal corticosteroids may cause increased intraocular pressure, blurred vision, glaucoma and/or cataracts. Growth velocity in pediatric patients may be reduced with intranasal corticosteroids.
- However, as a result of both the route of administration and the relatively low systemic bioavailability of these agents, intranasal corticosteroids are generally not associated with any clinically significant systemic adverse events. Moreover, drug interactions are limited when administered at recommended doses. The most common adverse events include nasal irritation and mild epistaxis.

(*Drug Facts and Comparisons 2017*)

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency		Comments
			Adults	Pediatric	
Beclomethasone (Beconase AQ, Qnasl)	Aerosol (Qnasl), Suspension (Beconase AQ)	IN	PAR, SAR: Aerosol: 2 actuations in each nostril once daily Suspension: 1 to 2 sprays in each nostril twice daily	Nasal polyps, nonallergic (vasomotor) rhinitis, PAR, SAR in children 6 to 12 years: Suspension: initial, 1 inhalation in each nostril twice daily; maximum, 2 inhalations in each nostril twice daily	The unit should be primed by releasing 6 sprays (suspension) or 4 sprays (aerosol) before initial use and reprime if not used for 7 days.

Drug	Available Formulations	Route	Usual Recommended Frequency		Comments
			Adults	Pediatric	
			Nasal polyps, nonallergic (vasomotor) rhinitis: Suspension: 1 to 2 sprays in each nostril twice daily	PAR, SAR in children 4 to 11 years: Aerosol: 1 actuation (40 µg strength) in each nostril once daily	
Budesonide (Rhinocort Allergy)	OTC suspension	IN	Hay fever or other upper respiratory allergies: OTC suspension: 2 sprays in each nostril once daily; once symptoms improve, reduce to 1 spray in each nostril once daily	Hay fever or other upper respiratory allergies in children 6 to 12 years: OTC suspension: 1 spray in each nostril once daily; maximum, 2 sprays in each nostril once daily	The unit should be primed by releasing 8 sprays and reprime if not used for 2 days.
Ciclesonide (Omnaris, Zetonna)	Aerosol (Zetonna), suspension (Omnaris)	IN	PAR, SAR: Aerosol: 1 inhalation in each nostril once daily Suspension: 2 sprays in each nostril once daily	SAR in children ≥ 6 years old: Suspension: 2 sprays in each nostril once daily	The unit should be primed by releasing 8 sprays (suspension) or 3 sprays (aerosol) and reprime if not used for 4 days (suspension) or 10 days (aerosol).
Flunisolide	Suspension	IN	PAR, SAR: Suspension: 2 sprays in each nostril twice daily; maximum, 8 sprays in each nostril per day	PAR, SAR in children 6 to 14 years: Suspension: 1 spray in each nostril 3 times daily or 2 sprays in each nostril twice daily; maximum, 4 inhalations in each nostril per day	The unit should be primed before initial use by releasing 5 or 6 sprays and reprime if not used for 5 days or more, or if it has been disassembled for cleaning.
Fluticasone furoate (Flonase Sensimist)	OTC suspension	IN	Hay fever or other upper respiratory allergies: OTC suspension: 2 sprays in each nostril once daily for 1 week; maintenance, 1 or 2 sprays in each nostril once daily, as needed to treat symptoms	Hay fever or other upper respiratory allergies in children 2 to 11 years: OTC suspension: 1 spray in each nostril once daily	The unit should be primed before initial use, when not used for 30 days or longer, or if the cap has been left off for 5 days or longer, by spraying until a fine mist appears.
Fluticasone propionate (Flonase Allergy Relief, fluticasone, Xhance)	Rx and OTC suspension	IN	Perennial nonallergic rhinitis: Rx suspension: 2 sprays in each nostril once daily or 1 spray in each nostril twice daily; may reduce to 1	Perennial nonallergic rhinitis in children ≥ 4 years old: Rx suspension: 1 spray in each nostril once daily; maximum, 2	The unit should be primed by releasing 6 sprays (Flonase or fluticasone) or 7 sprays (Xhance) until a fine spray appears before initial use and

Drug	Available Formulations	Route	Usual Recommended Frequency		Comments
			Adults	Pediatric	
			spray in each nostril once daily for maintenance therapy Hay fever or other upper respiratory allergies: OTC suspension: 2 sprays in each nostril once daily for 1 week; maintenance, 1 or 2 sprays in each nostril once daily, as needed to treat symptoms Nasal polyps (Xhance): 1 spray in each nostril twice daily; 2 sprays in each nostril twice daily may be effective in some	sprays in each nostril once daily Hay fever or other upper respiratory allergies in children 4 to 11 years: OTC suspension: 1 spray in each nostril once daily	if not used for a week or more.
Mometasone (Nasonex)	Suspension	IN	PAR, SAR: Suspension: 2 sprays in each nostril once daily Nasal polyps in adults ≥18 years old: Suspension: 2 sprays in each nostril once or twice daily	PAR, SAR in children 2 to 11 years: Suspension: 1 spray in each nostril once daily	The unit should be primed before initial use by actuating 10 times or until a fine spray appears. If unused for more than 7 days, it should be re-primed by actuating 2 times or until a fine spray appears.
Triamcinolone (triamcinolone, Nasacort Allergy 24HR)	Rx and OTC suspension	IN	SAR and PAR: Rx suspension: two sprays in each nostril once daily; maintenance, one spray in each nostril once daily. Hay fever or other upper respiratory allergies: OTC suspension: 2 sprays in each nostril once daily; maintenance, 1 inhalation in each nostril once daily	SAR and PAR in children 6 to 12 years old: One spray in each nostril once daily; maximum, two sprays in each nostril once daily SAR and PAR in children 2 to 5 years old: One spray in each nostril once daily Hay fever or other upper respiratory allergies in children 6 to 12 years: OTC Suspension: 1 spray in each nostril	The unit should be primed before initial use (5 sprays for Rx) and if not used for more than 2 weeks by spraying until a fine mist is produced.

Drug	Available Formulations	Route	Usual Recommended Frequency		Comments
			Adults	Pediatric	
				once daily; maximum, 2 sprays in each nostril once daily Hay fever or other upper respiratory allergies in children 2 to under 6 years: OTC Suspension: 1 spray in each nostril once daily	

See the current prescribing information for full details
Abbreviation: IN = intranasal or nasal inhalation, OTC = over the counter, PAR = perennial allergic rhinitis, Rx = prescription, SAR = seasonal allergic rhinitis

CONCLUSION

- Intranasal corticosteroids are used for the management of allergic rhinitis, some forms of nonallergic rhinitis and nasal polyps. They are generally well tolerated and are associated with limited drug interactions due to their localized administration and limited systemic absorption. Like other corticosteroids, intranasal corticosteroids carry warnings regarding use in patients with active infection and the development of signs of adrenal insufficiency, particularly with the administration of higher-than-recommended doses (Wallace et al, 2008).
- Intranasal corticosteroids are considered first-line agents for the treatment of allergic rhinitis, especially for patients with moderate to severe symptoms. Consensus guidelines do not recommend the use of one intranasal corticosteroid product over another (Bousquet et al, 2016; Brozek et al, 2017; Dykewicz et al, 2017; Seidman et al, 2015; Wallace et al, 2008).
- All available intranasal corticosteroids have demonstrated safety and efficacy for their respective indications. These agents have been shown to be effective in reducing rhinitis-related nasal symptoms such as congestion, rhinorrhea, sneezing, nasal itch, and postnasal drip. The differences in tolerability and sensory perceptions noted in clinical trials were minor and did not translate into differences in outcomes. The results of multiple head-to-head trials have generally failed to demonstrate clinically significant differences between products (Aasand et al, 1982; Al-Mohaimeid, 1993; Andersson et al, 1995; Bachert et al, 2004; Bachert et al; 2002; Berger et al, 2003; Day et al, 1998; Drouin et al. 1996; Graft et al, 1996; Gross et al, 2002; Haye et al, 1993; Hebert et al, 1996; LaForce et al, 1994; Langrick, 1984; Lumry et al, 2003; Mak et al, 2013; Mandl et al, 1997; McAllen et al, 1980; McArthur, 1994; Meltzer et al, 2005; Meltzer et al, 2008; Meltzer et al, 2010; Naclerio et al, 2003; Ratner et al, 1992; Sahay et al, 1980; Shah et al, 2003; Sipila et al, 1983; Small et al, 1997; Stern et al, 1997; Stokes et al, 2004; Svendsen et al, 1989; Van As et al, 1993; Vanzieleghem et al, 1987; Varshney et al, 2012; Welsh et al, 1987; Winder et al, 1993).
- Two nasal aerosol formulations, beclomethasone (Qnasl) and ciclesonide (Zetonna), have been approved by the FDA for the relief of symptoms associated with PAR and SAR. The other intranasal corticosteroid products are formulated as aqueous suspensions, which may be bothersome to patients due to the potential of the suspension to drip down or out of the nose following administration.

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Therapeutic Class Overview
Inhaled Corticosteroids

INTRODUCTION

- Inhaled corticosteroids (ICSs) are approved by the Food & Drug Administration (FDA) for the treatment of asthma. These agents are effective in the treatment of asthma due to their wide range of inhibitory activities against multiple cell types (e.g., mast cells and eosinophils) and mediators (e.g., histamine and cytokines) involved in the asthmatic response.
- Asthma is a chronic lung disease that inflames and narrows the airways, making it difficult to breathe. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing. Asthma affects people of all ages, but most often starts during childhood. In the United States, more than 25 million people are known to have asthma, including about 7 million children (*National Heart, Lung, and Blood Institute [NHLBI] 2014*).
- The exact cause(s) of asthma are unknown. A combination of factors such as genetics, certain respiratory infections during childhood, and contact with airborne allergens can contribute to its development. Most patients with asthma have allergies (*NHLBI 2014*).
- Current pharmacologic options for asthma management are categorized as: (1) long-term control medications to achieve and maintain control of persistent asthma, and (2) quick-relief medications used to treat acute symptoms and exacerbations (*NHLBI 2007*).
- Long-term control medications include (*NHLBI 2007*):
  - Corticosteroids (ICSs for long-term control; short courses of oral corticosteroids to gain prompt control of disease, long-term oral corticosteroids for severe persistent asthma)
  - Cromolyn sodium and nedocromil
  - Immunomodulators (i.e., omalizumab)
  - Leukotriene modulators
  - Long-acting β-agonists (LABAs)
  - Methylxanthines (i.e., theophylline)
- Quick-relief medications include (*NHLBI 2007*):
  - Short-acting β-agonists (SABAs) as the therapy of choice for relief of acute symptoms and prevention of exercise-induced bronchospasm
  - Anticholinergics (i.e. ipratropium bromide), as an alternative bronchodilator for those not tolerating a SABA
  - Systemic corticosteroids, although not short-acting, are used for moderate and severe exacerbations as part of initial treatment.
- In recent years, additional medications have been made available for select subsets of patients with asthma, including the interleukin-5 (IL-5) antagonists benralizumab, mepolizumab, and reslizumab for the management of severe asthma with an eosinophilic phenotype *(Prescribing information: Cinqair 2016, Fasrena 2017, Nucala 2017)*. Additionally, tiotropium, long used for chronic obstructive pulmonary disease (COPD), has been FDA-approved for the treatment of asthma *(Spiriva Respimat prescribing information 2017)*.
- ICSs are the most effective and most commonly recommended long-term control medications used for the treatment of asthma. The LABAs should not be used as monotherapy for the management of asthma due to increased risk for serious adverse events including death. However, they are effective adjunctive therapy in patients who are not adequately controlled with an ICS alone. Theophylline and mast-cell stabilizers have weak to low efficacy in asthma. Theophylline has an unfavorable side-effect profile and may be life-threatening at high doses. Mast-cell stabilizers have a more favorable safety profile. Tiotropium is an option for add-on therapy in patients with a history of exacerbations. An IL-5 antagonist or the immunoglobulin E (IgE) antagonist, omalizumab, may be added if patients require a higher level of care. Omalizumab is used in patients with moderate to severe allergic asthma while IL-5 antagonists are used for severe eosinophilic asthma. SABAs are the medication of choice for the relief of bronchospasm during acute exacerbations of asthma (*Fasrena prescribing information 2017, NHLBI 2007, Global Initiative for Asthma [GINA] 2017*).
- This review includes single-agent ICSs. While corticosteroids are commonly available in combination with other bronchodilators such as LABAs, combination agents are not included within this review. Although inflammation is also a component of COPD pathogenesis, no single-entity ICS has been FDA-approved for use in COPD.

- Of note, QVAR RediHaler, a new breath-actuated inhalation formulation of beclomethasone dipropionate manufactured by Teva, was approved by the FDA in August 2017 and is planned to replace the existing QVAR product, which will be eventually discontinued.
- Medispan class: Steroid Inhalants

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Aerospan (flunisolide)	-
Alvesco (ciclesonide)	-
ArmonAir RespiClick (fluticasone propionate)	-
Arnuity Ellipta (fluticasone furoate)	-
Asmanex HFA (mometasone furoate)	-
Asmanex Twisthaler (mometasone furoate)	-
Flovent Diskus (fluticasone propionate)	-
Flovent HFA (fluticasone propionate)	-
Pulmicort Flexhaler (budesonide)	-
Pulmicort Respules (budesonide)	✔
QVAR (beclomethasone dipropionate)	-
QVAR RediHaler (beclomethasone dipropionate)	-

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Drug	Maintenance treatment of asthma as prophylactic therapy
Aerospan (flunisolide)	✔ (age ≥6 years)
Alvesco (ciclesonide)	✔ (age ≥12 years)
ArmonAir RespiClick (fluticasone propionate)	✔ (age ≥12 years)
Arnuity Ellipta (fluticasone furoate)	✔ (age ≥12 years)
Asmanex HFA (mometasone furoate)	✔ (age ≥12 years)
Asmanex Twisthaler (mometasone furoate)	✔ (age ≥4 years)
Flovent Diskus & Flovent HFA (fluticasone propionate)	✔ (age ≥4 years)
Pulmicort Flexhaler (budesonide)	✔ (age ≥6 years)
Pulmicort Respules (budesonide)	✔ (age 12 months to 8 years)
QVAR (beclomethasone dipropionate)	✔ (age ≥5 years)
QVAR RediHaler (beclomethasone dipropionate)	✔ (age ≥4 years)

(*Prescribing information: Aerospan 2017, Alvesco 2013, ArmonAir RespiClick 2017, Arnuity Ellipta 2017, Asmanex HFA 2016, Asmanex Twisthaler 2014, Flovent Diskus 2017, Flovent HFA 2017, Pulmicort Flexhaler 2016, Pulmicort Respules 2016, QVAR 2017, QVAR RediHaler 2017*)

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

CLINICAL EFFICACY SUMMARY

- Several trials demonstrate the efficacy of ICSs compared to placebo for preventing exacerbations, improving FEV_1 and peak expiratory flow (PEF), improving symptoms, reducing use of SABAs, reducing oral corticosteroid requirements, and/or improving quality of life (*Amar et al 2017, Baker et al 1999, Bleecker et al 2014, Corren et al 2001, Fish et al 2000, Karpel et al 2007, Lotvall et al 2014, Meltzer et al 2009, Meltzer et al 2012, Nathan et al 2010, Nelson et al 1999, Rowe et al 1999, Sheffer et al 2005, Study #321, Study #322, Study #323/324, Study #3030, Study #3031*).
- Numerous head-to-head trials have compared various ICS regimens to one another. Several clinical trials demonstrated no significant differences between different ICSs:
  - A trial comparing budesonide 750 mcg twice daily to fluticasone propionate 375 mcg twice daily in children 5 to 16 years of age demonstrated no statistically significant differences between treatment groups in PEF, symptom scores, physician/patient/parent assessment of efficacy, or frequency of exacerbations (*Fitzgerald et al 1998*).
  - A trial comparing fluticasone propionate 250 mcg twice daily to various doses of mometasone furoate twice daily demonstrated comparable efficacy between fluticasone propionate and mometasone furoate for improvement in FEV_1, forced expiratory flow at 25 to 75% of forced vital capacity (FVC; i.e., forced expiratory flow $[FEF]_{25\text{ to }75\%}$), and PEF (*O'Connor et al 2001*).
  - A trial comparing fluticasone propionate 250 mcg twice daily to mometasone furoate 400 mcg every evening demonstrated no significant differences between groups in FEV_1, FVC, PEF, albuterol use, or asthma symptom scores (*Wardlaw et al 2004*).
  - A trial comparing fluticasone propionate 500 mcg twice daily to mometasone furoate 500 mcg twice daily demonstrated no significant differences in PEF, FEV_1, symptom scores, or rescue albuterol use (*Harnest et al 2008*).
  - A trial comparing beclomethasone dipropionate 168 mcg twice daily to mometasone furoate 100 or 200 mcg twice daily demonstrated no significant differences in FEV_1, PEF, asthma symptoms, nocturnal awakenings, or albuterol use (*Nathan et al 2001*).
  - A trial comparing ciclesonide 160 mcg every evening to budesonide 400 mcg every evening in children aged 6 to 11 years demonstrated no significant differences between groups in FEV_1, morning PEF, asthma symptom score, or need for rescue medication (*Von Berg et al 2007*).
  - A trial comparing fluticasone furoate 100 mcg daily to placebo also included fluticasone propionate 250 mcg twice daily as a reference arm; comparable results were seen between fluticasone propionate and fluticasone furoate for FEV_1, percentage of rescue-free days, and severe asthma exacerbations (*Lotvall et al* 2014).
  - A trial comparing fluticasone furoate 200 mcg daily to fluticasone propionate 500 mcg twice daily demonstrated that fluticasone furoate was non-inferior to fluticasone propionate based on effect on FEV_1 (*O'Byrne et al 2014*).
- Overall, comparative trials have not conclusively demonstrated one ICS to be significantly more effective than another. However, in several individual trials, significant differences in some endpoints were observed. For example, comparative trials have demonstrated:
  - In a trial comparing fluticasone propionate 200 mcg twice daily to budesonide 400 mcg twice daily in children 4 to 12 years of age, patients treated with fluticasone propionate had superior results for mean morning PEF compared to patients receiving budesonide (271 ± 82 and 259 ± 75 L/minute, respectively, P=0.002) (*Ferguson et al 1999*).
  - In a trial comparing budesonide 200 mcg twice daily to fluticasone propionate 100 mcg twice daily in children 6 to 9 years of age, effectiveness measures were comparable between groups; however, the mean growth velocity was significantly greater in the fluticasone propionate group (5.5 cm/year) compared to the budesonide group (4.6 cm/year) (*Ferguson et al 2007*).
  - A trial comparing beclomethasone dipropionate 168 or 336 mcg twice daily to fluticasone propionate 88 to 220 mcg twice daily demonstrated greater improvement in FEV_1 for fluticasone propionate-treated patients than beclomethasone dipropionate-treated patients. At endpoint, mean FEV_1 values in the low- and medium-dose fluticasone propionate groups improved by 0.31 (14%) and 0.36 L (15%), respectively, compared to improvements of 0.18 (8%) and 0.21 L (9%) in the low-and medium-dose beclomethasone dipropionate treatment groups, respectively. Improvements were also superior in the fluticasone propionate group for $FEF_{25\text{ to }75\%}$, FVC, morning PEF, and use of albuterol (*Raphael et al 1999*).
  - In a trial comparing budesonide 400 mcg twice daily to various doses of mometasone furoate twice daily, the FEV_1 was significantly improved from baseline in the mometasone furoate 200 and 400 mcg treatment groups compared to the budesonide treatment group. In addition, morning wheezing scores were significantly improved in the mometasone furoate 400 mcg twice daily group compared to the budesonide group, and patients treated with

mometasone furoate 200 or 400 mcg twice daily required significantly less albuterol compared to patients treated with budesonide (*Bousquet et al 2000*).
    - In a trial comparing budesonide 400 mcg once daily to mometasone furoate 440 mcg once daily, the mometasone furoate group had superior results for the percent change in FEV_1, $FEF_{25\ to\ 75\%}$, FVC, evening asthma symptom scores, albuterol use, percentage of asthma symptom-free days, and physician–evaluated response to therapy (*Corren et al 2003*).
- Meta-analyses have evaluated ciclesonide and mometasone furoate compared to other ICS agents:
    - A meta-analysis comparing ciclesonide to other ICS agents (budesonide or fluticasone propionate) in children with asthma demonstrated no significant differences between ciclesonide and budesonide on asthma symptom scores, symptom-free days, rescue medication-free days, or exacerbations. When ciclesonide and fluticasone propionate were compared, no significant differences were found in asthma symptoms or rescue medication-free days. One of the four studies of ciclesonide vs fluticasone propionate demonstrated a higher incidence of exacerbations with ciclesonide; however, the dose of fluticasone propionate was relatively higher in this study (*Kramer et al 2013*).
    - A meta-analysis comparing mometasone furoate to other ICS agents (beclomethasone dipropionate, budesonide, or fluticasone propionate) in patients with moderate to severe asthma demonstrated superior results with mometasone furoate for pulmonary function measures (FEV_1, FVC, $FEF_{25\ to\ 75\%}$, and morning PEF). Mometasone furoate was also shown to be superior on some symptom indices (morning difficulty breathing scores and rescue medication use), but not others (morning wheeze scores, morning cough scores, and nocturnal awakenings). However, based on the pooled results for the comparative arms, it is not possible to make conclusions about the relative efficacy of mometasone furoate compared to other individual agents (*Yang et al 2012*).
- Fluticasone propionate has also been compared to a leukotriene receptor, montelukast, in several randomized controlled trials in both adults and children. Although differences were not detected for all endpoints, in general these trials demonstrated superior outcomes for fluticasone propionate for FEV_1, symptom-free days, asthma symptom scores, nighttime awakenings, rescue albuterol use, physician's global assessments, frequency of exacerbations, and/or quality of life measures (*Busse et al 2001, Garcia et al 2005, Sorkness et al 2007, Szefler et al 2005, Zeiger et al 2006*).
- The safety and efficacy of ArmonAir RespiClick were evaluated in 2,130 patients with asthma, including two 12-week confirmatory trials, a 26-week safety trial, and two dose-ranging trials. The efficacy of ArmonAir RespiClick is based primarily on the dose-ranging and confirmatory trials (*Bernstein et al 2017, Kerwin et al 2017, Mansfield et al 2017, Raphael el at 2017, Sher et al 2017*).
    - The first Phase 3 trial (n=647, of which 389 were randomized to ArmonAir RespiClick or placebo) was a randomized, double-blind, placebo-controlled efficacy and safety study that compared ArmonAir RespiClick 55 mcg and 113 mcg one inhalation twice daily, AirDuo RespiClick (fluticasone propionate/salmeterol) 55/14 mcg and 113/14 mcg one inhalation twice daily, and placebo in patients ≥12 years of age with persistent symptomatic asthma despite low-dose or mid-dose ICS or ICS/LABA therapy. For the primary endpoint of change from baseline in trough FEV_1, a significantly greater improvement was seen in ArmonAir RespiClick 55 mcg and 113 mcg as compared to placebo at the end of 12 weeks (least squares means [LSM] change of 0.172 L, 0.204 L, and 0.053 L, respectively). Secondary endpoints of weekly average of daily trough morning PEF, total daily use of rescue medication, and Asthma Quality of Life Questionnaire improvement were also evaluated and supported efficacy of ArmonAir RespiClick (*Raphael el at 2017*).
    - The second Phase 3 trial (n=728, of which 437 were randomized to ArmonAir RespiClick or placebo) was similarly designed, but evaluated an increased ICS dose: ArmonAir RespiClick 113 mcg and 232 mcg, AirDuo RespiClick 113/14 mcg and 232/14 mcg, and placebo. Results for the primary endpoint of change from baseline in trough FEV_1 mirrored that of Trial 1, with significantly greater improvement in the ArmonAir RespiClick 113 mcg and 232 mcg groups as compared to placebo at the end of 12 weeks (LSM change of 0.119 L, 0.179 L, and -0.004 L, respectively). Secondary endpoints of weekly average of daily trough morning PEF and total daily use of rescue medication also supported efficacy of ArmonAir RespiClick (*Sher et al 2017*).
- The safety and efficacy of QVAR RediHaler were evaluated in 1,858 patients with persistent symptomatic asthma, including two 12-week and one 6-week Phase 3 confirmatory trials in patients ≥12 years of age, and one 12-week Phase 3 confirmatory in patients 4 to 11 years of age (*Amar et al 2016, Hampel et al 2017, QVAR RediHaler prescribing information 2017, Vandewalker et al 2017*).
    - The first 12-week Phase 3 trial (N=270) was a randomized, double-blind, placebo-controlled trial study that compared QVAR RediHaler 40 mcg and 80 mcg twice daily vs placebo in patients who previously used low-dose ICS or non-corticosteroid therapy. For the primary endpoint of change from baseline in trough FEV_1 area under the effect curve 0

to 12 weeks ($AUEC_{0\text{-}12wk}$), a significantly greater improvement was seen with QVAR RespiClick 80 mcg and 160 mcg as compared to placebo (difference of LSM from placebo of 0.124 L and 0.116 L, respectively). Both doses of QVAR RediHaler demonstrated improvements in asthma control as supported by significantly greater improvements in morning PEF and a reduction in asthma symptoms vs placebo (*Hampel et al 2017*).
  - The second 12-week Phase 3 trial (n=532) was a randomized, double-blind, placebo-controlled trial that compared QVAR RediHaler 160 mcg and 320 mcg twice daily vs QVAR 160 mcg and 320 mcg twice daily and placebo in patients who previously used mid- to high-dose ICS or ICS/LABA therapy. The baseline-adjusted trough morning FEV_1 $AUEC_{0\text{-}12wk}$ increased in all active treatment groups vs placebo, although the differences were not significant. Overall, the safety profiles of QVAR and QVAR RediHaler were comparable (*Amar et al 2016*).
  - The 6-week randomized, double-blind, parallel-group, placebo-controlled trial compared QVAR RediHaler 160 mcg and 320 mcg twice daily vs placebo, with a QVAR 160 mcg twice daily reference arm, in patients previously using non-corticosteroid, ICS ± LABA, or combination asthma therapy. For the primary endpoint of change from baseline in trough FEV_1 $AUEC_{0\text{-}6wk}$, a significantly greater improvement was seen with QVAR RespiClick 160 mcg and 320 mcg vs placebo (difference of LSM from placebo of 0.144 L and 0.150 L, respectively). Both doses of QVAR RediHaler demonstrated improvements in asthma control as supported by significantly greater improvements in morning PEF, reduced rescue medication use, and a reduction in asthma symptoms vs placebo, with similar results demonstrated with QVAR 160 mcg treatment (*QVAR RediHaler prescribing information 2017*).
  - The 12-week randomized, double-blind, parallel-group, placebo-controlled trial in pediatric patients compared QVAR RediHaler 40 mcg and 80 mcg twice daily vs placebo in patients who previously used non-corticosteroid or low-dose ICS ± LABA therapy. Treatment with the QVAR RediHaler did not demonstrate a statistically significant difference vs placebo for the primary endpoint of FEV_1 $AUEC_{0\text{-}12wk}$; however, the change in weekly average of daily morning PEF was 11.3 L/min and 8.5 L/min for the 80 mcg/day and 160 mcg/day doses of QVAR RediHaler, respectively, with nominal significance (*QVAR RediHaler prescribing information 2017, Vandewalker et al 2017*).

CLINICAL GUIDELINES

- The National Asthma Education and Prevention Program (NAEPP) guideline from the NHLBI states that the initial treatment of asthma should correspond to the appropriate asthma severity category, and it provides a stepwise approach to asthma management. Long-term control medications such as ICSs, long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline, and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. ICSs are the most potent and consistently effective long-term asthma control medication. Quick-relief medications such as SABAs and anticholinergics are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness, and wheezing. Systemic corticosteroids are important in the treatment of moderate or severe exacerbations because these medications prevent progression of the exacerbation, speed recovery, and prevent relapses (*NHLBI 2007*).
  - LABAs are used in combination with ICSs for long-term control and prevention of symptoms in moderate or severe persistent asthma.
  - Of the adjunctive treatments available, a LABA is the preferred option to combine with an ICS in patients 12 years of age and older. This combination is also an option in selected patients 5 to 12 years of age.
- The GINA guideline also provides a stepwise approach to asthma management. It recommends an ICS as a preferred controller medication choice, with an increased ICS dose and/or addition of a LABA for increasing symptom severity (higher steps). At the highest step, it is recommended that the patient be referred for add-on treatment (e.g., tiotropium, omalizumab, mepolizumab) (*GINA 2017*).

SAFETY SUMMARY

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

- The risk of oral corticosteroid withdrawal or adrenal insufficiency in patients transitioning from oral to ICS agents
- Paradoxical bronchospasm
- Reduction in bone mineral density with long-term use
- Reduction in growth velocity in pediatric patients

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

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Aerospan (flunisolide)	Inhalation Aerosol (HFA): 80 mcg per actuation	Inhalation	Adults and adolescents 12 years of age and older: initial, 160 mcg twice daily; maximum, 320 mcg twice daily	Children 6 to 11 years of age: initial, 80 mcg twice daily; maximum, 160 mcg twice daily
Alvesco (ciclesonide)	Inhalation Aerosol (HFA): 80 or 160 mcg per actuation	Inhalation	Patients treated previously with only bronchodilators: initial, 80 mcg twice daily; maximum, 160 mcg twice daily Patients treated previously with an ICS: initial, 80 mcg twice daily; maximum, 320 mcg twice daily Patients treated previously with oral corticosteroids: initial, 320 mcg twice daily; maximum, 320 mcg twice daily	Not indicated for children <12 years of age.
ArmonAir RespiClick (fluticasone propionate)	Dry powder inhaler: 55, 113, or 232 mcg per inhalation	Inhalation	Patients ≥ 12 years of age: initial, 55, 113, or 232 mcg twice daily (dependent on asthma severity); maximum, 232 mcg twice daily	Not indicated for children <12 years of age.
Arnuity Ellipta (fluticasone furoate)	Dry powder inhaler: 100 or 200 mcg per actuation	Inhalation	Patients not previously on an ICS: initial, 100 mcg once daily; maximum, 200 mcg once daily Patients treated previously with an ICS: Starting dose should be based on previous asthma drug therapy and disease severity, 100 mcg or 200 mcg once daily	Not indicated for children <12 years of age.
Asmanex HFA (mometasone furoate)	Inhalation aerosol (HFA): 100 or 200 mcg per actuation	Inhalation	Patients previously receiving a medium-dose ICS: 100 mcg, 2 inhalations twice daily	Not indicated for children <12 years of age.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Patients previously receiving a high-dose ICS: 200 mcg, 2 inhalations twice daily Patients currently receiving oral corticosteroids: 200 mcg, 2 inhalations twice daily	
Asmanex Twisthaler (mometasone furoate)	Dry powder inhaler: 110 or 220 mcg per actuation	Inhalation	Patients treated previously with bronchodilators alone or an ICS: initial, 220 mcg once daily in the evening; maximum, 440 mcg administered as once daily in the evening or as 220 mcg twice daily Patients treated previously with oral corticosteroids: initial, 440 mcg twice daily; maximum, 880 mcg per day	Children 4 to 11 years of age: initial, 110 mcg once daily in the evening; maximum, 110 mcg per day. When administered once daily, should be taken only in the evening.
Flovent Diskus (fluticasone propionate)	Dry powder inhaler: 50, 100, or 250 mcg per actuation	Inhalation	Patients who are not on an ICS: initial, 100 mcg twice daily; maximum, 1000 mcg twice daily For other patients and those who do not respond adequately to the starting dose after 2 weeks, higher dosages may provide additional control.	Children 4 to 11 years of age: initial, 50 mcg twice daily; maximum, 100 mcg twice daily
Flovent HFA (fluticasone propionate)	Inhalation Aerosol (HFA): 44, 110, or 220 mcg per actuation	Inhalation	Patients who are not on an ICS: initial, 88 mcg twice daily; maximum, 880 mcg twice daily For other patients and those who do not respond adequately to the starting dose after 2 weeks, higher dosages may provide additional control.	Children 4 to 11 years of age: 88 mcg twice daily
Pulmicort Flexhaler (budesonide)	Dry powder inhaler: 90 or 180 mcg per actuation	Inhalation	Patients ≥ 18 years of age: initial, 360 mcg twice daily (selected patients can be initiated at 180 mcg twice daily); maximum, 720 mcg twice daily	Children 6 to 17 years of age: initial, 180 mcg twice daily (selected patients can be initiated at 360 mcg twice daily); maximum, 360 mcg twice daily
Pulmicort Respules (budesonide)	Suspension for nebulization: 0.25 mg/2 mL, 0.5 mg/2 mL, or 1 mg/2 mL	Inhalation	Children 12 months to 8 years of age treated previously with only bronchodilators: initial, 0.5 mg total daily dose administered either once daily or divided into two doses; maximum, 0.5 mg total daily dose	Not indicated in adults.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Children 12 months to 8 years of age treated previously with an ICS: initial, 0.5 mg total daily dose administered either once daily or divided into two doses; maximum, 1 mg total daily dose Children 12 months to 8 years of age treated previously with an oral corticosteroid: initial, 1 mg total daily dose administered either as 0.5 mg twice daily or 1 mg once daily; maximum, 1 mg total daily dose	
QVAR (beclomethasone dipropionate)	Inhalation aerosol (HFA): 40 or 80 mcg per actuation	Inhalation	Patients not previously on an ICS: initial, 40 to 80 mcg twice daily; maximum, 320 mcg twice daily Patients treated previously with an ICS: initial, 40 to 320 mcg twice daily; maximum, 320 mcg twice daily	Children 5 to 11 years of age: initial, 40 mcg twice daily; maximum, 80 mcg twice daily regardless of previous therapy
QVAR RediHaler (beclomethasone dipropionate)	Inhalation aerosol: 40 or 80 mcg per actuation	Inhalation	Patients ≥ 12 years of age: initial, 40, 80, 160, or 320 mcg twice daily (dependent on prior asthma therapy and asthma severity); maximum, 320 mcg twice daily	Children 4 to 11 years of age: initial, 40 mcg twice daily; maximum, 80 mcg twice daily

See the current prescribing information for full details.

CONCLUSION

- ICS agents are considered the cornerstone of drug therapy for long-term asthma control. Consensus guidelines emphasize the important role of ICS agents as long-term controller medications. The NHLBI and GINA asthma guidelines agree that ICSs are the preferred treatment for initiating therapy in children and adults with persistent asthma. It is important to note that the current consensus guidelines do not give preference to one ICS over another (*GINA 2017, NHLBI 2007*).
- Although individual head-to-head clinical trials have demonstrated some differences among ICS agents on certain endpoints, results have not conclusively demonstrated one agent to be significantly more effective than another in the management of asthma. Contraindications, warnings/precautions, and adverse effects are also similar among products.
- There are several differences among products with respect to their available formulations, dosing, and use in the pediatric population. Notably, some products are available as dry-powder formulations, while others are available as inhalation aerosols. Most ICSs are dosed twice daily; however, Arnuity Ellipta is administered once daily. Asmanex Twisthaler and Pulmicort Respules may be administered either once or twice daily. Also, while most ICSs are approved for use in children, the starting age varies among products. Table 5 summarizes some of these key characteristics.

Table 5. Characteristics of ICS agents

Drug	Formulation	Advantages	Disadvantages/Limitations
Aerospan (flunisolide)	Inhalation aerosol	• Approved in children ≥6 years	• Pregnancy Category C
Alvesco (ciclesonide)	Inhalation aerosol	-	• Not approved in children <12 years of age • Pregnancy Category C
ArmonAir RespiClick (fluticasone propionate)	Dry powder inhaler	-	• Contraindicated with hypersensitivity to milk proteins • Not studied in pregnant women
Arnuity Ellipta (fluticasone furoate)	Dry powder inhaler	• Once daily dosing	• Not approved in children <12 years of age • Pregnancy Category C • Contraindicated with hypersensitivity to milk proteins
Asmanex HFA (mometasone furoate)	Inhalation aerosol	-	• Not approved in children <12 years of age • Not studied in pregnant women
Asmanex Twisthaler (mometasone furoate)	Dry powder inhaler	• Approved in children ≥4 years • May be given either once or twice daily	• Contraindicated with hypersensitivity to milk proteins • Pregnancy Category C
Flovent Diskus (fluticasone propionate)	Dry powder inhaler	• Approved in children ≥4 years	• Contraindicated with hypersensitivity to milk proteins • Not studied in pregnant women
Flovent HFA (fluticasone propionate)	Inhalation aerosol	• Approved in children ≥4 years	• Not studied in pregnant women
Pulmicort Flexhaler (budesonide)	Dry powder inhaler	• Approved in children ≥6 years • Pregnancy Category B	• Contraindicated with hypersensitivity to milk proteins
Pulmicort Respules (budesonide)	Suspension for nebulization	• Approved in children 12 months to 8 years • May be given either once or twice daily • Pregnancy Category B (although not indicated in adults) • Generic availability	• Pediatric only; not approved in ages >8 years
QVAR (beclomethasone dipropionate)	Inhalation aerosol	• Approved in children ≥5 years	• Not studied in pregnant women
QVAR RediHaler (beclomethasone dipropionate)	Inhalation aerosol	• Approved in children ≥4 years	• Not studied in pregnant women

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Therapeutic Class Overview
Inhaled Beta-Agonist Combination Agents

INTRODUCTION

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

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Beta$_2$-agonist & corticosteroid combinations	
ADVAIR DISKUS & ADVAIR HFA (fluticasone propionate/salmeterol)	-
AIRDUO RESPICLICK (fluticasone propionate/salmeterol)	✔ *
BREO ELLIPTA (fluticasone furoate/vilanterol)	-
DULERA (mometasone furoate/formoterol fumarate dihydrate)	-
SYMBICORT (budesonide/formoterol fumarate dihydrate)	-
Beta$_2$-agonist & anticholinergic combinations	
ANORO ELLIPTA (umeclidinium/vilanterol)	-
BEVESPI AEROSPHERE (glycopyrrolate/formoterol fumarate)	-
COMBIVENT RESPIMAT (ipratropium/albuterol)	-
DUONEB (ipratropium/albuterol)	✔
STIOLTO RESPIMAT (tiotropium/olodaterol)	-
UTIBRON NEOHALER (glycopyrrolate/indacaterol)	-
Triple combination	
TRELEGY ELLIPTA (fluticasone furoate/umeclidinium/vilanterol)	-

*Authorized generic

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

INDICATIONS

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

Indication	ADVAIR DISKUS	ADVAIR HFA	AIRDUO RESPICLICK	BREO ELLIPTA	DULERA	SYMBICORT
Treatment of asthma	✔ (age ≥4 years)	✔ (age ≥12 years)	✔ (age ≥12 years)	✔ (age ≥18 years)	✔ (age ≥12 years)	✔ (age ≥6 years)
Maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema	✔ (250/50 strength only)			✔ (100/25 strength only)		✔ (160/4.5 strength only)
To reduce exacerbations of COPD in patients with a history of exacerbations	✔ (250/50 strength only)			✔ (100/25 strength only)		✔ (160/4.5 strength only)

(Prescribing information: ADVAIR HFA, 2017; ADVAIR DISKUS, 2017; AIRDUO RESPICLICK, 2017; BREO ELLIPTA, 2017; DULERA, 2017; SYMBICORT, 2017)

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

Indication	ANORO ELLIPTA	BEVESPI AEROSPHERE	COMBIVENT RESPIMAT	DUONEB	STIOLTO RESPIMAT	UTIBRON NEOHALER
Long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema	✔				✔	
Long-term, twice-daily, maintenance treatment of airflow obstruction in patients with COPD		✔				✔
For use in patients with COPD on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator			✔			
For the treatment of bronchospasm associated with COPD in patients requiring more than one bronchodilator				✔		

(Prescribing information: ANORO ELLIPTA, 2017; BEVESPI AEROSPHERE, 2016; COMBIVENT RESPIMAT, 2016; DUONEB, 2012; STIOLTO RESPIMAT, 2016; UTIBRON NEOHALER, 2017)

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

Indication	TRELEGY ELLIPTA
Long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema, who are on a fixed-dose combination of fluticasone furoate and vilanterol for airflow obstruction and reducing exacerbations in whom additional treatment of airflow obstruction is desired or for patients who are already receiving umeclidinium and a fixed-dose combination of fluticasone furoate and vilanterol.	✔

(TRELEGY ELLIPTA prescribing information, 2017)

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

CLINICAL EFFICACY SUMMARY

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

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

- Numerous trials have compared the combination ICS/LABA products to their respective individual components as monotherapy, and in general, results have demonstrated that administration of the combination product is more effective than monotherapy for improving lung function and/or achieving control of symptoms in asthma and COPD (Bateman et al, 2001; Bateman et al, 2004; Bateman et al, 2006; Bateman et al, 2014; Berger et al, 2010; Bernstein et al, 2015; Bleecker et al, 2014; Calverley et al, 2003; Corren et al, 2007; Eid et al, 2010; FDA AirDuo RespiClick Medical Review, 2017; Gappa et al, 2009; Hanania et al, 2003; Jenkins et al, 2006; Kerwin et al, 2009; Kerwin et al, 2013; Kuna et al, 2006; Lalloo et al, 2003; Lundback et al, 2006; Martinez et al, 2013; Meltzer et al, 2012; Morice et al, 2007; Murphy et al, 2008; Nelson et al, 2003a; Nathan et al, 2006; Noonan et al, 2006; O'Byrne et al, 2014; Pearlman et al, 2004; Pearlman et al, 2017; Pohl et al, 2006; Raphael et al, 2016; Raphael et al, 2017; Rennard et al, 2009; Rodrigo et al, 2016; Rodrigo et al, 2017; Sharafkaneh et al, 2012; Sher et al, 2016; Sher et al, 2017; Tal et al, 2002; Tashkin et al, 2008; Vaessen-Verberne et al, 2010; Vestbo et al, 2005; Weinstein et al, 2010). Results for reducing COPD exacerbations have been inconsistent (Dransfield et al, 2013; Ohar et al, 2014).
- Although a synergistic effect of combination inhalers has been suggested by some data, overall there is similar efficacy between the administration of the combination ICS/LABA products and their individual components used in combination (Chapman et al, 1999; Jenkins et al, 2006; Marceau et al, 2006; Noonan et al, 2006; Nelson et al, 2003b; Perrin et al, 2010; Rosenhall et al, 2002). Improved adherence with combination inhalers has also been suggested but not shown conclusively (Marceau et al, 2006; Perrin et al, 2010).
- A large, double-blind, randomized trial (N=6,112) compared fluticasone propionate/salmeterol 500/50 mcg twice daily to its individual components and to placebo over a three-year period in patients with COPD (Calverley et al, 2007). The primary endpoint, time to death from any cause, for the combination vs placebo failed to reach statistical significance (12.6% vs 15.2%; P=0.052). However, the difference in mortality between the combination therapy and fluticasone monotherapy did reach statistical significance (12.6% vs 16%; P=0.007). Treatment with the combination regimen resulted in significantly fewer exacerbations, improved health status, and improved lung function compared with placebo.
- A large, double-blind, randomized trial (SUMMIT; N=16,590) evaluated the use of fluticasone furoate/vilanterol vs fluticasone furoate alone, vilanterol alone, or placebo in a population of patients with moderate COPD and heightened cardiovascular risk (age ≥60 years and receiving medication for >2 of the following: hypercholesterolemia, hypertension, diabetes mellitus, or peripheral arterial disease) (Vestbo et al, 2016a). Compared with placebo, there was no significant benefit or worsening in all-cause mortality with combination therapy (hazard ratio [HR], 0.88 [95% confidence interval (CI), 0.74 to 1.04; P=0.137]) or with the components (fluticasone furoate HR, 0.91 [95% CI, 0.77 to 1.08; P=0.284]; vilanterol HR, 0.96 [95% CI, 0.81 to 1.14; P=0.655]). Composite cardiovascular events were also similar in the four groups (3.9% to 4.4%). All treatments reduced the risk of moderate to severe COPD exacerbations compared to placebo, with percent reductions of 29% (95% CI, 22 to 35), 12% (95% CI, 4 to 19), and 10% (95% CI, 2 to 18) in the fluticasone furoate/vilanterol, fluticasone furoate, and vilanterol groups, respectively.

- A 12-month, randomized, open-label trial (Salford Lung Study; N=2,799) compared the use of fluticasone furoate/vilanterol 100/25 mcg daily to continuation of usual care in a real-world patient population in the United Kingdom (Vestbo et al, 2016b). Enrolled patients had COPD, had had one or more exacerbations in the previous three years, and were taking regular maintenance inhaler therapy (one or more long-acting bronchodilators; ICS alone or in combination with a long-acting bronchodilator; or a combination of ICS, LABA, and LAMA). The primary endpoint, the rate of moderate or severe exacerbations among patients who had had an exacerbation within one year before the trial, was 1.74 per year in the fluticasone furoate/vilanterol group and 1.90 per year in the usual-care group, for a difference of 8.4% (95% CI, 1.1 to 15.2; P=0.02). Serious adverse events, including pneumonia, were similar between the two groups.
- A meta-analysis of 19 trials evaluated the use of ICS/LABA combinations compared to placebo in patients with COPD, and demonstrated a significant reduction in exacerbation rate between fluticasone propionate/salmeterol and placebo and between budesonide/formoterol and placebo (Nannini et al, 2013). For the number of patients who experienced one or more exacerbations, the differences between fluticasone propionate/salmeterol vs placebo and mometasone furoate/formoterol 200/10 mcg strength vs placebo were not statistically significant; however, the mometasone furoate/formoterol 400/10 mcg strength was associated with a lower proportion of patients experiencing ≥1 exacerbation. This meta-analysis also demonstrated that when results for all combined inhalers vs placebo were pooled, there was an overall reduction in mortality (odds ratio [OR], 0.82; 95% CI, 0.68 to 0.99).
- A meta-analysis of 14 trials evaluated the use of ICS/LABA combinations compared to use of the same LABA as monotherapy in patients with COPD (Nannini et al, 2012). This analysis demonstrated that exacerbation rates were reduced with ICS/LABA combination therapy compared to LABA monotherapy (rate ratio, 0.76; 95% CI, 0.68 to 0.84). However, there was a significant increase in the incidence of pneumonia with combination therapy compared to LABA monotherapy (OR, 1.55; 95% CI, 1.2 to 2.01).
- A meta-analysis of 14 trials (total N=6,641) compared fluticasone furoate/vilanterol to placebo, fluticasone furoate monotherapy, fluticasone propionate monotherapy, vilanterol monotherapy, or fluticasone propionate/salmeterol in patients with asthma (Dwan et al, 2016). Primary endpoints included health-related quality of life (HRQoL) and severe asthma exacerbations (defined by hospital admission or treatment with oral corticosteroids). Fewer than half of the studies reported on these primary endpoints, and there were few opportunities to combine results from the included studies. One of the 14 studies evaluated HRQoL (as measured by the Asthma Quality of Life Questionnaire [AQLQ]) for fluticasone furoate/vilanterol 100/25 mcg vs placebo; it identified a significant advantage of fluticasone furoate/vilanterol (mean difference, 0.30; 95% CI, 0.14 to 0.46). Two studies compared fluticasone furoate/vilanterol 100/25 mcg vs placebo with respect to exacerbations; both studies reported no exacerbations in either treatment arm. No comparisons relevant to the primary outcomes were found for fluticasone furoate/vilanterol at a higher dose (200/25 mcg) vs placebo. There was insufficient evidence to assess whether once-daily fluticasone furoate/vilanterol had better or worse safety or efficacy compared to twice-daily fluticasone propionate/salmeterol. The authors stated that firm conclusions could not be drawn due to the limited number of studies, variety of endpoints, and short duration of most trials.
- Several large studies focused primarily on safety endpoints, with efficacy endpoints as secondary (Peters et al, 2016; Stempel et al, 2016a; Stempel et al, 2016b). The studies compared the use of ICS/LABA combinations to ICS monotherapy in patients with asthma. These studies each demonstrated non-inferiority of the ICS/LABA combination to ICS monotherapy for the risk of serious asthma-related events, offering reassurance for the safety of these agents.
  - A randomized, double-blind study (AUSTRI; N=11,679) enrolled adults and adolescents (age ≥12 years) with persistent asthma and a history of exacerbation within the previous year (Stempel et al, 2016a). Patients were randomized to receive fluticasone propionate/salmeterol or fluticasone propionate monotherapy for 26 weeks. Patients were stratified by their baseline asthma control questionnaire (ACQ)-6 score and current asthma medication to determine the fluticasone propionate dose (100, 250, or 500 mcg twice daily) and were randomized to receive this dose with or without concomitant salmeterol.
    - The primary safety endpoint was the first serious asthma-related event, a composite endpoint that included death, endotracheal intubation, and hospitalization. There were 36 events in 34 patients in the fluticasone propionate/salmeterol group and 38 events in 33 patients in the fluticasone propionate group (HR, 1.03; 95% CI, 0.64 to 1.66). Fluticasone propionate/salmeterol was shown to be non-inferior to fluticasone propionate for this endpoint. There were no asthma-related deaths.
    - The main efficacy endpoint was the first severe asthma exacerbation, defined as asthma deterioration leading to the use of systemic glucocorticoids for ≥3 days or an asthma-related hospitalization or emergency department visit leading to the use of systemic glucocorticoids. At least one severe asthma exacerbation was reported in 480

patients (8%) in the fluticasone propionate/salmeterol group and in 597 patients (10%) in the fluticasone propionate group (HR, 0.79; 95% CI, 0.70 to 0.89; P<0.001).
- A similarly designed trial (VESTRI; N=6,208) enrolled pediatric patients 4 to 11 years of age (Stempel et al, 2016b). Enrolled patients had a history of exacerbation within the previous year and consistent use of asthma medication during the 4 weeks before enrollment. Patients were randomized, on the basis of pretrial medication, Childhood Asthma Control Test (C-ACT) score, and exacerbation history, to receive fluticasone propionate/salmeterol 100/50 mcg or 250/50 mcg or fluticasone propionate alone 100 mcg or 250 mcg twice daily for 26 weeks.
  - The primary safety endpoint, the first serious asthma-related event (death, intubation, or hospitalization), occurred in 27 patients in the fluticasone propionate/salmeterol group and 21 patients in the fluticasone propionate group (HR, 1.28; 95% CI, 0.73 to 2.27); this demonstrated non-inferiority for fluticasone propionate/salmeterol compared to fluticasone propionate (P=0.006). All of the events were asthma-related hospitalizations; there were no deaths or asthma-related intubations in either group.
  - The primary efficacy endpoint was the first severe asthma exacerbation, defined as asthma deterioration leading to the use of systemic glucocorticoids for ≥3 days or a depot injection of glucocorticoids. One or more severe asthma exacerbations occurred in 8.5% of patients in the fluticasone propionate/salmeterol group and 10.0% of patients in the fluticasone propionate group (HR, 0.86; 95% CI, 0.73 to 1.01).
- An additional randomized, double-blind trial (N=11,693) compared the safety of formoterol/budesonide to budesonide alone in patients ≥12 years of age (Peters et al, 2016). Enrolled patients were receiving daily asthma medication and had had at least one exacerbation in the previous year. Patients were stratified to a dose level of budesonide on the basis of asthma control and prior treatment. Patients were then randomized to receive budesonide/formoterol (two actuations of 80/4.5 mcg or 160/4.5 mcg) or budesonide alone (two actuations of 80 mcg or 160 mcg) twice daily for 26 weeks.
  - The primary safety endpoint, the first serious adverse event (death, intubation, or hospitalization), occurred in 43 of 5,846 patients receiving budesonide/formoterol and 40 of 5,847 patients receiving formoterol alone (HR, 1.07; 95% CI, 0.70 to 1.65); this demonstrated non-inferiority for budesonide/formoterol vs budesonide alone. Two of the events (both in the budesonide/formoterol group) were asthma-related deaths; the remaining events were asthma-related hospitalizations.
  - The primary efficacy endpoint, the first asthma exacerbation (defined as a deterioration of asthma requiring systemic glucocorticoids for ≥3 days, inpatient hospitalization for asthma, or an emergency department visit for asthma that resulted in receipt of systemic glucocorticoids) occurred in 9.2% of patients in the budesonide/formoterol group and 10.8% of patients in the budesonide group (HR, 0.84; 95% CI, 0.74 to 0.94).

<u>Comparisons between different ICS/LABA combinations</u>

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

- A meta-analysis of five trials comparing fluticasone propionate/salmeterol 250/50 mcg twice daily vs varied doses of budesonide/formoterol twice daily failed to demonstrate significant differences in exacerbations, asthma-related serious adverse events, FEV_1, rescue medication use, symptom scores, or peak expiratory flow (Lasserson et al, 2011).
- A head-to-head trial comparing mometasone/formoterol to fluticasone propionate/salmeterol demonstrated non-inferiority for mometasone/formoterol for the primary endpoint of FEV_1 area under the curve (AUC) (0 to 12 hr) (Bernstein et al, 2011). Treatment with mometasone/formoterol demonstrated a rapid onset of action, with significantly greater effects on FEV_1 at all time points up to 30 minutes post-dose compared to fluticasone propionate/salmeterol. Other secondary endpoints were not significantly different between groups.
- A head-to-head trial comparing fluticasone furoate/vilanterol 100/25 mcg daily to fluticasone propionate/salmeterol 250/50 mcg twice daily demonstrated no significant differences between treatments on the primary endpoint, the wm FEV_1 (0 to 24 hr) (Woodcock et al, 2013). There were also no significant differences in key secondary endpoints, including the time to onset of bronchodilator effect, percentage of patients obtaining ≥12% and ≥200 mL increase from baseline in FEV_1 at 12 hours and 24 hours, and change from baseline in trough FEV_1.

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

- A double-blind, double-dummy, two-year trial (N=1,323) compared the use of fluticasone propionate/salmeterol 250/50 mcg twice daily to tiotropium 18 mcg daily in patients with COPD (Wedzicha et al, 2008). This trial demonstrated no significant difference between groups in the rate of exacerbations or post-dose FEV_1. The study demonstrated higher mortality in the tiotropium group (6%) compared to the fluticasone propionate/salmeterol group (3%). This study was limited by the high number of withdrawals, which were unevenly distributed between the study arms.
- A double-blind, double-dummy, 12-week trial (N=494) compared the use of umeclidinium/vilanterol 62.5/25 mcg daily to tiotropium 18 mcg daily in patients with COPD who had been treated with tiotropium monotherapy at the time of enrollment (Kerwin et al, 2017). The primary endpoint, trough FEV_1, showed improved efficacy in the group that stepped up to combination therapy, with a between-group difference of 88 mL (95% CI, 45 to 131; P<0.001). Improvements with umeclidinium/vilanterol were also observed in some secondary endpoints, including the use of rescue medication use and transition dyspnea index (TDI) score.
- A double-blind, double-dummy, 12-week trial (N=623) evaluated the use of fluticasone furoate/vilanterol 100/25 mcg daily and tiotropium 18 mcg daily in patients with moderate-to-severe COPD and an increased cardiovascular risk (Covelli et al, 2015). There was no significant difference in the primary endpoint, the change from baseline in wm FEV_1 (0 to 24 hr). Minor differences were noted in some secondary efficacy endpoints and in the safety profiles. Pneumonia occurred more frequently in the fluticasone furoate/vilanterol group, and two patients in the tiotropium group died following cardiovascular events. The duration of this trial was not long enough to allow any firm conclusions about the relative efficacy and safety of fluticasone furoate/vilanterol vs tiotropium.
- Several trials have evaluated the potential benefits of adding a combination ICS/LABA to tiotropium vs the use of tiotropium alone in patients with COPD. These trials generally demonstrated an improvement in FEV_1 and some other lung function, symptom score, and quality-of-life endpoints (Hanania et al, 2012; Lee et al, 2016; Welte et al, 2009). Some trials (Lee et al, 2016; Welte et al, 2009) also demonstrated a reduction in the risk of COPD exacerbations or severe exacerbations; however, other trials and a meta-analysis have not confirmed a significant benefit for exacerbations (Aaron et al, 2007; Hanania et al, 2012; Karner et al, 2011).

Beta$_2$-agonist/anticholinergic combinations for COPD

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

- Numerous trials have compared the combination beta$_2$-agonist/anticholinergic products to their respective individual components as monotherapy, and in general, results have demonstrated that administration of the combination product is more effective than monotherapy for improving lung function and/or achieving control of symptoms in COPD (Beeh et al, 2015; Bone et al, 1994; Buhl et al, 2015; Decramer et al, 2014; Donohue et al, 2013; Dorinsky et al, 1999; Friedman et al, 1999; Hanania et al, 2017; Mahler et al, 2015; Martinez et al, 2017).
- A systematic review of 23 studies of beta$_2$-agonist/anticholinergic combinations compared to their monocomponents and to other single-agent treatments in patients with COPD was conducted (Price et al, 2016). The analysis demonstrated that beta$_2$-agonist/anticholinergic combinations significantly improved lung function compared to their individual components. These combinations generally improved other outcomes compared to monotherapies as well, including

symptoms and health status, but there were some discrepancies between lung function results and these patient-reported outcomes.

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

- A 12-week, non-inferiority, randomized, double-blind, triple-dummy, parallel group study (N=967) compared umeclidinium/vilanterol (62.5/25 mcg once daily) to tiotropium (18 mcg once daily) plus indacaterol (150 mcg once daily) (Kalberg et al, 2016). When comparing trough FEV_1 on day 85, umeclidinium/vilanterol demonstrated non-inferiority to combination treatment with tiotropium and indacaterol. Other measures, including rescue medication use, TDI focal scores, and St. George's Respiratory Questionnaire (SGRQ) scores, were also similar between both treatment groups on day 85 (P values not provided).
- A meta-analysis of 26 randomized controlled trials comparing the efficacy of umeclidinium/vilanterol, indacaterol/glycopyrrolate, formoterol plus tiotropium, salmeterol plus tiotropium, or indacaterol plus tiotropium to tiotropium alone found that umeclidinium/vilanterol was comparable to other LAMA/LABA fixed dose combination agents with respect to trough FEV_1, SGRQ scores, TDI focal scores, and need for rescue medication use (Huisman et al, 2015).
- A meta-analysis of 27 trials (N=30,361) including 4 LAMA/LABA fixed-dose combination agents (aclidinium/formoterol 400/12 mcg [not FDA approved for use in the U.S.], glycopyrrolate/indacaterol 110/50 mcg, tiotropium/olodaterol 5/5 mcg, and umeclidinium/vilanterol 62.5/25 mcg) showed non-significant differences in efficacy, exacerbations, and discontinuation rates (Schlueter et al, 2016). Safety profiles were also similar among the products.

ICS/LABA compared to LAMA/LABA combinations for COPD

- A randomized, double-blind, 12-week trial (N=717) compared umeclidinium/vilanterol 62.5/25 mcg once daily to fluticasone propionate/salmeterol 500/50 mcg twice daily in patients with moderate to severe COPD and no exacerbations in the previous year (Singh et al, 2015). It should be noted that the dose of fluticasone propionate was higher than what is recommended in the U.S. for treatment of COPD. Treatment with umeclidinium/vilanterol resulted in greater improvement in lung function than fluticasone propionate/salmeterol, with a difference of 80 mL (95% CI, 46 to 113) in the wm FEV_1 (0 to 24 hr) and a difference of 90 mL (95% CI, 55 to 125) in trough FEV_1. Effects on rescue bronchodilator use, mean TDI focal score, and SGRQ total scores, and the incidence of adverse events, were similar between groups.
- Two randomized, double-blind, 12-week trials (N=707 and N=700; reported together) compared umeclidinium/vilanterol 62.5/25 mcg daily to fluticasone propionate/salmeterol 250/50 mcg twice daily in patients with moderate to severe COPD without exacerbations in the previous year (Donohue et al, 2015). These trials also demonstrated a greater improvement in lung function endpoints for umeclidinium/vilanterol compared to fluticasone propionate/salmeterol, with differences in wm FEV_1 (0 to 24 hr) and trough FEV_1 ranging from 74 to 101 mL ($P<0.001$ for all comparisons). Adverse event rates and effects on TDI score and SGRQ were similar between groups.
- A randomized, double-blind, 26-week trial (ILLUMINATE; N=523) compared indacaterol/glycopyrrolate 110/50 mcg daily to fluticasone propionate/salmeterol 500/50 mcg twice daily in patients with COPD and a history of at least one exacerbation during the previous year (Vogelmeier et al, 2013). The dosing regimens for indacaterol/glycopyrrolate and fluticasone propionate/salmeterol evaluated in this study are different from those available and/or recommended for COPD in the U.S. The primary endpoint, FEV_1 AUC (0 to 12 hr), was significantly higher with indacaterol/glycopyrrolate than fluticasone propionate/salmeterol, with a treatment difference of 138 mL (95% CI, 100 to 176; $P<0.0001$). Benefits were also seen for indacaterol/glycopyrrolate for some secondary endpoints, including additional lung function measures, change from baseline in rescue medication use, and TDI focal score; the difference in SGRQ was not statistically significant.
- A large, randomized, double-blind, 52-week trial (FLAME; N=3,362) compared indacaterol/glycopyrrolate 110/50 mcg daily to fluticasone propionate/salmeterol 500/50 mcg twice daily in patients with COPD and a history of at least one exacerbation during the previous year (Wedzicha et al, 2016). Again, these dosing regimens varied from U.S. recommendations. The primary endpoint, the annual rate of all COPD exacerbations, was 11% lower in the indacaterol/glycopyrrolate group than in the fluticasone propionate/salmeterol group (3.59 vs 4.03; rate ratio, 0.89; 95% CI, 0.83 to 0.96; P=0.003). Lung function was also improved to a greater extent with indacaterol/glycopyrrolate, with a difference in trough FEV_1 of 62 mL between groups ($P<0.001$).
- A randomized, double-blind, crossover trial (N=229) evaluated the use of tiotropium/olodaterol 2.5/5 mcg and 5/5 mcg once daily and fluticasone propionate/salmeterol 250/50 mcg and 500/50 mcg twice daily in patients with moderate to severe COPD; each patient received each of the four treatments for 6 weeks separated by 3-week washout periods

(Beeh et al, 2016). The lower dose of each combination is the dose available/recommended for COPD in the U.S. The primary endpoint, FEV_1 AUC (0 to 12 hr), was greater for the tiotropium/olodaterol regimens (range, 295 to 317 mL) than for the fluticasone propionate/salmeterol regimens (range, 188 to 192 mL) (P<0.0001). FEV_1 AUC (12 to 24 hr) and FEV_1 AUC (0 to 24 hr) also favored tiotropium/olodaterol. Rates of adverse events were similar among the treatments.

Triple combination for COPD

- Fluticasone furoate/umeclidinium/vilanterol is the first FDA-approved "closed triple" inhaler – an inhaler containing 3 active ingredients: an ICS, a LAMA, and a LABA. FDA approval was based primarily on the coadministration of umeclidinium plus the fluticasone furoate/vilanterol combination.
- Two 12-week randomized studies (N=619 and N=620; published together) evaluated the efficacy and safety of double-blind treatment with umeclidinium 62.5 mcg, umeclidinium 125 mcg, or placebo when added to open-label fluticasone furoate/vilanterol 100/25 mcg (Siler et al, 2015). In both studies, the primary endpoint, trough FEV_1, was significantly improved with the addition of umeclidinium, with improvements ranging from 111 to 128 mL (P<0.001 for all comparisons vs placebo). Improvement was also demonstrated on the secondary endpoint of wm FEV_1 (0 to 6 hr), with improvements ranging from 125 to 153 mL (P<0.001 for all comparisons vs placebo). SGRQ results were inconsistent. No substantial benefit was observed with umeclidinium 125 mcg over 62.5 mcg, which is consistent with findings in the umeclidinium monotherapy studies.
- Once-daily triple therapy with fluticasone furoate/umeclidinium/vilanterol has also been compared to twice-daily budesonide/formoterol 400/12 mcg in a 24-week, double-blind, double-dummy randomized trial (FULFIL; N=1810) (Lipson et al, 2017). The formulation/dosing regimen of budesonide/formoterol in this trial is different from the formulation available in the U.S. The trial demonstrated improvements in the change from baseline in trough FEV_1 (difference, 171 mL; 95% CI, 148 to 194; P<0.001), SGRQ (difference, -2.2; 95% CI, -3.5 to -1.0; P<0.001), and the rate of moderate/severe exacerbations (rate ratio, 0.65; 95% CI, 0.49 to 0.86; P=0.002). Although the comparator regimen is not available in the U.S., this trial further supports the efficacy of triple inhaler therapy with fluticasone furoate/umeclidinium/vilanterol.
- Preliminary information from the IMPACT study (N=10,335) has been made available from the fluticasone furoate/umeclidinium/vilanterol manufacturer (GlaxoSmithKline, 2017). This study demonstrated a reduction in moderate/severe exacerbations with fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 mcg (0.91 exacerbations per year) compared to each of two dual COPD therapies, fluticasone furoate/vilanterol 100/25 mcg (1.07 per year) and umeclidinium/vilanterol 62.5/25 mcg (1.21 per year); P<0.001 for comparisons of fluticasone furoate/umeclidinium/vilanterol to each dual therapy. Significant improvements were also seen in key secondary endpoints, including trough FEV_1 and SGRQ.

CLINICAL GUIDELINES

Asthma

- The National Asthma Education and Prevention Program (NAEPP) guideline from the NHLBI states that the initial treatment of asthma should correspond to the appropriate asthma severity category, and it provides a stepwise approach to asthma management. Long-term control medications such as ICS, long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline, and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. ICS are the most potent and consistently effective long-term asthma control medication. Quick-relief medications such as SABAs and anticholinergics are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness, and wheezing. Systemic corticosteroids are important in the treatment of moderate or severe exacerbations because these medications prevent progression of the exacerbation, speed recovery, and prevent relapses (NHLBI, 2007).
  - LABA are used in combination with ICS for long-term control and prevention of symptoms in moderate or severe persistent asthma.
  - Of the adjunctive treatments available, a LABA is the preferred option to combine with an ICS in patients 12 years of age and older. This combination is also an option in selected patients 5 to 12 years of age.
- The Global Initiative for Asthma (GINA) guideline also provides a stepwise approach to asthma management. It recommends an ICS as a preferred controller medication choice, with an increased ICS dose and/or addition of a LABA for increasing symptom severity (higher steps). At the highest step, it is recommended that the patient be referred for add-on treatment (eg, tiotropium, omalizumab, mepolizumab) (GINA, 2017).

- The available asthma guidelines are generally similar; however, one difference among them is the recommendation of ICS/formoterol as both maintenance and rescue therapy by the GINA guidelines. The NHLBI do not recommend LABA medications for the management of acute asthma symptoms or exacerbations (GINA, 2017; NHLBI, 2007).

COPD

- The 2017 GOLD guidelines underwent a significant update from prior guideline versions, and the 2018 GOLD report is a minor revision of the 2017 GOLD Report. 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, 2018):
  - Inhaled bronchodilators are recommended over oral bronchodilators.
  - LAMA and LABA 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.
  - Combination treatment with a LABA and LAMA reduces exacerbations compared to monotherapy or ICS/LABA.
  - LAMA have a greater effect on exacerbation reduction compared to LABA and decrease hospitalizations.
  - Combination treatment with a LABA and LAMA increases FEV_1 and reduces symptoms compared to monotherapy.
  - Combinations of LAMA and LABA in a single inhaler improve lung function compared to placebo; the improvement is greater than long-acting bronchodilator monotherapy, but less than fully additive of effects for the individual components. In studies where patient-reported outcomes are the primary endpoint or in pooled analyses, combination bronchodilators have a greater impact on these endpoints compared to monotherapies.
  - Long-term monotherapy with ICS is not recommended. Long-term treatment with ICS may be considered in association with LABA for patients with a history of exacerbations despite treatment with long-acting bronchodilators.
  - An ICS combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD. However, regular treatment with ICS increases the risk of pneumonia, especially in those with severe disease.
  - Triple inhaled therapy of ICS/LAMA/LABA improves lung function, symptoms, and health status and reduces exacerbations compared to ICS/LABA or LAMA monotherapy.
  - Treatment recommendations are given for patients with COPD based on their GOLD patient group (see Table 3 below).
    - Group A: Patients should be offered bronchodilator treatment (short- or long-acting). 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

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

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

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

SAFETY SUMMARY

Beta$_2$-agonist/corticosteroid combinations

- Beta$_2$-agonist/ICS combinations are generally contraindicated for the primary treatment of status asthmaticus or other acute episodes of asthma/COPD where intensive measures are required.
- Beta$_2$-agonist/ICS combinations are generally contraindicated in patients with hypersensitivity to any ingredients in the formulation. ADVAIR DISKUS, AIRDUO RESPICLICK, and BREO ELLIPTA are specifically contraindicated in patients with a severe hypersensitivity to milk proteins.
- Previously, ICS/LABA combinations had a boxed warning about an increased risk of asthma-related death, which had been observed with the LABA salmeterol. However, the boxed warning was removed from the prescribing information for ICS/LABA combinations in December 2017 based on an FDA review of four large clinical safety trials, which demonstrated that these combinations do not result in a significantly increased risk of asthma-related death, hospitalizations, or the need for intubation compared to ICS alone. There is still a warning/precaution in the prescribing information of ICS/LABA combinations related to the increased risk of asthma-related death with LABA monotherapy. A description of the clinical safety trials with ICS/LABA combinations has been added to the prescribing information for these products (FDA, 2017).
- Other key warnings and precautions include:
  - Significant cardiovascular effects and fatalities with excessive use of beta$_2$-agonists
  - Cardiovascular and/or central nervous system effects from beta-adrenergic stimulation (seizures, angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia)
  - Paradoxical bronchospasm
  - Hypercorticism and adrenal suppression due to systemic absorption of the corticosteroid
  - The need for caution when transferring patients from systemic corticosteroid therapy (deaths due to adrenal insufficiency have occurred)
  - Lower respiratory tract infections/pneumonia
  - Local infections of the mouth and pharynx with *candida albicans*
  - Reduced growth velocity in pediatric patients
  - The potential for drug interactions with strong cyp3a4 inhibitors; concomitant use is not recommended due to the potential for increased systemic effects
  - The potential for developing glaucoma, increased intraocular pressure, or cataracts
  - Immunosuppression
  - Hypersensitivity
  - Reduction in bone mineral density
- It is also important to note that ICS/LABA combinations should not be initiated in the setting of disease deterioration or potentially life-threatening episodes.
- Commonly reported adverse events (≥5% for at least one medication in the class) include oral candidiasis, hoarseness/dysphonia, nasopharyngitis/pharyngitis, pharyngolaryngeal/oropharyngeal pain, sinusitis, upper respiratory

tract infection, upper respiratory tract inflammation, bronchitis, cough, headache, gastrointestinal discomfort, and nausea/vomiting.

Beta$_2$-agonist/anticholinergic combinations

- Both albuterol/ipratropium combination products are contraindicated in patients with hypersensitivity to any component of the product, or hypersensitivity to atropine or its derivatives. ANORO ELLIPTA is contraindicated in patients with hypersensitivity to any component of the product, as well as in patients with severe hypersensitivity to milk proteins. BEVESPI AEROSPHERE and UTIBRON NEOHALER are contraindicated in patients with hypersensitivity to any component of the product. BEVESPI AEROSPHERE, STIOLTO RESPIMAT, and UTIBRON NEOHALER are all contraindicated in patients with asthma without use of a long-term asthma control medication (and are not indicated for the treatment of asthma).
- There are no boxed warnings for the albuterol/ipratropium combination products. ANORO ELLIPTA, BEVESPI AEROSPHERE, STIOLOTO RESPIMAT and UTIBRON NEOHALER have boxed warnings stating that LABA increase the risk of asthma-related death. Data from a large placebo-controlled U.S. trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including formoterol, one of the active ingredients in BEVESPI AEROSPHERE, indacaterol, one of the active ingredients in UTIBRON NEOHALER, vilanterol, one of the active ingredients in ANORO ELLIPTA, and olodaterol, one of the active ingredients in STIOLOTO RESPIMAT. The safety and efficacy of ANORO ELLIPTA, BEVESPI AEROSPHERE, STIOLOTO RESPIMAT, and UTIBRON NEOHALER in patients with asthma have not been established, and these products are not indicated for the treatment of asthma.
- Warnings and precautions are very similar among products, and include the following:
  - Paradoxical bronchospasm: May produce paradoxical bronchospasm, which can be life-threatening. If it occurs, the product should be discontinued and alternative therapy instituted.
  - Cardiovascular effect: Beta$_2$-agonists can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, and/or symptoms. If these symptoms occur, the product may need to be discontinued. In addition, electrocardiogram (ECG) changes may occur. These products should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
  - Ocular effects: Ipratropium and other anticholinergic agents may increase intraocular pressure, which may precipitate or worsen narrow-angle glaucoma. They should be used with caution in patients with narrow-angle glaucoma. In addition, patients should avoid spraying product into eyes, as this can cause eye pain and visual symptoms.
  - Urinary retention: Ipratropium and other anticholinergic agents may cause urinary retention. Caution is advised when administering to patients with prostatic hyperplasia or bladder-neck obstruction.
  - The recommended dose should not be exceeded: Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma.
  - Hypersensitivity reactions: Urticaria, angioedema, rash, pruritus, bronchospasm, laryngospasm, oropharyngeal edema, and anaphylaxis may occur. If such a reaction occurs, therapy should be discontinued and alternative treatment considered.
  - Coexisting conditions: Due to the beta$_2$-agonist component, caution is advised in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines.
  - Hypokalemia: β-agonists may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.
  - Drug interactions with strong cytochrome P4503A4 inhibitors; increased cardiovascular effects may occur (ANORO ELLIPTA only).
  - Reports of anaphylactic reactions in patients with severe milk protein allergy (ANORO ELLIPTA only).
  - Deterioration of disease and acute episodes; drug has not been studied in this setting and is not to relieve acute symptoms (ANORO ELLIPTA and STIOLTO RESPIMAT only).
- Adverse reactions are similar among products and include back pain, bronchitis, upper respiratory infection, lung disease, headache, dyspnea, nasopharyngitis/pharyngitis, and cough.
- In a 12-week trial comparing COMBIVENT RESPIMAT to COMBIVENT inhalation aerosol, rates of adverse reactions were very similar between groups. In a 48-week safety trial, most adverse reactions were similar in type and rate between treatment groups; however, cough occurred more frequently in patients enrolled in the COMBIVENT RESPIMAT group (7%) than the COMBIVENT inhalation aerosol group (2.6%).

- The choice of a specific LAMA/LABA fixed dose combination product is not based on any difference in the safety profile (Matera et al, 2016).

Triple combination

- TRELEGY ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or any ingredients in the formulation.
- TRELEGY ELLIPTA has a boxed warning noting that LABA such as vilanterol increase the risk of asthma-related death. TRELEGY ELLIPTA is not indicated for the treatment of asthma.
- Similar to other combination agents for COPD (and/or asthma), TRELEGY ELLIPTA has a number of additional warnings and precautions; these include:
  - Not initiating in patients with rapidly deteriorating COPD
  - Avoiding excessing use
  - Local effects of ICS
  - Risk of pneumonia
  - Immunosuppression
  - Using caution when transferring patients from systemic corticosteroid therapy
  - Hypercorticism and adrenal suppression
  - Drug interactions with strong cytochrome P450 3A4 inhibitors
  - Paradoxical bronchospasm
  - Hypersensitivity reactions
  - Cardiovascular effects
  - Reduction in bone mineral density
  - Glaucoma and cataracts
  - Urinary retention
  - Using caution in patients with certain coexisting conditions such as convulsive disorders or thyrotoxicosis
  - Hypokalemia and hyperglycemia
- The most common adverse reactions with TRELEGY ELLIPTA include headache, back pain, dysgeusia, diarrhea, cough, oropharyngeal pain, and gastroenteritis.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Components/ Dose Strengths	Route	Usual Recommended Frequency
Beta$_2$-agonist & corticosteroid combinations				
ADVAIR DISKUS	Inhalation powder	fluticasone propionate/salmeterol 100/50, 250/50 & 500 mcg	Inhalation	2 times daily
ADVAIR HFA	Aerosol inhaler	fluticasone propionate/salmeterol 45/21, 115/21 & 230/21 mcg	Inhalation	2 times daily
AIRDUO RESPICLICK	Inhalation powder	fluticasone propionate/salmeterol 55/14, 113/14 & 232/14 mcg	Inhalation	2 times daily
BREO ELLIPTA	Inhalation powder	fluticasone furoate/vilanterol 100/25 & 200/25 mcg	Inhalation	Once daily
DULERA	Aerosol inhaler	mometasone furoate/ formoterol fumarate dihydrate 100/5 & 200/5 mcg	Inhalation	2 times daily
SYMBICORT	Aerosol inhaler	budesonide/ formoterol fumarate dihydrate 80/4.5 & 160/4.5 mcg	Inhalation	2 times daily
Beta$_2$-agonist & anticholinergic combinations				
ANORO ELLIPTA	Inhalation powder	umeclidinium/vilanterol 62.5/25 mcg	Inhalation	Once daily

Drug	Available Formulations	Components/ Dose Strengths	Route	Usual Recommended Frequency
BEVESPI AEROSPHERE	Inhalation spray	glycopyrrolate/formoterol fumarate 9/4.8 mcg	Inhalation	2 times daily
COMBIVENT RESPIMAT	Inhalation spray	ipratropium bromide/albuterol 20/100 mcg	Inhalation	4 times daily
DUONEB	Nebulizer solution	ipratropium bromide/albuterol sulfate 0.5/3 mg	Inhalation (nebulizer)	4 times daily
STIOLTO RESPIMAT	Inhalation spray	tiotropium bromide/olodaterol 2.5/2.5 mcg	Inhalation	Once daily
UTIBRON NEOHALER	Inhalation powder	indacaterol/glycopyrrolate 27.5/15.6 mcg	Inhalation	2 times daily
Triple combination				
TRELEGY ELLIPTA	Inhalation powder	fluticasone furoate/ umeclidinium/vilanterol 100/62.5/25 mcg	Inhalation	Once daily

See the current prescribing information for full details.

CONCLUSION

- Inhaled medications are a mainstay of treatment for asthma and COPD, and a large amount of clinical evidence supports the safety and efficacy of beta$_2$-agonist combinations for these indications.
- Trials have demonstrated that the combination products have efficacy that is superior to the individual separate components given as monotherapy for the treatment of both asthma and COPD.
- For the treatment of asthma, current guidelines support the use of combination ICS/LABA products for long-term control and prevention of symptoms in patients who do not achieve sufficient symptom control with an ICS as monotherapy (GINA, 2017; NHLBI, 2007). Single-agent LABA therapy should not be used for asthma management due to the increased risk of asthma-related death, as well as asthma-related hospitalization in pediatric and adolescent patients. However, recent drug safety information from the FDA states that no significantly increased risk of serious asthma outcomes has been seen with the use of ICS/LABA combinations, and boxed warnings about this potential risk have been removed from the prescribing information for the ICS/LABA combinations (FDA, 2017).
  - A practical benefit of ICS/LABA combinations is that their use ensures that patients are not using a LABA without concomitant ICS.
- For the treatment of COPD, GOLD guidelines recommend the use of ICS/LABA products as an option for some patients at higher risk of exacerbations; however, the use of bronchodilator(s) without an ICS is recommended as first-line treatment for most COPD patients. The use of LAMA/LABA combination therapy as a first- or second-line treatment is recommended in most patients with COPD, with the exception of low-risk patients with milder symptoms (GOLD, 2018).
- None of the current asthma or COPD treatment guidelines recommend the use of one specific combination product over another (Criner et al, 2015; GINA, 2017; GOLD, 2018; NHLBI, 2007).
- Several single-ingredient inhalers containing beta$_2$-agonists, ICS, or anticholinergics are also available. Beta$_2$-agonist combinations offer improved convenience over the use of multiple separate inhalers.

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Therapeutic Class Overview
Antiemetics

INTRODUCTION

- Nausea, the sensation of anticipating vomiting, may occur with or without concomitant dyspepsia, other gastrointestinal (GI) symptoms, or vomiting, which is the forceful expulsion of gastric contents (*Longstreth 2018*).
- Chemotherapy-induced nausea and vomiting (CINV) is often viewed as the most severe and distressing form of nausea and vomiting (n/v) that occurs in patients with cancer. Additional causes of n/v in this population include surgery, opioid therapy, and radiation (*Hesketh, 2017[a]*).
- Normal function of the upper GI tract involves interactions between the gut and the central nervous system (CNS), with the motor function of the GI tract being controlled at the level of the parasympathetic and sympathetic nervous systems, enteric brain neurons, and smooth muscle cells (*Longstreth 2018*).
- Three distinct types of CINV have been defined, including (*Hesketh 2017[a], Hesketh 2017[b]*):
  - Acute emesis, which most commonly begins within 1 to 2 hours of chemotherapy and usually peaks in the first 4 to 6 hours
  - Delayed emesis, occurring beyond 24 hours after chemotherapy
  - Anticipatory emesis, occurring prior to treatment as a conditioned response in patients who have developed significant n/v during previous cycles of chemotherapy
- Approximately one-third of surgical patients have nausea, vomiting, or both after receiving general anesthesia, with increased risk associated with the female gender, nonsmoker status, previous history of postoperative n/v (PONV), and use of postoperative opioids (*Longstreth 2018*).
- Nausea and/or vomiting caused by radiation therapy (RT) is generally less severe than that caused by chemotherapy. The pathophysiology of radiation-induced n/v (RINV) remains unclear, but it is thought to be similar to that caused by chemotherapy (*Feyer et al 2017*).
- Nausea with or without vomiting is common in early pregnancy and affects 70 to 85% of pregnant women. Severe vomiting resulting in dehydration and weight loss is termed hyperemesis gravidarum and occurs less frequently. The treatment goals in patients with nausea and vomiting of pregnancy (NVP) are to reduce symptoms through changes in diet/environment and by medication, to correct consequences or complications of n/v such as dehydration, and to minimize the fetal effects of NVP treatment (*American College of Obstetrics and Gynecologists [ACOG] 2015, Smith et al 2017*).
- The mechanism of action for the 5-hydroxytryptamine (5-HT3, or serotonin) agents results from the blockade of 5-HT3 receptors in both the gastric area and the chemoreceptor trigger zone in the CNS. By blocking these receptors, these medications disrupt the signal to vomit and reduce the sensation of nausea (*Mannix et al 2006*).
- The substance P/neurokinin 1 (NK1) receptor antagonists cross the blood brain barrier and occupy the NK1 receptors in the brain, leading to reduced symptoms of n/v.
- Synthetic delta-9-tetrahydrocannabinol (THC) is the active ingredient in the THC derivative agents, also known as the cannabinoids. Cannabinoid receptors have been discovered in neural tissues, and these receptors may play a role in mediating the antiemetic effects of cannabinoids such as dronabinol and nabilone. These agents, like other cannabinoids, have the potential to be abused and produce psychological dependence. Both dronabinol and nabilone may produce alterations in mood (euphoria, detachment, depression, anxiety) and alterations in reality (distorted perceptions of objects and time and hallucinations).
- The mechanism of action of Diclegis and Bonjesta (doxylamine succinate/pyridoxine hydrochloride [HCl]) are unknown; however, doxylamine is known to compete with histamine for H1-receptor sites and block the chemoreceptor trigger zone thereby decreasing n/v (*Smith et al 2017*).
- The 5-HT3 receptor antagonists are Food and Drug Administration (FDA)-approved for the treatment of CINV, PONV, and/or RINV, although the medications and various dosage forms of each agent differ slightly with respect to these indications.
- The substance P/NK1 receptor antagonists are currently FDA-approved for the prevention of CINV. In addition, aprepitant is approved for the prevention of PONV.

- The combination product, Akynzeo, contains palonosetron, a 5-HT3 receptor antagonist, and netupitant, a substance P/NK1 receptor antagonist. This agent is approved for prevention of acute and delayed n/v associated with initial and repeat courses of cancer chemotherapy.
- Diclegis and Bonjesta are fixed-dose combination products of doxylamine succinate, an antihistamine, and pyridoxine HCl, a vitamin B6 analog. Diclegis and Bonjesta are indicated for the treatment of NVP in women who do not respond to conservative management. It should be noted that these agents have not been studied in hyperemesis gravidarum.
  - The combination of doxylamine and pyridoxine was previously available in the United States under the brand name Bendectin. However, this product was removed from the market in 1983 due to law suits alleging teratogenicity despite scientific evidence of the safety and efficacy of the medication. A meta-analysis *(*MA) of controlled studies on outcome of pregnancies exposed to Bendectin reported no increase in the incidence of birth defects (*Smith et al 2017*).
- The scope of this review will focus on the agents outlined in Table 1 for their respective FDA-approved indications as related to CINV. Other agents including anticholinergic agents, antihistamines, glucocorticoids, and dopamine receptor antagonists may also be effective antiemetics; however, they have been excluded from this review.
- Medispan Therapeutic Class: 5-HT3 Receptor Antagonists; Substance P/NK1 Receptor Antagonists; Antiemetics – Miscellaneous; Antiemetic Combinations – Two Ingredient.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Akynzeo (palonosetron/netupitant) capsule	–
Aloxi (palonosetron) IV solution*	✔ †
Anzemet (dolasetron) tablets	–
Bonjesta (doxylamine succinate/pyridoxine HCl) 20 mg extended-release tablets	–
Cesamet (nabilone) capsule	–
Civanti (aprepitant) IV emulsion	–
Diclegis (doxylamine succinate/pyridoxine HCl) 10 mg delayed-release tablets	✔ §
Emend (aprepitant) oral suspension	–
Emend (aprepitant) capsule, combination pack	✔
Emend (fosaprepitant) IV solution	–‖
granisetron injection, tablets	✔ ‡
Marinol (dronabinol) capsule	✔
Sancuso (granisetron) transdermal patch	–
Sustol (granisetron) extended-release injection	–
Syndros (dronabinol) oral solution	–
Varubi (rolapitant) tablet, IV emulsion	–
Zofran (ondansetron) IV solution, injection, oral solution, tablet	✔ ‡
Zofran ODT (ondansetron) ODT	✔ ‡
Zuplenz (ondansetron) oral soluble film	–

Abbrv: IV=intravenous, ODT=orally disintegrating tablet
*FDA approved ALOXI as an oral capsule on August 22, 2008, but neither Helsinn Healthcare nor Eisai have ever marketed ALOXI capsules. ALOXI oral capsules are listed on FDA's web site as "discontinued."
†Generics manufactured by Teva, Dr. Reddy's, and Cipla have launched. Sandoz, Exela, and Fresenius Kabi have also received FDA-approval to market a generic but launch plans are unknown.
‡Generic available in at least 1 dosage form and/or strength.
§Actavis received FDA approval for generic Diclegis on August 19, 2016; however, it is not yet marketed.
‖Sandoz received FDA approval for generic Emend injection on September 24, 2012. However, patents will likely protect Emend injection from generic competition until March 4, 2019, pending patent litigation.

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	5-HT$_3$ Receptor Antagonists				Substance P/NK$_1$ Receptor Antagonists			THC Derivatives		Combination Products	
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Aprepitant	Fosaprepitant	Rolapitant	Dronabinol	Nabilone	Palonosetron/ netupitant	Doxylamine succinate/ pyridoxine HCl
Anorexia in patients with AIDS											
Anorexia associated with weight loss in adults with AIDS								✔			
CINV											
N/V associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments								✔	✔		
Highly emetogenic cancer chemotherapy (HEC) – prevention of acute n/v associated with initial and repeat courses in adults				✔							
Prevention of acute and delayed n/v associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, HEC in patients ≥ 6 months of age					✔ (oral suspension)						
Prevention of acute n/v associated with initial and repeat courses of emetogenic chemotherapy, including HEC in pediatric patients aged 1 month to < 17 years				✔							
Prevention of acute and delayed n/v associated with initial and repeat courses of HEC, including high-dose cisplatin, in adults					✔ (IV emulsion)	✔ *	✔ *				
Prevention of acute and delayed n/v associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, HEC										✔	
Prevention of acute and delayed n/v associated with initial and repeat courses of HEC, including high-dose cisplatin, in patients ≥ 12 years of age					✔ * (capsule)						
Prevention of delayed n/v associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, HEC							✔ *				
Prevention of n/v associated with HEC including cisplatin ≥ 50 mg/m^2			✔ (tablet, ODT, oral solution,								

Indication	5-HT$_3$ Receptor Antagonists				Substance P/NK$_1$ Receptor Antagonists			THC Derivatives		Combination Products	
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Aprepitant	Fosaprepitant	Rolapitant	Dronabinol	Nabilone	Palonosetron/ netupitant	Doxylamine succinate/ pyridoxine HCl
			oral soluble film)								
Prevention of n/v associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin		✔ (injection, tablets)									
Prevention of n/v associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin, in patients ≥ 6 months of age			✔ (injection)								
Moderately emetogenic cancer (MEC) chemotherapy – prevention of acute and delayed n/v associated with initial and repeat courses in adults				✔	✔ (IV emulsion)						
Prevention of n/v in patients receiving MEC and/or HEC for up to 5 consecutive days		✔ (TD)									
Prevention of n/v associated with initial and repeat courses of MEC			✔ (tablet, ODT, oral solution, oral soluble film)								
Prevention of n/v associated with MEC, including initial and repeat courses in ages ≥ 2 years	✔										
Prevention of n/v associated with initial and repeat courses of MEC, in patients ≥ 6 months of age					✔ (oral suspension)						
Prevention of acute and delayed n/v associated with initial and repeat courses of MEC or anthracycline and cyclophosphamide combination chemotherapy regimens.		✔ * (ER injection)									
Prevention of n/v associated with initial and repeat courses of MEC						✔ *					
Prevention of n/v associated with initial and repeat courses of MEC in patients ≥ 12 years of age					✔ * (capsule)						
NVP											

Indication	5-HT$_3$ Receptor Antagonists				Substance P/NK$_1$ Receptor Antagonists			THC Derivatives		Combination Products	
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Aprepitant	Fosaprepitant	Rolapitant	Dronabinol	Nabilone	Palonosetron/ netupitant	Doxylamine succinate/ pyridoxine HCl
Treatment of NVP in women who do not respond to conservative management											✔
PONV											
Prevention of PONV for up to 24 hours following surgery; efficacy beyond 24 hours has not been demonstrated; as with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that n/v will occur post-operatively. In patients where n/v must be avoided postoperatively, Aloxi injection is recommended even where the incidence of PONV is low				✔							
Prevention of PONV in adults			✔ (tablet, ODT, oral solution)		✔ (capsule)						
Prevention of PONV; as with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that n/v will occur post-operatively. In patients where n/v must be avoided postoperatively, this drug is recommended even where the incidence of PONV is low.		✔ (injection)	✔ (injection†, oral soluble film)								
RINV											
Prevention of n/v associated with RT, including TBI and fractionated abdominal RT		✔ (tablets)									
Prevention of n/v associated with radiotherapy in patients receiving either TBI, single high-dose fraction to the abdomen, or daily fractions to the abdomen			✔ (tablet, ODT, oral solution, oral soluble film)								

Abbrv: 5-HT3 = serotonin (5-hydroxytryptamine) 3 receptor, AIDS = acquired immunodeficiency syndrome, ER = extended release, HEC = highly emetogenic cancer chemotherapy, MEC = moderately emetogenic cancer chemotherapy, n/v = nausea/vomiting, NVP = nausea and vomiting of pregnancy, NK1 = neurokinin 1, ODT = orally disintegrating tablet, PONV = postoperative nausea and vomiting, RINV = radiation-induced nausea and vomiting, RT = radiation therapy, TBI = total body irradiation, TD = transdermal patch, THC = delta-9-tetrahydrocannabinol

* When used in combination with other antiemetic agents.

† For patients who do not receive prophylactic Zofran injection and experience n/v postoperatively, Zofran injection may be given to prevent further episodes.

(*Prescribing information: Akynzeo 2016, Aloxi 2015, Anzemet tablets 2014, Bonjesta 2016, Cesamet 2015, Cinvanti 2017, Diclegis tablets 2013, Emend capsules and oral suspension 2017, Emend for injection 2017, granisetron injection 2015, granisetron tablets 2015, Marinol 2017, Sancuso 2017, Sustol 2016, Syndros 2017, Varubi 2017, Zofran injection 2017, Zofran tablets ODT oral solution 2017, Zuplenz 2017*)

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

CLINICAL EFFICACY SUMMARY

Anorexia in patients with AIDS

- A 2015 MA (N = 6,462; 79 trials) evaluated the efficacy and safety of cannabinoids in various conditions, including appetite stimulation in HIV/AIDS. Most trials were of low to moderate quality and compared cannabinoids to usual care, placebo, or no treatment across trials. Compared with placebo, cannabinoids were associated with a higher proportion of patients demonstrating a complete n/v response (47% vs 20%; odds ratio [OR], 3.82; 95% confidence interval [CI], 1.55 to 9.42; 3 trials), reduction in pain (37% vs 31%; OR, 1.41; 95% CI, 0.99 to 2.00; 8 trials), a greater average reduction in numerical rating scale pain assessment (on a 0 to 10 point scale; weighted mean difference [WMD], -0.46; 95% CI, -0.80 to -0.11; 6 trials), A total of 4 trials evaluated dronabinol for appetite stimulation in 255 patients with HIV infection or AIDS, key outcomes are outlined below (*Abrams et al 2003, Timpone et al 1997, Whiting et al 2015):*
  - Data from 1 small study (n = 139, of which only 88 were evaluable) demonstrated that a large proportion of patients experienced weight gain of ≥ 2 kg within 6 weeks vs placebo (OR, 2.2; 95% CI, 0.68 to 7.27). An active comparison trial found that megestrol acetate was associated with greater weight gain than dronabinol and that combining dronabinol with megestrol acetate did not lead to additional weight gain.
- A 2013 MA of 7 trials, mostly of poor quality, found similar results as *Whiting et al*. Randomized controlled trials (RCTs) included any cannabis intervention and were of a short duration, ranging from 21 to 84 days. Patients had a mean weight gain in the dronabinol group of 0.1 kg, compared with a weight loss of 0.4 kg in the placebo group (*Lutge et al 2013*).

CINV

- For the management of CINV, MAs and head-to-head trials have demonstrated that the cannabinoids, dronabinol and nabilone, are more effective compared to placebo and may be more effective than prochlorperazine and metoclopramide. There are no published clinical trials comparing dronabinol to nabilone for CINV. The effectiveness of Syndros (dronabinol) oral solution for its FDA-approved indications was based on studies of dronabinol capsules.
- In a study by *Lane et al,* the combination of dronabinol plus prochlorperazine significantly reduced the mean duration of vomiting per episode compared to either agent administered with placebo (*Lane et al 1991*).
- Dolasetron has been shown to be an effective therapy in the treatment of CINV in comparative studies with palonosetron, ondansetron, and placebo (*Eberhart et al 2004, Eisenberg et al 2003, Karamanlioglu et al 2003, Lofters et al 1997, Meyer et al 2005, Walker et al 2001*).
- Granisetron and ondansetron are generally recognized as equally efficacious in treating CINV and PONV. Various studies may show slight benefits of 1 over another, but this has not been a consistently proven outcome (*Billio et al 2010, Dabbous et al 2010, del Giglio et al 2000, Dempsey et al 2004, Gan et al 2005, Jaing et al 2004, Kalaycio et al 1998, Lacerda et al 2000, Orchard et al 1999, White et al 2006*).
- Sancuso (granisetron) patch was non-inferior to orally administered granisetron for CINV (*Boccia et al 2011*).
- Palonosetron was reported to be more effective than other medications in the class as well as placebo, particularly at preventing delayed emesis (*Aapro et al 2005, Billio et al 2010, Botrel et al 2011, Dong et al 2011, Eisenberg et al 2003, Gralla et al 2003, Kaushal et al 2010, Likun et al 2011, Massa et al 2009, Suzuki et al 2016*).
- The safety and efficacy of Sustol (granisetron) were evaluated in a pivotal Phase 3, double-blind (DB), double-dummy, multicenter (MC), RCT in adults receiving HEC or MEC (*Raftopoulos et al 2015[a], Raftopoulos et al 2015[b]*). In the modified intention-to-treat population, both granisetron ER 5 mg and 10 mg were noninferior to palonosetron in preventing acute CINV after HEC and MEC. The FDA-approved dose of granisetron ER 10 mg was non-inferior to palonosetron in preventing delayed CINV after MEC and was not superior in preventing delayed CINV after HEC (*Raftopoulos et al 2015[a], Raftopoulos et al 2015[b]*).
- All of the 5-HT3 receptor antagonists have been shown to be equally effective in preventing acute CINV in separate MAs and are superior to placebo (*Billio et al 2010, del Giglio et al 2000, George et al 2009, Singhal et al 2012, Tang et al 2012*). A 2016 MA comparing ondansetron to other 5-HT3 receptor antagonists used for CINV found that ondansetron exhibited similar efficacy to granisetron, but greater efficacy than dolasetron for acute vomiting; palonosetron exhibited greater efficacy than ondansetron for delayed nausea and acute and delayed vomiting (*Simino et al 2016*).
- A 2016 Cochrane review found that 5-HT3 receptor antagonists are effective in children who receive emetogenic chemotherapy. Granisetron or palonosetron may be more effective than ondansetron, and the addition of dexamethasone improves vomiting symptoms (*Phillips et al 2016*).

- A randomized, DB, non-inferiority study comparing single-dose palonosetron 20 mcg/kg to multi-dose ondansetron 150 mcg/kg x 3 doses for the prevention of CINV in pediatric patients, aged 0 to 17 years, receiving MEC or HEC found that palonosetron was non-inferior to ondansetron in the acute phase (0 to 24 hours post chemotherapy) (*Kovacs et al 2016*).
- A randomized, DB study in patients receiving HEC found that when used as part of combination therapy with dexamethasone and aprepitant, palonosetron IV was not more efficacious than granisetron IV at overall prevention of CINV. Combination therapy with palonosetron was, however, more efficacious than granisetron in controlling CINV in the delayed phase (24 to 120 hours post chemotherapy) (*Suzuki et al 2016*).
- One MC, DB, RCT evaluated dexamethasone compared to aprepitant in the prophylaxis of delayed CINV in patients with breast cancer who received chemotherapy containing anthracyclines and cyclophosphamide and the same antiemetic prophylaxis regimen. The primary endpoint was rate of complete response (ie, no vomiting or rescue treatment) from days 2 to 5 after chemotherapy. The results showed similar efficacy and toxicity between dexamethasone and aprepitant in the prevention of delayed emesis (*Roila et al 2014*).
- Aprepitant has been shown to be effective for the treatment of CINV as monotherapy and in combination with various 5-HT3 antagonists and/or dexamethasone (*Herrington et al 2008, Rapoport et al 2010, Yeo et al 2009, Herrstedt et al 2005, Warr et al 2005, Gralla et al 2005, De Wit et al 2004, Poli-Bigelli et al 2003, Hesketh et al 2003, Martin et al 2003, Gore et al 2009, Jordan et al 2009, Grunberg et al 2009*).
- In combination regimens with granisetron and dexamethasone, rolapitant has been shown to be more effective than placebo for the prevention of CINV due to MEC and HEC in clinical trials (*Rapoport et al 2015, Schwartzberg et al 2015*). In combinations with 5-HT3 antagonists and dexamethasone, addition of rolapitant has also been shown to be more effective at preventing CINV over multiple cycles of MEC or HEC, when compared to similar combinations without rolapitant (*Rapoport et al 2016*).
- The fixed-dose combination palonosetron and netupitant + dexamethasone has been shown to be significantly superior to each agent administered individually for CINV prevention following MEC (*Aapro et al 2014*); however, results from another study for CINV prevention revealed similar efficacy between the fixed-dose combination and each agent administered individually with dexamethasone (*Gralla et al 2014*).
- In a small study, *Meiri et al* reported that dronabinol and ondansetron were similarly effective for the management of delayed CINV, but combination therapy with these 2 agents was not more effective than either agent alone (*Meiri et al 2007*).
- In a large MA (13 dronabinol studies and 16 nabilone studies), treatment with cannabinoids was more effective for complete control of nausea in the first 24 hours of chemotherapy compared to alizapride, chlorpromazine, domperidone, haloperidol, metoclopramide, prochlorperazine, or thiethylperazine (relative risk [RR], 1.38; 95% confidence interval [CI], 1.18 to 1.62; number needed to treat [NNT] = 6) and for complete control of vomiting (RR, 1.28; 95% CI, 1.08 to 1.51; NNT = 8). Of note, cannabinoids were not more effective compared to other agents when the chemotherapy regimen was of very high- or very low-emetogenic risk (*Tramèr et al 2001*).
- In a second MA, authors concluded that with regard to antiemetic efficacy, dronabinol was no more effective compared to placebo (RR, 0.47; 95% CI, 0.19 to 1.16; p = 0.1) but was more effective compared to neuroleptics (RR, 0.67; 95% CI, 0.47 to 0.96; NNT = 3.4). Nabilone was not more effective than neuroleptics (RR, 0.88; 95% CI, 0.72 to 1.08; P = 0.21). With regard to patient preference and tolerability, cannabinoids were preferred over other study agents (RR, 0.33; 95% CI, 0.24 to 0.44; p < 0.00001; NNT = 1.8) (*Machado Rocha et al 2008*).
- In a MA of 23 RCTs (11 dronabinol studies and 12 nabilone studies), compared to placebo, treatment with cannabinoids resulted in a higher chance of reporting complete absence of n/v (RR, 2.9; 95% CI, 1.8 to 4.7; 3 studies); however, patients were more likely to withdraw due to an adverse event compared to placebo (2 trials; RR, 6.9; 95% CI, 1.96 to 24) and compared to prochlorperazine (RR, 3.9; 95% CI, 1.3 to 12; 5 studies). The proportion of patients who reported absence of n/v was not different between cannabinoids and prochlorperazine (*Smith et al 2015*).

NVP

- FDA-approvals of Diclegis and Bonjesta (doxylamine succinate/pyridoxine HCl) were based on 1 DB, randomized, multi-center, placebo-controlled study that evaluated the safety and efficacy of doxylamine succinate/pyridoxine HCl in pregnant adult women in the gestational age range of 7 to 14 weeks with n/v. Patients (N = 298) were randomized to 14 days of placebo or 2 tablets daily at bedtime and up to a maximum dose of 4 tablets of doxylamine succinate/pyridoxine HCl. Doxylamine succinate/pyridoxine hydrochloride treatment resulted in a statistically significant improvement in both the symptom and quality of life domains of the Pregnancy Unique-Quantification of Emesis (PUQE) score. There was a

4.8 point mean decrease from baseline in the symptom domain PUQE score at day 15 in the doxylamine succinate/pyridoxine HCl group compared to 3.9 point decrease in the placebo group (p = 0.006). For quality of life, there was also a 2.8 point mean increase from baseline in the score at day 15 in the Diclegis group compared to a 1.8 point decrease in the placebo group (P = 0.005) (*Koren et al 2010*).
  - A follow-up analysis of this trial was conducted in 2015 to evaluate the maternal safety of doxylamine/pyridoxine as compared to placebo. Based on the results of this analysis, doxylamine/pyridoxine was not associated with an overall increased in rate of adverse effects as compared to placebo (*Koren et al 2015*).

PONV
- In a MA, palonosetron was shown to be more effective for prevention of early and late postoperative nausea and late postoperative vomiting compared to ondansetron (*Xiong et al 2015*).
- A 2016 MA found that when compared to other 5-HT3 antagonists and NK1 antagonists, aprepitant reduces incidence of PONV, and need for rescue medications (*Singh et al 2016*).

RINV
- There are very few trials evaluating the prevention of RINV, and trials generally include patients with moderate to high risk RINV. The 5-HT3 receptor antagonists are the only agents in class which have demonstrated efficacy, and of these, only ondansetron and granisetron are FDA-approved.
- One DB, active-comparator trial compared oral ondansetron 8 mg to oral granisetron 2 mg in 34 bone marrow transplant patients receiving TBI, which is associated with high emetogenic risks. The study was only powered to demonstrate a difference between each active treatment groups and historical controls. In the intention-to-treat population, significantly more patients given granisetron (33.3%) or ondansetron (26.7%) had zero emetic episodes over 4 days, the primary efficacy end point, than those within the historical control group (0%) (p < 0.01) (*Spitzer et al 2000).*
- In a MA of 9 trials, fewer patients had residual emesis with 5-HT3 receptor antagonists compared with placebo (40% vs 57%; RR, 0.7; 95% CI, 0.57 to 0.86), and fewer required rescue medication (6.5% vs 36%; RR, 0.18; 95% CI, 0.05 to 0.60). Despite treatment, most patients did develop RT-induced nausea (70% vs 83%; RR 0.84; 95% CI, 0.73 to 0.96) (*Salvo et al 2012*).

CLINICAL GUIDELINES

- The 5-HT3 receptor antagonists are considered part of the standard of care in the management of CINV due to chemotherapeutic agents with moderate-to-high emetic risk, RINV, and PONV. Treatment of CINV or RINV generally involves the use of multiple agents that affect different receptor types (*American Gastroentrological Association [AGA], 2001, Herrstedt et al 2017, Hesketh et al 2017, Gan et al 2014, Gupta et al 2016, Roila et al 2010).*
- The 2016 expert opinion statement from the American Society for Enhanced Recovery (ASER) for the prophylaxis and management of PONV provides the following recommendations (*Gupta et al 2016*):
  - All patients should receive PONV prophylaxis during the perioperative period.
  - The number of risk factors should determine the number of medications used for treatment and prophylaxis for PONV.
- The 2017 American Society of Clinical Oncology (ASCO) antiemetic guidelines recommend the following for CINV (*Hesketh et al 2017*):
  - For the prevention of n/v induced by HEC, a 4 drug combination of an NK1 receptor antagonist, a 5-HT3 receptor antagonist dexamethasone, and olanzapine is recommended as first-line therapy.
  - For MEC other than carboplatin area under the curve (AUC) ≥ 4 mg/mL/min, a 2-drug combination of a 5-HT3 receptor antagonist and dexamethasone is recommended.
  - For MEC that includes carboplatin AUC ≥ 4 mg/mL/min, a 3-drug combination of a NK1 receptor antagonist, a 5-HT3 receptor antagonist and dexamethasone is recommended.
  - For children receiving HEC or MEC, a 3-drug combination of a 5-HT3 receptor antagonist, dexamethasone, and aprepitant is recommended. A 2-drug regimen of a 5-HT3 receptor antagonist and dexamethasone can be used if aprepitant cannot be given; palonosetron and aprepitant can be used if dexamethasone cannot be given.
  - Cannabinoids (eg, nabilone, dronabinol) are not listed as appropriate first-line antiemetics for any group of patients receiving chemotherapy of high to low emetic risk. These agents can be used in conjunction with standard regimens for patients who continue to have symptoms despite optimal prophylaxis (including use of olanzapine).
- The 2018 ACOG Practice Bulletin for NVP recommends the following algorithm (*ACOG 2018*):

- First-line non-pharmacologic options: Change the prenatal vitamin to 1 that contains only folic acid, ginger capsules, and P6 acupressure with wrist bands.
- If symptoms persist, escalate to first-line pharmacologic interventions: Pyridoxine (vitamin B6) monotherapy or pydridoxine in combination with doxylamine in various doses.
- If symptoms persist, oral dimenhydrinate, oral diphenhydramine, rectal prochlorperazine, or oral/rectal promethazine may be added.
- If there is no dehydration and symptoms persist, oral/intramuscular (IM) metoclopramide, oral ondansetron, oral/rectal/IM promethazine, or IM trimethobenzamide may be added.
- If there is dehydration, patients should receive IV fluid replacement. If symptoms persist, IV dimenhydrinate, IV metoclopramide, IV ondansetron, or IV promethazine may be added.
  - If symptoms continue to persist, IM/IV chlorpromazine or oral/IV methylprednisolone may be added.

SAFETY SUMMARY

- The 5-HT3 receptor antagonists and substance P/NK1 receptor antagonists are contraindicated with hypersensitivity, and overall these agents are generally well-tolerated.
- The 5-HT3 receptor antagonists are generally very well-tolerated. There is a warning and general precaution for dolasetron regarding the risk of arrhythmias. Ondansetron and granisetron have QTc prolongation as a general precaution, but the incidence of electrocardiogram (ECG) changes has been less than 1%. In addition, the development of serotonin syndrome has been reported with 5-HT3 receptor antagonists. Ondansetron may mask progressive ileus or gastric distention following abdominal surgery or in patients with CINV.
- Aprepitant and fosaprepitant are moderate inhibitors of CYP3A4 and CYP2C9. Netupitant is a substrate and moderate inhibitor of CYP3A4. Rolapitant inhibits CYP2D6; therefore, dose reductions may be warranted with these agents. Aprepitant, fosaprepitant, and rolapitant are contraindicated taking CYP substrates of the respective enzymes that have a narrow therapeutic index, pimozide and thioridazine. Increased plasma concentrations may result in QT prolongation and torsades de pointes.
- Fosaprepitant and aprepitant can cause serious hypersensitivity reactions, including anaphylaxis and anaphylactic shock, during or soon after infusion. If hypersensitivity reactions occur, discontinue the infusion and administer appropriate medical therapy. Do not reinitiate aprepitant or fosaprepitant IV in patients who experience hypersensitivity symptoms with first-time use.
- Dronabinol and nabilone have the potential to be abused and produce psychological dependence. Both dronabinol and nabilone may produce alterations in mood and alterations in reality (distorted perceptions of objects and time and hallucinations).
- Dronabinol and nabilone are contraindicated in individuals who are allergic to cannabinoids. Syndros (dronabinol oral solution) is contraindicated in patients with hypersensitivity to alcohol and in patients who have received products containing disulfiram or metronidazole within 14 days. Syndros contains dehydrated alcohol (50%, w/w) and propylene glycol (5.5%, w/w). Disulfiram- and metronidazole-containing products should not be administered within 7 days of completing Syndros treatment.
- Consider risks and benefits of using dronabinol in patients with a history of seizures. Patients with cardiac disorders may experience cardiac effects such as hypotension, hypertension, syncope, or tachycardia with cannabinoids.
- Dronabinol and nabilone may exacerbate or unmask symptoms of mania, depression, or schizophrenia.
- In both placebo and active controlled trials, > 10% of patients experienced dizziness, drowsiness, dry mouth, euphoria, and coordination disturbance with either cannabinoid.
- Syndros and Marinol both contain the same active ingredient, dronabinol, and the safety of Syndros oral solution was based on studies using dronabinol capsules. The Syndros prescribing information contains updated warnings and precautions, including:
  - Avoid Syndros in patients with a psychiatric history or monitor patients for new or worsening psychiatric symptoms if use of Syndros cannot be avoided.
  - Reduce the dose or discontinue if signs and symptoms of cognitive impairment occur.
  - Consider a dose reduction or discontinue in patients who develop worsening nausea, vomiting, or abdominal pain while taking Syndros.
- Doxylamine/pyridoxine is contraindicated when used with monoamine oxidase inhibitors (MAOI), as they intensify and prolong the adverse effects of the agent. The most common adverse effect observed with doxylamine/pyridoxine is somnolence. The warning section in the prescribing information states that activities requiring complete mental

alertness, such as driving or operating heavy machinery, while using doxylamine/pyridoxine, are not recommended (unless cleared to do so by the health care provider). Doxylamine/pyridoxine is also not recommended when using CNS depressants, such as alcohol. Doxylamine/pyridoxine has anticholinergic properties, so should be used with caution in women with asthma, increased intraocular pressure, narrow angle glaucoma, stenosis peptic ulcer, pyloroduodenal obstruction, and urinary bladder-neck obstruction.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
5-HT$_3$ Receptor Antagonists				
Dolasetron	Tablet	Oral	Take within 1 hour before chemotherapy.	Indicated in both pediatric (age 2 to 16 years based on adult PK data) and adults. Renal and hepatic dose adjustments required.
Granisetron	Tablet, injection, injection ER, TD patch	Oral, IV, SC, TD	Take orally within 1 hour before chemotherapy or radiation, or twice daily. Administer patch a minimum of 24 hours before chemotherapy (up to a maximum of 48 hours) and remove a minimum of 24 hours after chemotherapy completion Administer IV or SC within 30 minutes before chemotherapy or administer IV right before induction of anesthesia or immediately before reversal of anesthesia. Do not administer injection ER more frequently than once a week.	Injection approved for CINV in children 2 to 16 years. Tablet, injection ER, and TD patch have not studied in pediatrics. Do not use injection ER in severe renal impairment and adjust frequency in moderate renal impairment. Apply patch to upper outer arm. The patch may be worn for up to 7 days depending on the duration of the chemotherapy regimen.
Ondansetron	Tablet, oral solution, ODT, oral soluble film, IV solution, injection	Oral, lingual, IV, IM	Oral administrations vary: (1) Give within 30 minutes before HEC or; (2) given twice daily, with the first dose given 30 minutes before the start of emetogenic chemotherapy and a subsequent dose 8 hours later; then twice daily for 1 to 2 days after the completion of chemotherapy or; (3) give 1 to 2 hours before each fraction of radiotherapy administered each day or; (4) give 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for 1 to 2 days after completion of radiotherapy or; (5) give 1 hour before induction of anesthesia or; (6) for pediatric	Do not exceed 8 mg daily in patients with severe hepatic impairment (Child-Pugh score ≥10). There is no experience beyond first-day administration in these patients. Depending on indication and formulation, drug may be administered in patients aged ≥ 1 month.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			patients, give 3 times daily with the first dose given 30 minutes before the start of emetogenic chemotherapy and subsequent doses 4 and 8 hours later; then 3 times daily (every 8 hours) for 1 to 2 days after completion of chemotherapy. IV administrations vary: (1) administer IV over 15 minutes beginning 30 minutes before chemotherapy and subsequent doses are given 4 and 8 hours after the first dose or; (2) administer IV over 2 to 5 minutes immediately before induction of anesthesia, or postoperatively if the patient did not receive prophylactic antiemetics and experiences nausea and/or vomiting within 2 hours after surgery or; (3) for pediatric patients, (weighing ≤ 40 kg) administer as a single dose, or (weighing > 40 kg) administer IV over 2 to 5 min immediately prior to or following anesthesia induction, or postoperatively if the patient did not receive prophylactic antiemetics and experiences nausea and/or vomiting occurring within 2 hours after surgery. Administer IM as a single dose.	
Palonosetron	IV solution	IV	IV administrations vary: (1) administer IV over 30 seconds, approximately 30 minutes before the start of chemotherapy or; (2) administer IV over 10 seconds immediately before the induction of anesthesia or; (3) for pediatric patients, administer IV over 15 minutes, beginning approximately 30 minutes before the start of chemotherapy	IV solution approved for prevention of CINV in pediatric patients aged ≥ 1 month.
Substance P/NK_1 Receptor Antagonists				
Aprepitant	Capsule, combination pack, oral suspension, IV emulsion	Oral, IV	Take orally within 1 hour before chemotherapy and once daily for 2 additional days or; 3 hours prior to induction of anesthesia.	Given as part of a regimen that includes a corticosteroid and a 5-HT3 antagonist.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Administer IV over 30 minutes beginning 30 minutes before chemotherapy (for the 3-day regimen, continue capsules on day 2 and 3).	Oral suspension approved for prevention of CINV in pediatric patients aged 6 months to < 12 years. Give with or without food. Use with caution in severe hepatic impairment.
Fosaprepitant	IV solution	IV	Administer IV over 20 to 30 minutes before chemotherapy.	Given as part of a regimen that includes a corticosteroid and a 5-HT3 antagonist. Use with caution in severe hepatic impairment.
Rolapitant	Tablet, IV emulsion	Oral, IV	Administer orally or IV (over 30 minutes) 2 hours prior to chemotherapy.	Given as part of a regimen that includes a corticosteroid and a 5-HT3 antagonist. Use with caution in severe hepatic impairment.
THC derivatives				
Dronabinol	Capsule, oral solution	Oral	Take orally 1 to 3 hours before chemotherapy and subsequent doses every 2 to 4 hours after chemotherapy for a total of 4 to 6 doses/day or; take orally twice daily, prior to lunch and dinner.	If adverse effects occur and do not resolve in 1 to 3 days with continued use, consider dose reductions. In elderly, consider decreasing the initial dose to reduce risk of CNS adverse reactions. Capsules are not recommended for AIDS-related anorexia in pediatric patients, because safety and efficacy have not been established. Always use calibrated oral dosing syringe for administration; if the prescribed dose is > 5 mg, it must be divided in multiple doses. Take with 6 to 8 ounces of water.
Nabilone	Capsule	Oral	Take orally twice daily 1 to 3 hours before chemotherapy and subsequent doses 2 to 3 times daily.	
Combination products				
Palonosetron/ netupitant	Capsule	Oral	Take orally within 1 hour before chemotherapy	Given as part of a regimen that includes a corticosteroid. Do not use in severe renal impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Doxylamine succinate/ pyridoxine HCl	Tablet ER, tablet DR	Oral	Take orally at bedtime. Titrate dose to twice daily (for the 20/20 mg tablet ER) or 3 times daily (for the 10/10 mg tablet DR).	Bonjesta is available in 20/20 mg tablets ER and Diclegis is available in 10/10 mg tablets DR. Should be taken on an empty stomach with a glass of water.

Abbrv: DR = delayed release, ER = extended release, IV = intravenous, ODT = orally disintegrating tablet, PK = pharmacokinetic, SC = subcutaneously, TD = transdermal
See the current prescribing information for full details.

CONCLUSION

- Nausea and vomiting are significant problems, particularly in the treatment of cancer and following surgery. There are several classes of antiemetic drugs that may influence the neurotransmitter receptors involved in the pathway associated with n/v (*Longstreth 2018*)
- Choice of agents generally depends upon the relative emetogenic potential of the influencing agent, condition, or procedure, including chemotherapy or radiation therapy. Various formulations may be prescribed based on age of the patient, indication, and persistence of symptoms (*AGA 2001, ACOG 2018, Hesketh et al 2017, Longstreth 2018, Roila et al 2010).*
- Guideline recommendations vary according to indication. The 2017 ASCO antiemetic guidelines recommend a 4-drug combination of a NK1 receptor antagonist, a 5-HT3 receptor antagonist, dexamethasone, and olanzapine as first-line therapy for the prevention of CINV due to HEC. For MEC, a 2-drug combination of a 5-HT3 receptor antagonist plus dexamethasone is recommended for regimens other than carboplatin area AUC ≥ 4 mg/mL/min or a 3-drug combination of a NK1 receptor antagonist, a 5-HT3 receptor antagonist and dexamethasone for patients treated with a regimen that includes carboplatin AUC ≥ 4 mg/mL/min (*Hesketh et al 2017*). A 2016 expert opinion statement from ASER states that during the perioperative period, all patients should receive PONV prophylaxis (*Gupta et al 2016*). The clinical consensus guidelines for NVP from the ACOG recommend pyridoxine alone or in combination with doxylamine as first-line pharmacologic therapy (*ACOG 2018*).
- The 5-HT3 antagonists are the cornerstone of therapy for acute emesis with MEC to HEC agents in the management of CINV, in addition to RINV and PONV. These agents include dolansetron, granisetron, ondansetron, and palonosetron. Ondansetron is the most well studied medication; however, trials haven't demonstrated a clear treatment leader between dolansetron, granisetron, and ondansetron. Palonosetron has a longer half-life and a higher receptor binding affinity than the other 5-HT3 receptor antagonists. Single-dose therapy with palonosetron is reported to be more effective than other medications in the class, particularly at preventing delayed emesis. There are very few trials evaluating the prevention of RINV. The 5-HT3 receptor antagonists are the only agents in class which have demonstrated efficacy, and of these, only ondansetron and granisetron are FDA-approved. Oral formulations appear to have comparable efficacy to IV formulations in CINV. The 5-HT3 receptor antagonists are generally well tolerated, with mild headache the most frequent adverse event. Cardiac abnormalities ranging from ECG interval changes to torsade de pointes or QTc prolongation have been reported with dolansetron, granisetron, and ondansetron. In addition, the development of serotonin syndrome has been reported with 5-HT3 receptor antagonists (*Aapro et al 2005, AGA, 2001, Billio et al 2010, Botrel et al 2011, Dong et al 2011, Eisenberg et al 2003, Gan et al 2014, Gralla et al 2003, Gupta et al 2016, Herrstedt et al 2017, Hesketh et al 2017, Kaushal et al 2010, Kovacs et al 2016, Likun et al 2011, Longstreth 2018, Roila et al 2010, Salvo et al 2012, Simino et al 2016, Spitzer et al 2000, Suzuki et al 2016*).
  - All 5-HT3 antagonist formulations are available generically with the exception of Anzemet (dolansetron) tablets, Sancuso (granisetron) transdermal patch, Sustol (granisetron) extended-release injection, and Zuplenz (ondansetron) oral soluble film.
- The substance P/NK1 receptor antagonists are prescribed for both acute and delayed CINV, which is an advantage over first-generation serotonin antagonists which are generally effective for acute only emesis. The agents include aprepitant, fosaprepitant, and rolapitant. The substance P/NK1 receptor antagonists are most effective when used in combination with other agents, typically with a 5-HT3 antagonist, a glucocorticoid, with or without olanzapine, for patients receiving HEC. One MA concluded aprepitant reduces incidence of PONV and need for rescue medications compared to other 5-HT3 and NK1 antagonists. Aprepitant and fosaprepitant are moderate inhibitors of the CYP3A4 pathway and rolapitant

inhibits CYP2D6; therefore, dose reductions may be warranted. Anaphylaxis, anaphylactic shock, and other serious hypersensitivity reactions have also been reported in patients receiving IV formulations, some requiring hospitalization (*AGA 2001, Gralla et al 2005, Grunberg et al 2011, Hesketh et al 2017, Herrington et al 2008, Herrstedt et al 2005, Longstreth 2018, Rapoport et al 2010, Roila et al 2010, Singh et al 2016, Warr et al 2005, Yeo et al 2009)*.
    - The only substance P/NK1 receptor antagonist formulations available generically are aprepitant capsules and combination pack.
- The THC derivatives, also referred to as the cannabinoids, have been prescribed for CINV and also have properties that may contribute to weight gain. The agents include nabilone and dronabinol. Dronabinol is also FDA-approved for anorexia associated with weight loss in adults with AIDS. In terms of CINV, these agents have a modest antiemetic activity and a relatively unfavorable adverse event profile. Side effects include vertigo, xerostomia, hypotension, and dysphoria, particularly in elderly patients. Trials have demonstrated that the cannabinoids are more effective compared to placebo and may be more effective than metoclopramide and prochlorperazine; however, no head-to-head trials have been conducted. The cannabinoids have little clinical utility. Due to the availability of other agents that are more effective and better tolerated, dronabinol and nabilone are recommended for later line therapy *(Hesketh et al 2017, Lane et al 1991, Longstreth 2018, Meiri et al 2007, Machado Rocha et al 2008, Tramer et al 2001)*.
    - Only Marinol (dronabinol) oral capsules are available generically.
- Combination products include Diclegis and Bonjesta (doxylamine succinate/pyridoxine) and Akynzeo (palonosetron/netupitant). Doxylamine succinate/pyridoxine are the only agents in class FDA-approved for NVP and is guideline-recommended as first-line pharmacologic therapy. Diclegis and Bonjesta vary by fixed dose strengths; however, each individual component is available over-the-counter (*ACOG 2018)*. The fixed-dose combination Akynzeo (palonosetron/netupitant) with dexamethasone has been shown to be significantly superior to each agent administered individually for CINV prevention following MEC (*Aapro et al 2014*); however, results from another study for CINV prevention revealed similar efficacy between the fixed-dose combination and each agent administered individually with dexamethasone (*Gralla et al 2014*). Netupitant is also a moderate inhibitor of the CYP3A4 pathway and clinicians should be aware of potential drug interactions.

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Therapeutic Class Overview
Ophthalmic Prostaglandin Analogs

INTRODUCTION

- Glaucoma is an optic neuropathy that causes gradual degeneration of the cells making up the optic nerve. It is the leading cause of blindness and second leading cause of vision loss in the world *(Prum et al 2016)*. Open-angle glaucoma is the most common form; other forms include angle-closure, congenital, and secondary glaucoma *(Jacobs 2017[a], National Eye Institute Web site)*. Patients with open-angle glaucoma initially experience peripheral visual field loss, followed by central field loss, which may progress to irreversible blindness if untreated *(Jacobs 2018)*. The exact etiology of open-angle glaucoma is unknown *(Jacobs 2018)*. Major risk factors for developing open-angle glaucoma include advanced age, African or Hispanic/Latino descent, elevated intraocular pressure (IOP), family history of glaucoma, low ocular perfusion pressure, type 2 diabetes mellitus, and myopia *(Ellis et al 2000, Girkin et al 2004, Lesk et al 2007, Prum et al 2016)*.
- Elevated IOP is the one major risk factor for glaucoma that is treatable. Available evidence suggests that lowering IOP inhibits or reduces the progression of optic nerve damage *(Jacobs 2018)*. Treatment may be initiated in patients with a raised IOP despite having no visual field loss or optic nerve damage. An IOP > 22 mm Hg is generally considered to be elevated and would be treated by most clinicians; however, this number varies according to screening methods, risk factors, and disease progression. The target IOP should be individualized based on response to therapy and disease progression in order to maintain IOP within a range that is unlikely to adversely affect patients' health-related quality of life. The American Academy of Ophthalmology (AAO) recommends an initial target IOP reduction of 25% from pretreated baseline IOP. However, depending on the severity of disease, this target may vary since there is no consensus target IOP below which further visual loss and optic nerve damage will be prevented *(Prum et al 2016)*.
- The current treatment of glaucoma focuses on decreasing IOP by 1 of 3 methods: laser therapy, surgery, or medical intervention *(Prum et al 2016)*. Medical intervention is generally used as initial therapy prior to laser or surgical treatment *(Jacobs 2018)*. Medical intervention includes 5 classes of ophthalmic drugs used for the long-term management of glaucoma: alpha-$_2$ adrenergic agonists, beta adrenergic antagonists, carbonic anhydrase inhibitors, miotics or parasympathomimetics, and prostaglandin analogues *(Jacobs 2018, Micromedex 2018)*. These treatments reduce IOP by either decreasing the amount of aqueous humor produced by the ciliary body or by increasing uveoscleral outflow *(Micromedex 2018, Prum et al 2016)*. Miotics and prostaglandin analogues increase aqueous outflow, while beta adrenergic antagonists and carbonic anhydrase inhibitors decrease aqueous humor production *(Micromedex 2018)*. Alpha-$_2$ adrenergic agonists decrease the amount of aqueous humor formed and increase its outflow *(Micromedex 2018, Prum et al 2016)*.
- Guidelines published in 2010 by the American Optometric Association (AOA) do not recommend preferential use of any drug class, although current guidelines by the AAO generally recommend ophthalmic prostaglandin analogues as first-line pharmacologic therapy in patients with elevated IOP *(AOA 2010, Prum et al 2016)*. Combination or monotherapy with agents from an alternative pharmacologic class is recommended for patients that experience intolerable adverse events or who do not achieve the optimal IOP reduction with first-line agents *(Jacobs 2018)*.
- This class review consists of the ophthalmic prostaglandin analogs, which include Lumigan (bimatoprost), Travatan Z (travoprost), Vyzulta (latanoprostene bunod), Xalatan (latanoprost), and Zioptan (tafluprost). The drugs in this review are approved by the Food and Drug Administration (FDA) to reduce IOP in patients with open-angle glaucoma or ocular hypertension. Sucampo Pharma discontinued Rescula (unoprostone isopropyl solution/drops) in 2015; the discontinuation was not due to safety or efficacy concerns *(Drugs@FDA 2018)*. The branded product Latisse (bimatoprost 0.03%) has not been FDA-approved for IOP-reduction indications. Latisse is indicated to treat hypotrichosis of the eyelashes and will be discussed in this review in an abbreviated manner.
- Medispan Class: Prostaglandins – Ophthalmic

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Latisse (bimatoprost ophthalmic solution) 0.03%	✔

Drug	Generic Availability
Lumigan (bimatoprost ophthalmic solution) 0.01%¶	-
Travatan Z (travoprost ophthalmic solution) 0.004%†	-
Vyzulta (latanoprostene bunod ophthalmic solution) 0.024%	-
Xalatan (latanoprost ophthalmic solution) 0.005%	✔
Zioptan (tafluprost ophthalmic solution) 0.0015%	-
bimatoprost ophthalmic solution, 0.03%	✔

¶ Allergan discontinued brand Lumigan (bimatoprost) 0.03% in 2012; the discontinuation was not due to safety concerns. Generic bimatoprost 0.03% is available, but generic 0.01% is not.

†The original benzalkonium chloride-containing travoprost formulation (brand name: Travatan) was approved by the FDA on March 16, 2001; however, Travatan was discontinued by Alcon in June 2010. In March 2013, travoprost with benzalkonium chloride by Par Pharmaceuticals was approved by an abbreviated new drug application (ANDA); however, this generic product was discontinued on September 7, 2016 *(Clinical Pharmacology 2018)*. Only the brand product, Travatan Z, remains available.

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Latisse (bimatoprost)	Lumigan (bimatoprost)†	Travatan Z (travoprost)	Xalatan (latanoprost)	Vyzulta (latanoprostene bunod)	Zioptan (tafluprost)
Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension	-	✔	✔	✔	✔	✔
Hypotrichosis of the eyelashes by increasing their growth including length, thickness, and darkness	✔	-	-	-	-	-

† Generic bimatoprost 0.03% shares the same indication as brand Lumigan.

(Prescribing information: bimatoprost ophthalmic solution 0.03% 2017, Latisse 2017, Lumigan 2017, Travatan Z 2017, Xalatan 2017, Vyzulta 2017, Zioptan 2014)

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

CLINICAL EFFICACY SUMMARY

- Several comparative trials with the prostaglandin analogs have been published. Ophthalmic bimatoprost appears to have the greatest efficacy in reducing IOP; however, trials have not consistently demonstrated a difference in IOP reduction between travoprost and latanoprost *(Aptel et al 2008, Cantor et al 2006, Cheng et al 2008, Cheng et al 2009[a,b], Denis et al 2007, Li et al 2006, Parrish et al 2003, Sawada et al 2012, van der Valk et al 2009)*.
- A 2016 systematic review and network meta-analysis pooled results from 114 randomized controlled trials that compared a single topical treatment for glaucoma with placebo or active comparator *(Li et al 2016)*. The analysis reported the mean reductions (from greatest to least) in IOP at 3 months were achieved with bimatoprost, latanoprost, travoprost, and tafluprost. The authors concluded all first-line drugs, including prostaglandins, are effective compared to placebo, and that differences between drugs were small and may not be clinically significant. Another systematic review of 32 randomized controlled trials compared prostaglandin analogs for primary open-angle glaucoma, using the β-adrenergic antagonist timolol as a reference comparator. The analysis found that bimatoprost was most likely to achieve treatment success, defined as a 30% reduction in IOP (relative risk [RR], 1.59; 95% confidence interval [CI]: 1.28 to

1.98). The RR for treatment success with latanoprost was 1.32 (95% CI: 1.00 to 1.74), for travoprost was 1.33 (95% CI: 1.03 to 1.72), and for tafluprost was 1.1 (95% CI: 0.85 to 1.42). In terms of tolerability, bimatoprost was associated with the highest risk of developing hyperemia, while latanoprost had the lowest risk *(Lin et al 2014)*.

- A pooled analysis of 2 similarly designed, Phase 3, double-masked, active control (AC), multi-center (MC), noninferiority trials (APOLLO and LUNAR; N = 840 total) found that latanoprostene bunod 0.024% administered once daily led to greater reductions in mean IOP when compared to timolol maleate 0.5% (beta-adrenergic antagonist) administered twice daily at all evaluation time points (IOP was measured at 8 AM, 12 PM, and 4 PM at week 2, week 6, and months 3, 6, 9, and 12) [p < 0.001 for all] (*Weinreb et al 2018*). A greater proportion of patients treated with latanoprostene bunod vs timolol attained a mean IOP ≤ 18 mm Hg and an IOP reduction ≥ 25% from baseline (p < 0.001). Patients who switched over from timolol to latanoprostene bunod also experienced additional IOP lowering (p ≤ 0.009). Efficacy was maintained through 12 months of therapy.
- Latanoprostene bunod was also evaluated in a 28-day, Phase 2, randomized, investigator-masked, AC, MC, dose-ranging study (n = 413). The objective of the study was to assess the efficacy and safety of latanoprostene bunod vs latanoprost 0.005%, and to determine the optimum drug concentration(s) of latanoprostene bunod in reducing IOP. Patients were randomized into 1 of 5 treatment groups, including 4 different concentrations of latanoprostene bunod (0.006%, 0.012%, 0.024%, and 0.040%) and latanoprost 0.005% *(Weinreb et al 2015)*.
  - Efficacy for latanoprostene bunod was dose-dependent and reached a plateau at 0.024% to 0.040%. Latanoprostene bunod 0.024% led to significantly greater reductions in mean diurnal IOP compared with latanoprost 0.005% at day 28 (-9 mmHg vs -7.77 mmHg, respectively; p = 0.005).
  - A significantly greater proportion of patients had mean diurnal IOP ≤ 18 mmHg in the latanoprostene bunod 0.024% group at all measurement time points (p ≤ 0.046) compared to the latanoprost group.
- Available trials suggest that tafluprost may have a similar IOP-lowering effect as latanoprost, but less than that of travoprost *(Konstas et al 2013, Schnober et al 2010, Traverso et al 2010, Uusitalo et al 2010[b])*.
  - One trial found no significant difference in IOP reduction from baseline between tafluprost and travoprost following 6 weeks of treatment (difference, 0.17 mm Hg; 95% CI: -1.268 to 1.608; p = 0.811) *(Traverso et al 2010)*.
  - In a 6-week crossover trial, travoprost significantly reduced IOP from baseline compared to tafluprost (7.2 vs. 6.6 mm Hg; p = 0.01). Adverse events were similar between the treatment groups *(Schnober et al 2010)*.
  - In a randomized, double-blind trial (N = 533), tafluprost demonstrated noninferiority to latanoprost after 24 months (p < 0.05). No difference in the incidence of adverse events was reported between treatments *(Uusitalo et al 2010[b])*.
  - Results from a similar trial demonstrated a significantly lower incidence of ocular irritation/burning, tearing, itching, dry eye sensation, and conjunctival hyperemia when switched from latanoprost to tafluprost due to ocular intolerance (p < 0.001 for all). Tafluprost also significantly reduced IOP compared to baseline treatment with latanoprost (16.4 vs. 16.8 mm Hg; p = 0.049) *(Uusitalo et al 2010[a])*.
  - In a non-interventional trial by Erb and colleagues, patients with an inadequate response with prior glaucoma treatments achieved a significantly lower IOP after switching to tafluprost treatment for 6 to 12 weeks compared to baseline (16.4 ± 2.9 vs. 19.5 ± 4.4 mm Hg; p < 0.001) *(Erb et al 2011)*.
- In a trial comparing bimatoprost 0.03% and travoprost, the mean reduction in IOP was significantly greater with bimatoprost 0.03% at 9 AM (p < 0.014), but not at 1 PM (p = 0.213) or 4 PM (p ≥ 0.207) *(Cantor et al 2006)*. The results of a meta-analysis demonstrated that reductions in IOP were significantly greater with bimatoprost 0.03% compared to travoprost at 8 AM (p = 0.004) and 12 noon (p = 0.02), but not at 4 PM (p = 0.19) or 9 PM (p = 0.07). Bimatoprost 0.03% also demonstrated greater reductions in IOP compared to latanoprost at all time points. There were no statistically significant differences between latanoprost and travoprost at any time point *(Aptel et al 2008)*. In a trial evaluating bimatoprost 0.03%, latanoprost, and travoprost, the mean changes in IOP were comparable between all treatment groups at week 12 (p = 0.128); however, latanoprost was associated with fewer adverse events compared to bimatoprost (p < 0.001) *(Parrish et al 2003)*. In a meta-analysis of peak and trough IOP measurements, bimatoprost 0.03% demonstrated greater reductions in peak IOP compared to latanoprost; however, reductions were larger with latanoprost at the trough measurement *(Cheng et al 2009[a])*. Results from a similar meta-analysis by Li et al did not demonstrate a significant difference in IOP reductions between bimatoprost 0.03% and travoprost (p = 0.8) or latanoprost and travoprost (p = 0.07) *(Li et al 2006)*.
- A meta-analysis of 13 trials evaluating adverse events associated with the ophthalmic prostaglandin analogs showed that latanoprost had a lower incidence of conjunctival hyperemia compared to both bimatoprost 0.03% and travoprost (p < 0.0001 for both) *(Honrubia et al 2009)*. One trial evaluated the use of travoprost without the preservative benzalkonium chloride (BAK) and demonstrated a lower incidence of hyperemia compared to travoprost with BAK

(p-values not reported) *(Lewis et al 2007)*. The results from a second trial showed that travoprost without BAK was associated with lower Ocular Surface Disease Index (OSDI) scores compared to bimatoprost 0.03% and latanoprost ($p < 0.0001$) *(Henry et al 2008)*.

- The ophthalmic prostaglandin analogs have consistently demonstrated comparable or greater efficacy when compared to various combination therapies *(Cheng et al 2009[b], Coleman et al 2003, Fechtner et al 2004, Konstas et al 2008, Lesk et al 2008, Ozturk et al 2007, Sharpe et al 2008)*. Bimatoprost 0.03% significantly reduced IOP compared to dorzolamide/timolol in a 6-week crossover trial ($p = 0.03$) *(Sharpe et al 2008)*. In a meta-analysis of 14 trials, treatment with latanoprost or fixed-dose dorzolamide/timolol was associated with a similar reduction in IOP after 6 months ($p = 0.28$) *(Cheng et al 2009[b])*.
- In a randomized controlled trial, treatment with latanoprost was associated with greater reductions in IOP compared to betaxolol, carteolol, and nipradilol ($p < 0.05$ for all) *(Ikeda et al 2008)*. In addition, a meta-analysis of 11 randomized controlled trials showed significant reductions in IOP with latanoprost compared to timolol ($p < 0.001$) *(Zhang et al 2001)*. The ophthalmic prostaglandin analogs have consistently shown greater efficacy in reducing IOP compared to agents in other ophthalmic classes used as monotherapy *(Parrish et al 2003, Webers et al 2007, Zhang et al 2001)*. Only brimonidine reduced IOP to a similar degree as ophthalmic prostaglandin analog monotherapy ($p = 0.3$ vs. latanoprost) but with a higher incidence of adverse events (31 vs. 21%; $p = 0.0005$) *(Sonty et al 2008)*. The results from a meta-analysis by Cheng and colleagues demonstrated that brimonidine had the largest reduction in IOP at peak compared to all other glaucoma agents; however, brimonidine also had the smallest reduction in IOP at the trough time point *(Cheng et al 2009[a])*.

CLINICAL GUIDELINES

- Guidelines published in 2010 by the AOA (currently under review per the AOA website) do not recommend preferential use of any drug class, although current guidelines by the AAO generally recommend ophthalmic prostaglandin analogues as first-line pharmacologic therapy in patients with elevated IOP *(AOA 2010, Prum et al 2016)*.
- The AAO 2016 guidelines on primary open-angle glaucoma state that prostaglandin analogs are the most frequently prescribed initial eye drops because they are the most efficacious, well-tolerated products, and are administered once daily. The AAO guidelines do not recommend one ophthalmic prostaglandin analog over another *(Prum et al 2016)*.

SAFETY SUMMARY

- Class warnings include the risk of hyperpigmentation of ocular tissues and eyelash changes with darkening and thickening of eyelashes. Drugs in this class should be used with caution in patients with intraocular inflammation or macular edema. Patients should remove contact lenses prior to instillation and reinsert 15 minutes following the administration of all agents in this class except tafluprost, for which no information relating to contact lenses is available in the labeling.
- The most frequently reported adverse events associated with these agents are ocular in nature and include burning/stinging, hyperemia, pruritus, iris pigmentation changes, and growth and darkening of eyelashes.

DOSING AND ADMINISTRATION

- Administer other topical ophthalmic medications at least 5 minutes apart from the prostaglandin analogs.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Latisse (bimatoprost)	Ophthalmic solution/drops	Ophthalmic	Daily	Apply nightly directly to the skin of the upper eyelid margin at the base of the eyelashes using the accompanying applicators. Blot any excess solution beyond the eyelid margin. Dispose of the applicator after one use. Repeat for the opposite eyelid margin using a new sterile applicator.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				May be used in patients aged ≥ 5 years for hypotrichosis of the eyelashes. Bimatoprost has been studied in patients aged 5 to 17 years who were post-chemotherapy or had alopecia and ages 15 to 17 years with hypotrichosis not associated with a medical condition. Pregnancy: Unclassified†
Lumigan (bimatoprost) 0.01%; generic bimatoprost 0.03%	Ophthalmic solution/drops	Ophthalmic	Daily	Instill 1 drop into affected eye(s) once daily in the evening; the dosage should not exceed once daily. Use in pediatric patients < 16 years of age is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy: Unclassified†
Travatan Z (travoprost)	Ophthalmic solution/drops	Ophthalmic	Daily	Instill 1 drop into affected eye(s) once daily in the evening; the dosage should not exceed once daily. Use in pediatric patients < 16 years of age is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy Category C
Xalatan (latanoprost)	Ophthalmic solution/drops	Ophthalmic	Daily	Instill 1 drop into affected eye(s) once daily in the evening; the dosage should not exceed once daily. Safety and effectiveness in pediatric patients have not been established. Pregnancy Category C
Vyzulta (latanoprostene bunod)	Ophthalmic solution/drops	Ophthalmic	Daily	Instill 1 drop into affected eye(s) once daily in the

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				evening; the dosage should not exceed once daily. Use in pediatric patients < 16 years of age is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy: Unclassified†
Zioptan (tafluprost)	Ophthalmic solution/drops	Ophthalmic	Daily	Instill 1 drop into affected eye(s) once daily in the evening; the dosage should not exceed once daily. Use in pediatric patients is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy Category C

† In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

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

See the current prescribing information for full details

CONCLUSION

- Ophthalmic prostaglandin analogs currently available in the United States include bimatoprost, latanoprost, latanoprostene bunod, tafluprost, and travoprost. All are FDA-approved for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension. Latisse (bimatoprost) is indicated to treat hypotrichosis of the eyelashes.
- Study results have demonstrated statistically significant differences in IOP-lowering ability among agents in the class. However, the differences are generally small, and the clinical significance of these differences has not been established. Bimatoprost is generally considered to have the greatest IOP-reducing effect among the ophthalmic prostaglandin analogs *(Aptel et al 2008, Cheng et al 2008, Denis et al 2007, Kammer et al 2010, Li et al 2016, Lin et al 2014, van der Valk et al 2009, Weinreb et al 2018)*.
- In addition to conjunctival hyperemia, ocular adverse events with the prostaglandin analogs include eye irritation, increase in the number and length of eyelashes, and changes in iris and lash pigmentation; the latter 2 are most notable if only 1 eye is treated. The ophthalmic prostaglandin analogs are considered to be better tolerated compared to other classes of medications used for the management of glaucoma *(Jacobs 2018)*. Tafluprost is the only agent within the class that is formulated as preservative-free and may be associated with less ocular irritation compared to the other ophthalmic prostaglandin analogs *(Uusitalo et al 2010[b])*.
- Guidelines published in 2010 by the AOA (currently under review per the AOA website) do not recommend preferential use of any drug class, although current guidelines by the AAO generally recommend ophthalmic prostaglandin analogues as first-line pharmacologic therapy in patients with elevated IOP *(AOA 2010, Prum et al 2016)*.
- The results from various meta-analyses have demonstrated that prostaglandin analogs reduce IOP by up to 35% and to a further extent compared to alpha$_2$-adrenergic agonists, beta adrenergic antagonists, carbonic anhydrase inhibitors, and other recommended therapies *(van der Valk et al 2009)*. Combination therapy with agents from other therapeutic classes should be used if the reduction in IOP on monotherapy is unsatisfactory *(AOA 2010, Prum et al 2016)*.

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