BRIAN SANDOVAL
Governor

RICHARD WHITLEY, MS
Director

MARTA JENSEN
Administrator

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

NOTICE OF PUBLIC MEETING – PHARMACY AND THERAPEUTICS COMMITTEE

AGENDA

Date of Publication:	**February 22, 2018**
Date and Time of Meeting:	**Thursday, March 22, 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:** **Legislative Council Bureau** **401 S. Carson Street, Suite 2134** **Carson City, Nevada 89701** **South Nevada Location:** **Grant Sawyer Office Building** **555 E. Washington Avenue, Suite 4412** **Las Vegas, Nevada 89101** **Please check with staff to verify room location**
Teleconference:	**(775) 687-0999**
Access Code:	**43722**

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 cmclach@dhcfp.nv.gov in advance, but no later than two working days prior to the meeting so that arrangements may be conveniently made.

AGENDA

1. Call to Order and Roll Call

2. Public Comment

3. Administrative

a. **For Possible Action**: Review and Approve Meeting Minutes from December 7, 2017

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. 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. 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

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. Cardiovascular Agents – Antilipemics – HMG-CoA Reductase Inhibitors (Statins)

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. 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

e. 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

f. 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

g. Cardiovascular Agents – Antilipemics – Omega-3 Fatty Acids

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 five minutes.

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

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

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

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

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.]

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

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

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

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

(c) Anticonvulsant medications;

(d) Antirejection medications for organ transplants;

(e) Antidiabetic medications;

(f) Antihemophilic medications; and

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

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

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

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

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

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

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

Definition of "Therapeutic Alternative"

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

BRIAN SANDOVAL
Governor

RICHARD WHITLEY, MS
Director

MARTA JENSEN
Administrator

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

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.

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.

REFERENCES

- Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 2014;371:1189-1197.
- Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol*. 2014;133:1270-1277.
- Bjermer L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germinaro M. Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: a randomized phase 3 study. *Chest*. 2016;150(4):789-798.
- Bleecker ER, Fitzgerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomized, multicenter, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2115-2127.
- Buhl R, Solèr M, Matz J, et al. Omalizumab provides long-term control in patients with moderate-to-severe allergic asthma. *Eur Respir J*. 2002;20(1):73-78.
- Busse W, Corren J, Lanier BQ, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol*. 2001;108(2):184-90.
- Castro M, Wenzel SE, Bleecker ER, et al. Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomized dose-ranging study. *Lancet Respir Med*. 2014;2(11):879-890.
- Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med*. 2015;3(5):355-366.
- Cinqair prescribing information. Teva Pharmaceutical Industries Ltd. Frazer, PA. June 2016.
- Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43:343-373.
- Cockle SM, Stynes G, Gunsoy NB, et al. Comparative effectiveness of mepolizumab and omalizumab in severe asthma: An indirect treatment comparison. *Respir Med*. 2017;123:140-148.
- Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 study of reslizumab in patients with poorly controlled asthma: effects across a broad range of eosinophil counts. *Chest*. 2016;150(4):799-810.
- Corren J, Kavati A, Ortiz B, et al. Efficacy and safety of omalizumab in children and adolescents with moderate-to-severe asthma: a systematic literature review. *Allergy Asthma Proc*. 2017;38(4):250-263.
- DRUGS@FDA.com (database on the internet). Rockville (MD): U.S. Food and Drug Administration. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed November 20, 2017.
- Eisner MD, Zazzali JL, Miller MK, et al. Longitudinal changes in asthma control with omalizumab: 2-year interim data from the EXCELS study. *J Asthma*. 2012;49:642-648.
- Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. *Cochrane Database Syst Rev*. 2017 Sep 21;9:CD010834.
- Fasenra prescribing information. AstraZeneca Pharmaceuticals. Wilmington, DE. November 2017.
- Ferguson GT, Fitzgerald JM, Beecker ER, et al. Benralizumab for patients with mild to moderate, persistent asthma (BISE): a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2017;5(7):568-576.
- Fitzgerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomized, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2128-2141.
- Food and Drug Administration press release. FDA Drug Safety Communication: FDA approves label changes for asthma drug Xolair, including describing slightly higher risk of heart and brain adverse events. Published online September 26, 2014. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm414911.htm. Accessed November 20, 2017.

- Groh M, Pagnoux C, Baldini C, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. *Eur J Intern Med.* 2015;26(7):545-553.
- Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention (2017 update). 2017; www.ginasthma.org. Accessed November 20, 2017.
- Holgate S, Bousquet J, Wenzel S, et al. Efficacy of omalizumab, an antiimmunoglobulin E antibody, in patients with allergic asthma at high risk of serious asthma-related morbidity and mortality. *Curr Med Res Opin*. 2001;17(4):233-40.
- Holgate ST, Chuchalin AG, Hébert J, et al. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy*. 2004;34(4):632-8.
- Iribarren C, Rahmaoui A, Long AA, et al. Cardiovascular and cerebrovascular events among patients receiving omalizumab: Results from EXCELS, a prospective cohort study of moderate-to-severe asthma. *J Allergy Clin Immunol*. 2017;139(5):1489-1495.e5.
- Kaplan A, Ledford D, Ashby M, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *J Allergy Clin Immunol*. 2013;132:101-9.
- Khan DA. Chronic urticaria: treatment of refractory symptoms. UpToDate Web site. https://www.uptodate.com. Updated August 28, 2017. Accessed November 20, 2017.
- Lanier B, Bridges T, Kulus M, Taylor AF, Berhane I, Vidaurre CF. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. *J Allergy Clin Immunol*. 2009;124(6):1210-6.
- Lanier BQ, Corren J, Lumry W, et al. Omalizumab is effective in the long-term control of severe allergic asthma. *Ann Allergy Asthma Immunol*. 2003;91(2):154-9.
- Ledford D, Busse W, Trzaskoma B, et al. A randomized multicenter study evaluating Xolair persistence of response after long-term therapy. *J Allergy Clin Immunol*. 2017;140(1):162-169.e2.
- Li J, Wang F, Lin C, et al. The efficacy and safety of reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: a systematic review and meta-analysis. *J Asthma.* 2017;54(3):300-307.
- Long A, Rahmaoui A, Rothman KJ, et al. Incidence of malignancy in patients with moderate-to-severe asthma treated with or without omalizumab. *J Allergy Clin Immunol*. 2014;134:560-567.
- Lugogo N, Domingo C, Chanez P, et al. Long-term efficacy and safety of mepolizumab in patients with severe eosinophilic asthma: a multi-center, open-label, phase IIIb study. *Clin Ther*. 2016;38(9):2058-2070.
- Maurer M, Rosen K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med*. 2013;368:924-935.
- Maurer M, Kaplan A, Rosen K, et al. The XTEND-CIU study: long term use of omalizumab in chronic idiopathic urticaria [published online ahead of print November 10, 2017]. *J Allergy Clin Immunol.* doi: 10.1016/j.jaci.2017.10.018.
- Nachef Z, Krishnan A, Mashtare T, Zhuang T, Mador MJ. Omalizumab versus mepolizumab as add-on therapy in asthma patients not well controlled on at least an inhaled corticosteroid: a network meta-analysis. *J Asthma*. 2017 May 1:1-12. doi: 10.1080/02770903.2017.
- Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med*. 2017;376(25):2448-2458.
- National Heart, Lung, and Blood Institute. Expert Panel Report 3: Guidelines for the diagnosis and management of asthma (guideline on the Internet). NHLBI 2007. Available from http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed November 20, 2017.
- National Heart, Lung, and Blood Institute. What is Asthma? 2014. Available at: http://www.nhlbi.nih.gov/health/health-topics/topics/asthma. Accessed November 20, 2017.
- Normansell R, Walker S, Milan SJ, et al. Omalizumab for asthma in adults and children. Cochrane Database Syst Rev. 2014 Jan 13;(1):CD003559.
- Nucala prescribing information. GlaxoSmithKline LLC. Philadelphia, PA. December 2017.
- Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014;371(13):1198-1207.
- Ortega HG, Yancey SW, Mayer B, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. *Lancet Respir Med*. 2016;4(7):549-556.
- Pagnoux C, Groh M. Optimal therapy and prospects for new medicines in eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). *Expert Rev Clin Immunol;*2016;12(10):1059-1067.
- Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet.* 2012;380:651-659.
- Powell RJ, Leech SC, Till S, et al. BSACI guideline for the management of chronic urticaria and angioedema. *Clin Exp Allergy*. 2015;45(3):547-565.
- Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations. Available from https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411418.htm. Accessed November 20, 2017.
- Rodrigo GJ, Neffen H, Castro-Rodriguez JA. Efficacy and safety of subcutaneous omalizumab vs placebo as add-on therapy to corticosteroids for children and adults with asthma: a systematic review. *Chest*. 2011;139(1):28-35.
- Saini S. Chronic urticarial: clinical manifestations, diagnosis, pathogenesis, and natural history. UpToDate Web site. https://www.uptodate.com. Updated June 29, 2017. Accessed December 12, 2017.
- Saini SS, Bindslev-Jensen C, Maurer M, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. *J Invest Derm*. 2015;135:67-75.
- Schwartz J, Padmanabhan A, Aqui N, et al. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis: The seventh special issue. *J Clin Apher*. 2016;31(3):149-162.
- Solèr M, Matz J, Townley R, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J*. 2001;18(2):254-61.
- Walford HH, Doherty TA. Diagnosis and management of eosinophilic asthma: a US perspective. J Asthma and Allergy. 2014;7:53-65.
- Wechsler ME, Akuthota P, Jayne D, et al. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. *N Engl J Med*. 2017;376(20):1921-1932.
- Xolair prescribing information. Genentech, Inc. South San Francisco, CA and Novartis Pharmaceuticals. East Hanover, NJ. June 2017.

- Yancey SW, Ortega HG, Keene ON, et al. Meta-analysis of asthma-related hospitalization in mepolizumab studies of severe eosinophilic asthma. *J Allergy Clin Immunol*. 2017;139(4):1167-1175.
- Zhao ZT, Ji CM, Yu WJ, et al. Omalizumab for the treatment of chronic spontaneous urticaria: A meta-analysis of randomized clinical trials. *J Allergy Clin Immunol*. 2016;137(6):1742-1750.
- Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA/LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy*. 2014;69:868-887.

Publication Date: January 2, 2018

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*).

REFERENCES

- Afilalo M, Etropolski MS, Kuperwasser B, et al. Efficacy and safety of tapentadol extended release compared to oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study. Clin Drug Investig. 2010;30(8):489-505.
- Agarwal A, Polydefkis M, Block B, et al. Transdermal fentanyl reduces pain and improves functional activity in neuropathic pain states. Pain Medicine. 2007;8(7):554-62.
- Allan L, Hays H, Jensen NH, et al. Randomized crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. BMJ. 2001;322:1-7.
- Allan L, Richarz U, Simpson K, et al. Transdermal fentanyl vs sustained release oral morphine in strong-opioid naïve patients with chronic low back pain. Spine. 2005;30(22):2484-90.
- American Academy of Pain Medicine (AAPM) facts and figures on pain. The American Academy of Pain Medicine. Available at: http://www.painmed.org/patientcenter/facts_on_pain.aspx#incidence. Accessed October 4, 2017.
- Arymo ER prescribing information. Egalet US Inc. Wayne, PA. January 2017.
- Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol. 2010 Sep;17)9):1113-e88.
- Bao YJ, Hou W, Kong XY, et al. Hydromorphone for cancer pain. Cochrane Database Syst Rev. 2016;10:CD011108.
- Bekkering GE, Soares-Weiser K, Reid K, et al. Can morphine still be considered to be the standard for treating chronic pain? A systematic review including pair-wise and network meta-analyses. Curr Med Res Opin. 2011 Jul;27(7):1477-91.
- Bril V, England J, Franklin GM, et al. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology. 2011 May 17:76(20):1758-65.
- Bruera E, Palmer JL, Bosnak S, et al. Methadone vs morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study. J Clin Oncol. 2004;22(1):185-92.
- Butrans prescribing information. Purdue Pharma L.P. Stamford, CT. December 2016.
- Buynak R, Shapiro DY, Okamoto A, et al. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled Phase III study. Expert Opin Pharmacother. 2010 Aug;11(11):1787-804.
- Caldwell JR, Rappaport RJ, Davis JC, et al. Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and an open label extension trial. J Pain Symptom Manage. 2002;23:278-91.
- Caraceni A, Pigni A, Brunelli C. Is oral morphine still the first choice opioid for moderate to severe cancer pain? A systematic review within the European Palliative Care Research Collaborative guidelines project. Palliat Med. 2011 Jul;25(5):402-9.
- Centers for Medicare & Medicaid Services (CMS). Improving Drug Utilization Review Controls in Part D. Updated September 21, 2017. Available at: http://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/RxUtilization.html. Accessed October 4, 2017.
- Chou R, Cruciani RA, Fiellin DA, et al. Methadone safety: a clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society. J Pain. 2014;15(4):321-337.
- Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic non-cancer pain. J Pain. 2009 Feb;10(2):113-30.
- Chou R, Qaseem A, Snow V, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. Ann Int Med. 2007 Oct 2;147(7):478-91.
- Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. Ann Intern Med. 2015;162(4):276-86.

- Clark AJ, Ahmedzai SH, Allan LG, et al. Efficacy and safety of transdermal fentanyl and sustained-release oral morphine in patients with cancer and chronic non-cancer pain. Current Medical Research and Opinion. 2004;20(9):1419-28.
- Cohen SP, Srinivasa NR. Chapter 29. Pain. In: Goldman L, Schafer AI. eds. Goldman's Cecil Medicine, 24e. Philadelphia, PA: Elsevier, Inc.; 2012. Available by subscription at: www.clinicalkey.com. Originally accessed October 2, 2015.
- Conaghan PG, O'Brien CM, Wilson M, et al. Transdermal buprenorphine plus oral paracetamol vs an oral codeine-paracetamol combination for osteoarthritis of hip and/or knee: a randomized trial. Osteoarthritis Cartilage. 2011 Aug;19(8):930-8.
- Dolophine prescribing information. Roxane Laboratories, Inc. Columbus, OH. January 2017.
- Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain – United States, 2016. MMWR Recomm Rep 2016;65:1-49. Available at: http://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm?s_cid=rr6501e1_w#B1_down. Accessed October 4, 2017.
- Drug Enforcement Administration (DEA). FENTANYL (Trade Names: Actiq, Fentora, Duragesic). December 2016. Available at: http://www.deadiversion.usdoj.gov/drug_chem_info/fentanyl.pdf. Accessed October 4, 2017.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. March 22, 2017.
- Dubinsky RM, Kabbani H, El-Chami, et al; Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2004;63:959.
- Duragesic prescribing information. Janssen Pharmaceutical, Inc. Titusville, NJ. December 2016.
- Embeda prescribing information. King Pharmaceuticals, Inc. Bristol, TN. December 2016.
- Endo Pharmaceutics. Press Release. Endo Provides Update On Opana ER. July 6, 2017. Available at: http://phx.corporate-ir.net/phoenix.zhtml?c=231492&p=irol-newsArticle_print&ID=2284981. Accessed July 21, 2017.
- Exalgo prescribing information. Mallinckrodt LLC. Hazelwood, MO. December 2016.
- Food and Drug Administration (FDA). FDA statement: Original Opana ER relisting determination. May 10, 2013. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm351357.htm. Accessed October 3, 2017.
- FDA Drug Safety Communication: FDA warns about several safety issues with opioid pain medicines; requires label changes. March 22, 2016. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm489676.htm. Accessed October 3, 2017.
- FDA Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. August 21, 2016. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm518473.htm. Accessed October 3, 2017.
- FDA Industry Guidance. Guidance for Industry: Abuse-Deterrent Opioid – Evaluation and Labeling. April 2015. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf. Accessed October 3, 2017.
- FDA Industry Guidance. Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products (draft guidance). March 2016. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM492172.pdf. Accessed March 22, 2017.
- FDA Briefing Document. Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee Meeting. March 2017. Available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM545760.pdf. Accessed October 4, 2017.
- FDA Summary Minutes. Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee Joint Meeting. May 2016. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM509895.pdf. Accessed October 4, 2017.
- FDA Summary Review. Application number: 022272Orig1s027 (OxyContin). August 13, 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/022272Orig1s027SumR.pdf. Accessed October 4, 2017.
- FDA Summary Review. Application number: 022272Orig1s027 (Arymo ER). January 9, 2017. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208603Orig1s000SumR.pdf. Accessed October 4, 2017.
- Felden L, Walter C, Harder S, et al. Comparative clinical effects of hydromorphone and morphine: a meta-analysis. Br J Anaesth. 2011 Sep;107(3):319-28.
- Finkel JC, Finley A, Greco C, et al. Transdermal fentanyl in the management of children with chronic severe pain. Results from an international study. Cancer. 2005;104:2847-57.
- Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol. 2015;14(2):162-73.
- Gimbel JS, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy. Neurology. 2003;60:927-34.
- Gordon A, Rashiq S, Moulin DE, et al [a]. Buprenorphine transdermal system for opioid therapy in patients with chronic low back pain. Pain Res Manag. 2010 May-Jun;15(3):169-78.
- Gordon A, Callaghan D, Spink D, et al [b]. Buprenorphine transdermal system in adults with chronic low back pain: a randomized, double-blind, placebo-controlled crossover study, followed by an open-label extension phase. Clin Ther. 2010 May;32(5):844-60.
- Hale ME, Moe D, Bond M, Gasior M, Malamut R. Abuse-deterrent formulations of prescription opioid analgesics in the management of chronic noncancer pain. Pain Manag. 2016;6(5):497-508.
- Hale M, Tudor IC, Khanna S, et al. Efficacy and tolerability of once-daily OROS hydromorphone and twice-daily extended-release oxycodone in patients with chronic, moderate to severe osteoarthritis pain: results of a 6-week, randomized, open-label, non inferiority analysis. Clin Ther. 2007;29(5):874-88.
- Hale M, Khan A, Kutch M, et al. Once-daily OROS hydromorphone ER compared to placebo in opioid-tolerant patients with chronic low back pain. Curr Med Res Opin. 2010;26(6):1505-18.
- Hochberg MC, Altman RD, April KT, et al; American College of Rheumatology. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2012 Apr;64(4):455-74.
- Hysingla ER prescribing information. Purdue Pharmaceuticals, L.P. Stamford, CT. December 2016.
- Kadian prescribing information. Actavis Elizabeth LLC. Morristown, NJ. December 2016.

- Karlsson M, Berggren AC. Efficacy and safety of low-dose transdermal buprenorphine patches (5, 10, and 20 microg/h) vs prolonged-release tramadol tablets (75, 100, 150, and 200 mg) in patients with chronic osteoarthritis pain: a 12-week, randomized, open-label, controlled, parallel-group non inferiority study. Clin Ther. 2009 Mar;31(3):503-13.
- Katz N, Hale M, Morris D, et al. Morphine sulfate and naltrexone hydrochloride extended release capsules in patients with chronic osteoarthritis pain. Postgrad Med. 2010 Jul;122(4):112-28.
- Katz N, Kopecky EA, O'Connor M, Brown RH, Fleming Ab. A phase 3, multicenter, randomized, double-blind, placebo-controlled, safety, tolerability, and efficacy study of Xtampza ER in patients with moderate-to-severe chronic low back pain. Pain. 2015;156(12):2458-67.
- King SJ, Reid C, Forbes K, et al. A systematic review of oxycodone in the management of cancer pain. Palliat Med. 2011 Jul;25(5):454-70.
- Kivitz A, Ma C, Ahdieh H, et al. A 2-week, multicenter, randomized, double-blind, placebo-controlled, dose-ranging, phase III trial comparing the efficacy of oxymorphone extended release and placebo in adults with pain associated with osteoarthritis of the hip or knee. Clinical Therapeutics. 2006;38(3):352-64.
- Langford R, McKenna F, Ratcliffe S, et al. Transdermal fentanyl for improvement of pain and functioning in osteoarthritis. Arthritis & Rheumatism 2006;54(6):1829-37.
- Levorphanol prescribing information. Roxane Laboratories, Inc. Columbus, OH. September 2015.
- Ma K, Jiang W, Zhou Q, et al. The efficacy of oxycodone for management of acute pain episodes in chronic neck pain patients. Int J Clin Pract. 2008;62(2):241-7.
- Manchikanti L, Kaye AM, Knezevic NN, et al. Responsible, safe, and effective prescription of opioids for chronic non-cancer pain: American Society of Interventional Pain Physicians (ASIPP) Guidelines. Pain Physician. 2017;20(2S):S3-S92.
- *Medical Letter, Inc. Treatment guidelines from the Medical Letter: Drugs for Pain. 2013;11(128):31-42.*
- Mesgarpour B, Griebler U, Glechner A, et al. Extended-release opioids in the management of cancer pain: a systematic review of efficacy and safety. Eur J Pain. 2014;18(5):605-16.
- Melilli G, Samolsky Dekel BG, Frenquelli C, et al. Transdermal opioids for cancer pain control in patients with renal impairment. J Opioid Manag. 2014;10(2):85-93.
- Mercadante S, Porzio G, Ferrera P, et al. Low doses of transdermal fentanyl in opioid-naïve patients with cancer pain. Curr Med Research Opin. 2010;26(12):2765-8.
- Methadone oral solution prescribing information. Roxane Laboratories, Inc. Columbus, OH. March 2016.
- Methadose prescribing information. Mallinckrodt Inc. Hazelwood, MO. December 2016.
- Morley JS, Bridson J, Nash TP, et al. Low-dose methadone has an analgesic effect in neuropathic pain: a double-blind randomized controlled crossover trial. Palliative Medicine. 2003;17:576-87.
- Morphabond prescribing information. Inspirion Delivery Technologies LLC. Valley Cottage, NY. October 2015.
- MS Contin prescribing information. Purdue Pharma L.P. Stamford, CT. December 2016.
- Musclow SL, Bowers T, Vo H, et al. Long-acting morphine following hip or knee replacement: a randomized, double-blind and placebo-controlled trial (abstract). Pain Res Manag. 2012;17(2):83-8.
- National Academies of Sciences, Engineering, and Medicine. Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use. 2017. Available at: http://nationalacademies.org/hmd/Reports/2017/pain-management-and-the-opioid-epidemic.aspx. Accessed October 3, 2017.
- National Institute on Drug Abuse (NIDA). What is the Federal Government Doing to Combat the Opioid Abuse Epidemic? May 1, 2015. Available at: http://www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2015/what-federal-government-doing-to-combat-opioid-abuse-epidemic. Accessed October 4, 2017.
- Nicholson AB, Watson GR, Derry S, Wiffen PJ. Methadone for cancer pain. Cochrane Database Syst Rev. 2017;2:CD003971.
- Nucynta ER prescribing information. Janssen Pharmaceuticals, Inc. Titusville, NJ. December 2016.
- Office of Disease Prevention and Health Promotion. Pathways to Safer Opioid Use. October 6, 2015. Available at: http://health.gov/hcq/training-pathways.asp. Accessed October 4, 2017.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed October 4, 2017.
- OxyContin prescribing information. Purdue Pharma L.P. Stamford, CT. December 2016.
- Oxymorphone extended-release prescribing information. Mallinckrodt, Inc. Hazelwood, MO. November 2016.
- Park JH, Kim JH, Yun SC, et al. Evaluation of efficacy and safety of fentanyl transdermal patch (Duragesic D-TRANS) in chronic pain. Acta Neurochir. 2011;153:181-90.
- Pigni A, Brunelli C, Caraceni A. The role of hydromorphone in cancer pain treatment: a systematic review. Palliat Med. 2011 Jul;25(5):471-7.
- Qaseem A, Wilt TJ, McLean RM, Forciea MA; Clinical Guidelines Committee of the American College of Physicians. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2017. [Epub ahead of print]
- Quigley C. Hydromorphone for acute and chronic pain. Cochrane Database Syst Rev. 2002;(1):CD003447.
- Rauck RL, Nalamachu S, Wild JE, et al. Single-entity hydrocodone extended-release capsules in opioid-tolerant subjects with moderate-to-severe chronic low back pain: a randomized double-blind, placebo-controlled study. Pain Med. 2014 Feb [in press].
- Schwartz S, Etropolski M, Shapiro DY, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. Curr Med Res Opin. 2011 Jan;27(1):151-62.
- Slatkin NE, Rhiner MI, Gould EM, et al. Long-term tolerability and effectiveness of oxymorphone extended release in patients with cancer (abstract). J Opioid Manag. 2010;6(3):181-91.
- Sloan P, Slatkin N, Ahdieh H. Effectiveness and safety of oral extended-release oxymorphone for the treatment of cancer pain: a pilot study. Support Care Cancer. 2005;13:57-65.
- Summary of the Comprehensive Addiction and Recovery Act. American Society of Addiction Medicine (ASAM) Web site. http://www.asam.org/advocacy/issues/opioids/summary-of-the-comprehensive-addiction-and-recovery-act. Accessed October 4, 2017.

- US Department of Veterans Affairs. VA Accelerates Deployment of Nationwide Opioid Therapy Tool. March 9, 2015. Available at: http://www.va.gov/opa/pressrel/pressrelease.cfm?id=2681. Accessed October 4, 2017.
- Watson CPN, Moulin D, Watt-Watson J, et al. Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. Pain. 2003;105:71-8.
- Whittle SL, Richards BL, Husni E, et al. Opioid therapy for treating rheumatoid arthritis pain. Cochrane Database Syst Rev. 2011;(11):CD003113.
- Wiffen PJ, Wee B, Moore RA. Oral morphine for cancer pain (review). Cochrane Database Syst Rev. 2013;(7):CD003868.
- Wild JE, Grond S, Kuperwasser B, et al. Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain. Pain Pract. 2010 Sept-Oct;10(5):416-27.
- Whittle SL, Richards BL, Husnit E, et al. Opioid therapy for treatment rheumatoid arthritis pain (review). Cochrane Database Syst Rev. 2011;(11):CD003113.
- Xartemis XR prescribing information. Mallinckrodt Brand Pharmaceuticals, Inc. Hazelwood, MO. September 2017.
- Xtampza ER prescribing information. Patheon Pharmaceuticals. Cincinnati, OH. December 2016.
- Zohydro ER prescribing information. Zogenix, Inc. San Diego, CA. December 2016.

Publication date: October 4, 2017

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).

REFERENCES

- Andersen K, Weinberger MH, Egan B, et al. Comparative efficacy and safety of aliskiren, an oral direct renin inhibitor, and ramipril in hypertension: a 6-month, randomized, double-blind trial. J Hypertens. 2008;26(3):589-99.
- Basile J, Babazadeh S, Lillestol M, et al. Comparison of aliskiren/hydrochlorothiazide combination therapy with hydrochlorothiazide monotherapy in older patients with stage 2 systolic hypertension: results of the ACTION study. J Clin Hypertens (Greenwich). 2011 Mar;13(3):162-9.
- Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics – 2017 update: a report from the American Heart Association. Circulation. 2017;135(10):e146-e603.
- Black HR, Kribben A, Aguirre Palacios F, et al. Aliskiren alone or in combination with hydrochlorothiazide in patients with the lower ranges of stage 2 hypertension: The ACQUIRE randomized double-blind study. J Clin Hypertens (Greenwich). 2010 Dec;12(12):917-26.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed May 15, 2017.
- Duprez D, Munger M, Botha J, et al. Aliskiren for geriatric lowering of systolic hypertension: a randomized controlled trial (abstract). J Human Hyperten. 2010;24(9):600-8.
- FDA Drug Safety Communication: New warning and contraindication for blood pressure medicines containing aliskiren (Tekturna). April 2012. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm300889.htm. Accessed May 15, 2017.
- Ferdinand KC, Pool J, Weitzman R, et al. Peripheral and central blood pressure responses of combination aliskiren/hydrochlorothiazide and amlodipine monotherapy in African American patients with stage 2 hypertension: the ATLAAST trial. J Clin Hypertens (Greenwich). 2011;13(5):366-75.
- Gheorghiade M, Bohm M, Greene SJ, et al. Effect of aliskiren on postdischarge mortality and heart failure readmissions among patients hospitalized for heart failure (ASTRONAUT Randomized Trial). JAMA 2013;309(11):1125–1135.
- Go AS, Bauman M, King SM, et al. An Effective Approach to High Blood Pressure Control: A Science Advisory from the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention (AHA/ACC/CDC). Hypertension.2014;63(4):878-85.
- Gradman AH, Schmieder RE, Lins RL. Aliskiren, a novel orally effective renin inhibitor, provides dose-dependent antihypertensive efficacy and placebo-like tolerability in hypertensive patients. Circulation. 2005;111(8):1012-8.
- James PA, Oparil S, Carter BL, et al. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311(5):507-20.
- Krone W, Hanefeld M, Meyer HF, et al. Comparative efficacy and safety of aliskiren and irbesartan in patients with hypertension and metabolic syndrome. J Hum Hypertens. 2011;25(3):186-95.
- Kushiro T, Itakura H, Abo Y. Aliskiren, a novel oral renin inhibitor, provides dose-dependent efficacy and placebo-like tolerability in Japanese patients with hypertension. Hypertens Res. 2006;29(12):997-1005.
- Maggioni AP, Greene SJ, Fonarow GC, et al. Effect of aliskiren on post-discharge outcomes among diabetic and non-diabetic patients hospitalized for heart failure: insights from the ASTRONAUT trial. Eur Heart J. 2013;34(40):3117-27.
- Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34(28):2159-219.
- McMurray JJ, Krum H, Abraham WT, et al. Aliskiren, enalapril, or aliskiren and enalapril in heart failure. N Engl J Med. 2016;374(16):1521-1532.
- Musini V, Lawrence KA, Fortin PM, Bassett K, Wright JM. Blood pressure lowering efficacy of renin inhibitors for primary hypertension. Cochrane Database Syst Rev. 2017;(4):CD007066.
- Oh BH, Mitchell J, Herron JR. Aliskiren, an oral renin inhibitor, provides dose-dependent efficacy and sustained 24-hour blood pressure control in patients with hypertension. J Am Coll Cardiol. 2007;49(11):1157-63.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed May 15, 2017.
- Parving H, Brenner BM, McMurray JJ, et al. Cardiorenal End Points in a Trial of Aliskiren for Type 2 Diabetes (ALTITUDE). N Engl J Med. 2012;367(32):2204.
- Sanders GD, Coeytaux R, Dolor RJ, et al. Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin II Receptor Antagonists (ARBs), and Direct Renin Inhibitors for Treating Essential Hypertension: An Update. Comparative Effectiveness Review No. 34. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-02-0025.) AHRQ Publication No. 11-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. June 2011. Available at: http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=695. Accessed May 15, 2017.
- Schmieder R, Philipp T, Guerediaga J, et al. Aliskiren-based therapy lowers blood pressure more effectively than hydrochlorothiazide-based therapy in obese patients with hypertension: sub-analysis of a 52-week, randomized, double-blind trial. J Hyperten. 2009a;27(7):1493-1501.
- Schmieder R, Philipp T, Guerediaga J, et al. Long-term antihypertensive efficacy and safety of the oral direct renin inhibitor aliskiren: a 12-month randomized, double-blind comparator trial with hydrochlorothiazide. Circulation. 2009b;119(3):417-25.
- Stanton A, Jensen C, Nussberger J. Blood pressure lowering in essential hypertension with an oral renin inhibitor, aliskiren. Hypertension. 2003;42(6):1137-43.
- Strasser RH, Puig JG, Farsang C. A comparison of the tolerability of the direct renin inhibitor aliskiren and lisinopril in patients with severe hypertension. J Hum Hypertens. 2007;21(10):780-7.

- TEKTURNA HCT prescribing information. Novartis Pharmaceuticals Corporation; East Hanover, NJ. November 2016.
- TEKTURNA prescribing information. Novartis Pharmaceuticals Corporation; East Hanover, NJ. November 2016.
- Teo KK, Pfeffer M, Mancia G, et al. Aliskiren alone or with other antihypertensives in the elderly with borderline and stage 1 hypertension: the APOLLO trial. Eur Heart J. 2014;35(26):1743-51.
- Villa G, Le Breton S, Ibram G, et al. Efficacy, safety, and tolerability of aliskiren monotherapy administered with a light meal in elderly hypertensive patients: a randomized, double-blind, placebo-controlled, dose-response evaluation study. J Clin Pharmacol. 2012;52(12):1901-11.
- Weber MA, Schiffrin EL, White WB, et al. Clinical Practice Guidelines for the Management of Hypertension in the Community: A Statement by the American Society of Hypertension and the International Society of Hypertension (ASH/ISH). J Hypertens. 2014;32(1):3-15.
- Zhu JR, Sun NL, Yang K, et al. Efficacy and safety of aliskiren, a direct renin inhibitor, compared with ramipril in Asian patients with mild to moderate hypertension. Hypertens Res. 2012;35(1):28-33.

Publication Date: May 16, 2017

Therapeutic Class Overview
Statins (HMG-CoA Reductase Inhibitors)

INTRODUCTION

- The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (also known as statins) include single entity agents (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin), as well as fixed-dose combination products (amlodipine/atorvastatin, ezetimibe/atorvastatin, and ezetimibe/simvastatin). The statins work by inhibiting HMG-CoA reductase, which is the rate-limiting enzyme involved in hepatic cholesterol synthesis. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is a cholesterol precursor. Inhibition of HMG-CoA reductase decreases hepatic cholesterol synthesis, causing up-regulation of low-density lipoprotein cholesterol (LDL-C) receptors. Statins also decrease the release of lipoproteins from the liver.
- The statins are the most effective class of oral drugs to lower LDL-C. Depending on the agent selected, moderate-intensity statins can decrease LDL-C by 30 to 49% and high-intensity statins can decrease LDL-C levels ≥ 50%. The effects on LDL-C are dose-dependent and log-linear. Statins also decrease triglycerides (TG) and increase high-density lipoprotein cholesterol (HDL-C) by varying levels (Stone et al, 2013).
- Ezetimibe inhibits the intestinal absorption of cholesterol, which decreases the delivery of cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood.
- Amlodipine is a calcium channel blocker that is approved for the treatment of hypertension (HTN), chronic stable angina and vasospastic angina, as well as to reduce the risks of hospitalization or revascularization in patients with angiographically confirmed coronary artery disease (CAD).
- Statins that are included in this review are listed in Table 1. All products are now available in a generic formulation except for ALTOPREV® (lovastatin extended-release) (Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017).
- The combinations niacin/lovastatin (ADVICOR®) and niacin/simvastatin (SIMCOR®) were removed from the market because the Food and Drug Administration (FDA) determined that a reduction in TG and increase in HDL-C do not contribute to decreased cardiovascular events according to the newest evidence (AbbVie, 2016).
- 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.

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
ALTOPREV (lovastatin extended-release)	Covis Pharma	06/26/2002	-
CRESTOR (rosuvastatin)	AstraZeneca Pharmaceuticals	08/12/2003	✔
FLOLIPID (simvastatin oral suspension)	Salerno Pharmaceuticals LP	04/21/2016	-
LESCOL (fluvastatin)*	Novartis	12/31/1993	✔
LESCOL XL (fluvastatin extended-release)	Novartis	10/06/2000	✔
LIPITOR (atorvastatin)	Pfizer.	12/17/1996	✔
LIVALO, ZYPITAMAG (pitavastatin)€π	Kowa Company	08/03/2009	✔
MEVACOR (lovastatin)*	Merck & Co., Inc	08/31/1987	✔
PRAVACHOL (pravastatin)	Bristol Myers Squibb Company	10/31/1991	✔

Drug	Manufacturer	FDA Approval Date	Generic Availability
ZOCOR (simvastatin)	Merck & Co., Inc.	12/31/1991	✔
CADUET (amlodipine/ atorvastatin)	Pfizer	01/30/2004	✔
LIPTRUZET† (ezetimibe/atorvastatin)	Watson Labs Teva	04/26/2017	✔
VYTORIN® (ezetimibe/simvastatin)	Merck & Co., Inc.	07/23/2004	✔

*The brands, LESCOL and MEVACOR, have been discontinued, but the generic formulations are available.
†The brand, LIPTRUZET, by Merck was discontinued in 2015. A generic formulation by Watson Labs Teva was recently approved by the FDA.
€The brand NIKITA was discontinued.
πZYPITAMAG was FDA-approved July 2017; anticipated availability is currently unknown.

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

INDICATIONS

Table 2. FDA-approved indications

Indications	Single-Entity Agents							Combination Products		
	atorvastatin	fluvastatin	lovastatin	pitavastatin	pravastatin	rosuvastatin	simvastatin	amlodipine/ atorvastatin	ezetimibe/ atorvastatin	ezetimibe/ simvastatin
Hypertriglyceridemia										
Reduce elevated TG in patients with hypertriglyceridemia					✔		✔	✔ (atorvastatin)		
Treatment of adult patients with hypertriglyceridemia in combination with diet						✔				
Primary Hypercholesterolemia and Mixed Dyslipidemia										
Reduce elevated total cholesterol (TC), LDL-C, apolipoprotein B (apo B), and TG and to increase HDL-C in patients with primary hyperlipidemia or hypercholesterolemia and mixed dyslipidemia	✔	✔	✔ § (ER)	✔	✔	✔	✔	✔ (atorvastatin)	✔	✔
Reduce TC, LDL-C, and apo B levels in children with heterozygous familial hypercholesterolemia (HeFH) if after an adequate trial of diet therapy the following findings are present: LDL-C remains ≥189 (lovastatin only) or 190 mg/dL OR LDL-C remains ≥160 mg/dL and there is a positive family history of premature cardiovascular disease (CVD) or two or more other cardiovascular risk factors are present in the pediatric patient	✔ ¶	✔ #	✔ ** (IR)		✔ ††	✔ ††	✔ **	✔ (atorvastatin)		
Reduce elevated TG and very high LDL-C in patients with primary dysbetalipoproteinemia							✔			
Reduce TC and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH) as an adjunct to other lipid-lowering treatments or if such treatments are unavailable	✔						✔	✔ (atorvastatin)	✔	✔
Reduce TC, LDL-C, and apo B in adults with HoFH						✔				
Reduce LDL-C, TC, non HDL-C and apo B in children and adolescents with HoFH, as monotherapy or with other lipid-lowering therapies						✔ ~~A~~				
Reduction of elevated TC and LDL-C levels in patients with primary hypercholesterolemia			✔ § (IR)							

Treatment of patients with primary dysbetalipoproteinemia who do not respond adequately to diet	✔				✔	✔		✔ (atorvastatin)		
Prevention of CVD										
Adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower TC and LDL-C to target levels						✔				
Reduce the risk of myocardial infarction (MI) and stroke in patients with type 2 diabetes, and without clinically evident coronary heart disease (CHD), but with multiple risk factors for CHD such as retinopathy, albuminuria, smoking, or HTN	✔							✔ (atorvastatin)		
Reduce the risk of MI, stroke, revascularization procedures, and angina in adult patients without clinically evident CHD, but with multiple risk factors for CHD such as age, smoking, HTN, low HDL-C, or a family history of early CHD	✔							✔ (atorvastatin)		
Reduce the risk of MI, undergoing myocardial revascularization procedures, and cardiovascular mortality with no increase in death from noncardiovascular causes in patients with hypercholesterolemia without clinically evident CHD					✔					
Reduce the risk of MI, unstable angina, and coronary revascularization procedures in patients without symptomatic CVD			✔ ɣ							
Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for congestive heart failure, and angina in patients with clinically evident CHD	✔							✔ (atorvastatin)		
Reduce the risk of stroke, MI, and arterial revascularization procedures in patients without clinically evident CHD but with an increased risk of CVD based on age ≥50 years old in men and ≥60 years old in women, high sensitivity C-reactive protein ≥2 mg/L, and the presence of at least one additional CVD risk factor such as HTN, low HDL-C, smoking, or a family history of premature CHD						✔				
Reduce the risk of total mortality by reducing coronary death, MI, undergoing myocardial revascularization procedures, stroke and stroke/transient ischemic attack, and to slow the progression of coronary atherosclerosis in patients with clinically evident CHD					✔					
Reduce the risk of total mortality by reducing CHD deaths, non-fatal MI and stroke, and need for coronary and non-coronary							✔			

revascularization procedures in patients at high risk of coronary events because of existing CHD, diabetes, peripheral vascular disease, history of stroke or other cerebrovascular disease										
Reduce the risk of undergoing coronary revascularization procedures and slow the progression of coronary atherosclerosis in patients with clinically evident CHD		✔								
Slow the progression of coronary atherosclerosis in patients with CHD as part of a treatment strategy to lower TC and LDL-C to target levels			✔							
Other										
Reduce the risk of hospitalization for angina and to reduce the risk of a coronary revascularization procedure in patients with recently documented CAD by angiography and without heart failure or an ejection fraction <40%								✔ (amlodipine)		
Symptomatic treatment of chronic stable angina								✔ (amlodipine)		
Treatment of confirmed or suspected vasospastic angina								✔ (amlodipine)		
Treatment of HTN, to lower blood pressure								✔ (amlodipine)		

Abbrv: CAD=coronary artery disease, CHD=coronary heart disease, ER=extended-release, IR=immediate-release, HTN=hypertension, MI=myocardial infarction.
§When the response to diet restricted in saturated fat and cholesterol and to other nonpharmacological measures alone has been inadequate.
¶In boys and postmenarchal girls 10 to 17 years of age.
#In adolescent boys and adolescents girls who are at least one year post-menarche, 10 to 16 years of age.
**In adolescent boys and girls who are at least one year post-menarche, 10 to 17 years of age.
††In children and adolescent patients eight to 17 years of age
~~Ā~~In children and adolescents ages seven to 17
ɣFor ER lovastatin, for patients at high risk; for IR lovastatin, for patients with average to moderately elevated TC and LDL-C and below average HDL-C

(Prescribing information: ALTOPREV®, 2017; CADUET®, 2017; CRESTOR®, 2017; FLOLIPID, 2017; LESCOL®, 2017; LESCOL XL®, 2017; LIPITOR®, 2017; LIVALO®, 2016; MEVACOR®, 2017; PRAVACHOL®, 2017; VYTORIN®, 2016; ZOCOR®, 2015, ZYPITAMAG, 2017)
Clinical Pharmacology, 2017

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

CLINICAL EFFICACY SUMMARY

- Numerous clinical trials have demonstrated that the statins (single-entity and combination products) can effectively lower LDL-C, non-HDL-C, total cholesterol (TC), and TG, as well as positively impact other lipid/lipoprotein parameters. Additionally, many studies have compared active treatment to placebo or compared combination therapy to monotherapy. In these studies, the more aggressive treatment regimens often improved lipid parameters to a greater extent than the less-intensive treatment regimens (Ai et al, 2008; Alvarez-Sala et al, 2008; Arca et al, 2007; Avis et al, 2007; Avis et al, 2010; Ballantyne et al, 2003; Ballantyne et al, 2004; Ballantyne et al, 2005; Ballantyne et al, 2006; Ballantyne et al, 2007; Ballantyne et al, 2008; Bardini et al, 2010; Bays et al, 2004; Bays et al, 2010; Bays et al, 2013; Bays et al, 2008a; Bays et al, 2008b; Becker et al, 2008; Betteridge et al, 2007a; Betteridge et al, 2007b; Braamskamp et al, 2015; Brown et al, 1990; Bullano et al, 2006; Bullano et al, 2007; Calza et al, 2008; Catapano et al, 2006; Charland et al, 2010; Chenot et al, 2007; Clearfield et al, 2006; Coll et al, 2006; Conard et al, 2008; Constance et al, 2007; Davidson et al, 2002; Deedwania et al, 2007a; Derosa et al, 2009; Erdine et al, 2009; Eriksson et al, 1998; Eriksson et al, 2011; Faergeman et al, 2008; Farnier et al, 2007; Farnier et al, 2008; Farnier et al, 2009; Feldman et al, 2004; Feldman et al, 2006; Ferdinand et al, 2006; Ferdinand et al, 2012; Flack et al, 2008; Florentin et al, 2011; Foody et al, 2010; Fox et al, 2007a; Fox et al, 2007b; Gagné et al, 2002; Gaudiani et al, 2005; Goldberg et al, 2004; Goldberg et al, 2006; Goldberg et al, 2009; Grimm et al, 2010; Gumprecht et al, 2011; Hall et al, 2009; Harley et al, 2007; Hing Ling et al, 2012; Hobbs et al, 2009; Hogue et al, 2008; Hunninghake et al, 2001; Illingworth et al,1994; Insull et al, 2007; Jones et al, 2003; Jones et al, 2009a; Jones et al, 2009b; Kerzner et al, 2003; Kipnes et al, 2010; Knapp et al, 2001; Koshiyama et al, 2008; Kumar et al, 2009; Lee et al, 2007; Leiter et al, 2007; Leiter et al, 2008; Lewis et al, 2007; Lloret et al, 2006; Marais et al, 2008; May et al, 2008; Mazza et al, 2008; Melani et al, 2003; Meredith et al, 2007; Messerli et al, 2006; Milionis et al, 2006; Mohiuddin et al, 2009; Motomura et al, 2009; Neutel et al, 2009; Nicholls et al, 2010; Ose et al, 2007; Ose et al, 2009; Ose et al, 2010; Park et al, 2005; Park et al, 2010; Pearson et al, 2007; Piorkowski et al, 2007; Polis et al, 2009; Preston et al, 2007; Reckless et al, 2008; Robinson et al, 2009; Rodenburg et al, 2007; Roeters van Lennep et al, 2008; Rogers et al, 2007; Rosenson et al, 2009; Rotella et al, 2010; Roth et al, 2010; Saito et al, 2002; Sansanayudh et al, 2010; Sasaki et al, 2008; Shafiq et al, 2007; Stalenhoef et al, 2005; Stein et al, 2003; Stein et al, 2004; Stein et al, 2007; Stein et al, 2008; Viigimaa et al, 2010; Vuorio et al, 2014; Winkler et al, 2007; Winkler et al, 2009; Wlodarczyk et al, 2008; Wolffenbuttel et al, 2005; Yoshitomi et al, 2006; Zieve et al, 2010).
- All of the statins, with the exception of pitavastatin, have been shown to have beneficial effects on CHD outcomes, and the majority of them (atorvastatin, pravastatin, rosuvastatin, and simvastatin) have also been shown to decrease the risk of stroke (Afilalo et al, 2007; Afilalo et al, 2008; Ahmed et al, 2006; Amarenco et al, 2009a; Amarenco et al, 2009b; Asselbergs et al, 2004; Athyros et al, 2002; Athyros et al, 2007; Baigent et al, 2005; Barter et al, 2007; Briel et al, 2006; Bushnell et al, 2006; Byington et al; 1995; Cannon et al, 2004; Cannon et al, 2006; Cannon et al, 2015; Chan et al, 2010; Cholesterol Treatment Trialists' (CTT) Collaborators, 2008; Chonchol et al, 2007; Colhoun et al, 2004; Collins et al, 2003; Crouse et al, 2007; de Lemos et al, 2004; Deedwania et al, 2006; Deedwania et al, 2007b; Downs et al, 1998; Everett et al, 2010; Ford et al, 2007; Furberg et al, 1994; Hitman et al, 2007; Hulten et al, 2006; Khush et al, 2007; Knopp et al, 2006; Koenig et al, 2001; LaRosa et al, 2005; LaRosa et al, 2007; Liem et al, 2002; Meaney et al, 2009; Mood et al, 2007; Mora et al, 2010; Murphy et al, 2007; Nakamura et al, 2006; Neil et al, 2006; Nicholls et al, 2006; Nissen et al, 2004; Nissen et al, 2005; Nissen et al, 2006; No authors listed, 1994; No authors listed, 2002; No authors listed, 2007; Olsson et al, 2007; O'Regan et al, 2008; Pedersen et al, 2005; Pitt et al, 1999; Pitt et al, 2012; Ray et al, 2005; Ray et al, 2006; Ridker et al, 2008; Ridker et al, 2009; Ridker et al, 2010; Rossebø et al, 2008; Sacks et al,1996; Sakamoto et al, 2007; Sato et al, 2008; Schmermund et al, 2006; Schoenhagen et al, 2006; Schouten et al, 2009; Schwartz et al, 2005; Scirica et al, 2006; Serruys et al, 2002; Sever et al, 2003; Sever et al, 2005; Shah et al, 2008; Shepherd et al, 1995; Shepherd et al, 2007; Shepherd et al, 2006; Shepherd J et al, 2002; Strandberg et al, 2009; Tavazzi L et al, 2008; Taylor et al, 2013; The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002; The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group, 1998; The Pravastatin Multinational Study Group for Cardiac Risk Patients (PMS-CRP), 1993; Thompson et al, 2004; Tikkanen et al, 2009; Waters et al, 2006; Wenger et al, 2007; Yu et al, 2007).
- Two early primary prevention trials (West of Scotland Coronary Prevention Study [WOSCOPS] and Air Force/Texas Coronary Atherosclerosis Prevention Study [AFCAPS/TexCAPS) demonstrated that the use of statins significantly reduced the risk for major coronary events (Downs et al, 1998; Shepard et al, 1995).
- Specifically, the WOSCOPS trial (N=6959) demonstrated that compared to placebo, pravastatin (40 mg/day) was associated with a significant 31% reduction in the risk of the combined endpoint of CHD death and nonfatal MI (P<0.001). A reduction in the secondary endpoint of cardiovascular death was also significant in favor of pravastatin (32%; P=0.033) (Shepard et al, 1995).

- The AFCAPS/TexCAPs trial (N=6,605) demonstrated similar benefits but with lovastatin (20 to 40 mg/day). In this trial, lovastatin was associated with a significant 37% reduction in the risk of the combined endpoint of fatal or nonfatal MI, unstable angina or sudden cardiac death (P<0.001). The AFCAPS/TexCAPs trial contained too few events to perform survival analysis on cardiovascular and CHD mortality (Downs et al, 1998).
- The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT, N=10,305) was terminated early (median duration, 3.3 years) due to the significant benefits observed with atorvastatin. In this trial, patients had average cholesterol concentrations but were at an increased risk for CHD due to the presence of HTN and three additional CHD risk factors. Compared to placebo, atorvastatin significantly reduced the risk of the combined endpoint of CHD death and nonfatal MI by 35% (P=0.0005) (Sever et al, 2003).
- Despite not demonstrating any benefit on all-cause mortality within the ASCOT trial (P=0.1649), atorvastatin has been associated with significant reductions in all-cause mortality in other primary prevention trials (Colhoun et al, 2004; Sever et al, 2003; Sever et al, 2005).
- A benefit in all-cause mortality, as well as other cardiovascular outcomes, with rosuvastatin in primary prevention was demonstrated in the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial (N=17,802). This trial sought to evaluate the efficacy of rosuvastatin in reducing cardiac events in patients with elevated high sensitivity C-reactive protein levels, which they note as being a predictor for cardiac events. This trial was terminated early (median duration 1.9 years) due to the significant benefits observed with rosuvastatin. Compared to placebo, rosuvastatin significantly reduced the risk of a first major cardiovascular event (nonfatal MI, nonfatal stroke, hospitalization for unstable angina, revascularization procedure or cardiovascular death) by 44% (P<0.0001). When analyzed individually, rosuvastatin was associated with a significant benefit for all primary outcomes, as well as all-cause mortality (P=0.02) (Ridker et al, 2008).
- Meta-analyses support the findings observed in the individual primary prevention trials (Baigent et al, 2005; CTT Collaborators et al, 2008; Mora et al, 2010; O'Regan et al, 2008; Taylor et al, 2011, Nunes 2017).
- The Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL) trial (N=8,888) compared intensive lipid lowering therapy with atorvastatin 80 mg/day to moderate therapy with simvastatin 20 mg/day (with the potential to increase to 40 mg/day based on improvements in lipid profile). In this trial, atorvastatin did not significantly reduce the risk of the primary composite endpoint of CHD death, nonfatal MI, or cardiac arrest with resuscitation (hazard ratio [HR], 0.89; 95% confidence interval [CI], 0.78 to 1.01; P=0.07). Atorvastatin was associated with a significant reduction in the risk of major cardiovascular events compared to simvastatin (12.0 vs 13.7%; HR, 0.87; P=0.02). Atorvastatin was associated with a significant reduction in the risk of any CHD event compared to simvastatin (20.2 vs 23.8%; HR, 0.84; P<0.001) and for the risk of any cardiovascular events compared to simvastatin (26.5 vs 30.8%; HR, 0.84; P<0.001). For the individual events, atorvastatin had a lower rate of nonfatal acute MI than simvastatin (7.2% vs. 6.0%; HR, 0.83; 95% CI, 0.71 to 0.98; P=0.02), but the treatments were no different in terms of all-cause (P=0.81) or noncardiovascular (P=0.47) mortality. In addition, intensive therapy with atorvastatin 80 mg/day was associated with a significantly higher incidence of discontinuations due to adverse events (P<0.001) (Pedersen et al, 2005). A total of 94 patients (2.2%) receiving atorvastatin and 135 patients (3.2%) receiving simvastatin developed peripheral arterial disease (HR, 0.7; 95% CI, 0.53 to 0.91; P=0.007) (Stoekenbroek et al, 2015).
- Several trials have demonstrated that statins are effective in delaying the progression of atherosclerotic disease in patients with CHD. Included in these is the head-to-head REVERSAL trial that demonstrated that intensive lipid lowering with atorvastatin 80 mg/day was associated with a significantly lower median percentage change in atheroma volume compared to moderate lipid lowering with pravastatin 40 mg/day after 18 months (P=0.02) (Byington et al, 1995; Chan et al, 2010; Crouse et al, 2007; Furberg et al, 1994; Nicholls et al, 2006; Nissen et al, 2004; Nissen et al, 2005; Nissen et al, 2006; Schmermund et al, 2006; Schoenhagen et al, 2006).
- The majority of secondary prevention trials have evaluated the use of statins initiated three to six months after an acute cardiac event; however, evidence supports the use of these agents initiated right after an acute event (Briel et al, 2006; Cannon et al, 2004; de Lemos et al, 2004; Liem et al, 2002).
- The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial (N=3,086), a placebo-controlled trial with atorvastatin, is noteworthy as it demonstrated that when initiated in the hospital following an acute coronary syndrome (ACS), atorvastatin was safe and associated with a 16% reduction in the composite of death, nonfatal acute MI, resuscitated cardiac arrest, or recurrent symptomatic myocardial ischemia after 16 weeks (P=0.048) (Schwartz et al, 2005).
- Of the head-to-head trials, the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial (N=4,162) again compared intensive lipid therapy with atorvastatin 80 mg/day to standard therapy with pravastatin 40 mg/day (with a potential to increase to 80 mg/day based on

improvements in lipid profile). Patients who were hospitalized with an ACS within the preceding 10 days were enrolled. After two years, atorvastatin significantly reduced the combined endpoint of all-cause mortality, MI, unstable angina requiring hospitalization, coronary revascularization performed >30 days after randomization, and stroke by 16% compared to pravastatin (P=0.005). Among the individual endpoints, atorvastatin was significant for reducing the risk of revascularization (P=0.04) and unstable angina (P=0.02). In this trial, discontinuations due to adverse events were similar between the two treatments (P=0.11) (Cannon et al, 2004).

- A meta-analysis which assessed the efficacy of high dose atorvastatin in patients who underwent percutaneous coronary intervention (PCI) (N=2,850) found that atorvastatin significantly reduced the risk of MI in patients with PCI compared to placebo (RR, 0.62; 95% CI, 0.49 to 0.78) (Lu, 2017).
- A meta-analysis evaluated the efficacy and safety of dosing statins on alternative days (N=505) compared to daily dosing (N=518). Although there was no differences on TG, the reduction in TC (P<0.00001) and LDL-C (P=0.003) was significantly greater in the daily dosing group (Awad, 2017).
- A Cochrane review assessed the effectiveness of statins in children aged 4 to 18 years with HeFH and found that statin treatment is effective. Statin therapy was found to be safe with no significant safety issues in the short-term (Vuorio, 2017).

SAFETY SUMMARY

- Statins are contraindicated in documented hypersensitivity to the agent, unexplained elevations in serum transaminases, active liver disease, and patients who are pregnant or nursing.
- The statins are generally well-tolerated, and the most common side effects are gastrointestinal disturbances, headache, insomnia, myalgia, and rash. Muscle aches and weakness are reported by 1 to 2% of patients taking statins. The symptoms are usually mild and generally do not lead to discontinuation, however, myopathy can sometimes take the form of rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria. Rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. All statins can increase hepatic transaminase levels and creatinine kinase.
- Increases in hemoglobin A1c (HbA1c) and fasting serum glucose have been reported with statins. New-onset diabetes is increased in patients treated with statins; however, it is dose-related, occurs primarily in patients on metformin and a sulfonylurea, appears to be less common with pravastatin and possibly pitavastatin, and occurs overall to a lesser extent than the associated decrease in atherosclerotic cardiovascular disease (ASCVD) (Jellinger et al, 2017).
- Pravastatin is the only statin that does not undergo cytochrome (CYP) 450 metabolism, and is therefore associated with a lower risk for drug interactions. Atorvastatin (to a lesser extent), lovastatin, and simvastatin are primarily metabolized by the CYP3A4 isoenzyme, while fluvastatin, pitavastatin, and rosuvastatin are metabolized by the CYP2C9 isoenzyme, which may result in differences in their drug interaction profiles (Wiggins et al, 2016).
- The 2016 scientific statement written by the American Heart Association (AHA) stated that the risk for interactions between statins and other cardiovascular drugs may be unavoidable for heart patients, but it can be reduced with proper clinical management. A review of all of the medications that statin-treated patients are taking should be done at each patient visit, so that potential drug interactions can be identified early. Some key recommendations include:
    - Concomitant use of lovastatin, pravastatin, or simvastatin with gemfibrozil should be avoided. When gemfibrozil is used with other statins, a lower statin dose should be utilized.
    - A non-CYP3A4-metabolized statin should be used in combination with verapamil and diltiazem (calcium channel blockers). The dose of lovastatin or simvastatin should be limited to 20 mg daily or less when given with the calcium channel blocker amlodipine.
    - The concomitant use of cyclosporine, everolimus, sirolimus, or tacrolimus should be avoided with lovastatin, simvastatin, and pitavastatin, as the combination could be potentially harmful.
    - Numerous other drug interactions are listed, many of which require dose adjustment of statin therapy or drug level monitoring (e.g. digoxin) (Wiggins et al, 2016).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Single-Entity Agents				

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
atorvastatin	Tablet: 10 mg 20 mg 40 mg 80 mg	Hyperlipidemia: Tablet: initial, 10 to 40 mg once daily; maintenance, 10 to 80 mg/day Adjunct to diet for the treatment of patients with elevated serum TG levels, reduce TC and LDL-C in patients with HoFH as an adjunct to other lipid lowering treatments or if such treatments are unavailable, treatment of patients with primary dysbetalipoproteinemia: Tablet: 10 to 80 mg/day HeFH in pediatric patients 10 to 17 years old: Tablet: initial dose 10 mg/day, maximum dose 20 mg/day	After initiation and/or upon titration, lipid levels should be analyzed within two to four weeks and dosage adjusted accordingly.	May be administered with or without food. Tablets may be taken at any time during the day.
fluvastatin	Capsule: 20 mg 40 mg Extended-release tablet: 80 mg	Hypercholesterolemia (including HeFH and nonfamilial) and mixed dyslipidemia in adults: Capsule: 40 mg once daily or 40 mg twice daily Extended-release tablet: 80 mg once daily HeFH in pediatric patients: Capsule: 20 mg daily, maximum dose 40 mg twice daily Extended-release tablet: 80 mg once daily	After initiation and/or upon titration, lipid levels should be analyzed after four weeks and dosage adjusted accordingly.	Capsules should be taken in the evening if dosed once daily. If 80 mg/day is used, it should be administered in two divided doses (immediate-release capsule). May be administered with or without food. Tablets may be taken at any time during the day (extended-release tablet). Tablets should be swallowed whole. (extended-release tablet).
lovastatin	Extended-release tablet: 20 mg 40 mg 60 mg Tablet: 10 mg	Hyperlipidemia: Extended-release tablet: initial, 20 to 60 mg once daily; maintenance, 20 to 60 mg/day Tablet: initial, 20 mg once daily; maintenance, 10 to 80 mg/day in	Prior to initiation and periodically during therapy, lipid levels should be analyzed and dosage adjusted accordingly.	Extended-release tablet should be taken at bedtime. Extended-release tablets should be swallowed whole.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	20 mg 40 mg	single or two divided doses; maximum, 80 mg/day Prevention of CVD: Extended-release tablet: initial, 20 to 60 mg once daily; maintenance, 20 to 60 mg/day Tablet: initial, 20 mg once daily; maintenance, 10 to 80 mg/day in single or two divided doses; maximum, 80 mg/day		Immediate-release tablet should be taken with an evening meal.
pitavastatin	Tablet: 1 mg 2 mg 4 mg	Hyperlipidemia: Tablet: initial, 2 mg once daily; maintenance, 1 to 4 mg/day; maximum, 4 mg/day	After initiation and/or upon titration, lipid levels should be analyzed after four weeks and dosage adjusted accordingly. Do not exceed 4 mg once daily dosing due to increased risk of severe myopathy Max dose is 1 mg mg/day when used with erythromycin. Max dose is 2 mg mg/day when used with rifampin.	May be administered with or without food. Tablets may be taken at any time during the day.
pravastatin	Tablet: 10 mg* 20 mg 40 mg 80 mg	Hyperlipidemia: Tablet: initial, 40 mg once daily; maintenance, 40 to 80 mg once daily Prevention of CVD: Tablet: initial, 40 mg once daily; maintenance, 40 to 80 mg once daily Pediatric patients: Ages eight to 13 years old: 20 mg once daily Ages 14 to 18 years old: 40 mg once daily	After initiation and/or upon titration, lipid levels should be analyzed after four weeks and dosage adjusted accordingly. Max dose in patients taking cyclosporine is 20 mg/day. Max dose in patients taking	May be administered with or without food. Tablets may be taken at any time during the day.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			clarithromycin is 40 mg/day.	
rosuvastatin	Tablet: 5 mg 10 mg 20 mg 40 mg	Hyperlipidemia: Tablet: initial, 10 to 20 mg once daily; maintenance, 5 to 40 mg/day Reduce TC, LDL-C and apo B in patients with HoFH: Tablet: initial, 20 mg once daily; Ages seven to 17 years: Tablet: 20 mg once daily Reduce TC, LDL-C and apo B in pediatric patients with HeFH: Aged eight to less than 10 years: Tablet: maintenance, 5 to 10 mg/day Aged 10 to 17 years: Tablet: maintenance, 5 to 20 mg/day	After initiation and/or upon titration, lipid levels should be analyzed within two to four weeks and dosage adjusted accordingly. Dosing in Asian patients: initial, 5 mg once daily Max dose is 5 mg once daily when used with cyclosporine and 10 mg once daily when used with gemfibrozil, atazanavir/ ritonavir, lopinavir/ritonavir, or simeprevir.	May be administered with or without food. Tablets may be taken at any time during the day.
simvastatin	Tablet: 5 mg 10 mg 20 mg 40 mg 80 mg Oral suspension: 20 mg/5 mL 40 mg/5 mL	Hyperlipidemia: Tablet: initial, 10 or 20 mg once daily; maintenance, 5 to 40 mg/day Reduce TC and LDL-C in patients with HoFH as an adjunct to other lipid lowering treatments or if such treatments are unavailable: Tablet: 40 mg once daily Prevention of CVD: Tablet: initial, 10 or 20 mg once daily; maintenance, 5 to 40 mg/day Reduce TC, LDL-C and apo B in pediatric patients with HeFH: Aged 10 to 17 years: Tablet: initial, 10 mg/day; maintenance, 10 to 40 mg/day; maximum dose is 40 mg/day	After initiation and/or upon titration, lipid levels should be analyzed after four weeks and dosage adjusted accordingly. Dose should be decreased by 50% if initiating lomitapide. Simvastatin dosage should not exceed 20 mg/day (or 40 mg/day for patients who have previously taken simvastatin 80 mg/day chronically (e.g. for 12 months or	Tablets should be taken in the evening. The oral suspension should be taken on an empty stomach. Shake oral suspension bottle for at least 20 seconds. Use accurate measuring device. Due to the increased risk of myopathy, including rhabdomyolysis, particularly during the first year of treatment, use of the 80 mg dose should be restricted to patients who

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			more) without evidence of muscle toxicity) while taking lomitapide. Use caution in Chinese patients receiving doses >20 mg with niacin-containing products. Max dose is 10 mg/day when used with verapamil, diltiazem, or dronedarone. Max dose is 20 mg/day when used with amiodarone, amlodipine, or ranolazine.	have been taking the 80 mg dose chronically without evidence of muscle toxicity.
Combination Products				
amlodipine/ atorvastatin	Tablet: 2.5/10 mg 2.5/20 mg 2.5/40 mg 5/10 mg 5/20 mg 5/40 mg 5/80 mg 10/10 mg 10/20 mg 10/40 mg 10/80 mg	Dosage of amlodipine/atorvastatin must be individualized on the basis of both effectiveness and tolerance for each individual component in the treatment of hypertension/angina and hyperlipidemia. Select doses of amlodipine and atorvastatin independently. The usual starting dose for amlodipine is 5 mg daily and for atorvastatin 10 to 20 mg daily. The maximum dose is amlodipine 10 mg daily and atorvastatin 80 mg daily. Patients requiring large LDL-C reductions (>45%) should initiate atorvastatin therapy at 40 mg once daily. HeFH in pediatric patients 10 to 17 years old: *Atorvastatin*	After initiation and/or upon titration, lipid levels should be analyzed within two to four weeks and dosage adjusted accordingly. Dosage should be adjusted to achieve blood pressure goals. In general, wait seven to 14 days between titration steps. Titration may proceed more rapidly if clinically warranted, provided the	May be administered with or without food. Tablets may be taken at any time during the day.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		Tablet: initial dose 10 mg/day, maximum dose 20 mg/day *Amlodipine [age 6 to 7 years old]* Tablet: initial dose 2.5 to 5 mg maximum dose 5 mg	patient is assessed frequently.	
ezetimibe/ atorvastatin	Tablet: 10/10 mg 10/20 mg 10/40 mg 10/80 mg	Usual starting dose: 10/10 mg or 10/20 mg once daily. Usual dose range is 10/10 mg to 10/80 mg once daily. May initiate at 10/40 mg once daily for patients requiring a larger LDL-C reduction (> 55%). HoFH: 10/40 mg or 10/80 mg once daily.	After initiation or titration of doses, lipid levels may be analyzed after two or more weeks. For patients taking clarithromycin, itraconazole, saquinavir + ritonavir, darunavir + ritonavir, or fosamprenair alone or with ritonavir: Do not exceed 10/20 mg once daily. For patients taking nelfinavir: Do not exceed 10/40 mg once daily.	Tablets may be taken at any time of the day. May be administered with or without food.
ezetimibe/ simvastatin	Tablet: 10/10 mg 10/20 mg 10/40 mg 10/80 mg	Hyperlipidemia: Adjunct to diet to reduce elevated TC, LDL-C, apo B and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia, reduce TC and LDL-C in patients with HoFH as an adjunct to other lipid lowering treatments or if such treatments are unavailable: Tablet: initial, 10/10 or 10/20 mg once daily; maintenance, 10/10 to 10/40 mg/day	After initiation and/or upon titration, lipid levels should be analyzed within two or more weeks and dosage adjusted accordingly. Decrease dose of VYTORIN by 50% if initiating lomitapide. VYTORIN dosage should not exceed 10/20 mg once day (or 10/40 mg once daily	May be administered with or without food. Tablets should be taken in the evening. Due to the increased risk of myopathy, particularly during the first year of treatment, use of the 10/80 mg dose should be restricted to patients who have been taking the 10/80 mg dose chronically.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			for patients who have previously taken simvastatin 80 mg once day chronically, e.g., for 12 months or more, without evidence of muscle toxicity) while taking lomitapide. Max dose is 10/10 mg/day when used with verapamil, diltiazem, or dronedarone. Max dose is 10/20 mg/day when used with amiodarone, amlodipine, or ranolazine.	

*Pravachol 10 mg is no longer available, however, generic pravastatin 10 mg remains available.

Clinical Pharmacology, 2017.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
atorvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Approved for use in children 10 to 17 years of age for the treatment of HeFH. Doses of >20 mg have not been studied in this population. Safety and efficacy in children <10 years of age have not been established.	No dosage adjustment required.	Contraindicated in active liver disease or in patients with unexplained persistent elevations or serum transaminases.	Unclassified† Contraindicated in pregnant women. Contraindicated during breastfeeding.
fluvastatin	No evidence of overall differences in	Approved for use in children 9 to 16 years of age for	No dosage adjustment required in	Contraindicated in active liver disease or	Pregnancy Category X

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
	safety or efficacy observed between elderly and younger adult patients.	the treatment of HeFH. Safety and efficacy in children for other approved indications have not been established.	mild to moderate renal dysfunction. Use with caution in severe renal dysfunction; doses above 40 mg per day have not been studied.	unexplained persistent elevations in serum transaminases.	Potential excretion into breast milk; not recommended in breastfeeding women
lovastatin	No dosage adjustment required in the elderly. The initial starting dose of lovastatin extended-release should not exceed 20 mg/day (ALTOPREV).	Approved for use in children 10 to 17 years of age for the treatment of HeFH (MEVACOR); maximum dose of 40 mg/day. Safety and efficacy in children <10 years of age have not been established (MEVACOR). Safety and efficacy in children have not been established (ALTOPREV).	Renal dosage adjustment is required; for creatinine clearances <30 mL/minute, use with caution and carefully consider doses >20 mg/day.	No dosage adjustment required.	Pregnancy Category X No data on excretion in breast milk; not recommended.
pitavastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Safety and efficacy in children have not been established.	Renal dosage adjustment is required; for creatinine clearances 15 to 60 mL/ minute or end-stage renal disease receiving hemodialysis, an initial dose of 1 mg once daily and a maximum dose of 2 mg/day is re-commended.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Unclassified† Contraindicated in pregnant women. Contraindicated during breastfeeding.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
pravastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Approved for use in children eight to 18 years of age for the treatment of HeFH. Safety and efficacy in children <8 years of age have not been established.	Renal dosage adjustment is required in severe renal impairment; an initial dose of 10 mg/day is recommended.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Unclassified† Contraindicated in pregnant women. Pravastatin is present in breast milk; contraindicated during breastfeeding.
rosuvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Approved for use in children 8 to 17 years of age for the treatment of HeFH and 7 to 17 years of age for the treatment of HoFH. Safety and efficacy in children <7 years of age have not been established.	No dosage adjustment required in mild to moderate renal dysfunction. Renal dosage adjustment required; for creatinine clearances <30 mL/minute, an initial dose of 5 mg/day and a maximum dose of 10 mg/day are recommended.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Unclassified† Contraindicated in pregnant women. Limited data indicate that the drug is in breast milk; contraindicated during breastfeeding.
simvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Approved for use in children 10 to 17 years of age for the treatment of HeFH. Doses greater than 40 mg have not been studied in this population. Safety and efficacy in children <10 years of age have not been established.	No dosage adjustment required in mild to moderate renal dysfunction. Renal dosage adjustment required for severe renal impairment: an initial dose of 5 mg/day with close monitoring is recommended.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Pregnancy Category X Unknown whether excreted in breast milk; not recommended.
Combination Products					

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
amlodipine/ atorvastatin	Safety and efficacy in elderly patients have not been established.	Safety and efficacy in children have not been established. Safety and efficacy of atorvastatin in children <10 years and amlodipine in children <6 years of age have not been established	No dosage adjustment required.	Contraindicated in active liver disease.	Pregnancy Category X Unknown whether atorvastatin is excreted in breast milk; not recommended.
ezetimibe/ atorvastatin	The maximum dosage limit is 10/80 mg once daily for most patients.	Safety and efficacy have not been established.	No dosage adjustment is needed.	Contraindicated in patients with active hepatic disease or unexplained transaminase elevations.	Unclassified† Contraindicated for use during pregnancy and in women who may become pregnant. Contraindicated for use during breastfeeding.
ezetimibe/ simvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients; prescribe with caution.	Safety and efficacy in children < 10 years old have not been established.	Use with caution doses exceeding 10/20 mg in patients with moderate to severe renal dysfunction.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Pregnancy Category X Unknown whether excreted in breast milk; not recommended.

* Pregnancy Category X = Contraindicated in pregnant women due to evidence of fetal abnormalities from adverse effects data from investigational or marketing experience. Risks of use of the drug in pregnant women clearly outweigh potential benefits.

†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.

Clinical Pharmacology, 2017.

CONCLUSION

- Statins are approved for the treatment of a variety of lipid disorders, including primary hypercholesterolemia, mixed dyslipidemia, and hypertriglyceridemia.
- The fixed-dose combination products (CADUET [amlodipine/atorvastatin], ezetimibe/atorvastatin, and VYTORIN [ezetimibe/simvastatin]) are indicated for use when dual therapy is appropriate.
- Statins decrease LDL-C according to the intensity of statin used and TG by 7% to 30%, as well as increase HDL-C by 5% to 15% when administered as monotherapy. The effects on LDL-C are dose-dependent and log-linear. Statins also decrease TG and increase HDL-C by varying levels.

- All products in this review are now available in a generic formulation except for ALTOPREV® (lovastatin extended-release) and FLOLIPID (simvastatin oral suspension) (Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017).
- In general, therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia. When LDL-C lowering is required, initial treatment with a statin is recommended.
- In 2004, the National Cholesterol Education Program (NCEP) published guidelines on the Implications of Recent Clinical Trials for the NCEP Adult Treatment Panel III, which stated the following:
    - When LDL-C lowering drug therapy is employed in high-risk or moderately-high risk patients, it is advised that intensity of therapy be sufficient to achieve ≥30 to 40% reduction in LDL-C levels.
    - Standard statin doses are defined as those that lower LDL-C levels by 30 to 40%. The same effect may be achieved by combining lower doses of statins with other drugs or products such as bile acid sequestrants, ezetimibe, nicotinic acid, or plant stanols/sterols.
    - When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the statin dose may need to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals.
    - Fibrates may have an adjunctive role in the treatment of patients with high TG and low HDL-C, especially in combination with statins.
    - In high risk patients with high TG or low HDL-C levels, consideration can be given to combination therapy with fibrates or nicotinic acid and a LDL lowering agent.
    - For the treatment of HeFH, LDL-C lowering drugs should be initiated in young adulthood. Statins are considered first-line therapy. Two-drug and sometimes three-drug therapy may be needed (Grundy et al, 2004).
- The 2013 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines on Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults focus on primary and secondary atherosclerotic cardiovascular disease (ASCVD) risk reduction in adults (Stone et al, 2013).
    - These guidelines established four statin benefit groups: (1) individuals with clinical ASCVD (2) individuals with primary elevations of LDL–C >190 mg/dL (3) individuals with diabetes aged 40 to 75 years with LDL–C 70 to 189 mg/dL and without clinical ASCVD, and (4) individuals aged 40 to 75 years without clinical ASCVD or diabetes with LDL–C 70 to 189 mg/dL and estimated 10-year ASCVD risk >7.5%
    - Intensity of statin therapy (high, moderate, and low) is the new goal of treatment in the benefit groups for use in primary and secondary prevention of ASCVD.
    - A new cardiovascular risk tool, based on pooled cohort equations, has been created to estimate absolute 10-year ASCVD risk (defined as first occurrence nonfatal and fatal MI, and nonfatal and fatal stroke). The Pooled Cohort Equations should be used to estimate 10-year ASCVD risk for individuals without clinical ASCVD or diabetes and LDL–C 70 to189 mg/dL to guide the initiation of statin therapy. For the primary prevention of ASCVD in individuals with diabetes (diabetes mellitus type-1 and type-2), estimated 10-year ASCVD risk can also be used to guide the intensity of statin therapy. For those with clinical ASCVD or with LDL–C ≥190 mg/dL who are already in a statin benefit group, it is not necessary to estimate 10-year ASCVD risk (Stone et al, 2013).
    - Statins are the primary medications to utilize for ASCVD risk reduction according to the 2013 guidelines, which focus on treatments proven to reduce ASCVD and not comprehensive lipid management.
- The 2015 AHA Scientific Statement on Familial Hypercholesterolemia (FH) recommends aggressive pharmacological treatment for patients with HeFH beginning at age eight to 10 years. Pharmacological treatment may also be considered in younger patients (less than eight years of age) with extreme elevation of LDL-C or those with other major risk factors suggesting very premature CVD. In HeFH pediatric patients, LDL-C goals are not well defined; however, treatment is recommended based on LDL-C levels and not based on genetic abnormalities or other clinical features. In adult patients with HeFH, the initial goal is to reduce LDL-C by 50% and treatment with a high-intensity statin (rosuvastatin or atorvastatin) is recommended. If LDL-C levels remain above goal after three months, then ezetimibe may be added. If LDL-C continues to be above goal after three months of two-drug therapy, then the addition of a PCSK9 inhibitor, bile acid sequestrant, or niacin can be considered. In patients with HoFH, lipid-lowering therapy should be initiated as soon as possible, with statins providing a 10 to 25% reduction in LDL-C (Gidding et al, 2015).

- The 2016 United States Preventive Services Task Force (USPSTF) recommendations for preventive statin use for Primary Prevention of Cardiovascular Disease in Adults recommends the following:
    - Adults without a history of CVD should use a low- to moderate-dose statin for the prevention of CVD events and mortality when the following criteria are met: (1) they are aged 40 to 75 (2) they have one or more CVD risk factor such as dyslipidemia, diabetes, hypertension, or smoking (3) they have a calculated 10-year risk of a cardiovascular risk of 10% or more.
    - Although statin use may be beneficial for the primary prevention of CVD in some adults with a 10-year cardiovascular risk of <10%, the benefits are likely smaller. A low- to moderate-dose statin may be offered to certain adults without a history of CVD when all of the following criteria are met: (1) they are aged 40 to 75 years (2) they have one or more CVD risk factor (3) they have a calculated 10-year risk of a cardiovascular event of 7.5 to 10%.
    - There is insufficient evidence to assess the balance of benefits to risks of initiating a statin for the primary prevention of CVD and mortality in patients ≥76 years without a history of MI or stroke (US Preventative Task Force, 2016).
- In 2017, the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) recommended the addition of another agent when statin therapy alone does not achieve therapeutic goals; their guidance offers cholesterol absorption inhibitors, bile acid sequestrants, and proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors as options (Jellinger et al, 2017). The recommendations for statin therapy for managing dyslipidemia and prevention of cardiovascular disease are stated as the following:
    - Statin therapy is recommended as the primary pharmacologic agent to achieve target LDL-C goals on the bases of morbidity and mortality outcome trials.
    - For clinical decision making, mild elevations in blood glucose levels and/or an increased risk of new-onset type 2 diabetes mellitus associated with intensive statin therapy do not outweigh the benefits of statin therapy for ASCVD risk reduction.
    - In individuals within high-risk and very high-risk categories, further lowering of LDL-C beyond established targets with statins results in additional ASCVD event reduction and may be considered.
    - Very high-risk individuals with established coronary, carotid, and peripheral vascular disease, or diabetes who also have at least 1 additional risk factor should be treated with statins to target a reduced LDL-C treatment goal of <70 mg/dL.
    - Extreme-risk individuals should be treated with statins to target an even lower LDL-C treatment goal <55 mg/dL.
- Numerous clinical trials have demonstrated that the statins (single entity and combination products) can effectively lower LDL-C, non-HDL-C, TC, and TG, as well as positively impact other lipid/lipoprotein parameters. Many studies have compared active treatment to placebo or compared combination therapy to monotherapy. In these studies, the more aggressive treatment regimens often improved lipid parameters to a greater extent than the less-intensive treatment regimens.
- All of the statins, with the exception of pitavastatin, have been shown to have beneficial effects on CHD outcomes, while the majority of them (atorvastatin, pravastatin, rosuvastatin, and simvastatin) have also been shown to decrease the risk of stroke.
- Atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin have been shown to reduce cardiovascular events in patients with clinically evident CHD (secondary prevention). In addition, fluvastatin, lovastatin, pravastatin, and rosuvastatin have been shown to slow progression of coronary atherosclerosis in patients with CHD.
- No incremental benefit of the combination statin products on cardiovascular morbidity and mortality has been established over and above that demonstrated for the single entity statin products.
- The statins are generally well-tolerated, and the most common side effects are gastrointestinal disturbances, headache, insomnia, myalgia, and rash. Muscle aches and weakness are reported by one to two percent of patients taking statins. The symptoms are usually mild and generally do not lead to discontinuation. All statins can increase hepatic transaminase levels and creatinine kinase.
- Pravastatin is the only statin that does not undergo cytochrome (CYP) 450 metabolism, and is therefore associated with a lower risk for drug interactions. Atorvastatin (to a lesser extent), lovastatin, and simvastatin are primarily metabolized by the CYP3A4 isoenzyme, while fluvastatin, pitavastatin, and rosuvastatin are metabolized by the CYP2C9 isoenzyme, which may result in differences in their drug interaction profiles.
- There is insufficient evidence to support that one statin is safer or more efficacious than another statin.

Table 5. Advantages and Disadvantages of Statins

Drug	Advantages	Disadvantages
Atorvastatin	• Available generically both alone and in combination with ezetimibe • Has been documented to have more potency in cholesterol-lowering than certain other statins • Cardiovascular outcomes studies support the use of the 80 mg strength in certain populations (e.g., as secondary prophylaxis following ST elevation MI)	• Associated with drug-drug interactions through the CYP3A4 isoenzyme system
Fluvastatin	• Available generically • Available in an extended-release formulation • Not associated with drug-drug interactions through the CYP3A4 isoenzyme system	• Associated with drug-drug interactions through the CYP2C9 isoenzyme system
Lovastatin	• Available generically (immediate release formulation) • Available in an extended-release formulation	• Associated with drug-drug interactions through the CYP3A4 isoenzyme system
Pitavastatin	• Available generically • Not associated with drug-drug interactions through the CYP isoenzyme system	• Effect on cardiovascular morbidity and mortality has not been determined
Pravastatin	• Available generically • Not associated with drug-drug interactions through the CYP isoenzyme system	
Rosuvastatin	• Available generically • Has been documented to have more potency in cholesterol-lowering than certain other statins	
Simvastatin	• Available as an oral suspension • Tablet form is available generically • Available both alone and in combination with ezetimibe	• Associated with drug-drug interactions through the CYP3A4 isoenzyme system

REFERENCES

- AbbVie Inc; withdrawal of approval of new drug applications for ADVICOR and SIMCOR. Federal Register website. Available at: https://www.federalregister.gov/articles/2016/04/18/2016-08894/abbvie-inc-withdrawal-of-approval-of-new-drug-applications-for-advicor-and-simcor. Updated on April 18, 2016. Accessed November 12, 2017.
- Afilalo J, Duque G, Steele R, et al. Statins for secondary prevention in elderly patients: a hierarchical bayesian meta-analysis. J Am Coll Cardiol. 2008;51(1):37-45.
- Afilalo J, Majdan AA, Eisenberg MJ. Intensive statin therapy in acute coronary syndromes and stable coronary heart disease: a comparative meta-analysis of randomised controlled trials. Heart. 2007;93(8):914-21.
- Ahmed S, Cannon CP, Murphy SA, et al. Acute coronary syndromes and diabetes: Is intensive lipid lowering beneficial? Results of the PROVE IT-TIMI 22 trial. Eur Heart J. 2006;27(19):2323-9.
- Ai M, Otokozawa S, Asztalos BF, et al. Effects of maximal doses of atorvastatin vs rosuvastatin on small dense low-density lipoprotein cholesterol level. Am J Cardiol. 2008;101:315-8.
- ALTOPREV prescribing information. Covis Pharma. Zug, Switzerland. August 2017.
- Alvarez-Sala L, Cachofeiro V, Masana L, et al. Effects of fluvastatin extended-release (80 mg) alone and in combination with ezetimibe (10 mg) on low-density lipoprotein cholesterol and inflammatory parameters in patients with primary hypercholesterolemia: a 12-week, multicenter, randomized, open-label, parallel-group study. Clin Ther. 2008;30:84-97.
- Amarenco P, Benavente O, Goldstein LB, et al. Results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial by stroke subtypes. Stroke. 2009[a];40:1405-9.

- Amarenco P, Goldstein LB, Messig M, et al. Relative and cumulative effects of lipids and blood pressure control in Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial. Stroke. 2009[b];40:2486-92.
- American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions, O'Gara PT, Kushner FG, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;61(4):e78-140.
- Arca M, Montali A, Pigna G, et al. Comparison of atorvastatin vs fenofibrate in reaching lipid targets and influencing biomarkers of endothelial damage in patients with familial combined hyperlipidemia. Metabolism. 2007;56(11):1534-41.
- Asselbergs F, Diercks G, Hillege H, et al. Effects of fosinopril and pravastatin on cardiovascular events in patients with microalbuminuria. Circulation. 2004; Nov 2; 2809-16.
- Athyros VG, Mikhailidis DP, Liberopoulos EN, et al. Effect of statin treatment on renal function and serum uric acid levels and their relation to vascular events in patients with coronary heart disease and metabolic syndrome: a subgroup analysis of the GREek Atorvastatin and Coronary heart disease Evaluation (GREACE) Study. Nephrol Dial Transplant. 2007;22(1):118-27.
- Athyros VG, Papageorgiou AA, Mercouris BR, et al. Treatment with atorvastatin to the National Cholesterol Educational Program goal vs 'usual' care in secondary coronary heart disease prevention. The GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. Curr Med Res Opin. 2002;18(4):220-8.
- Avis HJ, Hutten BA, Gagne C, et al. Efficacy and safety of rosuvastatin therapy for children with familial hypercholesterolemia. J Am Coll Cardiol. 2010;55(11):1121-6.
- Avis HJ, Vissers MN, Stein EA, et al. A systematic review and meta-analysis of statin therapy in children with familial hypercholesterolemia. Arterioscler Thromb Vasc Biol. 2007;27(8):1803-10.
- Awad K, Mikhailidis DP, Toth PP, et al; Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group. Efficacy and safety of alternate-day versus daily dosing of statins: A systematic review and meta-analysis [published online ahead of print July 24, 2017]. Cardiovasc Drugs Ther. doi: 10.1007/s10557-017-6743-0.
- Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366(9493):1267-78.
- Ballantyne CM, Abate N, Yuan Z, et al. Dose-comparison study of the combination of ezetimibe and simvastatin (VYTORIN) vs atorvastatin in patients with hypercholesterolemia: the VYTORIN Vs Atorvastatin (VYVA) study. Am Heart J. 2005;149(3):464-73.
- Ballantyne CM, Bertolami M, Hernandez Garcia HR, et al. Achieving LDL cholesterol, non-HDL cholesterol, and apolipoprotein B target levels in high-risk patients: Measuring Effective Reductions in Cholesterol Using Rosuvastatin therapy (MERCURY) II. Am Heart J. 2006;151(5):975.e1-9.
- Ballantyne CM, Blazing MA, King TR, et al. Efficacy and safety of ezetimibe co-administered with simvastatin compared to atorvastatin in adults with hypercholesterolemia. Am J Cardiol. 2004;93(12):1487-94.
- Ballantyne CM, Davidson MH, McKenny J, et al. Comparison of the safety and efficacy of a combination tablet of niacin extended-release and simvastatin vs simvastatin monotherapy in patients with increased non-HDL cholesterol (from the SEACOAST I study). Am J Cardiol. 2008;101:1428-36.
- Ballantyne CM, Houri J, Notarbartolo A, et al. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Circulation. 2003;107(19):2409-15.
- Ballantyne CM, Pitt B, Loscalzo J, et al. Alteration of relation of atherogenic lipoprotein cholesterol to apolipoprotein B by intensive statin therapy in patients with acute coronary syndrome (from the Limiting UNdertreatment of lipids in ACS With Rosuvastatin [LUNAR] Trial). Am J Cardiol. 2013;111(4):506-9.
- Ballantyne CM, Weiss R, Moccetti T, et al. Efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe in patients at high risk of cardiovascular disease (results from the EXPLORER study). Am J Cardiol. 2007;99(5):673-80.
- Bardini G, Giorda CB, Pontiroli AE, et al. Ezetimibe+simvastatin vs doubling the dose of simvastatin in high cardiovascular risk diabetics: a multicenter, randomized trial (the LEAD study). Cardiovasc Diabetol. 2010;9(20):1-8.
- Barter P, Gotto AM, LaRosa JC, et al. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. N Engl J Med. 2007 Sep 27;357(13):1301-10.
- Bays H, Jones P, Mohiuddin S, et al. Long-term safety and efficacy of fenofibric acid in combination with statin therapy for the treatment of patients with mixed dyslipidemia. J Clin Lipidology. 2008[a];2:426-35.
- Bays H, Sapre A, Taggart W, et al. Long-term (48-week) safety of ezetimibe 10 mg/day coadministered with simvastatin compared to simvastatin alone in patients with primary hypercholesterolemia. Curr Med Res Opin. 2008[b];24(10):2953-66.
- Bays HD, Averna, Majul C, et al. Efficacy and safety of ezetimibe added to atorvastatin versus atorvastatin uptitration or switching to rosuvastatin in patients with primary hypercholesterolemia. Am J Cardiol. 2013;112(12):1885-95.
- Bays HE, Maki KC, McKenney J, et al. Long-term up to 24-month efficacy and safety of concomitant prescription omega-3-acid ethyl esters and simvastatin in hypertriglyceridemic patients. Curr Med Res Opin. 2010;26:907-15.
- Bays HE, Ose L, Fraser N, et al. A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared to ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia. Clin Ther. 2004;26(11):1758-73.
- Becker DJ, Gordon RY, Morris PB, et al. Simvastatin vs therapeutic lifestyle changes and supplements: randomized primary prevention trial. Mayo Clin Proc. 2008;83(7):758-64.
- Betteridge DJ, Gibson JM. Effects of rosuvastatin on lipids, lipoproteins and apolipoproteins in the dyslipidaemia of diabetes. Diabet Med. 2007 [a];24(5):541-9.
- Betteridge DJ, Gibson JM, Sager PT. Comparison of effectiveness of rosuvastatin vs atorvastatin on the achievement of combined C-reactive protein (<2 mg/L) and low-density lipoprotein cholesterol (< 70 mg/dl) targets in patients with type 2 diabetes mellitus (from the ANDROMEDA study). Am J Cardiol. 2007[b];100(8):1245-8.
- Braamskamp MJ, Langslet G, McCrindle BW, et al. Efficacy and safety of rosuvastatin therapy in children and adolescents with familial hypercholesterolemia: Results from the CHARON study. J Clin Lipidol. 2015;9(6):741-50.
- Briel M, Schwartz GG, Thompson PL, de Lemos JA, et al. Effects of early treatment with statins on short-term clinical outcomes in acute coronary syndromes: a meta-analysis of randomized controlled trials. JAMA. 2006 May 3;295(17):2046-56.

- Brown G, Albers JJ, Fisher LD, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. N Engl J Med. 1990;323:1289-98.
- Bullano MF, Kamat S, Wertz DA, et al. Effectiveness of rosuvastatin vs atorvastatin in reducing lipid levels and achieving low-density-lipoprotein cholesterol goals in a usual care setting. Am J Health Syst Pharm. 2007;64(3):276-84.
- Bullano MF, Wertz DA, Yang GW, et al. Effect of rosuvastatin compared to other statins on lipid levels and National Cholesterol Education Program goal attainment for low-density lipoprotein cholesterol in a usual care setting. Pharmacotherapy. 2006;26(4):469-78.
- Bushnell CD, Griffin J, Newby LK, et al. Statin use and sex-specific stroke outcomes in patients with vascular disease. Stroke. 2006 Jun;37(6):1427-31.
- Byington RP, Furberg CD, Crouse JR, 3rd, et al. Pravastatin, lipids, and atherosclerosis in the carotid arteries (PLAC-II). Am J Cardiol. 1995; 76:54C-9C.
- CADUET prescribing information. Pfizer Inc. New York, NY. June 2017.
- Calza L, Manfredi R, Colangeli V, et al. Rosuvastatin, pravastatin, and atorvastatin for the treatment of hypercholesterolemia in HIV-infected patients receiving protease inhibitors (abstract). Curr HIV Res. 2008;6(6):572-8.
- Cannon C, Braunwald E, McCabe C, et al. Intensive vs moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004;350;15;1495-504.
- Cannon CP, Steinberg BA, Murphy SA, et al. Meta-analysis of cardiovascular outcomes trials comparing intensive vs moderate statin therapy. J Am Coll Cardiol. 2006;48(3):438-45.
- Cannon CP, Blazing MA, Giugliano RP et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372:2387-97.
- Catapano AL, Davidson MH, Ballantyne CM, et al. Lipid-altering efficacy of the ezetimibe/simvastatin single tablet vs rosuvastatin in hypercholesterolemic patients. Curr Med Res Opin. 2006;22(10):2041-53.
- Chan KL, Teo K, Dumesnil JG, et al; ASTRONOMERS Investigators. Effect of lipid lowering with rosuvastatin on progression of aortic stenosis: results of the Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin (ASTONOMER) trial. Circulation. 2010;121:306-14.
- Charland SL, Malone DC. Prediction of cardiovascular event risk reduction from lipid changes associated with high potency dyslipidemia therapy. Curr Med Res Opin. 2010 Feb;26(2):365-75.
- Chenot F, Montant PF, Marcovitch O, et al. Co-administration of ezetimibe and simvastatin in acute myocardial infarction. Eur J Clin Invest. 2007 May;37(5):357-63.
- Cholesterol Treatment Trialists' (CTT) Collaborators, Kearney PM, Blackwell L, Collins R, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008 Jan 12;371(9607):117-25.
- Chonchol M, Cook T, Kjekshus J, et al. Simvastatin for secondary prevention of all-cause mortality and major coronary events in patients with mild chronic renal insufficiency. Am J Kidney Dis. 2007 Mar;49(3):373-82.
- Clearfield MB, Amerena J, Bassand JP, et al. Comparison of the efficacy and safety of rosuvastatin 10 mg and atorvastatin 20 mg in high-risk patients with hypercholesterolemia-Prospective study to evaluate the Use of Low doses of the Statins Atorvastatin and Rosuvastatin (PULSAR). Trials. 2006 Dec 21;7:35.
- Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc., http://www.clinicalpharmacology.com. Accessed November 12, 2017.
- Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004 Aug 21-27;364(9435):685-96.
- Coll B, Aragones G, Parra S, et al. Ezetimibe effectively decreases LDL-cholesterol in HIV-infection patients. AIDS. 2006 Aug;20(12):1675-7.
- Collins R, Armitage J, Parish S, et al; Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol-lowering with simvastatin in 5,963 people with diabetes: a randomized placebo-controlled trial. Lancet. 2003;361:2005-16.
- Conard SE, Bays HE, Leiter LA, et al. Efficacy and safety of ezetimibe added on to atorvastatin (20 mg) vs uptitration of atorvastatin (to 40 mg) in hypercholesterolemic patients at moderately high risk for coronary heart disease. Am J Cardiol 2008;102:1489-94.
- Constance C, Westphal S, Chung N, et al. Efficacy of ezetimibe/simvastatin 10/20 and 10/40 mg compared to atorvastatin 20 mg in patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2007 Jul;9(4):575-84.
- CRESTOR prescribing information. AstraZeneca Pharmaceuticals LP. Wilmington (DE). August 2017.
- Crouse JR 3rd, Raichlen JS, Riley WA, et al. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. JAMA. 2007 Mar 28; 297(12):1344-53.
- Davidson MH, McGarry T, Bettis R, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. J Am Coll Cardiol. 2002 Dec 18;40(12):2125-34.
- de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA. 2004 Sep 15;292(11):1307-16.
- Deedwania P, Barter P, Carmena R, et al. Reduction of low-density lipoprotein cholesterol in patients with coronary heart disease and metabolic syndrome: analysis of the Treating to New Targets study. Lancet. 2006 Sep 9;368(9539):919-28.
- Deedwania P, Stone PH, Bairey Merz CN, et al. Effects of intensive vs moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: results of the Study Assessing Goals in the Elderly (SAGE). Circulation. 2007[b] Feb 13;115(6):700-7.
- Deedwania PC, Gupta M, Stein M, et al. Comparison of rosuvastatin vs atorvastatin in South-Asian patients at risk of coronary heart disease (from the IRIS Trial). Am J Cardiol. 2007[a] Jun 1;99(11):1538-43.
- Derosa G, Maffioli P, Salvadeo SA, et al. Fenofibrate, simvastatin and their combination in the management of dyslipidaemia in type 2 diabetic patients. Curr Med Res Opin. 2009;25:1973-83.
- Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. Results of AFCAPS/TexCAPS. JAMA. 1998;279(20):1615-22.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available from: http://www.accessdata.fda.gov/scripts/cder/daf/. Accessed November 12, 2017.
- Erdine S, Ro YM, Tse HF, et al. Single-pill amlodipine/atorvastatin helps patients of diverse ethnicity attain recommended goals for blood pressure and lipids (the Gemini-AALA study). J Human Hypertens. 2009;23:196-210.

- Eriksson M, Budinski D, Hounslow N. Comparative efficacy of pitavastatin and simvastatin in high-risk patients: a randomized controlled trial. Adv Ther. 2011 Sep;28(9):811-23.
- Eriksson M, Hådell K, Holme I, et al. Compliance with and efficacy of treatment with pravastatin and cholestyramine: a randomized study on lipid-lowering in primary care. J Intern Med. 1998 May;243(5):373-80.
- Everett BM, Glynn RJ, MacFadyen JG, et al. Rosuvastatin in the prevention of stroke among men and women with elevated levels of C-reactive protein: Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER). Circulation. 2010;121:143-50.
- Faergeman O, Hill L, Windler E, et al. Efficacy and tolerability of rosuvastatin and atorvastatin when force-titrated in patients with primary hypercholesterolemia: results from the ECLIPSE study. Cardiology. 2008;111:219-28.
- Farnier M, Averna M, Missault L, et al. Lipid-altering efficacy of ezetimibe/simvastatin 10/20 mg compared to rosuvastatin 10 mg in high-risk hypercholesterolaemic patients inadequately controlled with prior statin monotherapy – the IN-CROSS study. Int J Clin Pract. 2009;63:534-5.
- Farnier M, Perevozskaya I, Taggart WV, et al. VAP II analysis of lipoprotein subclasses in mixed hyperlipidemic patients on treatment with ezetimibe/simvastatin and fenofibrate. J Lipid Res. 2008;49:2641-7.
- Farnier M, Roth E, Gil-Extremera B, et al. Efficacy and safety of the coadministration of ezetimibe/simvastatin with fenofibrate in patients with mixed hyperlipidemia. Am Heart J. 2007 Feb;153(2):335.e1-8.
- Feldman T, Davidson M, Shah A, et al. Comparison of the lipid-modifying efficacy and safety profiles of ezetimibe coadministered with simvastatin in older vs younger patients with primary hypercholesterolemia: a post Hoc analysis of subpopulations from three pooled clinical trials. Clin Ther. 2006 Jun;28(6):849-59.
- Feldman T, Koren M, Insull W Jr, et al. Treatment of high-risk patients with ezetimibe plus simvastatin co-administration vs simvastatin alone to attain National Cholesterol Education Program Adult Treatment Panel III low-density lipoprotein cholesterol goals. Am J Cardiol. 2004 Jun 15;93(12):1481-6.
- Ferdinand KC, Clark LT, Watson KE, et al. Comparison of efficacy and safety of rosuvastatin vs atorvastatin in African-American patients in a six-week trial. Am J Cardiol. 2006 Jan 15;97(2):229-35.
- Ferdinand KC, Davidson MH, Kelly MT, et al. One-year efficacy and safety of rosuvastatin + fenofibric acid combination therapy in patients with mixed dyslipidemia. Evaluation of dose response. Am J Cardiovasc Drugs. 2012;12(2):117-25.
- Flack JM, Victor R, Watson K, et al. Improved attainment of blood pressure and cholesterol goals using single-pill amlodipine/atorvastatin in African Americans: the CAPABLE trial. Mayo Clin Proc. 2008 Jan;83(1):35-45.
- FLOLIPID prescribing information. Salerno, Pharmaceuticals LP. Brooksville, FL. October 2017.
- Florentin M, Liberopoulos EN, Moutzouri E, et al. The effect of simvastatin alone vs simvastatin plus ezetimibe on the concentration of small density low-density lipoprotein cholesterol in subjects with primary hypercholesterolemia. Curr Med Res Opin. 2011;27(3):685-92.
- Foody JM, Brown WV, Zieve F, et al. Safety and efficacy of ezetimibe/simvastatin combination vs atorvastatin alone in adults ≥65 years of age with hypercholesterolemia and with or at moderately high/high risk for coronary heart disease (the VYTELD Study). Am J Cardiol. 2010;106:1255-63.
- Ford I, Murray H, Packard CJ, et al. Long-term follow-up of the West of Scotland Coronary Prevention Study. N Engl J Med. 2007 Oct 11;357(15):1477-86.
- Fox KM, Gandhi SK, Ohsfeldt RL, et al. Effectiveness of rosuvastatin in low-density lipoprotein cholesterol lowering and National Cholesterol Education Program Adult Treatment Panel guideline III LDL-C goal attainment compared to other statins among diabetes mellitus patients: a retrospective study using an electronic medical records dataset in the United States. Curr Med Res Opin. 2007[a];23(9):2125-33.
- Fox KM, Gandhi SK, Ohsfeldt RL, et al. Comparison of low-density lipoprotein cholesterol reduction after switching patients on other statins to rosuvastatin or simvastatin in a real-world clinical practice setting. Am J Manag Care. 2007 [b];13(Suppl 10):S270-5.
- Furberg CD, Adams HP, Applegate WB, et al. Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. Asymptomatic carotid artery progression study (ACAPS) research group. Circulation. 1994 Oct; 90(4):1679-87.
- Gagné C, Gaudet D, Bruckert E. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. Circulation. 2002 May 28;105(21):2469-75.
- Gaudiani LM, Lewin A, Meneghini L, et al. Efficacy and safety of ezetimibe co-administered with simvastatin in thiazolidinedione-treated type 2 diabetic patients. Diabetes Obes Metab. 2005 Jan;7(1):88-97.
- Gidding SS, Ann Champagne M, de Ferranti SD, et al. The Agenda for Familial Hypercholesterolemia: A Scientific Statement From the American Heart Association. Circulation. 2015 Dec 1;132(22):2167-92.
- Goldberg AC, Bays HE, Ballantyne CM, et al. Efficacy and safety of ABT-335 (fenofibric acid) in combination with atorvastatin in patients with mixed dyslipidemia. Am J Cardiol. 2009;103:515-22.
- Goldberg AC, Sapre A, Liu J, et al. Efficacy and safety of ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia: a randomized, double-blind, placebo-controlled trial. Mayo Clin Proc. 2004 May;79(5):620-9.
- Goldberg RB, Guyton JR, Mazzone T, et al. Ezetimibe/simvastatin vs atorvastatin in patients with type 2 diabetes mellitus and hypercholesterolemia: the VYTAL study. Mayo Clin Proc. 2006 Dec;81(12):1579-88.
- Grimm R, Malik M, Yunis C, et al; TOGETHER Investigators. Simultaneous treatment to attain blood pressure and lipid goals and reduced CV risk burden using amlodipine/atorvastatin single-pill therapy in treated hypertensive participants in a randomized controlled trial. Vasc Health Risk Manag. 2010;6:261-71.
- Grundy SM, Cleeman JI, Merz NB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation. 2004;110:227-39.
- Gumprecht J, Gosho M, Budinski D, et al. Comparative long-term efficacy and tolerability of pitavastatin 4 mg and atorvastatin 20-40 mg in patients with type 2 diabetes mellitus and combined (mixed) dyslipidaemia. Diabetes Obes Metab. 2011 Nov;13(11):1047-55.
- Hall AS, Jackson BM, Farrin AJ, et al. A randomized, controlled trial of simvastatin vs rosuvastatin in patients with acute myocardial infarction: the Secondary Prevention of Acute Coronary Events—Reduction of Cholesterol to Key European Targets Trial (abstract). Eur J Cardiovasc Prev Rehabil. 2009 Dec;16(6):712-21.
- Harley CR, Gandhi SK, Anoka N, et al. Understanding practice patterns and low-density lipoprotein cholesterol goal attainment implications of switching patients from simvastatin in a health plan setting. Am J Manag Care. 2007 Dec;13 Suppl 10:S276-81.

- Hing Ling PK, Civeira F, Dan AG, et al. Ezetimibe/simvastatin 10/40 mg vs atorvastatin 40 mg in high cardiovascular risk patients with primary hypercholesterolemia: a randomized, double-blind, active-controlled, multicenter study. Lipids Health Dis. 2012 Jan 31;11:18.
- Hitman GA, Colhoun H, Newman C, et al. Stroke prediction and stroke prevention with atorvastatin in the Collaborative Atorvastatin Diabetes Study (CARDS). Diabet Med. 2007 Dec;24(12):1313-21.
- Hobbs R, Gensini G, Mancini J, et al. International open-label studies to assess the efficacy and safety of single-pill amlodipine/atorvastatin in attaining blood pressure and lipid targets recommended by country-specific guidelines: the JEWEL programme (abstract). Eur J Cardiovasc Prev Rehabil. 2009 Aug;16(4):472-80.
- Hogue JC, Lamarche B, Tremblay AJ, et al. Differential effect of atorvastatin and fenofibrate on plasma oxidized low-density lipoprotein, inflammation markers, and cell adhesion molecules in patients with type 2 diabetes mellitus. Metabolism. 2008;57:380-6.
- Hulten E, Jackson JL, Douglas K, et al. The effect of early, intensive statin therapy on acute coronary syndrome: a meta-analysis of randomized controlled trials. Arch Intern Med. 2006 Sep 25;166(17):1814-21.
- Hunninghake D, Insull W Jr, Toth P, et al. Coadministration of colesevelam hydrochloride with atorvastatin lowers LDL cholesterol additively. Atherosclerosis. 2001 Oct;158(2):407-16.
- Illingworth DR, Stein EA, Mitchel YB, et al. Comparative effects of lovastatin and niacin in primary hypercholesterolemia. Arch Intern Med. 1994;154:1586-95.
- Insull W Jr, Ghali JK, Hassman DR, et al. Achieving low-density lipoprotein cholesterol goals in high-risk patients in managed care: comparison of rosuvastatin, atorvastatin, and simvastatin in the SOLAR trial. Mayo Clin Proc. 2007 May;82(5):543-50.
- Jellinger PS, Handelsman Y, Rosenbilt PD, et al. American Association Of Clinical Endocrinologists and American College Of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. Endocr Pract. 2017 Apr;23(Suppl 2):1-87.
- Jones P, Davidson M, Goldberg A, et al. Efficacy and safety of fenofibric acid in combination with a statin in patients with mixed dyslipidemia: pooled analysis of three phase 3, 12-week randomized, controlled studies. J Clin Lipidology. 2009[a];3:125-37.
- Jones P, Davidson M, Kashyap M, et al. Efficacy and safety of ABT-335 (fenofibric acid) in combination with rosuvastatin in patients with mixed dyslipidemia: A phase 3 study. Atherosclerosis. 2009[b];204:208-215.
- Jones P, Davidson M, Stein E, et al. Comparison of the efficacy and safety of rosuvastatin vs atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). Am J Cardiol. 2003;92:152-60.
- Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014; 45:2160-236.
- Kerzner B, Corbelli J, Sharp S, et al. Efficacy and safety of ezetimibe coadministered with lovastatin in primary hypercholesterolemia. Am J Cardiol. 2003 Feb 15;91(4):418-24.
- Khush KK, Waters DD, Bittner V, et al. Effect of high-dose atorvastatin on hospitalizations for heart failure: subgroup analysis of the Treating to New Targets (TNT) study. Circulation. 2007 Feb 6;115(5):576-83.
- Kipnes MS, Roth EM, Rhyme JM, et al. Year two assessment of fenofibric acid and moderate-dose statin combination. A Phase 3, open-label, extension study. Clin Drug Investig. 2010;30(10):51-61.
- Knapp HH, Schrott H, Ma P, et al. Efficacy and safety of combination simvastatin and colesevelam in patients with primary hypercholesterolemia. Am J Med. 2001 Apr;110(5):352-60.
- Knopp RH, d'Emden M, Smilde JG, et al. Efficacy and safety of atorvastatin in the prevention of cardiovascular endpoints in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). Diabetes Care. 2006 Jul;29(7):1478-85.
- Koenig W, Ridker PM. Rosuvastatin for primary prevention in patients with European systematic coronary risk evaluation risk ≥5% or Framingham risk >20%: post hoc analyses of the JUPITER trial requested by European health authorities. Eur Heart J. 2001;32:75-83.
- Koshiyama H, Taniguchi A, Tanaka K, et al. Effects of pitavastatin on lipid profiles and high-sensitivity CRP in Japanese subjects with hypercholesterolemia: Kansai Investigation of Statin for Hyperlipidemic Intervention in Metabolism and Endocrinology (KISHIMEN) investigators. J Atheroscler Thromb. 2008;15:345:50.
- Kumar SS, Lahey KA, Day A, et al. Comparison of the efficacy of administering a combination of ezetimibe plus fenofibrate vs atorvastatin monotherapy in the treatment of dyslipidemia. Lipids Health Dis. 2009;8(56):1-8.
- LaRosa JC, Grundy SM, Kastelein JJ, et al. Treating to New Targets (TNT) Steering Committee and Investigators. Safety and efficacy of Atorvastatin-induced very low-density lipoprotein cholesterol levels in Patients with coronary heart disease (a post hoc analysis of the treating to new targets [TNT] study). Am J Cardiol. 2007 Sep 1;100(5):747-52.
- LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005 Apr 7;352(14):1425-35.
- Lee SH, Chung N, Kwan J, et al. Comparison of the efficacy and tolerability of pitavastatin and atorvastatin: an 8-week, multicenter, randomized, open-label, dose-titration study in Korean patients with hypercholesterolemia. Clin Ther. 2007;29(11):2365-73.
- Leiter LA, Bays H, Conard S, et al. Efficacy and safety of ezetimibe added on to atorvastatin (40 mg) compared to uptitration of atorvastatin (to 80 mg) in hypercholesterolemic patients at high risk of coronary heart disease. Am J Cardiol. 2008;102:1495-501.
- Leiter LA, Rosenson RS, Stein E, et al. Efficacy and safety of rosuvastatin 40 mg vs atorvastatin 80 mg in high-risk patients with hypercholesterolemia: results of the POLARIS study. Atherosclerosis. 2007 Oct;194(2):e154-64.
- LESCOL and LESCOL XL prescribing information. Novartis Pharmaceuticals Corporation. East Hanover, NJ. August 2017.
- Lewis JH, Mortensen ME, Zweig S, et al. Efficacy and safety of high-dose pravastatin in hypercholesterolemic patients with well-compensated chronic liver disease: Results of a prospective, randomized, double-blind, placebo-controlled, multicenter trial. Hepatology. 2007 Nov;46(5):1453-63.
- Liem AH, van Boven AJ, Veeger NJ, et al. Effects of fluvastatin on ischemia following acute myocardial infarction: a randomized trial. Eur Heart J. 2002;23:1931-7.
- LIPITOR prescribing information. Pfizer, Inc. New York, NY. June 2017.
- LIVALO prescribing information. Kowa Pharmaceuticals America, Inc. Montgomery, AL: December 2016.
- Lloret R, Ycas J, Stein M, et al; STARSHIP Study Group. Comparison of rosuvastatin vs atorvastatin in Hispanic-Americans with hypercholesterolemia (from the STARSHIP trial). Am J Cardiol. 2006 Sep 15;98(6):768-73.

- Lu C, Jia H, Wang Z. High-dose atorvastatin reduces the risk of cardiovascular events in patients with percutaneous coronary intervention. Oncotarget. 2017 Jul 31;8(41):70356-70365
- Marais AD, Raal FJ, Stein EA, et al. A dose-titration and comparative study of rosuvastatin and atorvastatin in patients with homozygous familial hypercholesterolaemia. Atherosclerosis. 2008 Mar;197(1):400-6.
- May HT, Anderson JL, Pearson RR, et al. Comparison of effects of simvastatin alone vs fenofibrate alone vs simvastatin plus fenofibrate on lipoprotein subparticle profiles in diabetic patients with mixed dyslipidemia (from the Diabetes and Combined Lipid Therapy Regimen study). Am J Cardiol. 2008;101:486-9.
- Mazza F, Stefanutti C, Di Giacomo S, et al. Effects of low-dose atorvastatin and rosuvastatin on plasma lipid profiles: a long-term, randomized, open-label study in patients with primary hypercholesterolemia. Am J Cardiovasc Drugs. 2008;8:265-70.
- Meaney A, Ceballos G, Asbun J, et al. The VYTORIN on Carotid intima-media Thickness and Overall arterial Rigidity study (VYCTOR). J Clin Pharmacol. 2009;49:838-847.
- Melani L, Mills R, Hassman D, et al. Efficacy and safety of ezetimibe coadministered with pravastatin in patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Eur Heart J. 2003 Apr;24(8):717-28.
- Meredith KG, Horne BD, Pearson RR, et al. Comparison of effects of high (80 mg) vs low (20 mg) dose of simvastatin on C-reactive protein and lipoproteins in patients with angiographic evidence of coronary arterial narrowing. Am J Cardiol. 2007 Jan 15;99(2):149-53.
- Messerli FH, Bakris GL, Ferrera D, et al. Efficacy and safety of coadministered amlodipine and atorvastatin in patients with hypertension and dyslipidemia: results of the AVALON trial. J Clin Hypertens (Greenwich). 2006 Aug;8(8):571-81.
- MEVACOR prescribing information. Lupin Pharmaceuticals, Inc. Baltimore, MD. April 2017.
- Milionis HJ, Rizos E, Kostapanos M, et al. Treating to target patients with primary hyperlipidemia: comparison of the effects of ATOrvastatin and ROSuvastatin (the ATOROS study). Curr Med Res Opin. 2006 Jun;22(6):1123-31.
- Mohiuddin S, Pepine C, Kelly M, et al. Efficacy and safety of ABT-335 (fenofibric acid) in combination with simvastatin in patients with mixed dyslipidemia: a phase 3, randomized, controlled study. Am Heart J. 2009;157:195-203.
- Mood GR, Bavry AA, Roukoz H, et al. Meta-analysis of the role of statin therapy in reducing myocardial infarction following elective percutaneous coronary intervention. Am J Cardiol. 2007 Sep 15;100(6):919-23.
- Mora S, Glynn RJ, Hsia J, et al. Statins for the primary prevention of cardiovascular events in women with elevated high-sensitivity C-reactive protein dyslipidemia: results from the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) and meta-analysis of women from primary prevention trials. Circulation. 2010;121:1069-77.
- Motomura T, Okamoto M, Kitamura T, et al. Effects of pitavastatin on serum lipids and high sensitivity c-reactive protein in Type 2 diabetic patients. J Atheroscler Thromb. 2009;16:546-52.
- Murphy SA, Cannon CP, Wiviott SD, et al. Effect of intensive lipid-lowering therapy on mortality after acute coronary syndrome (a patient-level analysis of the Aggrastat to ZOCOR and Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 trials). Am J Cardiol. 2007 Oct 1;100(7):1047-51.
- Nakamura H, Arakawa K, Itakura H, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomized controlled study. Lancet. 2006;368:1155-63.
- Neil HA, DeMicco DA, Luo D, et al. Analysis of efficacy and safety in patients aged 65-75 years at randomization: Collaborative Atorvastatin Diabetes Study (CARDS). Diabetes Care. 2006 Nov;29(11):2378-84.
- Neutel JM, Bestermann WH, Dyess EM, et al. The use of a single-pill calcium channel blocker/statin combination in the management of hypertension and dyslipidemia: a randomized, placebo-controlled, multicenter study. J Clin Hypertens (Greenwich). 2009;11:22-30.
- Nicholls S, Brandrup-Wognsen G, Palmer M, et al. Meta-analysis of comparative efficacy of increasing dose of atorvastatin vs rosuvastatin vs simvastatin on lowering levels of atherogenic lipids (from VOYAGER). Am J Cardiol. 2010;105:69-76.
- Nicholls SJ, Tuzcu EM, Sipahi I, et al. Effects of obesity on lipid-lowering, anti-inflammatory, and antiatherosclerotic benefits of atorvastatin or pravastatin in patients with coronary artery disease (from the REVERSAL Study). Am J Cardiol. 2006 Jun 1;97(11):1553-7.
- NIKITA prescribing information. Lupin Pharmaceuticals, Inc. Baltimore, MD. August 2017.
- Nissen SE, Nicholls SJ, Sipahi I, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA. 2006 Apr 5;295(13):1556-65.
- Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared to moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial (REVERSAL). JAMA. 2004 Mar 3;291(9):1071-80.
- Nissen SE, Tuzcu EM, Schoenhagen P, et al; Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) Investigators. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med. 2005 Jan 6;352(1):29-38.
- No authors listed. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 356 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360:7-22.
- No authors listed. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian simvastatin survival study (4S). Lancet. 1994;344:1383-9.
- No authors listed. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions. J Vasc Surg. 2007 Apr;45(4):645-654.
- Nunes JP. Statins in primary prevention: impact on mortality. A meta-analysis study. Minerva Cardioangiol. 2017; 65(5):531-538.
- Olsson AG, Schwartz GG, Szarek M, et al. Effects of high-dose atorvastatin in patients > or =65 years of age with acute coronary syndrome (from the myocardial ischemia reduction with aggressive cholesterol lowering [MIRACL] study). Am J Cardiol. 2007 Mar 1;99(5):632-5.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring, MD: Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed November 12, 2017.
- O'Regan C, Wu P, Arora P, et al. Statin therapy in stroke prevention: a meta-analysis involving 121,000 patients. Am J Med. 2008 Jan;121(1):24-33.
- Ose L, Budinski D, Hounslow N, et al. Comparison of pitavastatin with simvastatin in primary hypercholesterolemia or combined dyslipidemia. Curr Med Res Opin. 2009;25(11):2755-64.
- Ose L, Budinski D, Hounslow N, et al. Long-term treatment with pitavastatin is effective and well tolerated by patients with primary hypercholesterolemia or combined dyslipidemia. Atherosclerosis. 2010;210:202-8.

- Ose L, Johnson-Levonas A, Reyes R, Lin J, et al. A multi-centre, randomized, double-blind 14-week extension study examining the long-term safety and efficacy profile of the ezetimibe/simvastatin combination tablet. Int J Clin Pract. 2007 Sep;61(9):1469-80.
- Park A, Kang HJ, Rim SJ, et al. A randomized, open-label study to evaluate the efficacy and safety of pitavastatin compared to simvastatin in Korean patients with hypercholesterolemia. Clin Ther. 2005;27(7):1074-82.
- Park JS, Kim YJ, Choi JY, et al. Comparative study of low doses of rosuvastatin and atorvastatin on lipid and glycemic control in patients with metabolic syndrome and hypercholesterolemia. Korean J Intern Med. 2010;25:27-35.
- Pearson T, Ballantyne C, Sisk C, et al. Comparison of effects of ezetimibe/simvastatin vs simvastatin vs atorvastatin in reducing C-reactive protein and low-density lipoprotein cholesterol levels. Am J Cardiol. 2007 Jun 15;99(12):1706-13.
- Pedersen TR, Faergeman O, Kastelein JJ, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA. 2005 Nov 16;294(19):2437-45.
- Piorkowski M, Fischer S, Stellbaum C, et al. Treatment with ezetimibe plus low-dose atorvastatin compared to higher-dose atorvastatin alone: is sufficient cholesterol-lowering enough to inhibit platelets? J Am Coll Cardiol. 2007 Mar 13;49(10):1035-42.
- Pitt B, Loscalzo J, Monyak J, et al. Comparison of lipid-modifying efficacy of rosuvastatin vs atorvastatin in patients with acute coronary syndrome (from the LUNAR study). Am J Cardiol. 2012 May 1;109(9):1239-46.
- Pitt B, Waters D, Brown WV, et al. Aggressive lipid-lowering therapy compared to angioplasty in stable coronary artery disease. Atorvastatin vs Revascularization Treatment Investigators. N Engl J Med. 1999 Jul 8;341(2):70-6.
- Polis AB, Abate N, Catapano AL, et al. Low-density lipoprotein cholesterol reduction and goal achievement with ezetimibe/simvastatin vs atorvastatin or rosuvastatin in patients with diabetes, metabolic syndrome, or neither disease, stratified by national cholesterol education program risk category. Metab Syndr Relat Disord. 2009;7(6):601-10.
- PRAVACHOL prescribing information. Bristol-Myers Squibb. Princeton, NJ. June 2017.
- Preston RA, Harvey P, Herfert O, et al. A randomized, placebo-controlled trial to evaluate the efficacy, safety, and pharmacodynamic interaction of coadministered amlodipine and atorvastatin in 1660 patients with concomitant hypertension and dyslipidemia: the respond trial. J Clin Pharmacol. 2007 Dec;47(12):1555-69.
- Ray KK, Bach RG, Cannon CP, et al. Benefits of achieving the NCEP optional LDL-C goal among elderly patients with ACS. Eur Heart J. 2006 Oct;27(19):2310-6.
- Ray KK, Cannon CP, McCabe CH, et al. Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes: results from the PROVE IT-TIMI 22 trial. J Am Coll Cardiol. 2005 Oct 18;46(8):1405-10.
- Reckless J, Henry P, Pomykaj T, et al. Lipid-altering efficacy of ezetimibe/simvastatin 10/40 mg compared to doubling the statin dose in patients admitted to the hospital for a recent coronary event (INFORCE). Int J Clin Pract. 2008;62:539-554.
- Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359:2195-207.
- Ridker PM, MacFadyen J, Cressman M, et al. Efficacy of rosuvastatin among men and women with moderate chronic kidney disease and elevated high-sensitivity C-reactive protein. J Am Coll Cardiol. 2010;55(12):1266-73.
- Ridker PM, MacFadyen JG, Fonseca FAH, et al. Number needed to treat with rosuvastatin to prevent first cardiovascular events and death among men and women with low-density lipoprotein cholesterol and elevated high-sensitivity c-reactive protein. Circ Cardiovasc Qual Outcomes. 2009;2:616-23.
- Robinson JG, Ballantyne CM, Grundy SM, et al. Lipid-altering efficacy and safety of ezetimibe/simvastatin vs atorvastatin in patients with hypercholesterolemia and the metabolic syndrome (VYMET). Am J Cardiol. 2009;103:1694-702.
- Rodenburg J, Vissers MN, Wiegman A, et al. Statin treatment in children with familial hypercholesterolemia: the younger, the better. Circulation. 2007 Aug 7;116(6):664-8.
- Roeters van Lennep H, Liem A, et al. The efficacy of statin monotherapy up-titration vs switching to ezetimibe/simvastatin (EASEGO). Curr Med Res Opin. 2008;24:685-694.
- Rogers SL, Magliano DJ, Levison DB, et al. A dose-specific meta-analysis of lipid changes in randomized controlled trials of atorvastatin and simvastatin. Clin Ther. 2007 Feb;29(2):242-52.
- Rosenson RS, Otvos JD, Hsia J, et al. Effects of rosuvastatin and atorvastatin on LDL and HDL particle concentrations in patients with metabolic syndrome: a randomized, double-blind, controlled study. Diabetes Care. 2009;32:1087-91.
- Rossebø AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis (SEAS). N Engl J Med. 2008;359:1343-56.
- Rotella CM, Zaninelli A, Le Grazie C, et al. Ezetimibe/simvastatin vs simvastatin in coronary heart disease patients with or without diabetes. Lipids Health Dis. 2010;9(80):1-8.
- Roth EM, Rosenson RS, Carlson DM, et al. Efficacy and safety of rosuvastatin 5 mg in combination with fenofibric acid 135 mg in patients with mixed dyslipidemia-a phase 3 study. Cardiovasc Drugs Ther. 2010;24:421-8.
- Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. The Cholesterol and Recurrent Events Trial (CARE). N Engl J Med.1996 Oct; 335(14):1001-9.
- Saito Y, Yamada N, Teramoto T, et al. A randomized, double-blind trial comparing the efficacy and safety of pitavastatin vs pravastatin in patients with primary hypercholesterolemia. Atherosclerosis. 2002;162:373-9.
- Sakamoto T, Kojima S, Ogawa H, et al. Usefulness of hydrophilic vs lipophilic statins after acute myocardial infarction: subanalysis of MUSASHI-AMI. Circ J. 2007 Sep;71(9):1348-53.
- Sansanayudh N, Wongwiwatthananukit S, Putwai P, et al. Comparative efficacy and safety of low-dose pitavastatin vs atorvastatin in patients with hypercholesterolemia. Ann Pharmacother. 2010;44:415-23.
- Sasaki J, Ikeda Y, Kuribayashi T, et al. A 52-week, randomized, open-label, parallel-group comparison of the tolerability and effects of pitavastatin and atorvastatin on high-density lipoprotein cholesterol levels and glucose metabolism in Japanese patients with elevated levels of low-density lipoprotein cholesterol and glucose intolerance. Clin Ther. 2008;30(6):1089-100.
- Sato H, Kinjo K, Ito H, et al. Effect of early use of low-dose pravastatin on major adverse cardiac events in patients with acute myocardial infarction: the OACIS-LIPID Study. Circ J. 2008;72:17-22.
- Schmermund A, Achenbach S, Budde T, et al. Effect of intensive vs standard lipid-lowering treatment with atorvastatin on the progression of calcified coronary atherosclerosis over 12 months: a multicenter, randomized, double-blind trial. Circulation. 2006 Jan 24;113(3):427-37.

- Schoenhagen P, Tuzcu EM, Apperson-Hansen C, et al. Determinants of arterial wall remodeling during lipid-lowering therapy: serial intravascular ultrasound observations from the Reversal of Atherosclerosis with Aggressive Lipid Lowering Therapy (REVERSAL) trial. Circulation. 2006 Jun 20;113(24):2826-34.
- Schouten O, Boersma E, Hoeks S, et al. Fluvastatin and perioperative events in patients undergoing vascular surgery. N Engl J Med. 2009;361:980-989.
- Schwartz GG, Olsson AG, Szarek M, et al. Relation of characteristics of metabolic syndrome to short-term prognosis and effects of intensive statin therapy after acute coronary syndrome: an analysis of the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial. Diabetes Care. 2005 Oct;28(10):2508-13.
- Scirica BM, Morrow DA, Cannon CP, et al. Intensive statin therapy and the risk of hospitalization for heart failure after an acute coronary syndrome in the PROVE IT-TIMI 22 study. J Am Coll Cardiol. 2006 Jun 6;47(11):2326-31.
- Serruys PW, de Feyter P, Macaya C, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. LESCOL Intervention Prevention Study (LIPS). JAMA. 2002;287(24):3215-22.
- Sever PS, Dahlöf B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet. 2003 Apr 5;361(9364):1149-58.
- Sever PS, Poulter NR, Dahlöf B, et al. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial--lipid-lowering arm (ASCOT-LLA). Diabetes Care. 2005 May;28(5):1151-7.
- Shafiq N, Bhasin B, Pattanaik S, et al. A meta-analysis to evaluate the efficacy of statins in children with familial hypercholesterolemia. Int J Clin Pharmacol Ther. 2007 Oct; 45(10):548-55.
- Shah SJ, Waters DD, Barter P, et al. Intensive lipid-lowering with atorvastatin for secondary prevention in patients after coronary artery bypass surgery. J Am Coll Cardiol. 2008;51:1938-43.
- Shepherd J, Barter P, Carmena R, et al. Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study. Diabetes Care. 2006 Jun;29(6):1220-6.
- Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomized controlled trial. Lancet. 2002;360:1623-30.
- Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. The West of Scotland Coronary Prevention Study (WOSCOPS). NEJM. 1995;333(20):1301-7.
- Shepherd J, Hunninghake DB, Barter P, et al. Guidelines for lowering lipids to reduce coronary artery disease risk: a comparison of rosuvastatin with atorvastatin, pravastatin, and simvastatin for achieving lipid-lowering goals. Am J Cardiol. 2003 Mar 6;91(5A):11C-7C.
- Shepherd J, Kastelein JJ, Bittner V, et al. Effect of intensive lipid lowering with atorvastatin on renal function in patients with coronary heart disease: the Treating to New Targets (TNT) study. Clin J Am Soc Nephrol. 2007 Nov;2(6):1131-9.
- Stalenhoef A, Ballantyne C, Sarti C, et al. A comparative study with rosuvastatin in subjects with metabolic syndrome: Results of The Comets Study. Eur Heart J. 2005;1093:822-9.
- Stein E, Ballantyne C, Windler E, et al. Efficacy and tolerability of fluvastatin XL 80 mg alone, ezetimibe alone, and the combination of fluvastatin XL 80 mg with ezetimibe in patients with a history of muscle-related side effects with other statins. Am J Cardiol. 2008;101:490-496.
- Stein E, Stender S, Mata P, Sager P, et al. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: Efficacy and safety of ezetimibe co-administered with atorvastatin. Am Heart J. 2004 Sep;447-55.
- Stein EA, Amerena J, Ballantyne CM, et al. Long-term efficacy and safety of rosuvastatin 40 mg in patients with severe hypercholesterolemia. Am J Cardiol. 2007 Nov 1;100(9):1387-96.
- Stein EA, Strutt K, Southworth H, et al. Comparison of rosuvastatin versus atorvastatin in patients with heterozygous familial hypercholesterolemia. Am J Cardiol. 2003 Dec 1;92(11):1287-93.
- Stoekenbroek RM, Boekholdt SM, Fayyad R, et al. High-dose atorvastatin is superior to moderate-dose simvastatin in preventing peripheral arterial disease. Heart. 2015;101:356-62.
- Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in Adults: A report of the American College of Cardiology/American Heart Association. Circulation. 2014 Jun 24;129(25 Suppl 2):S1-45.
- Strandberg TE, Holme I, Faergeman O, et al. Comparative effect of atorvastatin (80 mg) vs simvastatin (20 to 40 mg) in preventing hospitalizations for heart failure in patients with previous myocardial infarction. Am J Cardiol. 2009;103:1381-5.
- Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet. 2008;372:1231-9.
- Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews. 2013, Jan 31;(1):CD004816. doi: 10.1002/14651858.CD004816.pub5.
- The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care. The antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT-LLT). JAMA. 2002;288(23):2998-3007.
- The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med. 1998;339(19):1349-57.
- The Pravastatin Multinational Study Group for Cardiac Risk Patients (PMS-CRP). Effects of pravastatin in patients with serum total cholesterol levels from 5.2 to 7.8 mmol/liter (200 to 300 mg/dL) plus two additional atherosclerotic risk factors. Am J Cardiol. 1993;72:1031-7.
- Thompson P, Meredith I, Anerena J, et al. Effect of pravastatin compared to placebo initiated within 24 hours of onset of acute myocardial infarction or unstable angina: The Pravastatin in Acute Coronary Treatment (PACT) trial. Am Heart J. 2004 Jul;148(1):e2.
- Tikkanen MJ, Holme I, Cater NB, et al. Comparison of efficacy and safety of atorvastatin (80 mg) to simvastatin (20 to 40 mg) in patients aged <65 vs ≥65 years with coronary heart disease (from the Incremental Decrease through Aggressive Lipid Lowering [IDEAL] study). Am J Cardiol. 2009;103:577-82.
- US Preventive Services Task Force. Statin Use for the Primary Prevention of Cardiovascular Disease in Adults US Preventive Services Task Force Recommendation Statement. *JAMA.* 2016;316(19):1997-2007. *Circulation*. 2016;134:e468-e495.

- Viigimaa M, Vaverkova H, Farnier M, et al. Ezetimibe/simvastatin 10/20 mg vs rosuvastatin 10 mg in high-risk hypercholesterolemic patients stratified by prior statin treatment potency. Lipids Health Dis. 2010 Nov 4;9:127.
- Vuorio A, Kuoppala J, Kovanen PT, et al. Statins for children with familial hypercholesterolemia. Cochrane Database of Systematic Reviews. 2014, Jul 7; (7): CD006401. doi: 10.1002/14651858.CD006401.pub3.
- VYTORIN prescribing information. Merck & Co, Inc. Whitehouse Station, NJ. October 2016.
- Waters DD, LaRosa JC, Barter P, et al. Effects of high-dose atorvastatin on cerebrovascular events in patients with stable coronary disease in the TNT (treating to new targets) study. J Am Coll Cardiol. 2006 Nov 7;48(9):1793-9.
- Wenger NK, Lewis SJ, Herrington DM, et al; Treating to New Targets Study Steering Committee and Investigators. Outcomes of using high- or low-dose atorvastatin in patients 65 years of age or older with stable coronary heart disease. Ann Intern Med. 2007 Jul;147(1):1-9.
- Wiggins B, Saseen J, Page R, et al. Recommendations for Management of Clinically Significant Drug-Drug Interactions With Statins and Select Agents Used in Patients With Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation*. 2016;134:e468-e495.
- Winkler K, Ablethauser CB, Gimpelewicz C, et al. Risk reduction and tolerability of fluvastatin in patients with the metabolic syndrome: a pooled analysis of thirty clinical trials. Clin Ther. 2007;29:1987-2000.
- Winkler K, Schewe T, Putz G, et al. Fluvastatin/fenofibrate vs simvastatin/ezetimibe in patients with metabolic syndrome: different effects on LDL-profiles. Eur J Clin Invest. 2009;39(6):463-70.
- Wlodarczyk J, Sullivan D, Smith M. Comparison of benefit and risks of rosuvastatin vs atorvastatin for a meta-analysis of head-to-head randomized controlled trials. Am J Cardiol. 2008;102:1654-62.
- Wolffenbuttel BH, Franken AA, Vincent HH. Cholesterol-lowering effects of rosuvastatin compared to atorvastatin in patients with type 2 diabetes: the CORALL study. J Intern Med. 2005 Jun;257(6):531-9.
- Wongwiwatthananukit S, Sansanayudh N, Dhummauppakorn R, et al . Efficacy and safety of rosuvastatin every other day compared to once daily in patients with hypercholesterolemia. Ann Pharmacother. 2006 Nov;40(11):1917-23.
- Yoshitomi Y, Ishii T, Kaneki M, et al. Efficacy of a low dose of pitavastatin compared to atorvastatin in primary hyperlipidemia: results of a 12-week, open label study. J Atheroscler Thromb. 2006;13(2):108-13.
- Yu CM, Zhang Q, Lam L, et al. Comparison of intensive and low-dose atorvastatin therapy in the reduction of carotid intima-medial thickness in patients with coronary heart disease. Heart. 2007 Aug;93(8):933-9.
- Zieve F, Wenger NK, Ben-Yehuda O, et al. Safety and efficacy of ezetimibe added to atorvastatin vs up titration of atorvastatin to 40 mg in patients >or = 65 years of age (ZETELD). Am J Cardiol. 2010;105:656-63.
- ZOCOR prescribing information. Merck & Co, Inc. Whitehouse Station, NJ. March 2015.
- ZYPITAMAG prescribing information. Zydus Pharmaceuticals Inc. Pennington, NJ. July 2017.

Publication Date: January 5, 2018

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.

REFERENCES

- American Diabetes Association. Diabetes Basics: Type 2 (2017[a]). http://www.diabetes.org/diabetes-basics/type-2/?loc=util-header_type2. Accessed July 31, 2017.
- American Diabetes Association. Standards of Medical Care in Diabetes – 2017. Diabetes Care. 2017[b];40(suppl 1):S1-S135 http://care.diabetesjournals.org/content/diacare/suppl/2016/12/15/40.Supplement_1.DC1/DC_40_S1_final.pdf. Accessed July 31, 2017.
- Araki E, Tanizawa Y, Tanaka Y, et al. Long-term treatment with empagliflozin as add-on to oral anti-diabetes therapy in Japanese patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2015;17(7):665-74.
- Bailey CJ, Gross JL, Pieters A, Bastien A, List JF. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomized, double-blind, placebo-controlled trial. Lancet. 2010;375:2223-2233.
- Bailey CJ, Iqbal N, T'Joen C, et al. Dapagliflozin monotherapy in drug-naive patients with diabetes: a randomized-controlled trial of low-dose range. Diabetes Obes Metab. 2012;14(10):951-959.
- Bailey CJ, Morales-Villegas EC, Woo, V, et al. Efficacy and safety of dapagliflozin monotherapy in people with type 2 diabetes: a randomized double-blind placebo-controlled 102-week trial. Diabet Med. 2015;32:531-41.
- Barnett AH, Mithal A, Manassie J, et al. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomize, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2014;2(5):369-84.

- Bilezikian JP, Watts NB, Usiskin K, et al. Evaluation of bone mineral density and bone biomarkers in patients with Type 2 diabetes treated with canagliflozin. J Clin Endocrinol Metab. 2016;101(1):44-51.
- Bode B, Stenlof K, Harris S, et al. Long-term efficacy and safety of canagliflozin over 104 weeks in patients aged 55-80 years with type 2 diabetes. Diabetes Obes Metab. 2015;17:294-303.
- Bode B, Stenlof K, Sullivan D, Fung A, Usiskin K. Efficacy and safety of canagliflozin treatment in older subjects with type 2 diabetes mellitus: a randomized trial. Hosp Pract. 1995;41:72-84.
- Bolen S, Tseng E, Hutfless S, Segal JB, Suarez-Cuervo C, Berger Z, Wilson LM, Chu Y, Iyoha E, Maruthur NM. Diabetes Medications for Adults With Type 2 Diabetes: An Update. Comparative Effectiveness Review No. 173. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2012-00007-I.) AHRQ Publication No. 16-EHC013-EF. Rockville, MD: Agency for Healthcare Research and Quality; April 2016. www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed July 31, 2017.
- Cefalu W, Leiter L, Yoon KH L, et al. Efficacy and safety of canagliflozin vs glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. Lancet. 2013;182-941-950.
- Centers for Disease Control and Prevention (CDC). National Diabetes Statistics Report; 2017. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. Updated July 17, 2017. Accessed July 31, 2017.
- ClinicalTrials.gov Web site. http://clinicaltrials.gov/. Accessed July 31, 2017.
- Copeland KC, Silverstein J, Moore KR, et al. Management of newly diagnosed type 2 diabetes mellitus (T2DM) in children and adolescents. Pediatrics. 2013;131:364-382.
- Davies MJ, Trujillo A, Vijapurkar U, et al. Effect of canagliflozin on serum uric acid in patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2015;17:426-429.
- DeFronzo RA, Lewin A, Patel S, et al. Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. Diabetes Care. 2015;38:384-393.
- Del Prato S, Nauck M, Duran-Garcia S, et al. Long-term glycaemic response and tolerability of dapagliflozin vs a sulphonylurea as add-on therapy to metformin in type 2 diabetes patients: 4-year data. Diabetes Obes Metab. 2015;17(6):581-90.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed July 31, 2017.
- Farxiga Prescribing Information. AstraZeneca Pharmaceuticals LP. Wilmington, DE. March 2017.
- FDA Drug Safety Communications. Canagliflozin (Invokana, Invokamet): Drug Safety Communication – Clinical Trial Results Find Increased Risk of Leg and Foot Amputations. May 18, 2016[a]. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm501565.htm. Accessed July 31, 2017.
- FDA Drug Safety Communications. FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR). May 16, 2017. https://www.fda.gov/downloads/Drugs/DrugSafety/UCM558427.pdf. Accessed July 24, 2017.
- FDA Drug Safety Communications. FDA revises label of diabetes drug canagliflozin (Invokana, Invokamet) to include updates on bone fracture risk and new information on decreased bone mineral density. September 10, 2015. https://www.fda.gov/downloads/Drugs/DrugSafety/UCM461790.pdf. Accessed July 25, 2017.
- FDA Drug Safety Communications. FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR). June 14, 2016[b]. http://www.fda.gov/drugs/drugsafety/ucm505860.htm. Accessed July 31, 2017.
- Ferrannini E, Berk A, Hantel S, et al. Long-term safety and efficacy of empagliflozin, sitagliptin, and metformin: an active-controlled, parallel-group, randomized, 78-week open-label extension study in patients with type 2 diabetes. Diabetes Care. 2013;36(12):4015-21.
- Ferrannini E, Jimenez Ramos S, Salsali A, Tang W, List J. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise. Diabetes Care. 2010;33:2217-2214.
- Forst T, Guthrie R, Goldenberg R, et al. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes on background metformin and pioglitazone. Diabetes Obes Metab. 2014;16(5):467-77.
- Fulcher G, Matthews DR, Perkovic V, et al. Efficacy and safety of canagliflozin used in conjunction with sulfonylurea in patients with type 2 diabetes mellitus: a randomized, controlled trial. Diabetes Ther. 2015 Sep;6(3):289-302.
- Garber AJ, Abrahamson MJ, Barzilay JI, et al. Rosenblit PD, Umpierrez GE. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm - 2017 Executive Summary. Endocr Pract. 2017 Feb;23(2):207-238.
- Glyxambi prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. March 2017.
- Haring HU, Merker L, Seewaldt-Becker E, et al. Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care. 2014;37:1650-9.
- Haring HU, Merker L, Seewaldt-Becker E, et al. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care. 2013;36:3396-3404.
- Henry RR, Murray AV, Marmolejo MH, Hennicken D, et al. Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomized controlled trial. Int J Clin Pract. 2012;66:446-456.
- Inagaki N, Kondo K, Yoshinari T, et al. Japanese patients with type 2 diabetes inadequately controlled with diet and exercise: a 24-week, randomized, double-blind, placebo-controlled, Phase III study. Expert Opin Pharmacother 2014;15:1501-1515.
- Invokamet prescribing information. Janssen Pharmaceuticals, Inc. Titusville, NJ. July 2017.
- Invokamet XR prescribing information. Janssen Pharmaceuticals, Inc. Titusville, NJ. July 2017.
- Invokana prescribing information. Janssen Pharmaceuticals, Inc. Titusville, NJ. July 2017.
- Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2015;38(1):140-149. http://care.diabetesjournals.org/content/38/1/140.full.pdf+html. Accessed July 31, 2017.
- Jabbour A, Hardy E, Sugg J, Parikh S. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. Diabetes Care. 2014;37(3):740-50.
- Jardiance prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. December 2016.

- Kohan DE, Fioretto P, Tang W, et al. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. Kidney Int. 2014 Apr;85(4):962-71.
- Kosiborod M, Cavender MA, Fu AZ, et al.; CVD-REAL Investigators and Study Group*. Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors). Circulation. 2017 Jul 18;136(3):249-259.
- Kovacs CS, Seshiah V, Merker L, et al. Empagliflozin as add-on therapy to pioglitazone with or without metformin in patients with type 2 diabetes mellitus. Clin Ther. 2015 Aug;37(8):1773-88.
- Kovacs CS, Seshiah V, Swallow R, et al. Empagliflozin improves glycemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: a 24-week, randomized, placebo-controlled trial. Diabetes Obes Metab. 2014;16:147-58.
- Lavalle-Gonzalez, et al. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomized trial. Diabetologia. 2013;56:2582-2592.
- Leiter LA, Cefalu WT, Tjerk W, et al. Dapagliflozin added to usual care in individuals with type 2 diabetes mellitus with preexisting cardiovascular disease: a 24-week, multicenter, randomized, double-blind, placebo-controlled study with a 28-week extension. J Am Geriatr Soc. 2014;62:1252-62.
- Leiter, LA, Yoon HK, Arias P et al. Canagliflozin provides durable glycemic improvements and body weight reduction over 104 weeks versus glimepiride in patients with type 2 diabetes on metformin: a randomized, double-blind, phase 3 study. Diabetes Care. 2015;38(3):355-64.
- Liakos A, Karagiannis T, Athanasiadou E, et al. Efficacy and safety of empagliflozin for type 2 diabetes: a systematic review and meta-analysis. Diabetes Obes Metab. 2014;16:984-993.
- Matthaei S, Aggarwal N, Garcia-Hernandez P, et al. One-year efficacy and safety of saxagliptin add-on in patients receiving dapagliflozin and metformin. Diabetes Obes Metab. 2016;18(11):1128-1133.
- Matthaei S, Bowering K, Rohwedder K, et al. Dapagliflozin improves glycemic control and reduces body weight as add-on therapy to metformin plus sulfonylurea: a 24-week randomized, double-blind clinical trial. Diabetes Care. 2015;38:365-372.
- Matthaei S, Catrinoiu D, Celiński A, et al. Randomized, double-blind trial of triple therapy with saxagliptin add-on to dapagliflozin plus metformin in patients with type 2 diabetes. Diabetes Care. 2015;38(11):2018-24.
- Mathieu C, Herrera Marmolejo M, González González JG, et al. Efficacy and safety of triple therapy with dapagliflozin add-on to saxagliptin plus metformin over 52 weeks in patients with type 2 diabetes. Diabetes Obes Metab. 2016;18(11):1134-1137.
- Mathieu C, Ranetti AE, Li D, et al. Randomized, double-blind, phase 3 trial of triple therapy with dapagliflozin add-on to saxagliptin plus metformin in type 2 diabetes. Diabetes Care. 2015;38(11):2009-17.
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Diabetic Kidney Disease: What is diabetic kidney disease? 2017. https://www.niddk.nih.gov/health-information/diabetes/overview/preventing-problems/diabetic-kidney-disease. Updated February 2017. Accessed July 31, 2017.
- Nauck MA, Del Prato S, Duran-Garcia A, et al. Durability of glycaemic efficacy over 2 years with dapagliflozin versus glipizde as add-on therapies in patients whose type 2 diabetes mellitus is inadequately controlled with metformin. Diabetes Obes Metab. 2014;16(11):1111-20.
- Nauck MA, Del Prato S, Meier JJ, et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin. Diabetes Care. 2011;34:2015-2022.
- Neal B, Perkovic V, Mahaffey KW, et al.; CANVAS Program Collaborative Group. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017 Jun 12. doi: 10.1056/NEJMoa1611925. [Epub ahead of print]
- Neal B, Perkovic V, de Zeeuw D et al. Efficacy and safety of canagliflozin, an inhibitor of sodium-glucose cotransporter 2, when used in conjunction with insulin therapy in patients with type 2 diabetes. Diabetes Care. 2015;38:403-411.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed July 31, 2017.
- Orme M, Fenici P, Duprat-Lomon I, et al. A systematic review and mixed-treatment comparison of dapagliflozin with existing anti-diabetes treatments for those with type 2 diabetes mellitus inadequately controlled by sulfonylurea monotherapy. Diabetol Metab Syndr. 2014 Jun 11;6:73.
- Ptaszynska A, Johnsson KM, Parikh SJ, et al. Safety profile of dapagliflozin for type 2 diabetes: pooled analysis of clinical studies for overall safety and rare events. Drug Saf. 2014;37(10):815-29.
- Qtern prescribing information. AstraZeneca Pharmaceuticals LP. Wilmington, DE. February 2017.
- Ridderstrale M, Andersen KR, Zeller C, et al. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomized, active-controlled, double-blind, phase 3 trial. Lancet Diabetes Endrocrinol. 2014;2:691-700.
- Roden M, Weng J, Eilbracht J, et al. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol. 2013;1(3):208-19.
- Rosenstock J, Chuck L, Gonzalez-Ortiz M, et al. Initial combination therapy with canagliflozin plus metformin versus each component as monotherapy for drug-naïve type 2 diabetes. Diabetes Care. 2016;39(3):353-62.
- Rosenstock J, Hansen L, Zee P, et al. Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. Diabetes Care. 2015[a];38:376-83.
- Rosenstock J, Jelaska A, Frappin G, et al. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. Diabetes Care. 2014;37:1815-23.
- Rosenstock J, Jelaska A, Zeller C, et al for the EMPA-REG BASALTM trial investigators. Impact of empagliflozin added on to basal insulin in type 2 diabetes inadequately controlled on basal insulin: a 78-week randomized, double-blind, placebo-controlled trial. Diabetes Obes Metab. 2015[b] Oct;17(10):936-48.
- Rosenstock J, Seman LJ, Jelaska A, et al. Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycaemia. Diabetes Obes Metab. 2013;15:1154-60.
- Rosenstock J, Vico M, Wei L, Salsali A, List JF. Effects of dapagliflozin, an SGLT2 inhibitor, on HbA1c, body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. Diabetes Care. 2012;35:1473-1478.
- Ross S, Thamer C, Cescutti J, et al. Efficacy and safety of empagliflozin twice daily versus once daily in patients with type 2 diabetes inadequately controlled on metformin: a 16-week, randomized, placebo-controlled trial. Diabetes Obes Metab. 2015;17:699-702.

- Schernthaner G, Gross JL, Rosenstock J, Guarisco M, Fu M, Yee J, Kawaguchi M, Canovatchel W, Meininger G. Canagliflozin Compared With Sitagliptin for Patients With Type 2 Diabetes Who Do Not Have Adequate Glycemic Control With Metformin Plus Sulfonylurea: A 52-week randomized trial. Diabetes Care. 2013;36:2508-2515.
- Shyangdan DS, Uthman OA, Waugh N. SGLT-2 receptor inhibitors for treating patients with type 2 diabetes mellitus: a systematic review and network meta-analysis. BMJ Open. 2016 Feb 24;6(2):e009417.
- Sinclair A, Bode B, Harris S, et al. Efficacy and safety of canagliflozin compared with placebo in older patients with type 2 diabetes mellitus: a pooled analysis of clinical studies. BMC Endocrine Disorders. 2014;14:37.
- Sinclair AJ, Bode B, Harris S, et al. Efficacy and safety of canagliflozin in individuals aged 75 and older with Type 2 Diabetes Mellitus: A pooled analysis. J Am Geriatr Soc. 2016;64:543-552.
- Stenlöf K, Cefalu WT, Kim KA, Alba M, Usiskin K, Tong C, Canovatchel W, Meininger G. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab. 2013;15(4):372-82.
- Strojek K, Yoon KH, Elze M, Langkilde AM, Parikh S. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. Diabetes Obes Metab. 2011;13:928-938.
- Strojek K, Yoon KH, Hruba V, et al. Dapagliflozin added to glimepiride in patients with type 2 diabetes mellitus sustains glycemic control and weight loss over 48 weeks: a randomized, double-blind, parallel-group, placebo-controlled trial. Diabetes Ther. 2014;5:267-83.
- Supplement to: Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. DOI: 10.1056/NEJMoa1611925.
- Sun Y, Zhou Y, Chen X et al. The efficacy of dapagliflozin combined with hypoglycaemic drugs in treating type 2 diabetes mellitus: meta-analysis of randomised controlled trials. BMJ Open. 2014 Apr 7;4(4):e004619.
- Synjardy prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. December 2016.
- Synjardy XR prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. December 2016.
- Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med. 2016;375(4):323-334.
- Watts NB, Bilezikian JP, Usiskin K, et al. Effects of canagliflozin on fracture risk in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab. 2016;101(1):157-166.
- Weir MR, Januszewicz A, Gilbert RE et al. Effect of canagliflozin on blood pressure and adverse events related to osmotic diuresis and reduced intravascular volume in patients with type 2 diabetes mellitus. J Clin Hypertens. 2014;16:875-882.
- Wilding J, Charpentier G, Hollander P, et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sulphonylurea. Int J Clin Pract. 2013;67:1267-1282.
- Wilding JP, Woo V, Soler N, et al. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin. Ann Intern Med. 2012;156:405-415.
- Xigduo XR prescribing information. AstraZeneca Pharmaceuticals LP. Wilmington, DE. March 2017.
- Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab. 2013;14:463-479.
- Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab. 2014;16:1016-1027.
- Yang XP, Lai D, Zhong XY, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes: systematic review and meta-analysis. Eur J Clin Pharmacol. 2014;70:1149-1158.
- Zaccardi F, Webb DR, Htike ZZ, Youssef D, Khunti K, Davies MJ. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. Diabetes Obes Metab. 2016 Aug;18(8):783-94.
- Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117-2128.

Publication Date: August 4, 2017

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.

REFERENCES

- Aasand G, Etholm BO, Skjostad M, Volden J. Flunisolide nasal spray compared to beclomethasone dipropionate in the treatment of seasonal rhinitis. Rhinology. 1982;20(4):205-11.
- Al-Mohaimeid H. A parallel-group comparison of budesonide and beclomethasone dipropionate for the treatment of perennial allergic rhinitis in adults. J Int Med Res. 1993;21(2):67-73.
- Andersson M, Berglund R, Greiff L, et al. A comparison of budesonide nasal dry powder with fluticasone propionate aqueous nasal spray in patients with perennial allergic rhinitis. Rhinology. 1995;33(1):18-21.
- Bachert C, El-Akkad T. Patient preferences and sensory comparisons of 3 intranasal corticosteroids for the treatment of allergic rhinitis. Ann Allergy Asthma Immunol. 2002;89:292-7.

- Bachert C, Lukat KF, Lange B. Effect of intranasal fluticasone propionate and triamcinolone acetonide on basal and dynamic measures of hypothalamic-pituitary-adrenal-axis activity in healthy volunteers. Clin Exp Allergy. 2004;34:85-90.
- Beconase AQ prescribing information. GlaxoSmithKline. Research Triangle Park, NC. September 2015.
- Berger WE, Jacobs RL, Amar NJ, et al. Efficacy and safety of beclomethasone dipropionate nasal aerosol in children with perennial allergic rhinitis. Ann Allergy Asthma Immunol. 2015 Aug;115(2):130-6.
- Berger WE, Kaiser H, Gawchik SM, et al. Triamcinolone acetonide aqueous nasal spray and fluticasone propionate are equally effective for relief of nasal symptoms in patients with seasonal allergic rhinitis. Otolaryngol Head Neck Surg. 2003 Jul;129(1):16-23.
- Berger WE, Mohar DE, LaForce C, et al. A 26-week tolerability study of ciclesonide nasal aerosol in patients with perennial allergic rhinitis. Am J Rhinol Allergy. 2012 Jul;26(4):302-7.
- Bousquet J, Schunemann HJ, Hellings PW, et al. MACVIA clinical decision algorithm in adolescents and adults with allergic rhinitis. J Allergy Clin Immunol. 2016;138(2):367-374.e2.
- Brozek JL, Bousquet J, Agache I, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines—2016 revision. J Allergy Clin Immunol. 2017;140(4):950-958.
- Chong LY, Head K, Hopkins C, et al. Different types of intranasal steroids for chronic rhinosinusitis. Cochrane Database Syst Rev. 2016 Apr 26;4:CD011993. doi: 10.1002/14651858.CD011993.pub2.
- Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc; 2017. Available at: http://www.clinicalpharmacology.com. Accessed November 13, 2017.
- Day J, Carrillo T. Comparison of the efficacy of budesonide and fluticasone propionate aqueous nasal spray for once daily treatment of perennial allergic rhinitis. J Allergy Clin Immunol. 1998;102(6):902-8.
- Devillier P, Dreyfus JF, Demoly P, Calderon MA. A meta-analysis of sublingual allergen immunotherapy and pharmacotherapy in pollen-induced seasonal allergic rhinoconjunctivitis. BMC Medicine. 2014, 12:71. DOI: 10.1186/1741-7015-12-71.
- Drouin M, Yang WH, Bertrand B, et al. Once daily mometasone furoate aqueous nasal spray is as effective as twice daily beclomethasone dipropionate for treating perennial allergic rhinitis patients. Ann Allergy Asthma Immunol. 1996:77(2):153-60.
- Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2017. Available at: https://fco.factsandcomparisons.com. Accessed November 12, 2017.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/daf/. Accessed November 12, 2017.
- Durham SR, Creticos PS, Nelson HS, et al. Treatment effect of sublingual immunotherapy tablets and pharmacotherapies for seasonal and perennial allergic rhinitis: pooled analyses. J Allergy Clin Immunol. 2016;138(4):1081-1088.
- Dykewicz MS, Wallace DV, Baroody F, et al. Treatment of seasonal allergic rhinitis: an evidence-based focused 2017 guideline update [published online ahead of print November 2, 2017]. Ann Allergy Asthma Immunol. doi: 10.1016/j.anai.2017.08.012
- Flonase Allergy Relief drug facts. GlaxoSmithKline. August 2017. Available https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205434Orig1s005lbl.pdf/. Accessed November 13, 2017.
- Flonase Sensimist Allergy Relief drug facts. GlaxoSmithKline. April 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022051Orig1s014lbl.pdf. Accessed November 13, 2017.
- Flunisolide prescribing information. Bausch & Lomb Inc. Tampa, FL. June 2016.
- Fluticasone propionate prescribing information. West-Ward Pharmaceuticals Corp. Eatontown, NJ. June 2016.
- Glacy J, Putnam K, Godfrey S, et al. Treatments for seasonal allergic rhinitis. Comparative Effectiveness Review No. 120. (Prepared by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. 290-2007-10058-I.) AHRQ Publication No. 13-EHC098-EF. Rockville, MD: Agency for Healthcare Research and Quality; July 2013.
- GlaxoSmithKline (GSK) press release. GSK Consumer Healthcare Launches Flonase Sensimist Allergy Relief Nationwide. Website. February 8, 2017. Available at: http://us.gsk.com/en-us/media/press-releases/2017/gsk-consumer-healthcare-launches-flonase-sensimist-allergy-relief-nationwide/. Accessed November 13, 2017.
- Graft D, Aaronson D, Chervinsky P, et al. A placebo- and active-controlled randomized trial of prophylactic treatment of seasonal allergic rhinitis with mometasone furoate aqueous nasal spray. Journal of Allergy and Clinical Immunology. 1996:98(4):724-31.
- Gross G, Jacobs RL, Woodworth TH, et al. Comparative efficacy, safety, and effect on quality of life of triamcinolone acetonide and fluticasone propionate aqueous nasal sprays in patients with fall seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2002;89(1):56-62.
- Haye R, Gomez EG. A multicentre study to assess long-term use of fluticasone propionate aqueous nasal spray in comparison with beclomethasone dipropionate aqueous nasal spray in the treatment of perennial rhinitis. Rhinology. 1993;31(4):169-74.
- Hebert JR, Nolop K, Lutsky BN. Once-daily mometasone furoate aqueous nasal spray (Nasonex™) in seasonal allergic rhinitis: an active- and placebo-controlled study. Allergy. 1996;51:569-76.
- Kalish L, Snidvongs K, Sivasubramaniam R, et al. Topical steroids for nasal polyps. Cochrane Database of Systematic Reviews. 2012, Issue 12. Art. No.: CD006549. DOI: 10.1002/14651858.CD006549.pub2.
- Khanna P, Shah A. Assessment of sensory perceptions and patient preference for intranasal corticosteroid sprays in allergic rhinitis. Am J Rhinol. 2005;19(3):316-21.
- LaForce C, van Bavel J, Meltzer EO, et al. Efficacy and safety of ciclesonide hydrofluoroalkane nasal aerosol once daily for the treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2009 Aug;103(2):166-73.

- LaForce CF, Dockhorn RJ, Findlay SR, et al. Fluticasone propionate: an effective alternative treatment for seasonal allergic rhinitis in adults and adolescents. J Fam Pract. 1994;38:145-52.
- Langrick AF. Comparison of flunisolide and beclomethasone dipropionate in seasonal allergic rhinitis. Curr Med Res Opin. 1984;9:290-5.
- Lumry W, Hampel F, LaForce C, et al. A comparison of once-daily triamcinolone acetonide aqueous and twice-daily beclomethasone dipropionate aqueous nasal sprays in the treatment of seasonal allergic rhinitis. Allergy Asthma Proc. 2003;24:203-10.
- Mak KK, Ku MS, Lu KH, et al. Comparison of mometasone furoate monohydrate (Nasonex) and fluticasone propionate (Flixonase) nasal sprays in the treatment of dust mite-sensitive children with perennial allergic rhinitis. Pediatr Neonatol. 2013 Aug; 54:239-245. DOI: 10.1016/j.pedneo.2013.01.007.
- Mandl M, Nolop K, Lutsky BN. Comparison of once daily mometasone furoate (Nasonex) and fluticasone propionate aqueous nasal sprays for the treatment of perennial rhinitis. The 194-079 Study Group. Ann Allergy Asthma Immunol. 1997:79(3):237-45.
- McAllen MK, Portillo PR, Parr EJ, et al. Intranasal flunisolide, placebo and beclomethasone dipropionate in perennial rhinitis. Br J Dis Chest. 1980;74:32-6.
- McArthur JG. A comparison of budesonide and beclomethasone dipropionate sprays in the treatment of seasonal allergic rhinitis. Clin Otolaryngol Allied Sci. 1994;19(6):537-42.
- Meltzer E, Andrews C, Journeay G, et al. Comparison of patient preference for sensory attributes of fluticasone furoate or fluticasone propionate in adults with seasonal allergic rhinitis: a randomized, placebo-controlled, double blind study. Ann Allergy Asthma Immunol. 2010;104:331-8.
- Meltzer E, Stahlman J, Leflein J, et al. Preferences of adult patients with allergic rhinitis for the sensory attributes of fluticasone furoate vs fluticasone propionate nasal sprays: a randomized, multicenter, double-blind, single-dose, crossover study. Clin Ther. 2008;30:271-9.
- Meltzer EO, Bardelas J, Goldsobel A, Kaiser H. A preference evaluation study comparing the sensory attributes of mometasone furoate and fluticasone propionate nasal sprays by patients with allergic rhinitis. Treat Respir Med. 2005;4(4):289-96.
- Meltzer EO, Jacobs RL, LaForce CF, et al. Safety and efficacy of once-daily treatment with beclomethasone dipropionate nasal aerosol in subjects with perennial allergic rhinitis. Allergy Asthma Proc. 2012 May-Jun;33(3):249-57.
- Mohar D, Berger WE, LaForce C, et al. Efficacy and tolerability study of ciclesonide nasal aerosol in patients with perennial allergic rhinitis. Allergy Asthma Proc. 2012 Jan-Feb;33(1):19-26.
- Naclerio RM, Baroody FM, Bidani N, et al. A comparison of nasal clearance after treatment of perennial allergic rhinitis with budesonide and mometasone. Otolaryngol Head Neck Surg. 2003;128:220-7.
- Nasacort Allergy 24HR drug facts. Chattem. August 2016. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020468Orig1s042lbl.pdf. Accessed November 13, 2017.
- Nasonex prescribing information. Schering Corporation. Whitehouse Station, NJ. March 2013.
- Omnaris prescribing information. Sunovion Pharmaceuticals. Marlborough, MA. March 2013.
- Optinose press release. Optinose Announces FDA Approval of XHANCE™ (fluticasone propionate) Nasal Spray for the Treatment of Nasal Polyps. Optinose website. September 18, 2017. Available at: http://www.optinose.com/press-releases/optinose-announces-fda-approval-xhance-fluticasone-propionate-nasal-spray-treatment-nasal-polyps. Accessed November 12, 2017.
- Qnasl prescribing information. Teva Respiratory. Frazer, PA. July 2017.
- Ratner P, Jacobs R, Mohar D, et al. Evaluation of the efficacy and safety of ciclesonide hydrofluoroalkane nasal aerosol, 80 or 160 µg once daily, for the treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2010 Dec;105(6):471-9. DOI: 10.1016/j.anai.2010.09.024.
- Ratner PH, Andrews C, Martin B, et al. A study of the efficacy and safety of ciclesonide hydrofluoroalkane nasal aerosol in patients with seasonal allergic rhinitis from mountain cedar pollen. Allergy Asthma Proc. 2012 Jan-Feb;33(1):27-35.
- Ratner PH, Paull BR, Findlay SR, et al. Fluticasone propionate given once daily is as effective for seasonal allergic rhinitis as beclomethasone dipropionate given twice daily. J Allergy Clin Immunol. 1992;90:285-91.
- Rhinocort Allergy drug facts. AstraZeneca. May 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020746Orig1s037lbl.pdf. Accessed November 13, 2017.
- Sahay JN, Chatterjee SS, Engler C. A comparative trial of flunisolide and beclomethasone dipropionate in the treatment of perennial allergic rhinitis. Clin Allergy. 1980;10:65-70.
- Seidman MD, Gurgel RK, Lin ST, et al. Clinical practice guideline: allergic rhinitis. Otolaryngol Head Neck Surg. 2015;152(1 Suppl):SI-S43.
- Shah SR, Miller C, Pethick N, et al. 2 multicenter, randomized, single-blind, single-dose, crossover studies of specific sensory attributes of budesonide aqueous nasal spray and fluticasone propionate nasal spray. Clin Ther. 2003;25(8):2198-214.
- Sipila P, Sorri M, Ojala K, Palva A. Comparative trial of flunisolide and beclomethasone dipropionate nasal sprays in patients with seasonal allergic rhinitis. Allergy. 1983;38:303-7.
- Small P, Houle PA, Day JH, et al. A comparison of triamcinolone acetonide nasal aerosol spray and fluticasone propionate aqueous solution spray in the treatment of spring allergic rhinitis. J Allergy Clin Immunol. 1997;100(5):592-5.Snyder-Bulik B. GSK looks for another OTC allergy crossover hit in newly launched Flonase Sensimist. Website. FiercePharma. Feburary 14, 2017. Available at: http://www.fiercepharma.com/marketing/gsk-launches-another-otc-allergy-crossover-flonase-sensimist-and-supporting-ad-campaign. Accessed November 13, 2017.
- Stern MA, Dahl R, Nielsen LP, et al. A comparison of aqueous suspensions of budesonide nasal spray (128 µg and 256 µg once daily) and fluticasone propionate nasal spray (200 µg once daily) in the treatment of adult patients with seasonal allergic rhinitis. Am J Rhinol. 1997;11(4):323-30.
- Stokes M, Amorosi SL, Thompson D, et al. Evaluation of patients' preferences for triamcinolone acetonide aqueous, fluticasone propionate, and mometasone furoate nasal sprays in patients with allergic rhinitis. Otolaryngol Head Neck Surg. 2004;131:225-31.
- Storms WW, Segall N, Mansfield LE, et al. Efficacy and safety of beclomethasone dipropionate nasal aerosol in pediatric patients with seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2013;111(5):408-414.e1.

- Svendsen UG, Frolund L, Madsen F, et al. Beclomethasone dipropionate vs flunisolide as topical steroid treatment in patients with perennial rhinitis. Clin Otolaryngol Allied Sci. 1989;14(5):441-5.
- Triamcinolone acetonide prescribing information. Winthrop U.S. Bridgewater, NJ. July 2013.
- Van As A, Bronsky EA, Dockhorn RJ, et al. Once daily fluticasone propionate is as effective for perennial allergic rhinitis as twice daily beclomethasone dipropionate. J Allergy Clin Immunol. 1993;91(6):1146-54.
- Vanzieleghem MA, Juniper EF. A comparison of budesonide and beclomethasone dipropionate nasal aerosols in ragweed-induced rhinitis. J Allergy Clin Immunol. 1987;79(6):887-92.
- Varshney J, Varshney H, Dutta SK, Hazra A. Comparison of sensory attributes and immediate efficacy of intranasal ciclesonide and fluticasone propionate in allergic rhinitis: a randomized controlled trial. Indian J Pharmacol. 2012 Sep-Oct;44(5):550-4. DOI: 10.4103/0253-7613.
- Wallace DV, Dykewicz MS, Bernstein DI, et al. The diagnosis and management of rhinitis: An updated practice parameter of the joint task force on practice parameters for allergy and immunology. J Allergy Clin Immunol. 2008;122:S1-S84. Available at: http://www.allergyparameters.org/published-practice-parameters/alphabetical-listing/rhinitis-download/. Accessed November 13, 2017.
- Welsh PW, Stricker WE, Chu C, et al. Efficacy of beclomethasone nasal solution, flunisolide, and cromolyn in relieving symptoms of ragweed allergy. Mayo Clin Proc. 1987;62:125-34.
- Winder J, Bell T, Brodsky L. A comparative study of intranasal triamcinolone acetonide aerosol and intranasal beclomethasone dipropionate aqueous spray in perennial allergic rhinitis. Immunol Allergy Pract. 1993;15(7):203-9.
- Y1zaki M, Akiyama K, Karaki M, et al. Preference evaluation and perceived sensory comparison of fluticasone furoate and mometasone furoate intranasal sprays in allergic rhinitis. Auris Nasus Larynx. 2016;43(3):292-7.
- Xhance prescribing information. OptiNose, Inc. Yardley, PA. September 2017.
- Zetonna prescribing information. Sunovion Pharmaceuticals. Marlborough, MA. October 2014.

Publication Date: December 29, 2017

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 $[FEF]_{25\ to\ 75\%}$), 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 $FEF_{25\ to\ 75\%}$, 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 ($AUEC_{0-12wk}$), 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 $AUEC_{0-12wk}$ 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 $AUEC_{0-6wk}$, 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 $AUEC_{0-12wk}$; 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

REFERENCES

- Aerospan prescribing information. Meda Pharmaceuticals. Somerset, NJ. November 2017.
- Alvesco prescribing information. Sunovion Pharmaceuticals, Inc. Marlborough, MA. January 2013.
- Amar NJ, Moss MH, Kerwin EM, et al. Safety and efficacy of beclomethasone dipropionate delivered by breath-actuated or metered-dose inhaler for persistent asthma. Allergy Asthma Proc. 2016;37(5):359-69. doi: 10.2500/aap.2016.37.3983.
- Amar NJ, Shekar T, Varnell TA, et al. Mometasone furoate (MF) improves lung function in pediatric asthma: A double-blind, randomized controlled dose-ranging trial of MF metered-dose inhaler. Pediatr Pulmonol. 2017;52(3):310-318.

- ArmonAir RespiClick prescribing information. Teva Respiratory, LLC. Frazer, PA. October 2017.
- Arnuity Ellipta prescribing information. GlaxoSmithKline. Research Triangle Park, NC. May 2017.
- Asmanex HFA prescribing information. Merck & Co., Inc. Whitehouse Station, NJ. July 2016.
- Asmanex Twisthaler prescribing information. Merck Sharp & Dohme Corp. Whitehouse Station, NJ. September 2014.
- Baker JW, Mellon M, Wald J, et al. A multiple-dosing, placebo-controlled study of budesonide inhalation suspension given once or twice daily for treatment of persistent asthma in young children and infants. Pediatrics. 1999 Feb;103(2):414-21.
- Bernstein DI, Gillespie M, Song S, et al. Safety, efficacy, and dose response of fluticasone propionate delivered via the novel MDPI in patients with severe asthma: a randomized, controlled, dose-ranging study. J Asthma. 2017;54(6):559-569.
- Bleecker ER, Lotvall J, O'Byrne PM, et al. Fluticasone furoate-vilanterol 100-25 mcg compared with fluticasone furoate 100 mcg in asthma: a randomized trial. J Allergy Clin Immunol Pract. 2014;2:553-561.
- Bousquet J, D'Urzo A, Hebert J, et al. Comparison of the efficacy and safety of mometasone furoate dry powder inhaler to budesonide Turbuhaler®. Eur Respir J. 2000;16:808-16.
- Busse W, Raphael GD, Galant S, et al. Low-dose fluticasone propionate compared to montelukast for first-line treatment of persistent asthma: a randomized clinical trial. J Allergy Clin Immunol. 2001 Mar;107(3):461-8.
- Cinqair prescribing information. Teva. Frazer, PA. March 2016.
- Corren J, Berkowitz R, Murray JJ, et al. Comparison of once-daily mometasone furoate vs once-daily budesonide in patients with moderate persistent asthma. Int J Clin Pract. 2003;57(7):567-72.
- Corren J, Nelson H, Greos LS, et al. Effective control of asthma with hydrofluoroalkane flunisolide delivered as an extrafine aerosol in asthma patients. Ann Allergy Asthma Immunol. 2001;87:405-411.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2016. Available from: http://www.accessdata.fda.gov/scripts/cder/daf/. Accessed December 11, 2017.
- Fasrena prescribing information. AstraZeneca Pharmaceuticals LP. Frazer, PA. Wilmington, DE. November 2017.
- Ferguson AC, Van Bever HP, Teper AM, et al. A comparison of the relative growth velocities with budesonide and fluticasone propionate in children with asthma. Respiratory Medicine. 2007;101:118-29.
- Ferguson AC, Spier S, Manjra A, et al. Efficacy and safety of high-dose inhaled steroids in children with asthma: A comparison of fluticasone propionate with budesonide. J Pediatr. 1999;134(4):422-7.
- Fish JE, Karpel JP, Craig TJ, et al. Inhaled mometasone furoate reduces oral prednisone requirements while improving respiratory function and health-related quality of life in patients with severe persistent asthma. J Allergy Clin Immunol. 2000;106:852-60.
- Fitzgerald D, Van Asperen P, Mellis C, et al. Fluticasone propionate 750 µg/day vs beclomethasone dipropionate 1500 µg/day: comparison of efficacy and adrenal function in pediatric asthma. Thorax. 1998;53(8):656-61.
- Flovent Diskus prescribing information. GlaxoSmithKline. Research Triangle Park, NC. July 2017.
- Flovent HFA prescribing information. GlaxoSmithKline. Research Triangle Park, NC. July 2017.
- Garcia ML, Wahn U, Gilles L, et al. Montelukast compared to fluticasone for control of asthma among six to 14-year-old patients with mild asthma: the MOSAIC study. Pediatrics. 2005 Aug;116(2):360-9.
- Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention 2017. Available from: http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention. Accessed December 11, 2017.
- Hampel FC Jr, Carr W, Gillespie M, Small CJ. Evaluation of beclomethasone dipropionate (80 and 160 micrograms/day) delivered via a breath-actuated inhaler for persistent asthma. Allergy Asthma Proc. 2017;38(6):419-430. doi: 10.2500/aap.2017.38.4089.
- Harnest U, Price D, Howes T, Sussman G. Comparison of mometasone furoate dry powder inhaler and fluticasone propionate dry powder inhaler in patients with moderate to severe persistent asthma requiring high-dose inhaled corticosteroid therapy: findings from a non inferiority trial. Journal of Asthma. 2008;45:215-20.
- Karpel JP, Nayak A, Lumry W, et al. Inhaled mometasone furoate reduces oral prednisone usage and improves lung function in severe persistent asthma. Respir Med. 2007;101:628-637.
- Kerwin EM, Gillespie M, Song S, et al. Randomized, dose-ranging study of a fluticasone propionate multidose dry powder inhaler in adolescents and adults with uncontrolled asthma not previously treated with inhaled corticosteroids. J Asthma. 2017;54(1):89-98.
- Kramer S, Rottier BL, Scholten RJPM, et al. Ciclesonide versus other inhaled corticosteroids for chronic asthma in children. Cochrane Database of Systematic Reviews. 2013, Issue 2. Art. No.: CD010352. doi: 10.1002/14651858.CD010352.
- Lotvall J, Bleecker ER, Busse WW, et al. Efficacy and safety of fluticasone furoate 100 µg once-daily in patients with persistent asthma: a 24-week placebo and active-controlled randomized trial. Respir Med. 2014;108:41-49.
- Mansfield L, Yiu G, Sakov A, et al. A 6-month safety and efficacy study of fluticasone propionate and fluticasone propionate/salmeterol multidose dry powder inhalers in persistent asthma. Allergy Asthma Proc. 2017;38(4):264-276.
- Meltzer E, Korenblat P, Weinstein S, et al. Efficacy and safety evaluation of ciclesonide in mild to moderate persistent asthma previously treated with inhaled corticosteroids. Allergy & Asthma Proceedings. 2009;30(3):293-303.
- Meltzer EO, Kuna P, Nolte H, et al. Mometasone furoate/formoterol reduces asthma deteriorations and improves lung function. Eur Respir J. 2012;39:279-289.
- Nathan RA, Nayak AS, Graft DF, et al. Mometasone furoate: efficacy and safety in moderate asthma compared to beclomethasone dipropionate. Ann Allergy Asthma Immunol. 2001;86:203-10.

- Nathan RA, Nolte H, Pearlman DS, et al. Twenty-six-week efficacy and safety study of mometasone furoate/formoterol 200/10 microg combination treatment in patients with persistent asthma previously receiving medium-dose inhaled corticosteroids. Allergy Asthma Proc. 2010;31(4):269-279.
- National Heart, Lung, and Blood Institute. Expert Panel Report 3: Guidelines for the diagnosis and management of asthma (guideline on the Internet). NHLBI 2007. Available from http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed December 11, 2017.
- National Heart, Lung, and Blood Institute. What is Asthma? August 2014. Available at: http://www.nhlbi.nih.gov/health/health-topics/topics/asthma. Accessed December 11, 2017.
- Nelson HS, Busse WW, deBoisblanc BP, et al. Fluticasone propionate powder: Oral corticosteroid-sparing effect and improved lung function and quality of life in patients with severe chronic asthma. J Allergy Clin Immunol. 1999;103(2 pt 1):267-75.
- Nucala prescribing information. GlaxoSmithKline. Research Triangle Park, NC. February 2017.
- O'Byrne PM, Bleecker ER, Bateman ED, et al. Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma. Eur Respir J. 2014;43:773-782.
- O'Connor B, Bonnaud G, Haahtela T, et al. Dose-ranging study of mometasone furoate dry powder inhaler in the treatment of moderate persistent asthma using fluticasone propionate as an active comparator. Ann Allergy Asthma Immunol. 2001;86:397-404.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2016. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed December 11, 2017.
- Pulmicort Flexhaler prescribing information. AstraZeneca. Wilmington, DE. October 2016.
- Pulmicort Respules prescribing information. AstraZeneca. Wilmington, DE. October 2016.
- QVAR prescribing information. Teva Respiratory, LLC. Horsham, PA. October 2017.
- QVAR RediHaler prescribing information. Teva Respiratory, LLC. Frazer, PA. August 2017.
- Raphael GD, Lanier RQ, Baker J, et al. A comparison of multiple doses of fluticasone propionate and beclomethasone dipropionate in subjects with persistent asthma. J Allergy Clin Immunol. 1999;103(5):796-803.
- Raphael G, Yiu G, Sakov A, et al. Randomized, double-blind trial evaluating the efficacy and safety of fluticasone propionate and fluticasone propionate/salmeterol delivered via multidose dry powder inhalers in patients with persistent asthma aged 12 years and older. J Asthma. 2017;Aug 1:1-11.
- Rowe BH, Bota GW, Fabris L, et al. Inhaled budesonide in addition to oral corticosteroids to prevent asthma relapse following discharge from the emergency department. JAMA. 1999;281(22):2119-26.
- Sheffer AL, Silverman M, Woolcock AJ, et al. Long-term safety of once-daily budesonide in patients with early-onset mild persistent asthma: results of the inhaled steroid treatment as regular therapy in early asthma (START) study. Ann Allergy Asthma Immunol. 2005;94(1):48-54.
- Sher LD, Yiu G, Sakov A, et al. Fluticasone propionate and fluticasone propionate/salmeterol multidose dry powder inhalers compared with placebo for persistent asthma. Allergy Asthma Proc. 2017;38(5):343-353.
- Sorkness CA, Lemanske RF Jr, Mauger DT, et al. Long-term comparison of three controller regimens for mild-moderate persistent childhood asthma: the pediatric asthma controller trial. J Allergy Clin Immunol. 2007 Jan;119(1):64-72.
- Spiriva Respimat prescribing information. Boehringer Ingelheim. Ridgefield, CT. February 2017.
- Szefler SJ, Phillips BR, Martinez FD, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. J Allergy Clin Immunol. 2005 Feb;115(2):233-42.
- Vandewalker M, Hickey L, Small CJ. Efficacy and safety of beclomethasone dipropionate breath-actuated or metered-dose inhaler in pediatric patients with asthma. Allergy Asthma Proc. 2017;38(5):354-364. doi: 10.2500/aap.2017.38.4078.
- von Berg A, Engelstätter R, Minic P, et al. Comparison of the efficacy and safety of ciclesonide 160 µg once daily vs budesonide 400 µg once daily in children with asthma. Pediatr Allergy Immunol. 2007;18:391-400.
- Wardlaw A, Larivee P, Eller J, et al. Efficacy and safety of mometasone furoate dry powder inhaler vs fluticasone propionate metered-dose inhaler in asthma subjects previously using fluticasone propionate. Ann Allergy Asthma Immunol. 2004;93:49-55.
- Yang D, Wang J, Bunjhoo H, et al. Comparison of the efficacy and safety of mometasone furoate to other inhaled steroids for asthma: a meta-analysis. Asian Pac J Allergy Immunol. 2012;31:26-35.
- Zeiger RS, Szefler SJ, Phillips BR, et al. Response profiles to fluticasone and montelukast in mild-to-moderate persistent childhood asthma. J Allergy Clin Immunol. 2006 Jan;117(1):45-52.

Publication Date: December 14, 2017

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.

REFERENCES

- Aalbers R, Backer V, Kava TT, et al. Adjustable maintenance dosing with budesonide/formoterol compared to fixed-dose salmeterol/fluticasone in moderate to severe asthma. Curr Med Res Opin. 2004;20(2):225-40.
- Aaron SD, Vandemheen KL, Fergusson D, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med. 2007;146(8):545-55.
- ADVAIR DISKUS prescribing information. GlaxoSmithKline. Research Triangle Park, NC. December 2017.
- ADVAIR HFA prescribing information. GlaxoSmithKline. Research Triangle Park, NC. December 2017.
- Agusti A, de Teresa L, De Backer W, et al. A comparison of the efficacy and safety of once-daily fluticasone furoate/vilanterol with twice-daily fluticasone propionate/salmeterol in moderate to very severe COPD. Eur Respir J. 2014;43(3):763-72.
- AIRDUO RESPICLICK prescribing information. Teva Respiratory, LLC. Frazer, PA. December 2017.
- ANORO ELLIPTA prescribing information. GlaxoSmithKline. Research Triangle Park, NC. October 2017.

- Bateman ED, Boushey HA, Bousquet J, et al. Can guideline-defined asthma control be achieved? The gaining optimal asthma control study. Am J Respir Crit Care Med. 2004;170(8):836-44.
- Bateman ED, Jacques L, Goldfrad C, et al. Asthma control can be maintained when fluticasone/salmeterol in a single inhaler is stepped down. J Allergy Clin Immunol. 2006;117(3):563-70.
- Bateman ED, O'Byrne PM, Busse WW, et al. Once-daily fluticasone furoate (FF)/vilanterol reduces risk of severe exacerbations in asthma versus FF alone. Thorax. 2014;69:312-19.
- Bateman ED, Silins V, Bogolubov M. Clinical equivalence of salmeterol/fluticasone propionate in combination (50/100 microg twice daily) when administered via a chlorofluorocarbon-free metered dose inhaler or dry powder inhaler to patients with mild-to-moderate asthma. Respir Med. 2001;95:136-46.
- Beeh KM, Derom E, Echave-Sustaeta J, et al. The lung function profile of once-daily tiotropium and olodaterol via Respimat is superior to that of twice-daily salmeterol and fluticasone propionate via Accuhaler (ENERGITO study). Int J Chron Obstruct Pulmon Dis. 2016;11:193-205.
- Beeh KM, Westerman J, Kirsten AM, et al. The 24-h lung-function profile of once-daily tiotropium and olodaterol fixed-dose combination in chronic obstructive pulmonary disease. Pulm Pharmacol Ther. 2015; 32:53-9.
- Berger WE, Bleecker ER, O'Dowd L, et al. Efficacy and safety of budesonide/formoterol pressurized metered-dose inhaler: randomized controlled trial comparing once- and twice-daily dosing in patients with asthma. Allergy Asthma Proc. 2010;31:49-59.
- Bernstein DI, Bateman ED, Woodcock A, et al. Fluticasone furoate (FF)/vilanterol (100/25 mcg or 200/25 mcg) or FF (100 mcg) in persistent asthma. J Asthma. 2015;52(10):1073-83.
- Bernstein DI, Hebert J, Cheema A, et al. Efficacy and Onset of Action of Mometasone Furoate/Formoterol and Fluticasone Propionate/Salmeterol Combination Treatment in Subjects With Persistent Asthma. Allergy Asthma Clin Immunol. 2011;7(1):21.
- BEVESPI AEROSPHERE prescribing information. AstraZeneca. Wilmington, DE. April 2016.
- Bleecker ER, Lötvall J, O'Byrne PM, et al. Fluticasone furoate-vilanterol 100-25 mcg compared with fluticasone furoate 100 mcg in asthma: a randomized trial. J Allergy Clin Immunol Pract. 2014;2:553-61.
- Bone R, Boyars M, Braun S, et al. In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone an 85-day multicenter trial. Chest. 1994;105:1411-9.
- BREO ELLIPTA prescribing information. GlaxoSmithKline. Research Triangle Park, NC. December 2017.
- Buhl R, Maltais F, Abrahams R, et al. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2-4). Eur Respir J. 2015;45:869-71.
- Busse WW, Shah SR, Somerville L, et al. Comparison of adjustable- and fixed-dose budesonide/ formoterol pressurized metered-dose inhaler and fixed-dose fluticasone propionate/salmeterol dry powder inhaler in asthma patients. J Allergy Clin Immuno. 2008;121:1407-14.
- Calverley PMA ,Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007;356(8):775-89.
- Calverley P, Pauwels R, Vestbo J, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomized controlled trial. Lancet. 2003;361:449-56.
- Centers for Disease Control and Prevention. Chronic obstructive pulmonary disease (COPD). Updated August 24, 2017. Available at: https://www.cdc.gov/copd/index.html. Accessed December 28, 2017.
- Chapman KR, Ringdal N, Backer V, et al. Salmeterol and fluticasone propionate (50/250 microg) administered via combination Diskus inhaler: as effective as when given via separate Diskus inhalers. Can Respir J. 1999;6:45-51.
- COMBIVENT RESPIMAT prescribing information. Boehringer Ingelheim. Ridgefield, CT. June 2016.
- Corren J, Korenblat PE, Miller CJ, et al. Twelve-week, randomized, placebo-controlled, multicenter study of the efficacy and tolerability of budesonide and formoterol in one metered-dose inhaler compared to budesonide alone and formoterol alone in adolescents and adults with asthma. Clin Ther. 2007;29(5):823-43.
- Covelli H, Pek B, Schenkenberger I, et al. Efficacy and safety of fluticasone furoate/vilanterol or tiotropium in subjects with COPD at cardiovascular risk. Int J Chron Obstruct Pulmon Dis. 2015;11:1-12.
- Criner GJ, Bourbeau J, Diekemper RL, et al. Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society Guideline. Chest. 2015;147(4):894-942.
- Dahl R, Chuchalin A, Gor D, et al. EXCEL: a randomized trial comparing salmeterol/fluticasone propionate and formoterol/budesonide combinations in adults with persistent asthma. Resp Med. 2006; 100:1152-62.
- Decramer M, Anzueto A, Kerwin E, et al. Efficacy and safety of umeclidinium plus vilanterol versus tiotropium, vilanterol, or umeclidinium monotherapies over 24 weeks in patients with chronic obstructive pulmonary disease: results from two multicentre, blinded, randomised controlled trials. Lancet Respir Med. 2014;2:472-86.
- Donohue JF, Maleki-Yazdi MR, Kilbride S, et al. Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. Respir Med. 2013;107:1538-46.
- Donohue JF, Worsley S, Zhu CQ, et al. Improvements in lung function with umeclidinium/vilanterol versus fluticasone propionate/salmeterol in patients with moderate-to-severe COPD and infrequent exacerbations. Respir Med. 2015;109:870-881.
- Dorinsky PM, Reisner C, Ferguson G, et al. The combination of ipratropium and albuterol optimizes pulmonary function reversibility testing in patients with COPD. Chest. 1999;115:966-71.
- Dransfield MT, Bourbeau J, Jones PW, et al. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. Lancet Respir Med. 2013;1:210-23.

- Dransfield MT, Feldman G, Korenblat P, et al. Efficacy and safety of once-daily fluticasone furoate/vilanterol (100/25 mcg) versus twice-daily fluticasone propionate/salmeterol (250/50 mcg) in COPD patients. Respir Med. 2014;108:1171-79.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed December 28, 2017.
- DULERA prescribing information. Merck Sharp & Dohme. Whitehouse Station, NJ. December 2017.
- DUONEB prescribing information. Dey Pharma, L.P. Napa, CA. June 2012.
- Dwan K, Milan SJ, Bax L, et al. Vilanterol and fluticasone furoate for asthma. Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.: CD010758. DOI: 10.1002/14651858.CD010758.pub2.
- Eid NS, Noonan MJ, Chipps B, et al. Once- vs twice-daily budesonide/formoterol in 6- to 15-year old patients with stable asthma. Pediatrics. 2010;126:e565-e75.
- FDA AirDuo RespiClick Medical Review. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208799Orig1s000TOC.cfm. Accessed December 28, 2017.
- FDA. FDA drug safety communication: FDA review finds no significant increase in risk of serious asthma outcomes with long-acting beta agonists (LABAs) used in combination with inhaled corticosteroids (ICS). https://www.fda.gov/Drugs/DrugSafety/ucm589587.htm?utm_campaign=New%20FDA%20Drug%20Safety%20Communication%20update%20on%20long-acting%20beta%20agonists%20%28LABAs%29&utm_medium=email&utm_source=Eloqua. December 20, 2017. Accessed December 27, 2017.
- FitzGerald MJ, Boulet LP, Follows RM. The CONCEPT trial: A 1-year, multicenter, randomized, double-blind, double-dummy comparison of a stable dosing regimen of salmeterol/fluticasone propionate with an adjustable maintenance dosing regimen of formoterol/budesonide in adults with persistent asthma. Clin Ther. 2005;27(4):393-406.
- Friedman M, Serby CW, Menjoge SS, et al. Pharmacoeconomic evaluation of a combination of ipratropium plus albuterol compared with ipratropium alone and albuterol alone in COPD. Chest. 1999;115:635-41.
- Gappa M, Zachgo W, von Berg A, et al. Add-on salmeterol compared to double dose fluticasone in pediatric asthma: a double-blind, randomized trial (VIAPAED). Pediatr Pulmonol. 2009;44:1132-42.
- GlaxoSmithKline. GSK and Innoviva report positive headline results from IMPACT study showing single inhaler triple therapy Trelegy Ellipta reduced COPD exacerbations (press release). http://www.gsk.com/en-gb/media/press-releases/gsk-and-innoviva-report-positive-headline-results-from-impact-study-showing-single-inhaler-triple-therapy-trelegy-ellipta-reduced-copd-exacerbations/. September 20, 2017. Accessed December 27, 2017.
- Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention 2017. Available from: ginasthma.org. Accessed December 28, 2017.
- Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2018 report. Revised 2017. Available at: http://goldcopd.org/. Accessed December 28, 2017.
- Hanania NA, Crater GD, Morris AN, et al. Benefits of adding fluticasone propionate/salmeterol to tiotropium in moderate to severe COPD. Respir Med. 2012;106:91-101.
- Hanania NA, Darken P, Horstman D, et al. The efficacy and safety of fluticasone propionate (250 microg)/salmeterol (50 microg) combined in the discus inhaler for the treatment of COPD. Chest. 2003;124(3):834-43.
- Hanania NA, Tashkin DP, Kerwin EM, et al. Long-term safety and efficacy of glycopyrrolate/formoterol metered dose inhaler using novel co-suspension delivery technology in patients with chronic obstructive pulmonary disease. Respir Med. 2017;126:1050115.
- Huisman EL, Cockle SM, Ismaila AS, et al. Comparative efficacy of combination bronchodilator therapies in COPD: a network meta-analysis. Int J Chron Obstruct Pulm Dis. 2015;10:1863-81.
- Jenkins C, Kolarikova R, Kuna P, et al. Efficacy and safety of high-dose budesonide/formoterol (Symbicort) compared to budesonide administered either concomitantly with formoterol or alone in patients with persistent symptomatic asthma. Respirology. 2006;11:276-86.
- Kalberg C, O'Dell D, Galkin D, et al. Dual bronchodilator therapy with umeclidinium/vilanterol versus tiotropium plus indacaterol in chronic obstructive pulmonary disease: a randomized controlled trial. Drug R D. 2016;16:217-27.
- Karner C, Cates CJ. Combination inhaled steroid and long-acting beta$_2$-agonist in addition to tiotropium versus tiotropium or combination alone for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews. 2011; Issue 3. Art. No.: CD008532. DOI: 0.1002/14651858.CD008532.pub2.
- Kerwin EM, Kalberg CJ, Galkin DV, et al. Umeclidinium/vilanterol as step-up therapy from tiotropium in patients with moderate COPD: a randomized, parallel-group, 12-week study. Int J Chron Obstruct Pulmon Dis. 2017;12:745-755.
- Kerwin EM, Oppenheimer JJ, LaForce C, et al. Efficacy and tolerability of once-daily budesonide/formoterol pressurized metered-dose inhaler in adults and adolescents with asthma previously stable with twice-daily budesonide/formoterol dosing. Ann Allergy Asthma Immunol. 2009;103:62-72.
- Kerwin EM, Scott-Wilson C, Sanford L, et al. A randomized trial of fluticasone furoate/vilanterol (50/25 µg; 100/25 µg) on lung function in COPD. Respir Med. 2013;107:560-69.
- Kuna P, Creemers JPHM, Vondra V, et al. Once-daily dosing with budesonide/formoterol compared to twice-daily budesonide/formoterol and once-daily budesonide in adults with mild to moderate asthma. Respir Med. 2006;100(12):2151-9.
- Lalloo U, Malolepszy J, Kozma D, et al. Budesonide and formoterol in a single inhaler improves asthma control compared to increasing the dose of corticosteroid in adults with mild-to-moderate asthma. Chest. 2003;123:1480-7.
- Lasserson TJ, Ferrara G, Casali L. Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children. Cochrane Database of Systematic Reviews 2011, Issue 12. Art. No.: CD004106. DOI: 10.1002/14651858.CD004106.pub4.

- Lee SD, Xie CM, Yunus F, et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium compared with tiotropium alone in patients with severe or very severe COPD: a randomized, multicentre study in East Asia. Respirology. 2016; 21(1):119-127.
- Lipson DA, Barnacle H, Birk R, et al. FULFIL trial: once-daily triple therapy for patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2017;196(4):438-446.
- Lundback B, Ronmark E, Lindberg A, et al. Control of mild to moderate asthma over 1-year with the combination of salmeterol and fluticasone propionate. Respir Med. 2006;100:2-10.
- Mahler DA, Kerwin E, Ayers T, et al. FLIGHT1 and FLIGHT2: Efficacy and safety of QVA149 (indacaterol/glycopyrrolate) versus its monocomponents and placebo in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2015;192(9):1068-79.
- Marceau C, Lemiere C, Berbiche D, et al. Persistence, adherence, and effectiveness of combination therapy among adult patients with asthma. J Allergy Clin Immunol. 2006;118:574-81.
- Martinez FJ, Boscia J, Feldman G, et al. Fluticasone furoate/vilanterol (100/25; 200/25 µg) improves lung function in COPD: a randomized trial. Respir Med. 2013;107:550-9.
- Martinez FJ, Rabe KF, Ferguson GR, et al. Efficacy and safety of glycopyrrolate/formoterol MDI formulated using co-suspension delivery technology in patients with COPD. Chest. 2017;151(2):340-57.
- Matera MG, Rogliani P, Calzetta L, et al. Safety considerations with dual bronchodilator therapy in COPD: an update. Drug Saf. 2016;39(6):501-8.
- Meltzer EO, Kuna P, Nolte H, et al., on behalf of the P04073 Study Investigators. Mometasone furoate/formoterol reduces asthma deteriorations and improves lung function. Eur Respir J. 2012;39:279-89.
- Morice AH, Peterson S, Beckman O, Osmanliev D. Therapeutic comparison of a new budesonide/formoterol pMDI with budesonide pMDI and budesonide/formoterol DPI in asthma. Int J Clin Pract. 2007;61(11):1874-83.
- Murphy K, Nelson H, Parasuraman B, et al. The effect of budesonide and formoterol in one pressurized metered-dose inhaler on patient-reported outcomes in adults with mild-to-moderate persistent asthma. Curr Med Res Opin. 2008;24(3):879-94.
- Nannini LJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta$_2$-agonist in one inhaler versus long-acting beta$_2$-agonists for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews. 2012; Issue 9. Art. No.: CD006829. DOI: 10.1002/14651858.CD006829.pub 2.
- Nannini LJ, Poole P, Milan SJ, et al. Combined corticosteroid and long-acting beta2-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2013, Issue 11. Art. No.: CD003794. DOI: 10.1002/14651858.CD003794.pub4.
- Nathan RA, Rooklin A, Schoaf L, et al. Efficacy and tolerability of fluticasone/salmeterol administered twice daily via hydrofluoroalkane 134a metered-dose inhaler in adolescents and adult patients with persistent asthma: a randomized, double blind, placebo-controlled, 12-week study. Clin Ther. 2006;28:73-85.
- National Heart, Lung, and Blood Institute. Asthma. Available at: http://www.nhlbi.nih.gov/health/health-topics/topics/asthma. 2017. Accessed December 28, 2017.
- National Heart, Lung, and Blood Institute. Expert Panel Report 3: Guidelines for the diagnosis and management of asthma (guideline on the Internet). NHLBI 2007. Available from http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines. Accessed December 28, 2017.
- Nelson HS, Chapman KR, Pyke SD, et al. Enhanced synergy between fluticasone and salmeterol inhaled from a single inhaler vs separate inhalers. J Allergy Clin Immunol. 2003(b);112:29-36.
- Nelson HS, Wolfe JD, Gross G, et al. Efficacy and safety of fluticasone propionate 44 microg/salmeterol 21 microg administered in a hydrofluoroalkane metered-dose inhaler as an initial asthma maintenance treatment. Ann Allergy Asthma Immunol. 2003(a);91:263-9.
- Noonan M, Rosenwasser LJ, Martin P, et al. Efficacy and safety of budesonide and formoterol in one pressurized metered-dose inhaler in adults and adolescents with moderate to severe asthma. Drugs. 2006;66(17):2235-54.
- O'Byrne PM, Bleecker ER, Bateman ED, et al. Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma. Eur Respir J. 2014;43(3):773-82.
- Ohar JA, Crater GD, Emmett A, et al. Fluticasone propionate/salmeterol 250/50 µg versus salmeterol 50 µg after chronic obstructive pulmonary disease exacerbation. Respir Res. 2014;15:105. DOI:10.1186/s12931-014-0105-2.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2016. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed December 28, 2017.
- Palmqvist M, Arvidsson P, Beckman O, et al. Onset of bronchodilation with budesonide/formoterol and salmeterol/fluticasone in single inhalers. Pulm Pharmacol Ther. 2001;14(1):29-34.
- Partridge MR, Schuermann W, Beckman O, et al. Effect on lung function and morning activities of budesonide/formoterol vs salmeterol/fluticasone in patients with COPD. Ther Adv Respir Dis. 2009;3(4):147-57.
- Pearlman DS, Eckerwall G, McLaren J, et al. Efficacy and safety of budesonide/formoterol pMDI vs budesonide pMDI in asthmatic children (6-<12 years). Ann Allergy Asthma Immunol. 2017;118:489-499.
- Pearlman DS, Peden D, Condemi JJ, et al. Efficacy and safety of fluticasone/salmeterol HFA 134A MDI in patients with mild-moderate persistent asthma. J Asthma. 2004;41:797-806.
- Perrin K, Williams M, Wijesinghe M, et al. Randomized controlled trial of adherence with single or combination inhaled corticosteroid/long-acting β-agonist inhaler therapy in asthma. J Allergy Clin Immunol. 2010;126:505-10.
- Peters SP, Bleecker ER, Canonica GW, et al. Serious asthma events with budesonide plus formoterol vs. budesonide alone. N Engl J Med. 2016;375:850-60.

- Pohl WR, Vetter N, Zwick H, et al. Adjustable maintenance dosing with budesonide/formoterol or budesonide: double blind study. Respir Med. 2006;100(3):551-60.
- Price D, Østrem A, Thomas M, Welte T. Dual bronchodilation in COPD: lung function and patient-reported outcomes – a review. Int J Chron Obstruct Pulmon Dis. 2016;12:141-168.
- Price DB, Williams AE, Yoxall S. Salmeterol/fluticasone stable-dose treatment compared to formoterol-budesonide adjustable maintenance dosing: impact on health-related quality of life. Respir Res. 2007;8:46.
- Raphael G, Yiu G, Sakov A, et al. Fluticasone propionate and fluticasone propionate/salmeterol delivered via multidose dry powder inhalers for persistent asthma [abstract no. P142]. Ann Allergy Asthma Immunol. 2016; 5(117):S63.
- Raphael G, Yiu G, Sakov A, et al. Patient-reported outcomes and quality of life improved with fluticasone propionate and fluticasone propionate/salmeterol multidose dry powder inhalers versus placebo in patients with persistent asthma [abstract no. 31]. Abstract presented at AAAAI Annual Meeting; March 3-6, 2017; Atlanta, Georgia.
- Rennard SI, Tashkin DP, McElhattan J, et al. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. Drugs. 2009;69(5):549-65.
- Rodrigo GJ, Neffen H. A systematic review with meta-analysis of fluticasone furoate/vilanterol combination for the treatment of stable COPD. Pulm Pharmacol Ther. 2017;42:1-6.
- Rodrigo GJ, Plaza V, et al. Once-daily fluticasone furoate and vilanterol for adolescents and adults with symptomatic asthma: a systematic review and meta-analysis. Ann Allergy Asthma Immunol. 2016;116:565-70.
- Rosenhall L, Heinig JH, Lindqvist A, et al. Budesonide/formoterol (Symbicort) is well tolerated and effective in patients with moderate persistent asthma. Int J Clin Pract. 2002;56(6):427-33.
- Schlueter M, Gonzalez-Rojas N, Baldwin M, et al. Comparative efficacy of fixed-dose combinations of long-acting muscarinic antagonists and long-acting β2-agonists: a systematic review and network meta-analysis. Ther Adv Respir Dis. 2016;10(2):89-104.
- Sharafkhaneh A, Southard JG, Goldman M, Uryniak T, Ubaldo JM. Effect of budesonide/formoterol pMDI on COPD exacerbations: a double-blind, randomized study. Respir Med. 2012;106:257-68.
- Sher L, Yiu G, Sakov A, et al. Fluticasone propionate and fluticasone/salmeterol multidose dry powder inhalers compared with placebo for persistent asthma [abstract no. P139]. Ann Allergy Asthma Immunol. 2016; 5(117):S61-2.
- Sher L, Yiu G, Sakov A, et al. Treatment of asthmatic patients with fluticasone propionate and fluticasone propionate/salmeterol multidose dry powder inhalers compared with placebo: patient-reported outcomes and quality of life [abstract no. 306]. Abstract presented at AAAAI Annual Meeting; March 3-6, 2017; Atlanta, Georgia.
- Siler TM, Kerwin E, Sousa AR, et al. Efficacy and safety of umeclidinium added to fluticasone furoate/vilanterol in chronic obstructive pulmonary disease: results of two randomized studies. Respir Med. 2015;109(9):1155-63.
- Singh D, Worsley S, Zhu CQ, et al. Umecledinium/vilanterol versus fluticasone propionate/salmeterol in COPD: a randomised trial. BMC Pulm Med. 2015;15:91.
- Stempel DA, Raphiou IH, Kral KM, et al. Serious adverse events with fluticasone plus salmeterol versus fluticasone alone. N Engl J Med. 2016(a);374:1822-30.
- Stempel DA, Szefler SJ, Pedersen S, et al. Safety of adding salmeterol to fluticasone propionate in children with asthma. N Engl J Med. 2016(b);375:840-9.
- STIOLTO Respimat prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. June 2016.
- SYMBICORT prescribing information. AstraZeneca. Wilmington, DE. December 2017.
- Tal A, Simon G, Vermeulen, JH, et al. Budesonide/formoterol in a single inhaler vs inhaled corticosteroids alone in the treatment of asthma. Pediatr Pulmonol. 2002;34:342-50.
- Tashkin DP, Rennard SI, Martin P, et al. Efficacy and safety of budesonide and formoterol in one pressurized metered-dose inhaler in patients with moderate to very severe chronic obstructive pulmonary disease: results of a 6-month randomized clinical trial. Drugs. 2008;68(14):1975-2000.
- TRELEGY ELLIPTA prescribing information. GlaxoSmithKline. Research Triangle Park, NC. September 2017.
- UTIBRON NEOHALER Inhalation Powder prescribing information. Novartis. East Hanover, NJ. January 2017.
- Vaessen-Verberne AAPH, van den Berg NJ, van Nierop JC, et al. Combination therapy salmeterol/fluticasone vs doubling dose of fluticasone in children with asthma. Am J Respir Crit Care Med. 2010;182:1221-7.
- Vestbo J, Anderson JA, Brook RD, et al. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. Lancet. 2016(a);387:1817-26.
- Vestbo J, Leather D, Bakerly ND, et al. Effectiveness of fluticasone furoate-vilanterol for COPD in clinical practice. N Engl J Med. 2016(b);375:1253-60.
- Vestbo J, Pauwels R, Anderson J, et al. Early onset of effect of salmeterol and fluticasone propionate in chronic obstructive pulmonary disease. Thorax. 2005;60:301-4.
- Vogelmeier CF, Bateman ED, Pallante J, et al. Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol-fluticasone in patients with chronic obstructive pulmonary disease (ILLUMINATE): a randomised, double-blind, parallel group study. Lancet Respir Med. 2013;1:51-60.
- Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. N Engl J Med. 2016;374(23):2222-34.
- Wedzicha JA, Calverley PMA, Seemungal TA, et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med. 2008;177:19-26.

- Weinstein SF, Corren J, Murphy K, et al. Twelve–week efficacy and safety study of mometasone furoate/formoterol 200/10 microg and 400/10 microg combination treatments in patients with persistent asthma previously receiving high-dose inhaled corticosteroids. Allergy Asthma Proc. 2010;31:280-9.
- Welte T, Miravitlles M, Hernandez P, et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009;180:741-50.
- Woodcock A, Bleecker ER, Lötvall J, et al. Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: a randomized trial. Chest. 2013;144(4):1222-9.

Publication Date: January 4, 2018

Therapeutic Class Overview
Omega-3 Fatty Acids

INTRODUCTION

- The independent relationship of triglycerides (TGs) to the risk of future cardiovascular disease (CVD) events has long been controversial (Miller et al, 2011).
- Rich sources of omega-3-fatty acids come from fatty fish and plant sources, and fish oil has eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).
    - When administered at high doses, they can reduce levels of TGs by approximately 50% (National Cholesterol Education Program [NCEP], 2002; Rosensen, 2013; Tangney, 2013).
    - Select clinical trials suggest that relatively high doses of omega-3-fatty acids, in the form of fish, fish oils or high-linolenic acid oils, will reduce the risk for major coronary events in persons with established coronary heart disease; however, the overall body of literature does not offer convincing evidence that fish oil supplements are beneficial for preventing cardiovascular disease or improving outcomes (NCEP, 2002; Institute for Clinical Systems Improvement, 2017; Smith et al, 2011).
- The scope of this review will focus on LOVAZA®, OMTRYG™ and TRIKLO (omega-3-acid ethyl esters), VASCEPA® (icosapent ethyl), and EPANOVA® (omega-3-carboxylic acids) for their respective Food and Drug administration (FDA)-approved indications, which are outlined in Table 1.
- LOVAZA, OMTRYG and TRIKLO (omega-3-acid ethyl esters), VASCEPA (icosapent ethyl), and EPANOVA (omega-3 carboxylic acids) are FDA-approved prescription omega-3 fatty acids. These products are approved as adjunct therapy to diet to reduce TGs in adults with severe (≥500 mg/dL) hypertriglyceridemia.
    - LOVAZA (omega-3-acid ethyl esters) is available as a 1 gram soft-gelatin capsule, containing approximately 375 mg and 465 mg of DHA and EPA, respectively. TRIKLO is a branded generic product for LOVAZA.
    - VASCEPA (icosapent ethyl) is available as a soft-gelatin capsule, containing ≥95% icosapent ethyl, an esterified formation of EPA (Rosensen, 2013).
    - EPANOVA (omega-3 carboxylic acids) is available as a coated, soft-gelatin capsule, containing at least 850 mg of polyunsaturated fatty acids, including multiple omega-3 fatty acids (predominantly EPA and DHA).
    - OMTRYG (omega-3-acid ethyl esters) is available as a 1.2 gram, transparent, soft-gelatin capsule filled with yellow oil containing 375 mg and 465 mg of DHA and EPA, respectively.
    - Of note, there are several over-the-counter products containing omega-3 fatty acids that are marketed as nutritional supplements. These products do not have FDA-approved indications and may not contain the same amount of the active ingredient (Facts and Comparisons, 2017).
- Omega-3 fatty acids have the potential to be used off-label for the treatment of coronary arteriosclerosis, familial combined hyperlipidemia, heart failure and hyperlipidemia with TG levels < 500 mg/dL (Micromedex, 2017).
- The 2013 American College of Cardiology/American Heart Association (ACC/AHA) Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults focuses more heavily on a patient's overall atherosclerotic cardiovascular disease (ASCVD) risk versus achieving target LDL-C and/or non-HDL-C levels to guide appropriate treatment. The guidelines also state that adherence to lifestyle and to statin therapy should be re-emphasized before considering the addition of a non-statin drug (Stone et al, 2014). Recent ACC/AHA recommendations on non-statin use do not consider the use of omega-3 fatty acids as they did not include therapies for severe hypertriglyceridemia (Lloyd-Jones et al, 2016; Lloyd-Jones et al, 2017).
- The National Lipid Association recommends omega-3 fatty acids, fibric acid derivatives, or niacin as first-line agents for patients with TG levels of 1000 mg/dL or greater. These agents may also be considered for patients with contraindications for, or intolerance to, statin therapy (Jacobson et al, 2015).
- The Endocrine Society Clinical Practice Guidelines state that omega-3 fatty acids, fibrates, and niacin may be considered as monotherapy or in combination with statins in patients with TG levels that are moderate (200 to 999 mg/dL, based on the Endocrine Society criteria) to severe (1,000 to 1999 mg/dL, based on the Endocrine Society criteria) (Berglund et al, 2012).

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
EPANOVA (omega-3-carboxylic acids capsule)	AstraZeneca	05/05/2014	-
LOVAZA (omega-3-acid ethyl esters capsule)	GlaxoSmithKline	11/10/2004	✔
OMTRYG (omega-3-acid ethyl esters Type A capsule)	Trygg Pharma, Inc.	04/23/2014	-*
TRIKLO (omega-3-acid ethyl esters capsule)	Key Therapeutics, LLC	08/08/2017	✔ **
VASCEPA (icosapent ethyl capsule)	Amarin Pharma, Inc.	07/26/2012	-

*OMTRYG was FDA-approved in 2014, but current availability of the product is unclear.
**Branded generic for LOVAZA.
(Drugs@FDA, 2017; Facts and Comparisons, 2017; Clinical Pharmacology, 2017; TRIKLO prescribing information, 2017)

INDICATIONS

Table 2. FDA-Approved Indications

Indication	EPANOVA (omega-3-carboxylic acids)	LOVAZA (omega-3-acid ethyl esters)	TRIKLO (omega-3-acid ethyl esters)	OMTRYG (omega-3-acid ethyl esters)	VASCEPA (icosapent ethyl)
Adjunctive treatment to diet to reduce TG levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia	✔	✔	✔	✔	✔

(Prescribing information: EPANOVA, 2017; LOVAZA, 2015; OMTRYG, 2016; TRIKLO, 2017; VASCEPA, 2017)

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

CLINICAL EFFICACY SUMMARY

- There are currently no head-to-head efficacy trials comparing EPANOVA (omega-3-carboxylic acids), LOVAZA and OMTRYG (omega-3-acid ethyl esters), or VASCEPA (icosapent ethyl). One study compared the effects of an acylglycerol omega-3 formulation, which is often available in non-prescription omega-3 supplements to LOVAZA. In this double-blind trial in patients with TG concentrations of 150 to 500 mg/dL, 120 patients were randomized to 5563 mg acylglycerol omega-3 daily, LOVAZA 4 g daily, or placebo (olive oil). Both omega-3 groups had decreased TG concentrations compared with placebo (P<0.001), but no difference was found between active treatments (28% reduction with acylglycerol omega-3 and 22% with LOVAZA; P=0.785). Unfortunately, patients included in this study had mild to moderate elevations in TG at baseline, and it is unclear if the acylglycerol omega-3 formulation would have similar results in patients with severe hypertriglyceridemia (Hedengran et al, 2015).
- EpanoVa fOr Lowering Very high triglyceridEs (EVOLVE) was a 12-week, double-blind, placebo (olive oil)-controlled, randomized trial that evaluated the safety and lipid-altering efficacy of EPANOVA (omega-3-carboxylic acids) in 399 adult patients with average serum TG concentrations of ≥500 mg/dL but <2,000 mg/dL at screening (one and two weeks before random assignment). Patients were either treatment-naïve for dyslipidemia or using a stable (for at least six weeks before the first qualifying lipid measurement) dosage of a statin, cholesterol absorption inhibitor (CAI), or their combination. They were randomized to one of four treatment groups: placebo (olive oil) (n=99), or EPANOVA 2 g (n=100), 3 g (n=101), or 4 g (n=99). The EPANOVA 3 g group demonstrated a lower TG reduction than the other two active treatment groups. Treatment with EPANOVA 2 g and EPANOVA 4 g compared to placebo led to statistically significant reductions in fasting TG levels (P<0.01 and P<0.001, respectively) and in non-HDL-C levels (P<0.05 and

P<0.01, respectively). However, there was a statistically significant increase in LDL-C levels in both active treatment groups (P<0.001 for both) (Kastelein et al, 2014).

- The ESPRIT trial was a six-week, double-blind, parallel-group trial of 647 diet-stable patients with fasting TG levels ≥200 mg/ dL and <500 mg/dL (treated with a maximally tolerated dose of statin or statin with ezetimibe) and at high risk for CVD who were randomized to receive placebo (olive oil) capsules (n=216), EPANOVA 2 g daily (n=215), or EPANOVA 4 g daily (n=216) to assess the TG and non-HDL-C lowering efficacy of adding EPANOVA to existing statin therapy. Compared to placebo, both EPANOVA 2 g and 4 g treatment groups demonstrated significant reductions in non-HDL-C levels (P<0.05 for both) and TG levels (P<0.001 for both). LDL-C was significantly increased compared to placebo in the EPANOVA 2 g group only (P<0.025) (Maki et al, 2013).
- LOVAZA (omega-3-acid ethyl esters) and VASCEPA (icosapent ethyl) (studied under the investigational name, AMR-101) were consistently associated with decreases in TG levels from baseline compared to placebo in studies of hypertriglyceridemia (Ballantyne et al, 2012; Bays et al, 2011; Bays, Maki et al, 2010; Bays, McKenny et al, 2010; Calabresi et al, 2000; Calabresi et al, 2004; Davidson et al, 2007; Durrington et al, 2001; Eritsland et al, 1996; GISSI-Prevenzione Investigators,1999; Johansen et al,1999; Koh et al, 2012; Macchia et al, 2013; Maki et al, 2008; Maki et al, 2010; McKeone et al,1997; Nilsen et al, 2001; Nordoy et al, 1998; Peters et al, 2012; Pownall et al,1999; Risk and Prevention Study Collaborative Group et al, 2013; Roth et al, 2009; Stalenhoef et al, 2000; Van Dam et al, 2001).
- In select placebo-controlled trials, LOVAZA (omega-3-acid ethyl esters) was associated with an increase in low density lipoprotein cholesterol (LDL-C) levels from baseline compared to placebo (Bays, Maki et al, 2010; Calabresi et al, 2000; Calabresi et al, 2004; Koh et al, 2012; Maki et al, 2010; Pownall et al, 1999; Roth et al, 2009; Stalenhoef et al, 2000).
- LOVAZA (omega-3-acid ethyl esters) was generally associated with an additive decrease in TG and total cholesterol (TC) levels when added to a regimen containing a statin or a fibric acid derivative (Bays, Maki et al, 2010 COMBOS; Bays, McKenny et al, 2010; Davidson et al, 2007; Durrington et al, 2001; Maki et al, 2008; Maki et al, 2010 COMBOS; Nordoy et al, 1998; Peters et al, 2012; Roth et al, 2009).
- When compared in head-to-head trials, LOVAZA (omega-3-acid ethyl esters) was associated with similar decreases in cholesterol parameters from baseline compared to fenofibrate. When compared to gemfibrozil, one randomized controlled trial demonstrated similar cholesterol decreases. However, a second randomized controlled trial demonstrated that this agent was associated with a significantly smaller decrease in TG levels from baseline (–28.9 vs –51.2%, respectively; P=0.007) (Koh et al, 2012; Stalenhoef et al, 2000; Van Dam et al, 2001).
- In placebo-controlled trials, VASCEPA (icosapent ethyl) was not associated with an increase in LDL-C levels from baseline compared to placebo (Ballantyne et al, 2012; Bays et al, 2011).
- Outcomes data with LOVAZA (omega-3-acid ethyl esters) have demonstrated mixed results when evaluating reduction in the risk of cardiovascular events.
    - The GISSI-Prevenzione trial demonstrated the beneficial effects of omega-3 acid ethyl esters in patients who have experienced a recent myocardial infarction (MI); omega-3-acid ethyl esters significantly reduced the risk of death, nonfatal MI, and nonfatal stroke compared to vitamin E. Treatment with omega-3 poly unsaturated fatty acids (PUFA), but not vitamin E, significantly lowered the risk of the composite of death, nonfatal MI, and nonfatal stroke (relative risk [RR], 0.10; 95% confidence interval [CI], 0.01 to 0.18; P=0.048 by 2-way analysis and RR, 0.15; 95% CI, 0.20 to 0.25; P=0.023 by 4-way analysis) (GISSI-Prevenzione Investigators, 1999).
    - A randomized controlled trial comparing LOVAZA (omega-3-acid ethyl esters) to dietary therapy in patients admitted for coronary artery bypass grafting demonstrated a lower incidence of vein graft occlusion rate in the treatment group. After one year of therapy, the vein graft occlusion rate per distal anastomoses was 27% in the group receiving LOVAZA (omega-3-acid ethyl esters) compared to 33% in the control group (odds ratio [OR], 0.77; 95% CI, 0.60 to 0.99; P=0.034) (Eritsland et al, 1996).
    - A randomized controlled trial comparing LOVAZA (omega-3-acid ethyl esters) to placebo in patients who were scheduled for elective coronary angioplasty demonstrated no difference in the rate of restenosis. This event occurred in 40.6% of the treated stenoses in the LOVAZA (omega-3-acid ethyl esters) group and in 35.4% of the treated stenoses in the placebo group (OR, 1.25; 95% CI, 0.87 to 1.80; P=0.21) (Johansen et al, 1999).
    - A randomized, controlled trial comparing LOVAZA (omega-3-acid ethyl esters) to placebo in patients with an acute MI demonstrated no difference in the rate of cardiovascular events and revascularizations. Of the patients receiving LOVAZA (omega-3-acid ethyl esters), 28% experienced at least one cardiac event compared to 24% of patients in the placebo group (P=0.74). There was no significant difference between the groups with regards to the number, type, or severity of cardiac events (Nilsen et al, 2001).

- The Risk and Prevention Study compared LOVAZA (omega-3-acid ethyl esters) to placebo in patients evaluated to be at a high cardiovascular risk and demonstrated no difference in the rate of death, nonfatal MI, and nonfatal stroke. The primary end point occurred in 1,478 of 12,505 patients included in the analysis (11.8%), of whom 733 of 6,239 (11.7%) had received omega-3 PUFA and 745 of 6,266 (11.9%) had received placebo (hazard ratio [HR], 0.97; 95% CI, 0.88 to 1.08; P=0.58) (Risk and Prevention Study Collaborative Group et al, 2013).
- A randomized controlled trial comparing LOVAZA (omega-3-acid ethyl esters) to placebo in patients with confirmed symptomatic paroxysmal atrial fibrillation (AF) that required cardioversion, who had at least two episodes of AF in the six months before randomization, or both, demonstrated no significant difference in the rate of recurrence of symptomatic AF. At 12 months, 56 of 297 participants (18.9%) in the placebo group and 69 of 289 participants (24%) in the omega-3 PUFA group had a recurrent symptomatic AF (HR, 1.28; 95% CI, 0.90 to 1.83; P=0.17) (Macchia et al, 2013).

- There are no published trials evaluating VASCEPA (icosapent ethyl) as an adjunctive therapy to treat hypercholesterolemia or evaluating the cardiovascular outcomes with this agent. However, a formulation of icosapent ethyl has been marketed in Japan since 1994 under the trade name EPADEL® (ethyl-eicosapentaenoic acid, the active metabolite of icosapent ethyl). Published studies have evaluated this formulation as an adjunctive therapy with estriol and statins and the cardiovascular outcomes of this agent.
  - In a prospective observational, 48-week trial, EPADEL (ethyl-eicosapentaenoic acid) 1,800 mg daily added to estriol 2 mg daily was compared to estriol 2 mg daily alone. TC decreased significantly from baseline in both groups. Serum levels of TGs decreased significantly from 194.5 to 141.5 mg/dL (-27. 2%; P=0.001) in the study group but increased slightly from 192.9 to 207.4 mg/dL (+7.5%) in the control group at week 48 in the women whose level of TGs was not <150 mg/dL (Kurabayashi et al, 2000).
  - In an open-label trial, 900 to 1,800 mg/day of EPADEL (ethyl-eicosapentaenoic acid) was administered to patients with hyperlipidemia who had been treated with statins for an average of 30 months. Serum TC and TG concentrations were significantly decreased three months after the administration of EPADEL (ethyl-eicosapentaenoic acid) (from 5.63 to 5.02 mmol/L, P<0.05; from 2.07 to 1.08 mmol/L; P<0.01, respectively) (Nakamura et al, 1999).
  - In the Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS), a prospective, open label, blinded endpoint trial, 18,645 patients were randomly assigned to receive either 1,800 mg of EPADEL (ethyl-eicosapentaenoic acid) daily with a statin or statin therapy alone. The primary endpoint was any major coronary event, including sudden cardiac death, fatal and non-fatal MI, and other non-fatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting. At mean follow-up of 4.6 years, the primary endpoint occurred less frequently in the EPADEL (ethyl-eicosapentaenoic acid) group compared to the control group (262 [2.8%] vs. 324 [3.5%], respectively; RR=0.19; P=0.011) (Yokoyama et al, 2007).
  - Seven sub-analyses have been published of the JELIS study.
    - The reduction in cardiovascular risk was greater in the EPADEL (ethyl-eicosapentaenoic acid) group compared to the control group in patients unable to attain LDL-C and/or high density lipoprotein cholesterol (HDL-C) goals (-38% reduced risk; P=0.007), those with peripheral artery disease (HR, 0.44, 95% CI, 0.19 to 0.97; P=0.041), those with preexisting coronary artery disease (CAD) and a TC ≥250 mg/dL (8.7% vs. 10.7%, respectively; HR, 0.77, 95% CI, 0.63 to 0.96; P=0.017) and regardless of the number of cardiovascular risk factors (hypercholesterolemia, obesity, high TG or low HDL-C, diabetes, and hypertension) (P<0.05 for all comparisons) (Ishikawa et al, 2010; Matsuzaki et al, 2009; Saito et al, 2008, Sasaki et al, 2012).
    - The use of EPADEL (ethyl-eicosapentaenoic acid) was associated with a significantly greater decrease in CAD compared to the control group in patients with impaired glucose metabolism, but not normoglycemic patients (P=0.048 and P=0.062, respectively) (Oikawa et al, 2009).
    - Adherence to ≥80% of the medication regimen was associated with a decreased incidence of cardiovascular endpoints compared to those exhibiting <80% adherence to study medications (P=0.041) (Origasa et al, 2010).
    - The incidence of secondary stroke was lower in the EPADEL (ethyl-eicosapentaenoic acid) group compared to the control group (6.8 vs 10.5%, respectively; HR, 0.80; 95% CI, 0.64 to 0.997; P=0.047); however, there was no difference between groups in the incidence of primary stroke (1.5 vs 1.3%, respectively; HR, 1.08; 95% CI, 0.95 to 1.22; P=0.244) (Tanaka et al, 2008).

- The authors of a Cochrane systematic review that examined the effects of omega-3 fatty acids on the prevention and treatment of CVD concluded that it is unclear whether dietary or supplemental omega-3 fats reduce or increase total mortality or combined cardiovascular events in people with, or at risk of, CVD or in the general population (Hooper et al, 2004).
- The 2013 ACC/AHA guidelines emphasize adherence to lifestyle and to statin therapy before considering the addition of a nonstatin drug (Stone et al, 2013). Other guidelines suggest a potential role for other lipid-lowering therapies when treating hypertriglyceridemia including fibric acid derivatives, niacin, and omega-3 fatty acids (Jellinger et al, 2012; Jacobson et al, 2015).

SAFETY SUMMARY

- Omega-3 fatty acids have precautions for use in patients with hepatic impairment and fish allergy. LOVAZA, TRIKLO, OMTRYG (omega-3 acid ethyl esters) and EPANOVA (omega-3-carboxylic acids) may be associated with increases in LDL-C. Additionally, LOVAZA, TRIKLO, and OMTRYG have a possible association with atrial fibrillation or flutter.
- The most common adverse reactions associated with LOVAZA, TRIKLO, and OMTRYG (incidence >3% and greater than placebo) were eructation, dyspepsia, and taste perversion.
- The most common adverse reactions with EPANOVA (incidence ≥ 3% and greater than placebo) were eructation, nausea, diarrhea, and abdominal pain. Additional adverse reactions include vomiting, flatulence, and taste perversion.
- The most common adverse reaction associated with VASCEPA (incidence >2% and greater than placebo) was arthralgia.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
EPANOVA (omega-3-carboxylic acids)	Coated soft gelatin capsule: 1 g	Adjunct to diet to reduce TG levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia: 2 g or 4 g once daily depending on individual patient response and tolerability	Assess TG levels carefully before initiating therapy. Identify other causes (e.g., diabetes mellitus, hypothyroidism, or medications) of high TG levels and manage as appropriate. Patients should be placed on an appropriate lipid-lowering diet prior to receiving treatment and should continue diet during therapy.	In clinical trials, this agent was administered without regard to meals. Swallow capsules whole. Do not break open, crush, dissolve, or chew. Gelatin source: porcine
LOVAZA and TRIKLO (omega-3-acid ethyl esters)	Soft-gelatin capsule: 1 g	Adjunct to diet to reduce TG levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia: 4 g/day administered once daily or in two divided doses	Assess TG levels carefully before initiating therapy. Identify other causes (e.g., diabetes mellitus, hypothyroidism, or medications) of high TG levels and manage as appropriate. Patients should be placed on an appropriate lipid-lowering diet prior to receiving treatment and should continue diet during therapy.	In clinical trials, this agent was administered with meals. Swallow capsules whole. Do not break open, crush, dissolve, or chew.
OMTRYG (omega-3-acid ethyl esters)	Soft-gelatin capsule: 1.2 g (containing	Adjunct to diet to reduce TG levels in adult patients with severe	Assess TG levels carefully before initiating therapy. Identify other causes (e.g.,	Should be administered with food.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	≥900 mg ethyl esters of omega-3 fatty acids)	(≥500 mg/dL) hypertriglyceridemia: 4 capsules/day administered once daily or in two divided doses	diabetes mellitus, hypothyroidism, or medications) of high TG levels and manage as appropriate. Patients should be placed on an appropriate lipid-lowering diet prior to receiving treatment and should continue diet during therapy.	Swallow capsules whole. Do not break open, crush, dissolve, or chew.
VASCEPA (icosapent ethyl)	Soft-gelatin capsule: 0.5 g, 1 g	Adjunct to diet to reduce TG levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia: 4 g/day administered in two divided doses	Assess TG levels carefully before initiating therapy. Identify other causes (e.g., diabetes mellitus, hypothyroidism, or medications) of high TG levels and manage as appropriate. Patients should be placed on an appropriate lipid-lowering diet prior to receiving treatment and should continue diet during therapy.	Should be administered with food. Swallow capsules whole. Do not break open, crush, dissolve, or chew.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
EPANOVA (omega-3-carboxylic acids)	Clinical trials did not include sufficient numbers of patients ≥65 years of age to determine if they have a different response than younger patients. In general, therapy should be initiated at the lower end of the dosing range for elderly patients.	Safety and efficacy have not been established.	Safety and efficacy have not been established.	Safety and efficacy have not been established.	Unclassified† No studies in pregnant women: data insufficient to inform risk. No information regarding presence in human breast milk or effects on breast-fed infants. Limited studies show that omega-3 fatty acids are present in human milk at levels higher than plasma concentrations.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
LOVAZA, TRIKLO, and OMTRYG (omega-3-acid ethyl esters)	The efficacy and safety profile among those ≥60 years of age did not appear to differ from the efficacy and safety profile observed in younger patients.	Safety and efficacy have not been established.	Safety and efficacy have not been established.	Safety and efficacy have not been established.	Pregnancy Category C Caution should be exercised in lactating mothers.
VASCEPA (icosapent ethyl)	No overall differences in safety or effectiveness were observed between subjects ≥65 years of age and younger subjects.	Safety and efficacy have not been established.	Safety and efficacy have not been established.	Safety and efficacy have not been established.	Pregnancy Category C Caution should be exercised in lactating mothers.

*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.
†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.

CONCLUSION

- Prescription omega-3 fatty acids are approved by the FDA for the treatment of severe hypertriglyceridemia. There is a generic formulation of LOVAZA (omega-3-acid ethyl esters) currently available, as well as a branded generic product (TRIKLO).
- In patients with an elevated TG level (≥500 mg/dL), a fibric acid derivative or niacin should be initiated before LDL-C lowering therapy to prevent pancreatitis. Omega-3-acid fatty acids represent an alternative to fibric acid derivatives and niacin for the treatment of hypertriglyceridemia. Select clinical trials suggest that relatively high doses of omega-3-fatty acids, in the form of fish, fish oils or high-linolenic acid oils, will reduce the risk for major coronary events in persons with established coronary heart disease; however, the overall body of literature does not offer convincing evidence that fish oil supplements are beneficial for preventing cardiovascular disease or improving outcomes.
- Clinical trials have demonstrated that prescription omega-3 acid ethyl esters can effectively lower TGs, as well as positively impact other lipid/lipoprotein parameters when used as monotherapy or in combination with fenofibrate or statins.
- In select placebo-controlled trials, both LOVAZA and OMTRYG (omega-3-acid ethyl esters) and EPANOVA (omega-3 carboxylic acids) were associated with an increase in LDL-C levels from baseline compared to placebo.
- In placebo-controlled trials, VASCEPA (icosapent ethyl) was not associated with an increase in LDL-C levels from baseline compared to placebo.
- Select cardiovascular outcomes studies have suggested a decrease in cardiovascular outcomes with LOVAZA (omega-3 acid ethyl esters) and VASCEPA (icosapent ethyl); however, certain trials have demonstrated no benefit compared to a control group.
- EPANOVA (omega-3-carboxylic acids) is the first FDA-approved prescription omega-3 in free fatty acid form, which produces higher bioavailability than esterified forms. Unlike the other prescription omega-3 fatty acids, EPANOVA can be taken without regard to meals. It does have a similar safety profile as the existing available products.
- The 2013 ACC/AHA guidelines emphasize adherence to lifestyle and to statin therapy before considering the addition of a nonstatin drug. When EPA and/or DHA are used to treat severe hypertriglyceridemia, it is reasonable to evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding (Stone et al, 2013).

Table 5. Advantages and Disadvantages of Omega-3 Fatty Acids

Drug	Advantages	Disadvantages
EPANOVA (omega-3-carboxylic acids)	• First FDA-approved prescription omega-3 in free fatty acid form • Can be taken with or without food • Dosing option may be as few as two capsules once daily	• May be associated with an increase in LDL-C levels • The effects of the agent on the risk of pancreatitis or cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia have not been determined.
LOVAZA, TRIKLO, and OMTRYG (omega-3-acid ethyl esters)	• Clinical trials have established that this agent is associated with a decrease in TG levels and select other lipid parameters.	• May be associated with an increase in LDL-C levels • The effects of the agent on the risk of pancreatitis or cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia have not been determined. • The absorption is greater when given with high-fat high-calorie meals. Since many patients with hypertriglyceridemia are advised to stick to a low-fat diet, this could negatively affect absorption.
VASCEPA (icosapent ethyl)	• Clinical trials have established that this agent is associated with a decrease in TG levels and select other lipid parameters. • May not be associated with an increase in LDL-C levels	• The effects of the agent on the risk of pancreatitis or cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia have not been determined.

REFERENCES

- Ballantyne CM, Bays HE, Kastelein JJ, et al. Efficacy and safety of eicosapentaenoic acid ethyl ester (AMR101) therapy in statin-treated patients with persistent high TGs (from the ANCHOR study). Am J Cardiol. 2012 Oct 1;110(7):984-92.
- Bays HE, Ballantyne CM, Kastelein JJ, et al. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the Multi-center, plAcebo-controlled, Randomized, double-blINd, 12-week study with an open-label Extension [MARINE] trial). Am J Cardiol. 2011;108(5):682-90.
- Bays HE, Maki KC, McKenny J, et al. Long-term up to 24-month efficacy and safety of concomitant prescription omega-3-acid ethyl esters and simvastatin in hypertriglyceridemic patients. Curr Med Res Opin. 2010 Apr;26(4):907-15.
- Bays HE, McKenny J, Maki KC, et al. Effects of prescription omega-3-acid ethyl esters on non-high-density lipoprotein cholesterol when coadministered with escalating doses of atorvastatin. Mayo Clin Proc. 2010 Feb;85(2):122-8.
- Berglund L, Brunzell JD, Goldberg AC. Evaluation and treatment of hypertriglyceridemia: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2012;97(9):2969-2989.
- Calabresi L, Donati D, Pazzucconi F, et al. Omacor in familial combined hyperlipidemia: effects on lipids and low density lipoprotein subclasses. Atherosclerosis. 2000;148:387-96.
- Calabresi L, Villa B, Canavesi M, et al. An omega-3 polyunsaturated fatty acid concentrate increases plasma high-density lipoprotein 2 cholesterol and paraoxonase levels in patients with familial combined hyperlipidemia. Metabolism. 2004 Feb;53(2):153-8.
- Clinical Pharmacology [database on the Internet]. Gold Standard, 2017. Available from www.clinicalpharmacology.com. Accessed November 10, 2017.
- Davidson MH, Stein EA, Bays HE, et al. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. Clin Ther. 2007 Jul;29(7):1354-67.
- Durrington PN, Bhatnagar D, Mackness MI, et al. An omega-3 polyunsaturated fatty acid concentrate administered for one year decreased triglycerides in simvastatin treated patients with coronary heart disease and persisting hypertriglyceridemia. Heart. 2001;85:544–548.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available from: http://www.accessdata.fda.gov/scripts/cder/daf/. Accessed November 10, 2017.
- EPANOVA prescribing information. AstraZeneca. Wilmington, DE. March 2017.
- Eritsland L, Arnesen H, Gronseth K, et al. Effect of dietary supplementation with n-3 fatty acids on coronary artery bypass graft patency. Am J Cardiol. 1996;77:31–36.
- Facts & Comparisons eAnswers [database on the Internet]. St. Louis, MO: Wolters Kluwer; 2017. Available from: https://fco.factsandcomparisons.com/. Accessed November 13, 2017.
- GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet. 1999 Aug 7;354(9177):447-55.
- Grundy SM, Cleeman JI, Merz NB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation. 2004; 110:227-39.
- Hedengran A, Szecsi PB, Dyerberg J, Harris WS, Stender S. n-3 PUFA esterified to glycerol or as ethyl esters reduce non-fasting plasma triacylglycerol in subjects with hypertriglyceridemia: a randomized trial. Lipids. 2015;50(2):165-175.
- Hooper L, Harrison RA, Summerbell CD. Omega 3 fatty acids for prevention and treatment of cardiovascular disease. Cochrane Database Syst Rev. 2004;10:CD003177.

- Ishikawa Y, Yokoyama M, Saito Y, et al. Preventive effects of eicosapentaenoic acid on coronary artery disease in patients with peripheral artery disease. Circ J. 2010 Jul;74(7):1451-7.
- Jacobson TA, Ito MK, Maki KC, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1—full report. J Clin Lipidol. 2015;9(2):129-169.
- Jellinger PS, Smith DA, Mehta AE, et al. American Association of Clinical Endocrinologists' Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis. Endocr Pract. 2012 Mar-Apr;18 Suppl 1:1-78.
- Johansen O, Brekke M, Seljeflot I, et al., Coronary Angioplasty Restenosis Trial. n-3 fatty acids do not prevent re stenosis after coronary angioplasty: Results from the CART study. J Am Coll Cardiol. 1999; 33:1619–1626.
- Kastelein JJ, Maki KC, Susekov A, et al. Omega-3 free fatty acids for the treatment of severe hypertriglyceridemia: the EpanoVa fOr Lowering Very high triglyceridEs (EVOLVE) trial. J Clin Lipidol. 2014;8(1):94-106. doi: 10.1016/j.jacl.2013.10.003.
- Koh KK, Quon MJ, Shin KC, et al. Significant differential effects of omega-3 fatty acids and fenofibrate in patients with hypertriglyceridemia. Atherosclerosis. 2012;220:537-44.
- Kurabayashi T, Okada M, Tanaka K. Eicosapentaenoic acid effect on hyperlipidemia in menopausal Japanese women. The Niigata Epadel Study Group. Obstet Gynecol. 2000 Oct;96(4):521-8.
- Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular risk. J Am Coll Cardiol. 2016;68(1):92-125.
- Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol*. 2017 Oct;70(14):1785-1822.
- LOVAZA prescribing information. GlaxoSmithKline, Research Triangle Park, NC. September 2015.
- Macchia A, Grancelli H, Varini S, et al. Omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: results of the FORWARD (Randomized Trial to Assess Efficacy of PUFA for the Maintenance of Sinus Rhythm in Persistent Atrial Fibrillation) trial. J Am Coll Cardiol. 2013 Jan 29;61(4):463-8. doi: 10.1016/j.jacc.2012.11.021.
- Maki KC, Dicklin MR, Davidson MH, et al. COMBination of prescription omega-3 with simvastatin (COMBOS) Investigators. Am J Cardiol. 2010 May;105(10):1409-12.
- Maki KC, McKenny JM, Reeves MS, et al. Effects of adding prescription omega-3 acid ethyl esters to simvastatin (20 mg/day) on lipids and lipoprotein particles in men and women with mixed dyslipidemia. Am J Cardiol. 2008;102:429-33.
- Maki KC, Orloff DG, Nicholls SJ, et al. A highly bioavailable omega-3 free fatty acid formulation improves the cardiovascular risk profile in high-risk, statin-treated patients with residual hypertriglyceridemia (the ESPRIT trial). Clin Ther. 2013;35(9):1400-11.e1-3. doi: 10.1016/j.clinthera.2013.07.420.
- Matsuzaki M, Yokoyama M, Saito Y, et al. Incremental effects of eicosapentaenoic acid on cardiovascular events in statin-treated patients with coronary artery disease. Circ J. 2009 Jul;73(7):1283-90.
- McCrindle BW, Urbina EM, Dennison BA, et al. Drug therapy of high-risk lipid abnormalities in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing. Circulation. 2007 Apr;115(14):1948-67.
- McKeone BJ, Osmundsen K, Brauchi D, Pao Q, Payton-Ross C, Kilinc C, et al. Alterations in serum phosphatidylcholine fatty acyl species by eicosapentaenoic and docosahexaenoic ethyl esters in patients with severe hypertriglyceridemia. J Lipid Res. 1997;38:429-36.
- Micromedex [database on the Internet]. Greenwood Village, CO: Truven Health Analytics; 2017. Available from: http://www.micromedexsolutions.com. Accessed November 13, 2017.
- Miller M, Stone NJ, Ballantyne C, et al. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2011;123(20):2292-2333.
- Nakamura N, Hamazaki T, Ohta M, et al. Joint effects of HMG-CoA reductase inhibitors and eicosapentaenoic acids on serum lipid profile and plasma fatty acid concentrations in patients with hyperlipidemia. Int J Clin Lab Res. 1999;29(1):22-5.
- National Cholesterol Education Program (NCEP). Detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report, 2002 [guideline on the internet]. Available at: https://www.nhlbi.nih.gov/files/docs/guidelines/atp3xsum.pdf. Accessed November 13, 2017.
- Nilsen DWT, Albrelasen G, Landmark K, et al. Effects of a high-dose concentration of n-3 fatty acids or corn oil introduced early after an acute myocardial infarction on serum triacylglycerol and HDL cholesterol. Am J Clin Nutr. 2001;74:50–56.
- Nordoy A, Bonaa KH, Nilsen H, et al. Effects of simvastatin and omega-3 fatty acids on plasma lipoproteins and lipid peroxidation in patients with combined hyperlipidemia. J Intern Med. 1998;243:163–170.
- Oikawa S, Yokoyama M, Origasa H, et al. Suppressive effect of EPA on the incidence of coronary events in hypercholesterolemia with impaired glucose metabolism: Sub-analysis of the Japan EPA Lipid Intervention Study (JELIS). Atherosclerosis. 2009 Oct;206(2):535-9. doi: 10.1016/j.atherosclerosis.2009.03.029.
- OMTRYG prescribing information. Trygg Pharma, Inc. Arlington, VA. March 2016.
- Origasa H, Yokoyama M, Matsuzaki M, et al. JELIS Investigators. Clinical importance of adherence to treatment with eicosapentaenoic acid by patients with hypercholesterolemia. Circ J. 2010 Mar;74(3):510-7.
- Peters BS, Wierzbicki AS, Moyle G, et al. The effect of a 12-week course of omega-3 polyunsaturated fatty acids on lipid parameters in hypertriglyceridemic adult HIV-infected patients undergoing HAART: a randomized, placebo-controlled pilot trial. Clin Ther. 2012;34:67-76.
- Pownall HJ, Brauchi D, Kilinc C, et al. Correlation of serum triglyceride and its reduction by omega-3 fatty acids with lipid transfer activity and the neutral lipid compositions of high-density and low-density lipoproteins. Atherosclerosis. 1999;143:285-97.
- Risk and Prevention Study Collaborative Group, Roncaglioni MC, Tombesi M, Avanzini F, et al. n-3 fatty acids in patients with multiple cardiovascular risk factors. N Engl J Med. 2013 May 9;368(19):1800-8. doi: 10.1056/NEJMoa1205409.
- Roth EM, Bays HE, Forker AD, et al. Prescription omega-3 fatty acid as an adjunct to fenofibrate therapy in hypertriglyceridemic patients. J Cardiovasc Pharmacol. 2009;54:196-203.

- Saito Y, Yokoyama M, Origasa H, et al. Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS). Atherosclerosis. 2008 Sep;200(1):135-40. doi: 10.1016/j.atherosclerosis.2008.06.003.
- Sasaki J, Yokoyama M, Matsuzaki M, et al. Relationship between coronary artery disease and non-HDL-C, and effect of highly purified EPA on the risk of coronary artery disease in hypercholesterolemic patients treated with statins: sub-analysis of the Japan EPA Lipid Intervention Study (JELIS). J Atheroscler Thromb. 2012;19(2):194-204.
- Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. J Am Coll Cardiol. 2011 Nov 29;58(23):2432-46.
- Stalenhoef AFH, de Graaf J, Wittekoek ME, et al. The effect of concentrated n-3 fatty acids vs gemfibrozil on plasma lipoproteins, low density lipoprotein heterogeneity and oxidizability in patients with hypertriglyceridemia. Atherosclerosis. 2000;153:129-38.
- Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American College of Cardiology/American Heart Association. Circulation. 204;129(25 Suppl 2):S1-S45.
- Tanaka K, Ishikawa Y, Yokoyama M, et al. Reduction in the recurrence of stroke by eicosapentaenoic acid for hypercholesterolemic patients: subanalysis of the JELIS trial. Stroke. 2008 Jul;39(7):2052-8. doi: 10.1161/STROKEAHA.107.509455.
- TRIKLO prescribing information. Key Therapeutics, LLC. Flowood, MS. August 2017.
- Van Dam M, Stalenhoef AFH, Wittekoek J, et al. Efficacy of concentrated omega-3 fatty acids in hypertriglyceridemia: A comparison with gemfibrozil. Clin Drug Invest. 2001;21:175–181.
- VASCEPA prescribing information. Amarin Pharma Inc. Bedminster, NJ. February 2017.
- Woolley T, Canoniero M, Conroy W, et al. Institute for Clinical Systems Improvement. Lipid Management in Adults. Updated February 2017. Available at: https://www.icsi.org/_asset/qz5ydq/LipidMgmt-Interactive1111.pdf. Accessed November 13, 2017.
- Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet. 2007 Mar 31;369(9567):1090-8.

Publication Date: January 3, 2018