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NOTICE OF PUBLIC MEETING – PHARMACY AND THERAPEUTICS COMMITTEE

AGENDA

Date of Publication:	**November 1, 2017**
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 Street, Suite 3A** **Carson City, NV 89701**
Place of Meeting:	**South Nevada Location:** **Silver State Health Insurance Exchange** **150 N. Stephanie Street, Suite 100** **Henderson, NV 89074** **Please check with staff to verify room location**
Webinar Registration:	https://optum.webex.com/optum/onstage/g.php?MTID=e7c160bfb8cdc5e1705129744ebe4f8c9 **OR** www.webex.com, select "Join," enter Meeting Number 319 354 044, your name and email and then select "Join." A Password should not be necessary, but if asked, enter, "q2TyYC56" **OR**

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

Event Number: **319 354 044**

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

Reasonable efforts will be made to assist and accommodate physically challenged persons desiring to attend the meeting. Please call Colleen McLachlan at: (775) 684-3722 or email 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 September 28, 2017

b. Status Update by the DHCFP

1. Public Comment

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

a. Gastrointestinal Agents – Functional Gastrointestinal Disorder Drugs

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

b. Ophthalmic Agents – Ophthalmic Antihistamines

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. 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

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

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

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

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 Long-Acting Antimuscarinic/Long-Acting Beta-Agonist 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. 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

5. Established Drug Classes

a. Dermatological Agents – Topical Analgesics

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

b. Biologic Response Modifiers – Immunomodulators – Targeted Immunomodulators

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
   c. Approve exception to a trial of two preferred agent requirement.
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. Report by OptumRx on New Drugs to Market, New Generic Drugs to Market and New Line Extensions

7. 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) FENTANYL PATCH BUTRANS®	**PA required for Fentanyl Patch** **General PA Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-59.pdf Quantity limits apply to all Opioids	AVINZA® DOLOPHINE® DURAGESIC® PATCHES EXALGO® KADIAN® METHADONE METHADOSE® MS CONTIN® NUCYNTA® ER OPANA ER® OXYCODONE SR OXYMORPHONE SR XARTEMIS XR® ZOHYDRO ER®
Opiate Agonists - Abuse Deterrent		
EMBEDA® HYSINGLA ER®	Quantity limits apply to all Opioids	OXYCONTIN® 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® SOVALDI® ZEPATIER®	**PA required: (see below)** http://dhcfp.nv.gov/uploadedFiles/dhcfpnvgov/content/Resources/AdminSupport/Manuals/MSMCh1200Packet6-11-15(1).pdf https://www.medicaid.nv.gov/Downloads/provider/Pharmacy_Announcement_Viekira_2015-0721.pdf	DAKLINZA® OLYSIO® TECHNIVIE® VIEKIRA® PAK
Ribavirins		
RIBAVIRIN		RIBASPHERE RIBAPAK® MODERIBA® REBETOL®
Anti-Herpetic Agents		
ACYCLOVIR FAMVIR® VALCYCLOVIR		
Influenza Agents		
AMANTADINE TAMIFLU® RIMANTADINE RELENZA®		
Cephalosporins		
Second-Generation Cephalosporins		
CEFACLOR CAPS and SUSP CEFACLOR ER CEFUROXIME TABS and SUSP CEFPROZIL SUSP		CEFTIN® CECLOR® CECLOR CD® CEFZIL
Third-Generation Cephalosporins		
CEFDINIR CAPS / SUSP CEFPODOXIME TABS and SUSP		CEDAX® CAPS and SUSP CEFDITOREN OMNICEF® SPECTRACEF® SUPRAX® VANTIN®
Macrolides		
AZITHROMYCIN TABS/SUSP CLARITHROMYCIN TABS/SUSP		BIAXIN® DIFICID®

Preferred Products	PA Criteria	Non-Preferred Products
ERYTHROMYCIN BASE ERYTHROMYCIN ESTOLATE ERYTHROMYCIN ETHYLSUCCINATE ERYTHROMYCIN STEARATE		ZITHROMAX® ZMAX®
Quinolones		
Quinolones - 2nd Generation		
CIPROFLOXACIN TABS CIPRO® SUSP		FLOXIN® OFLOXACIN
Quinolones - 3rd Generation		
AVELOX® AVELOX ABC PACK® LEVOFLOXACIN		LEVAQUIN®
Autonomic Agents		
Sympathomimetics		
Self-Injectable Epinephrine		
AUVI-Q® * EPINEPHRINE® EPIPEN® EPIPEN JR.®	* PA required	ADRENACLICK® QL
Biologic Response Modifiers		
Immunomodulators		
Targeted Immunomodulators		
CIMZIA® COSENTYX® ENBREL® HUMIRA® 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	ACTEMRA® ENTYVIO® ILARIS® INFLECTRA® REMICADE® STELARA® TALTZ®
Multiple Sclerosis Agents		
Injectable		
AVONEX® AVONEX® ADMIN PACK BETASERON® COPAXONE® QL EXTAVIA® REBIF® QL TYSABRI®	*Trial of only one agent is required before moving to a non-preferred agent*	GLATOPA® LEMTRADA® PLEGRIDY® ZINBRYTA®
Oral		
AUBAGIO®		

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

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

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

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

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

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

Preferred Products	PA Criteria	Non-Preferred Products
		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	
Injectable		
ARIXTRA® ENOXAPARIN FRAGMIN®		FONDAPARINUX INNOHEP® LOVENOX®
Erythropoiesis-Stimulating Agents		
ARANESP® QL PROCRIT® QL	PA required Quantity Limit	EPOGEN® QL OMONTYS® QL
Platelet Inhibitors		
AGGRENOX® ANAGRELIDE ASPIRIN BRILINTA® * QL CILOSTAZOL®	* PA required	ASPIRIN/DIPYRIDAMOLE DURLAZA® EFFIENT® * QL PLAVIX® ZONTIVITY®

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

Preferred Products	PA Criteria	Non-Preferred Products
HUMALOG® HUMULIN® LANTUS® LEVEMIR ® NOVOLIN® NOVOLOG® TRESIBA FLEX INJ		BASAGLAR® NEW 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® XIGDUO XR®
Sulfonylureas		
AMARYL® CHLORPROPAMIDE DIABETA® GLIMEPIRIDE (Amaryl®) GLIPIZIDE (Glucotrol®) GLUCOTROL® GLUCOVANCE® GLIPIZIDE EXT-REL (Glucotrol XL®) GLIPIZIDE/METFORMIN (Metaglip®) GLYBURIDE MICRONIZED (Glynase®) GLYBURIDE/METFORMIN (Glucovance®) GLUCOTROL XL® GLYBURIDE (Diabeta®) GLYNASE® METAGLIP® TOLAZAMIDE TOLBUTAMIDE		
Thiazolidinediones		
ACTOPLUS MET XR® ACTOS®		

Preferred Products	PA Criteria	Non-Preferred Products
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® DIDRONEL® ETIDRONATE IBANDRONATE SKELID®
Nasal Calcitonins		
MIACALCIN®		FORTICAL® CALCITONIN-SALMON
Restless Leg Syndrome Agents		
PRAMIPEXOLE REQUIP XL		HORIZANT® MIRAPEX®

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

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

Preferred Products	PA Criteria	Non-Preferred Products
PHENYTOIN PRODUCTS		
Anti-Migraine Agents		
Serotonin-Receptor Agonists		
RELPAX® RIZATRIPTAN ODT SUMATRIPTAN NASAL SPRAY SUMATRIPTAN INJECTION SUMATRIPTAN TABLET	PA required for exceeding Quantity Limit	AMERGE® AXERT® FROVA® IMITREX® MAXALT® TABS MAXALT® MLT NARATRIPTAN SUMAVEL® TREXIMET® ZECUITY® TRANSDERMAL ZOMIG® ZOMIG® ZMT
Antiparkinsonian Agents		
Non-ergot Dopamine Agonists		
PRAMIPEXOLE ROPINIROLE ROPINIROLE ER		MIRAPEX® MIRAPEX® ER NEUPRO® REQUIP® REQUIP XL®
Ophthalmic Agents		
Antiglaucoma Agents		
Carbonic Anhydrase Inhibitors/Beta-Blockers		
ALPHAGAN P® AZOPT® BETAXOLOL BETOPTIC S® BRIMONIDINE CARTEOLOL COMBIGAN® DORZOLAM DORZOLAM / TIMOLOL LEVOBUNOLOL METIPRANOLOL SIMBRINZA® TIMOLOL DROPS/ GEL SOLN		ALPHAGAN® BETAGAN® BETOPTIC ® COSOPT® COSOPT PF® OCUPRESS® OPTIPRANOLOL® TIMOPTIC® TIMOPTIC XE® TRUSOPT®
Ophthalmic Prostaglandins		
LATANOPROST LUMIGAN® TRAVATAN®		TRAVOPROST XALATAN® ZIOPTAN®

Preferred Products	PA Criteria	Non-Preferred Products
TRAVATAN Z®		
Ophthalmic Antihistamines		
ALAWAY® BEPREVE® KETOTIFEN PAZEO® ZADITOR OTC®		AZELASTINE ALOMIDE ALOCRIL ELESTAT® EMADINE® EPINASTINE LASTACRAFT® OPTIVAR® PATADAY® PATANOL®
Ophthalmic Anti-infectives		
Ophthalmic Macrolides		
ERYTHROMYCIN OINTMENT		
Ophthalmic Quinolones		
BESIVANCE® CIPROFLOXACIN LEVOFLOXACIN MOXEZA® VIGAMOX®		CILOXAN® OFLOXACIN® ZYMAXID®
Ophthalmic Anti-infective/Anti-inflammatory Combinations		
NEO/POLY/DEX PRED-G SULF/PRED NA SOL OP TOBRADEX OIN TOBRA/DEXAME SUS % ZYLET SUS		BLEPHAMIDE MAXITROL NEO/POLY/BAC OIN /HC NEO/POLY/HC SUS OP TOBRADEX SUS TOBRADEX ST SUS
Ophthalmic Anti-inflammatory Agents		
Ophthalmic Corticosteroids		
ALREX® DEXAMETHASONE DUREZOL® FLUOROMETHOLONE LOTEMAX® PREDNISOLONE		FLAREX® FML® FML FORTE® MAXIDEX® OMNIPRED® PRED FORTE® PRED MILD® VEXOL®
Ophthalmic Nonsteroidal Anti-inflammatory Drugs (NSAIDs)		
DICLOFENAC FLURBIPROFEN ILEVRO®		ACULAR® ACULAR LS® ACUVAIL®

Preferred Products	PA Criteria	Non-Preferred Products
KETOROLAC NEVANAC®		BROMDAY® BROMFENAC® PROLENSA®
Ophthalmics for Dry Eye Disease		
RESTASIS® NEW		XIIDRA® NEW
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® INTUNIV® METADATE CD® METHYLIN® METHYLIN ER® METHYLPHENIDATE METHYLPHENIDATE ER (All forms generic extended release) METHYLPHENIDATE SOL PROCENTRA® QUILLICHEW® QUILLIVANT® XR SUSP RITALIN LA® STRATTERA® VYVANSE®	**PA required for entire class** **Children's Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-69.pdf **Adult Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-68.pdf	ADDERALL® AMPHETAMINE SALT COMBO XR APTENSIO XR® CONCERTA® DAYTRANA® DESOXYN® DEXEDRINE® DEXTROAMPHETAMINE SOLUTION EVEKEO® FOCALIN® KAPVAY® METADATE ER® RITALIN® ZENZEDI®
Antidepressants		
Other		
BUPROPION BUPROPION SR	PA required for members under 18 years old	APLENZIN® BRINTELLIX®

Preferred Products	PA Criteria	Non-Preferred Products
BUPROPION XL DULOXETINE MIRTAZAPINE MIRTAZAPINE RAPID TABS PRISTIQ® TRAZODONE VENLAFAXINE (ALL FORMS)	* PA required *No PA required if ICD-10 - M79.1; M60.0-M60.9, M61.1.*	CYMBALTA® DESVENLAFAXINE FUMARATE EFFEXOR® (ALL FORMS) FETZIMA® FORFIVO XL® KHEDEZLA® VIIBRYD® WELLBUTRIN®
Selective Serotonin Reuptake Inhibitors (SSRIs)		
CITALOPRAM ESCITALOPRAM FLUOXETINE PAROXETINE PEXEVA® SERTRALINE	PA required for members under 18 years old	CELEXA® FLUVOXAMINE QL LEXAPRO® LUVOX® PAXIL® PROZAC® SARAFEM® ZOLOFT®
Antipsychotics		
Atypical Antipsychotics - Oral		
ARIPIPRAZOLE CLOZAPINE FANAPT® LATUDA® NUPLAZID®* Preferred for ICD-10 code G31.83 OLANZAPINE QUETIAPINE REXULTI® RISPERIDONE SAPHRIS® SEROQUEL XR® ZIPRASIDONE	**PA required for Ages under 18 years old** **PA Forms:** https://www.medicaid.nv.gov/Downloads/provider/FA-70A.pdf (ages 0-5) https://www.medicaid.nv.gov/Downloads/provider/FA-70B.pdf (ages 6-18) *(No PA required Parkinson's related psychosis ICD code on claim)	ABILIFY® CLOZARIL® FAZACLO® GEODON® INVEGA® PALIPERIDONE QUETIAPINE XR NEW RISPERDAL® SEROQUEL® VRAYLAR® ZYPREXA®
Anxiolytics, Sedatives, and Hypnotics		
ESTAZOLAM FLURAZEPAM ROZEREM®	No PA required if approved diagnosis code transmitted on claim (All agents in this class)	AMBIEN® AMBIEN CR® BELSOMRA®

Preferred Products	PA Criteria	Non-Preferred Products
TEMAZEPAM TRIAZOLAM ZALEPLON ZOLPIDEM ZOLPIMIST®		DORAL® ESZOPICLONE EDLUAR® HETLIOZ® INTERMEZZO® LUNESTA® SILENOR® SOMNOTE® SONATA® ZOLPIDEM CR
	PA required for members under 18 years old	
Psychostimulants		
Narcolepsy Agents		
Provigil® *	* (No PA required for ICD-10 code G47.4)	MODAFINIL NUVIGIL® XYREM®
Respiratory Agents		
Nasal Antihistamines		
ASTEPRO® DYMISTA® PATANASE®		AZELASTINE OLOPATADINE
Respiratory Anti-inflammatory Agents		
Leukotriene Receptor Antagonists		
MONTELUKAST ZAFIRLUKAST		ACCOLATE® SINGULAIR®
Respiratory Corticosteroids		
ARNUITY ELLIPTA® ASMANEX® FLOVENT DISKUS® QL FLOVENT HFA® QL PULMICORT FLEXHALER® PULMICORT RESPULES®* QVAR®	*No PA required if < 4 years old	ALVESCO® AEROSPAN HFA® BUDESONIDE NEBS*
Nasal Corticosteroids		
FLUTICASONE NASONEX®		BECONASE AQ® FLONASE® FLUNISOLIDE NASACORT AQ® OMNARIS® QNASL® RHINOCORT AQUA® TRIAMCINOLONE ACETONIDE VERAMYST®

Preferred Products	PA Criteria	Non-Preferred Products
		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 NEW PROAIR® HFA PROAIR RESPICLICK® VENTOLIN HFA® XOPENEX® Solution* QL
Respiratory Corticosteriod/Long-Acting Beta-Agonist Combinations		
ADVAIR DISKUS® ADVAIR HFA® DULERA® SYMBICORT®		BREO ELLIPTA®
Respiratory Long-Acting Antimuscarinic/Long-Acting Beta-Agonist Combinations		
ANORO ELLIPTA® STIOLTO RESPIMAT®		UTIBRON NEOHALER ®
Toxicology Agents		
Antidotes		
Opiate Antagonists		
NALOXONE NARCAN® NASAL SPRAY		
Substance Abuse Agents		
Mixed Opiate Agonists/Antagonists		
BUNAVAIL® SUBOXONE® ZUBSOLV®	PA required for class	BUPRENORPHINE/NALOXONE

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

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

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

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

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

(b) Antirejection medications for organ transplants;

(c) Antihemophilic medications; and

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

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

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

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

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

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

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

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

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

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

(b) Maintains continuous eligibility for Medicaid; and

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

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

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

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

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

(c) Anticonvulsant medications;

(d) Antirejection medications for organ transplants;

(e) Antidiabetic medications;

(f) Antihemophilic medications; and

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

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

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

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

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

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

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

Definition of "Therapeutic Alternative"

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

BRIAN SANDOVAL
Governor

RICHARD WHITLEY, MS
Director

MARTA JENSEN
Acting Administrator

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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PHARMACY AND THERAPEUTICS COMMITTEE

Meeting Minutes

Date and Time of Meeting: **Thursday, September 28, 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:
Division of Public & Behavioral Health
4150 Technology Way, Rm 301
Carson City, NV 89701

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

Please check with staff to verify room location

Webinar Registration:

https://optum.webex.com/optum/onstage/g.php?MTID=e698cdc3c4cbcc31d4c379331a1f8cebe

OR

www.webex.com, select "Join", enter Meeting Number 644 525 531, your name and email and then select, "Join".

A Password should not be necessary, but if asked, enter, "9MMZuC88"

OR

Audio Only: **1-763-957-6300**

Event Number: 644 525 531

Event Number: **644 525 531**

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

Attendees

Board Members (Present)	**Board Members (Absent)**
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.	
DHCFP:	
Duane Young, Chief, DHCFP	Gabe Lither, DAG
Holly Long, Social Services Program Sp	
DXC:	
Beth Slamowitz, Pharm.D.	
OptumRx:	
Carl Jeffery, Pharm.D.	Rob Earnest, Pharm.D., JD
Kevin Whittington, RPh	Daniel Medina
Public (Las Vegas):	
Toya Malone Davis, MD, Neurology	Fatima Sadut, Otsuka
Rob Bigham, Shire	Rupa Shah, Purdue Pharma
Mark Schwartz, GSK	Christian Heirner, Rhodes
Nick Casale, Indivior	Nana Numapan, BI
George Dzwikaski, Indivior	Dan Tubridy, BI
Krystal Joy, Otsuka	William Lam, BI
Cynthia Albert, Merck	Lee Stout Chiesi
Charissa Anne, J&J	Patrick Moty, Horizon
Cathy Gross, Purdue	Jennifer Lauper, BMS
Chet Steckler, Purdue	Nindhana Paranthaman, BMS
Jill Sugg, USB	Tony Locke, Tris Pharma
Chioma Ezenduka, UCB	Melissa Walsh, Novartis
Fern Leal, UCB	Lovell Robinson, Abbvie
Elaine Defelice, UCB	Jignesa Patel, Novo
Kelvin Yamebute, Sanofi	Karen Jackson, Trividia
Zulma Schlossberg, Tris Pharma	Danielle Marano, Epilepsy Foundation
Karen Nguyen, Allergan	Steven Zona, Janssen
Jane Stephan, Allergan	Ryan Bitton, HPN

Karen Enbinder, Novo
Kaysen Bala, Biogen
Christy Lemons, Orexo
Sandy Sierawski, Pfizer
Mark Rueckert, Pfizer
Mike Markette, Pfizer
Lori Howarth, Bayer
James Marx, MD
James Kotusky, Gilead
Michael Virtuoso, Student

Public (Carson City):
Aimee Doran, United Therapeutics

Public (Teleconference):
Dave West
Rhigel Tan
Kim Jacoby, Lundbeck
Chad MacGregor
Robert Horn
Vanessa Castillo
Tanya Phares
Colin Carey
Tom Beranek, SilverSummit
Jeannine Murray, Amerigroup
Rob Bigham, Shire
Michael Faithe, Amgen
Jaclyn Weise, Genentech

1. Call to Order and Roll Call

Dr. Nagy called the Meeting to order at 1:00PM. Roll call was taken and a quorum established.

2. Public Comment

Dr. Nagy called for public comment. None

3. Administrative

a. **For Possible Action**: Review and Approve Meeting Minutes from March 23, 2017

A motion was made to approve the minutes as submitted, the motion was seconded. The Board voted to accept the minutes. The motion carried.

b. Status Update by DHCFP
   i. Public Comment

Mr. Young provides an update from DHCFP. Gave an overview of new Behavior Health programs that were effective July 1, 2017. The legislation from the current session allowed for rate changes and adding services to the state plan, will be effective January 1, 2018. Behavior Health parody assessment was completed.

Dr. Nagy called for public comment.

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

a. Analgesics - Opiate Agonists

Dr. Nagy called for public comment.

Dr. Rupa Shaw, clinical pharmacist with Purdue Pharma. Provided comment for Hysingla ER.

Dr. Jeffery notified Dr. Shaw the abuse deterrent opioids will be reviewed in December.

Dr. Shaw had no further comments.

Dr. Jeffery provided overview of the generic buprenorphine patch. Dr. Jeffery reminded the board the abuse deterrent opioids will be reviewed in December. Optum recommended the class be considered clinically and therapeutically equivalent.

A motion was made, seconded and voted to approve. The motion carried.

Dr. Jeffery recommended the generic buprenorphine patch be considered non-preferred, the rest of the class remain the same.

A motion was made, seconded and voted to approve. The motion carried.

b. Anti-infective Agents - Antivirals - Influenza Agents

Dr. Nagy called for public comment

Dr. Jeffery provided information for the generic Tamiflu, an AB rated generic. Optum recommended the board consider the drugs in the class clinically and therapeutically equivalent.

A motion was made to accept the recommendation, seconded and voted to approve. The motion carried.

Dr. Jeffery recommended to the board the generic remain non-preferred and the brand as preferred.

A motion was made to accept Optum's recommendation, seconded and voted to approve. The motion carried.

c. Anti-infective Agents - Quinolones - Quinolones - 3rd Generation

Dr. Nagy asked for public comment.

Dr. Jeffery gave an overview of moxifloxacin generic. Another new agent, also available, Baxdela was briefly discussed. It has similar cure rates, but not available yet on the market. Optum recommended the board consider the drugs in this class clinically and therapeutically equivalent.

A motion was made to accept Optum's recommendation, seconded and voted to approve. The motion carried.

Dr. Jeffery recommended to the board the generic moxifloxacin and Baxdela be considered non-preferred.

A motion to accept Optum's recommendations was made, seconded and voted as approved. The motion carried.

d. Autonomic Agents - Sympathomimetics - Self-Injectable Epinephrine

Dr. Nagy asked for public comment.

Dr. Jeffery gave an overview of the changes to the class including the authorized generic from Teva for EpiPen. The new generic is made by the same company as EpiPen. The generic is BX rated, so not interchangeable at the pharmacy. Auvi Q is available again after being off the market for some time. Dr. Jeffery recommended the board consider the products in this class clinically and therapeutically equivalent.

A motion to accept Optum's recommendation was made, seconded and voted as approved. The motion carried.

Dr. Jeffery recommended moving Auvi-Q, Epipen and Epipen Jr. to non-preferred and list the generic epinephrine auto injector as preferred.

A motion to accept the recommendation was made, seconded and voted as approved. The motion carried.

e. Biologic Response Modifiers - Immunomodulators - Targeted Immunomodulators

Dr. Nagy asked for public comment.

Nindhana Paranthaman from the Medical Affairs team at Bristol Myers Squibb offered information on two new updates for Orencia with new indications. Covered dosing and studies of efficacy.

Sandy Sierawski, a pharmacist with Pfizer in the medical outcomes division, provided information for Xeljanz and Xeljanz XR.

Steven Zona with medical outcomes from Janssen, presented information for Stelara and Tremfya and asked the Board to consider adding them to the preferred drug list. Provided information on Stelara, including mechanism of action, dosing and administration, studies showing efficacy and safety information. Provided information for Tremfya including mechanism of action, dosing and administration, studies showing superiority to Humira in psoriasis, adverse drug events and warnings.

Dr. Jeffery presented information on new agents, Kevzara an IL6 indicated for rheumatoid arthritis, Renflexis, a biosimilar to Remicade, Siliq an IL17 for plaque psoriasis and Tremfya an IL23 for plaque psoriasis. Recommended the board consider the drugs in the class be considered clinically and therapeutically equivalent.

A motion was made to accept Optum's recommendation, the motion was seconded and voted as approved. The motion carried.

Dr. Jeffery recommended to the board the new agents Kevzara, Renflexis, Siliq and Tremfya be considered non-preferred.

Dr. Decerbo asked if failure of only one agent is required before moving to a non-preferred agent.

Dr. Jeffery answered that two preferred agents would have to be tried first.

Mr. Lither suggested the board defer changing the requirement to failing a single agent to a future meeting.

Dr. Adashek requested this topic be on the next agenda to consider requiring only a single preferred agent before getting a non-preferred agent.

A motion was made to accept the proposed drug list by Optum. The motion was seconded and voted as approved. The motion carried.

f. Biologic Response Modifiers - Multiple Sclerosis Agents - Injectable

Dr. Nagy called for public comment.

Dr. Jeffery started by reminding the board that only one preferred agent trial be tried first. Presented information on a new agent in the class Ocrevus. Gave an overview of administration and indication. Recommended the board consider this class clinically and therapeutically equivalent.

A motion is made to accept the recommendation from Optum. The motion was seconded and voted as approved. The motion carried.

Dr. Jeffery recommended to the board Ocrevus be listed as preferred.

Dr. Decerbo asked how Ocrevus will be billed.

Dr. Jeffery responded that specialty pharmacies may bill and then ship to the provider for administration rather than the physician's office billing for it directly.

A motion was made to accept Optum's recommendation. The motion was seconded and voted as approved. The motion carried.

g. Cardiovascular Agents - Antilipemics - Cholesterol Absorption Inhibitors

Dr. Nagy asked for public comment.

Dr. Jeffery provided information on the new AB rated generic of Zetia. Optum recommends the board consider these agents clinically and therapeutically equivalent.

A motion was made to accept the recommendation from Optum. The motion was seconded and voted as approved, the motion carried.

Dr. Jeffery recommended brand Zetia remain preferred and ezetimibe be listed as non-preferred.

A motion was made to accept Optum's recommendation. The motion was seconded and voted as approved. The motion carried.

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

Dr. Nagy called for public comment.

Dr. Jeffery provided information on the new AB rated generic Vytorin and Crestor. Recommended the board consider the medications in this class be considered clinically and therapeutically equivalent.

A motion was made to accept the recommendation. The motion was seconded and voted as approved, the motion carried.

Dr. Jeffery recommended the generic ezetimibe-simvastatin and rosuvastatin be considered non-preferred.

A motion to accept the recommendation was made. The motion was seconded and voted as approved, the motion carried.

i. Dermatological Agents - Antipsoriatic Agents - Topical Vitamin D Analogs

Dr. Nagy called for public comment.

Dr. Jeffery provided information for some new products, Enstilar. Recommended the board consider the agents in this class clinically and therapeutically equivalent.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

Dr. Jeffery recommended some changes to include Sorilux, Taclonex, Vectical ointment be considered preferred and Calcipotriene, calcipotriene/betamethasone and Enstilar as non-preferred.

A motion was made to accept the recommendations. The motion was seconded and voted as approved. The motion carried.

j. Dermatological Agents - Topical Anti-infectives - Topical Antivirals

Dr. Nagy called for public comment.

Dr. Jeffery provided information on the new agent Xerese and Zovirax ointment. Discussed national guidelines and OTC availability. Recommended these agents be considered clinically and therapeutically equivalent.

Dr. Adeshek asked if there are any studies comparing the oral agents vs the topical agents.

Dr. Jeffery responded that he was not aware of any head-to-head studies.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

Dr. Jeffery recommended the new product Xerese be preferred and Acyclovir ointment and Denavir as non-preferred.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

k. Dermatological Agents - Topical Anti-infectives - Topical Scabicides

Dr. Nagy called for public comment.

Dr. Jeffery provided information for Ulesfia and spinosad. Recommended the board consider these clinically and therapeutically equivalent.

A motion was made to accept the recommendation. The motion was seconded and voted as preferred. The motion carried.

Dr. Jeffery recommended Ulesfia be moved to preferred and spinosad be non-preferred.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

l. Gastrointestinal Agents - Antiulcer Agents - Proton Pump Inhibitors (PPIs)

Dr. Nagy called for public comment.

Dr. Jeffery presented information on the new generics of esomeprazole. Recommended the agents in the class be considered clinically and therapeutically equivalent.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

Dr. Jeffery recommended the new generic esomeprazole be non-preferred, everything else remain the same.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

m. Gastrointestinal Agents - Gastrointestinal Anti-inflammatory Agents

Dr. Nagy called for public comment.

Dr. Jeffery provided information on new generics for Lialda and Asacol, both mesalamine. Recommended the medications in the class be considered clinically and therapeutically equivalent.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

Dr. Jeffery recommended moving brand names Apriso, Asacol HD and Lialda as preferred and the Melalamine, generics for Lialda and Asacol HD as non-preferred.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

n. Hematological Agents - Anticoagulants - Injectable

Dr. Nagy called for public comment.

Dr. Jeffery stated there are no changes recommended to the class. The class will be included with the review at the end.

o. Hormones and Hormone Modifiers - Antidiabetic Agents - Biguanides

Dr. Nagy called for public comment.

Dr. Jeffery provided information on the new generic for Glumetza. Reminded the board of the statute of anything on the market before June 30, 2010 has to be preferred. Recommended the medications in the class be considered clinically and therapeutically equivalent.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

Dr. Jeffery recommended the generic Glumetza metformin be considered non-preferred.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

p. Hormones and Hormone Modifiers - Antidiabetic Agents - Incretin Mimetics

Dr. Nagy called for public comment.

Dr. Jeffery provided information on some new medication in the class, Adlyxin, Soliqua and Xultophy. Covered administration and product details. Discussed rationale for including the combination products, Soliqua and Xultophy in the class. Recommended the medications in the class be considered clinically and therapeutically equivalent.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

Dr. Jeffery recommended the new agents Adlyxin, Soliqua and Xultophy be considered non-preferred.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

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

Dr. Nagy called for public comment.

Nana Numapau with Boehringer Ingelheim in the health economics and outcomes group. Provided information for Synjardy and Synjardy XR. Reminded the board Synjardy is the only agent to reduce cardiovascular death. Covered other studies and outcomes. Covered other agents, Glyxambi, Synjardy and Synjardy XR. Asked the board the add Synjardy and Synjardy XR as preferred because of the available data.

Steven Zona offered to answer any questions from the board about Invokana.

Dr. Jeffery provided information on Synjardy XR. Recommended the medications in the class be considered clinically and therapeutically equivalent.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

Dr. Jeffery recommended keeping the combination agents as non-preferred and keeping Synjardy XR as non-preferred. Reminded the board that only a single preferred agent needs to be tried before getting a non-preferred.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

r. Musculoskeletal Agents - Bone Resorption Inhibitors - Bisphosphonates

Dr. Nagy called for public comment.

Dr. Jeffery recommended no changes to the class and include with the global approval section at the end.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

s. Neurological Agents - Anti-Migraine Agents - Serotonin-Receptor Agonists

Dr. Nagy called for public comment.

Dr. Jeffery provided information on the generic Relpax, eletriptan. Recommended the medications in the class be considered clinically and therapeutically equivalent.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

Dr. Jeffery recommended making the new generic eletriptan non-preferred and keeping the rest of the class the same.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

t. Ophthalmic Agents - Ophthalmic Anti-infectives - Ophthalmic Quinolones

Dr. Nagy called for public comment.

Dr. Jeffery provided information on the new generic for Vigamox, moxifloxacin. Recommended the medications in the class be considered clinically and therapeutically equivalent.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

Dr. Jeffery recommended the new generic moxifloxacin be added as non-preferred and keep the rest of the class the same.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

u. Psychotropic Agents - ADHD Agents

Dr. Nagy called for public comment.

Christina Heiner, representing Rhodes Pharmaceuticals, asked the board to consider adding Aptensio XR to the preferred drug list. Covered indications, dosage forms, administration, pharmacokinetics, and clinical studies.

Dr. Jeffery provided information on the new products in the class, Cotempla XR, Mydayis, Vyvanse Chewable and generic atomoxetine. Discussed the different dosage forms and clinical differences. Recommended the medications in the class be considered clinically and therapeutically equivalent.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

Dr. Jeffery recommended Intuniv be moved to non-preferred and the generic guanfacine ER to preferred. Atomoxetine, Cotempla XR and Mydayis will be added as non-preferred. The new dosage form of Vyvnase be included with the other Vyvanse products already listed as preferred.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

v. Psychotropic Agents - Antipsychotics - Atypical Antipsychotics - Oral

Dr. Nagy called for public comment.

Karen Nguyen, a pharmacist and scientific liaison at Allergan. Provided information on Vraylar including mechanism of action, indications, clinical studies, clinical guidelines and asked Vraylar be preferred for Nevada Medicaid.

[Name unintelligible] psychiatrist in Las Vegas. Provided clinical experience with Vraylar in his practice.

Dr. Jeffery referred the board to the letters regarding Vraylar passed out at the meeting. Provided information on generic quetiapine ER and Vraylar. Recommended the medications in the class be considered clinically and therapeutically equivalent.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

Dr. Jeffery recommended to the Board to make quetiapine XR preferred and brand Seroquel XR as non-preferred.

Dr. Adashek referenced the letters from the physicians asking for Vraylar to be made preferred, asked if there was any reason to not make it preferred.

Dr. Jeffery responded that it is a good medication, but there are other medications that are also effective.

Dr. Decerbo asked if this class only requires the failure of a single preferred agent before getting a non-preferred. They would just need to fail a single preferred agent.

Dr. Jeffery responded just one preferred agent must be tried.

A motion was made to make Vraylar preferred and accept the remainder of the recommendation. The motion was seconded.

Dr. Decerbo asked to make separate motions.

A motion was made to make Vraylar preferred. The motion was seconded, voted as approved, the motion carried.

A motion was made to accept the rest of the recommendations. The motion was seconded and voted as approved. The motion carried.

w. Respiratory Agents - Respiratory Anti-inflammatory Agents - Leukotriene Receptor Antagonists

Dr. Nagy called for public comment.

Dr. Jeffery provided information for Zyflo, Zyflo CR and a generic zileuton ER. Recommended the medications in the class be considered clinically and therapeutically equivalent.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

Dr. Jeffery recommended Zyflo, Zyflo CR be made preferred and zileuton ER be non-preferred, and keep the rest of the class the same.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

x. Respiratory Agents - Respiratory Corticosteriod/Long-Acting Beta-Agonist Combinations

Dr. Nagy called for public comment.

Dr. Jeffery provided a brief overview of the new agents in the class, Airduo and fluticasone propionate/salmeterol. The same ingredients as in Advair, but a different delivery mechanism. Recommended the medications in the class be considered clinically and therapeutically equivalent.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

Dr. Jeffery recommended the new agents Airduo and fluticasone propionate/salmeterol be made non-preferred and keep the rest of the class the same.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

5. Annual Review – Established Drug Classes

a. Cardiovascular Agents - Antihypertensive Agents - Angiotensin II Receptor Antagonists

Dr. Jeffery recommended this class be included in the review with no recommended changes.

Dr. Nagy agreed and moved the agenda item to the no recommended changes.

b. Cardiovascular Agents - Antihypertensive Agents - Calcium-Channel Blockers

Dr. Jeffery recommended this class be included in the review with no recommended changes.

Dr. Nagy agreed and moved the agenda item to the no recommended changes.

c. Cardiovascular Agents - Antihypertensive Agents - Vasodilators – Oral

Dr. Nagy called for public comment.

Dr. Jeffery provided a brief overview of the class. Letairis is in the same class as Tracleer, a preferred medication. Recommended the medications in the class be considered clinically and therapeutically equivalent.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

Dr. Jeffery recommended Latairis move to non-preferred and grandfather anyone currently on Letairis to continue without PA requirements.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

d. Gastrointestinal Agents - Antiemetics - Miscellaneous

Dr. Jeffery recommended this class be included in the review with no recommended changes.

Dr. Nagy agreed and moved the agenda item to the no recommended changes.

e. Hematological Agents - Anticoagulants - Oral

Dr. Nagy called for public comment.

Dr. Jeffery provided information on the new agent in the class, Bevyxxa. Covered indication and dosing. Recommended the medications in the class be considered clinically and therapeutically equivalent.

Dr. Decerbo asked if Yosprala, aspirin/omeprazole should be included.

Dr. Jeffery answered that medication is included in another class, the antiplatelets.

A motion was made to accept the recommendation minus the Yosprala. The motion was seconded and voted as approved. The motion carried.

Dr. Jeffery recommended Bevyxxa be made non-preferred due to the limited indications.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

f. Hematological Agents - Platelet Inhibitors Public Comment

Dr. Nagy called for public comment.

Dr. Jeffery provided an overview of the new agents, prasugrel and Yosprala. Recommended the medications in the class be considered clinically and therapeutically equivalent.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

Dr. Jeffery recommended prasugrel and Yosprala be made non-preferred and the rest of the class remain the same.

Dr. Decerbo asked for clarification that brand Effient will remain non-preferred as with the new generic prasugrel.

Dr. Jeffery confirmed.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

g. Hormones and Hormone Modifiers - Pituitary Hormones - Growth hormone modifiers

Dr. Jeffery recommended this class be included in the review with no recommended changes.

Dr. Nagy agreed and moved the agenda item to the no recommended changes.

h. Neurological Agents - Anticonvulsants

Dr. Nagy called for public comment.

Danielle Marano, executive director for the Epilepsy Foundation of Nevada. Asked the board to open access to all anti-epileptics so patients do not have to fail or try other agents first.

Toya Malone Davis, neurologist and epileptologist in Las Vegas. Asked to board to open access to all medications. Explained difficulty of having to step through preferred agents for certain patients. Advocated to have as open access as possible.

Fern Leal, Medical Director with UCB Pharma. Provided information on Briviact, including epilepsy basics, treatment guidelines, pharmacokinetics of different drugs, drug interactions and mechanisms of actions. Clinical studies were presented. Informed the board of new indications including monotherapy. Asked the Board to provide access to Briviact.

Dr. Jeffery asked if the indication was updated to include monotherapy.

Dr. Leal responded that Briviact is indicated for monotherapy.

Dr. Jeffery provided information on the change of indication for Fycompa that included monotherapy. Briviact also was mentioned with the updated indication for monotherapy. Recommended the medications in the class be considered clinically and therapeutically equivalent.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

Dr. Jeffery recommended to move Fycompa and Briviact to preferred to keep consistent with drugs with indications for monotherapy.

Dr. Decerbo offered information that there are several products available and moving Briviact will keep the list consistent with practices of the past to have monotherapy products as preferred.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

i. Ophthalmic Agents - Ophthalmic Anti-infective/Anti-inflammatory Combinations

Dr. Nagy called for public comment.

Dr. Jeffery provided information of why this class is being reviewed. Recommended the medications in the class be considered clinically and therapeutically equivalent.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

Dr. Jeffery recommended the board move Tobradex Suspension preferred and the generic tobramycin/dexamethasone suspension as non-preferred.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

j. Psychotropic Agents - Anxiolytics, Sedatives, and Hypnotics

Dr. Nagy called for public comment.

Dr. Jeffery provided a brief overview of Zolpimist, the nasal spray of zolpidem. Recommended the medications in the class be considered clinically and therapeutically equivalent.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

Dr. Jeffery recommended moving Zolpimst to non-preferred.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

k. Respiratory Agents - Nasal Antihistamines

Dr. Nagy called for public comment.

Dr. Jeffery provided a brief overview of Astepro and olopatadine. Recommended the medications in the class be considered clinically and therapeutically equivalent.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

Dr. Jeffery recommended Astepro be moved from preferred to non-preferred and the rest of the class remain the same.

A motion was made to accept the recommendation. The motion was seconded and voted as approved. The motion carried.

l. Respiratory Agents - Respiratory Anti-inflammatory Agents - Nasal Corticosteroids

Dr. Jeffery recommended this class be included in the review with no recommended changes.

Dr. Nagy agreed and moved the agenda item to the no recommended changes.

6. Annual Review – Drug Classes Without Proposed Changes

Dr. Nagy called for public comment.

Dr. Jeffery reviewed the classes with no recommended changes.

a. Public Comment
b. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the division of Health Care Financing and Policy Without Changes
    i. Analgesics - Analgesic/Miscellaneous - Neuropathic Pain/Fibromyalgia Agents
    ii. Analgesics - Analgesic/Miscellaneous - Tramadol and Related Drugs
    iii. Analgesics - Opiate Agonists - Abuse Deterrent
    iv. Analgesics - Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) - Oral
    v. Antihistamines - H1 blockers - Non-Sedating H1 Blockers
    vi. Anti-infective Agents - Antivirals - Alpha Interferons
    vii. Anti-infective Agents - Antivirals - Anti-hepatitis Agents - Polymerase Inhibitors/Combination Products
    viii. Anti-infective Agents - Antivirals - Anti-hepatitis Agents - Ribavirins
    ix. Anti-infective Agents - Antivirals - Anti-Herpetic Agents
    x. Anti-infective Agents - Cephalosporins - Second-Generation Cephalosporins
    xi. Anti-infective Agents - Cephalosporins - Third-Generation Cephalosporins
    xii. Anti-infective Agents - Macrolides
    xiii. Anti-infective Agents - Quinolones - Quinolones - 2nd Generation
    xiv. Biologic Response Modifiers - Multiple Sclerosis Agents - Oral
    xv. Biologic Response Modifiers - Multiple Sclerosis Agents - Specific Symptomatic Treatment
    xvi. Cardiovascular Agents - Antihypertensive Agents - Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors)
    xvii. Cardiovascular Agents - Antihypertensive Agents - Beta-Blockers
    xviii. Cardiovascular Agents - Antihypertensive Agents - Direct Renin Inhibitors
    xix. Cardiovascular Agents - Antihypertensive Agents - Vasodilators - Inhaled
    xx. Cardiovascular Agents - Antilipemics - Bile Acid Sequestrants
    xxi. Cardiovascular Agents - Antilipemics - Fibric Acid Derivatives
    xxii. Cardiovascular Agents - Antilipemics - Niacin Agents
    xxiii. Cardiovascular Agents - Antilipemics - Omega-3 Fatty Acids
    xxiv. Dermatological Agents - Topical Analgesics
    xxv. Dermatological Agents - Topical Anti-infectives - Acne Agents: Topical, Benzoyl Peroxide, Antibiotics and Combination Products

xxvi. Dermatological Agents - Topical Anti-infectives - Impetigo Agents: Topical
xxvii. Dermatological Agents - Topical Anti-infectives - Topical Antifungals (onychomycosis)
xxviii. Dermatological Agents - Topical Anti-inflammatory Agents - Immunomodulators: Topical
xxix. Dermatological Agents - Topical Antineoplastics - Topical Retinoids
xxx. Electrolytic and Renal Agents - Phosphate Binding Agents
xxxi. Gastrointestinal Agents - Antiemetics - Serotonin-receptor antagonists/Combo
xxxii. Gastrointestinal Agents - Antiulcer Agents - H2 blockers
xxxiii. Gastrointestinal Agents - Functional Gastrointestinal Disorder Drugs (New)
xxxiv. Gastrointestinal Agents - Gastrointestinal Enzymes
xxxv. Genitourinary Agents - Benign Prostatic Hyperplasia (BPH) Agents - 5-Alpha Reductase Inhibitors
xxxvi. Genitourinary Agents - Benign Prostatic Hyperplasia (BPH) Agents - Alpha-Blockers
xxxvii. Genitourinary Agents - Bladder Antispasmodics
xxxviii. Hematological Agents - Erythropoiesis-Stimulating Agents
xxxix. Hormones and Hormone Modifiers - Androgens
xl. Hormones and Hormone Modifiers - Antidiabetic Agents - Alpha-Glucosidase Inhibitors/Amylin analogs/Misc.
xli. Hormones and Hormone Modifiers - Antidiabetic Agents - Dipeptidyl Peptidase-4 Inhibitors
xlii. Hormones and Hormone Modifiers - Antidiabetic Agents - Insulins (Vials, Pens and Inhaled)
xliii. Hormones and Hormone Modifiers - Antidiabetic Agents - Meglitinides
xliv. Hormones and Hormone Modifiers - Antidiabetic Agents - Sulfonylureas
xlv. Hormones and Hormone Modifiers - Antidiabetic Agents - Thiazolidinediones
xlvi. Hormones and Hormone Modifiers - Progestins for Cachexia
xlvii. Musculoskeletal Agents - Antigout Agents
xlviii. Musculoskeletal Agents - Bone Resorption Inhibitors - Nasal Calcitonins
xlix. Musculoskeletal Agents - Restless Leg Syndrome Agents
l. Musculoskeletal Agents - Skeletal Muscle Relaxants
li. Neurological Agents - Alzheimers Agents
lii. Neurological Agents - Anticonvulsants - Barbiturates
liii. Neurological Agents - Anticonvulsants - Benzodiazepines
liv. Neurological Agents - Anticonvulsants - Hydantoins
lv. Neurological Agents - Antiparkinsonian Agents - Non-ergot Dopamine Agonists
lvi. Ophthalmic Agents - Antiglaucoma Agents - Carbonic Anhydrase Inhibitors/Beta-Blockers
lvii. Ophthalmic Agents - Antiglaucoma Agents - Ophthalmic Prostaglandins
lviii. Ophthalmic Agents - Ophthalmic Antihistamines
lix. Ophthalmic Agents - Ophthalmic Anti-infectives - Ophthalmic Macrolides
lx. Ophthalmic Agents - Ophthalmic Anti-inflammatory Agents - Ophthalmic Corticosteroids

lxi. Ophthalmic Agents - Ophthalmic Anti-inflammatory Agents - Ophthalmic Nonsteroidal Anti-inflammatory Drugs (NSAIDs)
lxii. Ophthalmic Agents - Ophthalmics for Dry Eye Disease
lxiii. Otic Agents - Otic Anti-infectives - Otic Quinolones
lxiv. Psychotropic Agents - Antidepressants - Other
lxv. Psychotropic Agents - Antidepressants - Selective Serotonin Reuptake Inhibitors (SSRIs)
lxvi. Psychotropic Agents - Psychostimulants - Narcolepsy Agents
lxvii. Respiratory Agents - Respiratory Anti-inflammatory Agents - Respiratory Corticosteroids
lxviii. Respiratory Agents - Respiratory Anti-inflammatory Agents - Phosphodiesterase Type 4 Inhibitors
lxix. Respiratory Agents - Respiratory Antimuscarinics
lxx. Respiratory Agents - Respiratory Beta-Agonists - Long-Acting Respiratory Beta-Agonist
lxxi. Respiratory Agents - Respiratory Beta-Agonists - Short-Acting Respiratory Beta-Agonist
lxxii. Respiratory Agents - Respiratory Long-Acting Antimuscarinic/Long-Acting Beta-Agonist Combinations
lxxiii. Toxicology Agents - Antidotes - Opiate Antagonists
lxxiv. Toxicology Agents - Substance Abuse Agents - Mixed Opiate Agonists/Antagonists

c. **For Possible Action**: Committee Discussion and Approval of the Drug Classes without Changes

A motion was made to accept the drug classes without changes. The motion was seconded and voted as approved. The motion carried.

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

Dr. Jeffery referenced some agents that will be coming out in the immunomodulator classes.

8. Closing Discussion

Dr. Nagy called for public comment.

The date of the next meeting will be December 7th. The location is to be determined.

Dr. Nagy adjourned the meeting 3:15PM.

INTRODUCTION

- Irritable bowel syndrome (IBS) is a gastrointestinal disorder that most commonly manifests as chronic abdominal pain and altered bowel habits in the absence of any organic disorder (Wald, 2017).
- IBS may consist of diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), IBS with a mixed symptomatology (IBS-M), or unclassified IBS (IBS-U). Switching between the subtypes of IBS is also possible (Ford et al, 2014).
- IBS is a functional disorder of the gastrointestinal tract characterized by abdominal pain, discomfort, and bloating, as well as disturbed bowel habit. The exact pathogenesis of the disorder is unknown; however, it is believed that altered gastrointestinal tract motility, visceral hypersensitivity, autonomic dysfunction, and psychological factors indicate disturbances within the enteric nervous system, which controls the gastrointestinal system (Ford, 2009; Andresen, 2008).
- Prevalence estimates of IBS range from 5% to 15%, and it typically occurs in young adulthood (Ford et al, 2014). IBS-D is more common in men, and IBS-C is more common in women (World Gastroenterology Organization [WGO], 2015).
- Symptoms of IBS often interfere with daily life and social functioning (WGO, 2015).
- The general goals of therapy are to alleviate the patient's symptoms and to target any specific exacerbating factors (e.g., medications, dietary changes), concerns about serious illness, stressors, or potential psychiatric comorbidities that may exist.
- Non-pharmacological interventions to combat IBS symptoms include dietary modifications such as exclusion of gas-producing foods (e.g., beans, prunes, brussel sprouts, bagels, etc.), trials of gluten avoidance, consumption of probiotics, as well as psychosocial therapies (e.g., hypnosis, biofeedback, etc.) (Ford et al, 2014).
- Depending upon the clinical presentation of an individual's IBS condition, a number of therapies exist to help alleviate the constellation of disease symptoms. Commonly used agents that are often initiated for disease control include poorly absorbable antibiotics such as rifaximin; laxative agents, including stimulant laxatives (bisacodyl, etc.) and osmotic laxatives (polyethylene glycol [PEG], lactulose, etc.); antispasmodics (e.g., dicyclomine, hyoscine, etc.); selective chloride channel activators (e.g. lubiprostone); serotonin-3 receptor antagonists (e.g., alosetron); guanylate cyclase-c agonists (e.g., linaclotide); antidepressants such as tricyclic antidepressants and selective serotonin reuptake inhibitors; select probiotics; and peppermint oil (Ford et al, 2014).
- In addition to treatment of IBS-C, AMITIZA® (lubiprostone), LINZESS® (linaclotide), and TRULANCE™ (plecanatide) are indicated for the treatment of chronic idiopathic constipation (CIC). Symptoms of constipation are common with a prevalence of approximately 16% in adults overall and 33% in adults >60 years of age. Constipation is defined as fewer than three bowel movements (BMs) per week with symptoms that may include hard stools, a feeling of incomplete evacuation, abdominal discomfort, bloating, and distention. Initial treatment typically includes osmotic laxatives, stimulant laxatives, and increased fiber intake (American Gastroenterological Association [AGA] Medical Position Statement, 2013; Bharucha et al, 2013).
- AMITIZA (lubiprostone) is also Food and Drug Administration (FDA)-approved for the treatment of opioid-induced constipation (OIC) in adults with chronic, non-cancer related pain. OIC is a frequent adverse event of opioid therapy. Opioids exert their action on the enteric nervous system causing dysmotility, decreased fluid secretion and sphincter dysfunction. Laxatives are typically prescribed but often are inadequate to completely relieve constipation (Brock et al, 2012).
- Three other products are approved for use in OIC:
  - RELISTOR® (methylnatrexone) injection is an opioid receptor antagonist indicated for treatment of OIC in adults with chronic non-cancer pain and in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. RELISTOR has also been FDA-approved in a tablet formulation, which is indicated for the treatment of OIC in adults with chronic non-cancer pain.
  - MOVANTIK® (naloxegol) and SYMPROIC® (naldemedine) are once-daily oral peripherally acting mu-opioid receptor antagonists (PAMORA) indicated for the treatment of OIC in adult patients with chronic non-cancer pain.

- LOTRONEX® (alosetron) is FDA-approved with restrictions for the treatment of women who exhibit severe IBS-D and have failed conventional therapy.

- ZELNORM® (tegaserod) was approved in July 2002 for short-term treatment of IBS-C in women and in August 2004 for treatment of CIC in men and women <65 years of age. In March 2007, the FDA requested the manufacturer to discontinue the marketing of ZELNORM due to safety concerns related to increased rate of heart attack, stroke, and worsening heart-related chest pain. In July 2007, ZELNORM became available for use as a treatment investigational new drug (IND) protocol for IBS-C and CIC in women < 55 years of age meeting specific guidelines; however, in April 2008, the manufacturer discontinued the availability as a treatment IND. ZELNORM is currently available for use only in emergency situations with FDA authorization (Clinical Pharmacology, 2016).
- IBS-D is an IBS subtype characterized mainly by loose or watery stools at least 25% of the time. In May 2015, two new treatments with different mechanisms of action were approved for use in the treatment of IBS-D, VIBERZI® (eluxadoline) and XIFAXAN® (rifaximin). VIBERZI is a mu-opioid receptor agonist, and XIFAXAN is a rifamycin antibacterial (FDA News Release, 2015). VIBERZI is a schedule IV controlled substance.
- The scope of this review will focus upon AMITIZA (lubiprostone), LINZESS (linaclotide), LOTRONEX (alosetron), MOVANTIK (naloxegol), RELISTOR (methylnaltrexone bromide), SYMPROIC (naldemedine), TRULANCE (plecanatide), VIBERZI (eluxadoline), and XIFAXAN (rifaximin) for their respective FDA-approved indications, which are outlined in Table 2.
- Medispan Classes: Agents for CIC (TRULANCE); Gastrointestinal Chloride Channel Activators (AMITIZA); IBS Agents (LOTRONEX, LINZESS, VIBERZI); Peripheral Opioid Receptor Antagonists (MOVANTIK, RELISTOR, SYMPROIC); Anti-infective Agents – Misc (XIFAXAN)

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
AMITIZA (lubiprostone)	Sucampo Pharmaceuticals, Inc./Takeda	01/31/2006	-
LINZESS (linaclotide)	Ironwood Pharmaceuticals/ Forest Pharmaceuticals	08/30/2012 (145 and 290 mcg capsules) 1/25/2017 (72 mcg capsule)	-
LOTRONEX (alosetron)	Prometheus Laboratories, Inc.	02/09/2000	✔
MOVANTIK (naloxegol)	AstraZeneca	09/16/2014	-
RELISTOR (methylnaltrexone bromide)	Salix Pharmaceuticals	04/24/2008 (injection) 07/19/2016 (tablet)	-
SYMPROIC® (naldemedine)	Shionogi Inc.	3/23/2017	-
TRULANCE (plecanatide)	Synergy Pharmaceuticals Inc.	1/19/2017	-
VIBERZI (eluxadoline)	Patheon Pharmaceuticals/Forest Pharmaceuticals (now Actavis)	05/27/2015	-
XIFAXAN (rifaximin)	Salix Pharmaceuticals	05/25/2004 (200 mg tablet) 03/24/2010 (550 mg tablet)	-

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

INDICATIONS

Table 2. FDA Approved Indications

Indication	AMITIZA (lubiprostone)	LINZESS (linaclotide)	LOTRONEX (alosetron)	MOVANTIK (naloxegol)	RELISTOR (methylnaltrexone bromide)	SYMPROIC (naldemedine)	TRULANCE (plecanatide)	VIBERZI (eluxadoline)	XIFAXAN (rifaximin)
Treatment of CIC in adults	✔	✔					✔		
Treatment of OIC in adults with chronic, non-cancer pain	✔*			✔	✔	✔			
Treatment of OIC in patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation.	✔			✔	✔	✔			
Treatment of OIC in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient or pain caused by active cancer which requires opioid dosage escalation for palliative care					✔†				
Treatment of IBS-C in women ≥18 years of age	✔								
Treatment of IBS-C in adults		✔							
Treatment of IBS-D in adults								✔	✔‡
Women with severe IBS-D who have: • chronic IBS symptoms (generally lasting six months or longer) • had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and not responded adequately to conventional therapy§			✔						

*Effectiveness of AMITIZA in the treatment of opioid-induced constipation in patients taking diphenylheptane opioids such as methadone has not been established.

†Injection formulation only. Use of RELISTOR beyond four months in treatment of OIC in patients with advanced illness has not been studied.

‡XIFAXAN has additional indications for treatment of traveler's diarrhea (TD) caused by noninvasive strains of *Escherichia coli* in adult and pediatric patients 12 years of age and older, and reduction in risk of overt hepatic encephalopathy (HE) recurrence in adults. Do not use XIFAXAN in patients with TD complicated by fever or blood in the stool or diarrhea due to pathogens other than *E. coli*.

§IBS-D is severe if it includes diarrhea and one or more of the following: frequent and severe abdominal pain/discomfort, frequent bowel urgency or fecal incontinence, disability or restriction of daily activities due to IBS.

(Prescribing information: AMITIZA, 2017; LINZESS, 2017; LOTRONEX, 2016; MOVANTIK, 2017; RELISTOR, 2017; SYMPROIC 2017; TRULANCE, 2017; VIBERZI, 2017; XIFAXAN, 2017)

- LOTRONEX was approved by the FDA in February of 2000 and was later withdrawn from the market due to numerous reports of serious and fatal gastrointestinal adverse events. Approval of a supplemental New Drug Application (sNDA) was accepted in July 2002 by the FDA to allow restricted marketing of LOTRONEX to treat only women with severe IBS-D. Physicians are required to complete training before prescribing alosetron to ensure that the benefits and risks of the agent are considered before administering it to patients (LOTRONEX FDA press release, 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

- There are currently no head-to-head trials comparing the available agents used in the treatment of CIC, OIC, IBS-C, and IBS-D.

CIC

- A network meta-analysis demonstrated linaclotide and lubiprostone to be superior to placebo for the treatment of CIC. Treatment with linaclotide resulted in a significant increase in the proportion of patients with ≥3 complete spontaneous bowel movements (CSBMs)/week compared with placebo with a relative risk (RR) of 1.96 (95% confidence interval [CI], 1.12 to 3.44), and was superior vs placebo with an increase over baseline by ≥1 CSBM/week (RR 1.72; 95% CI, 1.18 to 2.52). For change from baseline in the number of SBMs/week, the weighted mean difference (WMD) with lubiprostone was 1.91 (95% CI, 1.41 to 2.41) and WMD with linaclotide was 2.11 (95% CI, 1.68 to 2.54) (Nelson et al, 2017).
- A meta-analysis demonstrated the total pooled treatment effect of spontaneous bowel movements (SBMs)/week in patients with CIC or IBS-C was greater in lubiprostone-treated patients compared with placebo (combined standardized difference in means, 0.419; 95% CI, 0.088 to 0.750; P<0.001) (Li et al, 2016).
- In another meta-analysis, treatment with linaclotide 145 mcg demonstrated significant improvements in the weekly frequency of CSBMs from baseline compared with placebo in patients with CIC (RR, 3.80; 95% CI, 2.20 to 6.55). Results were similar for abdominal discomfort or bloating responders for linaclotide 145 mg vs placebo, with pooled RRs of 1.57 (95% CI, 1.26 to 1.97) and 1.97 (95% CI, 1.44 to 2.69), respectively (Videlock et al, 2013).
- Results from a long-term safety study illustrated that overall lubiprostone was well tolerated. The most commonly reported events were diarrhea, nausea, urinary tract infection, sinusitis, abdominal distension, and headache. Significant changes from baseline in hematology, laboratory values, vital signs, weight, body mass index and physical examination were not seen over the study duration (Chey et al, 2012).
- For the recently approved linaclotide 72 mcg, a double-blind, placebo-controlled, multicenter, randomized controlled trial demonstrated that linaclotide improved the weekly frequency of CSBMs compared with placebo, with 13% of linaclotide-treated patients meeting responder requirements compared with 9% in the placebo group (95% CI, 4.8% to 12.5%) (LINZESS prescribing information, 2017).
- Two double-blind, placebo-controlled, multicenter, randomized controlled trials demonstrated that treatment with plecanatide 3 mg significantly increased weekly CSBM frequency as measured by the overall CSBM responder rate vs placebo (Study 1: 21.0% vs 10.2%; P<0.001; Study 2: 20.1% vs 12.8%; P=0.004) (Miner et al [abstract], 2016; Miner et al, 2017).

IBS

- In 2 meta-analyses, linaclotide demonstrated significant improvements in the FDA-defined composite endpoint of improvement in both daily worst abdominal pain scores and CSBM frequency from baseline compared to placebo after 12 weeks and demonstrated a similar result when compared over 26 weeks (Atluri et al, 2014; Videlock et al, 2013). More patients in the placebo treatment arm failed to achieve the FDA endpoint compared with patients treated with linaclotide (82.6% vs 66%; RR of failure to respond 0.80; 95% CI, 0.76 to 0.85).
- For the treatment of IBS-C, placebo-controlled trials demonstrated that lubiprostone had a significantly higher percentage of overall responders (Drossman et al, 2007; Drossman et al, 2009; Johanson et al, 2008b). In multiple 12-week studies, lubiprostone-treated patients reported significant improvements in abdominal pain/discomfort, stool consistency, straining, constipation severity, and quality of life (Drossman et al, 2007; Drossman et al, 2009; Johanson et al, 2008b).
- Treatment with alosetron is associated with a significantly greater proportion of patients reporting adequate relief of IBS pain and discomfort, and improvements in bowel function compared to placebo (Camilleri et al, 2000; Camilleri et al, 2001; Chey et al, 2004; Lembo et al, 2001; Lembo et al, 2004; Rahimi et al, 2008; Watson et al, 2001).
- A meta-analysis concluded that the 5-HT3 antagonists as a class significantly improve symptoms of non-constipating or IBS-D in both men and women compared to placebo; however, these agents were also associated with a greater increase in the risk of causing constipation compared to placebo (Andresen et al, 2008).
- Alosetron treatment has been shown to positively impact global symptoms, as well as pain and discomfort in non-constipated females with IBS. This analysis further supports the increased chance of developing constipation with alosetron compared to placebo (Cremonini et al, 2003).
- The safety and efficacy of eluxadoline for treatment of IBS-D were established in two randomized, multicenter, multinational, double-blind, placebo-controlled, phase 3 clinical trials in which 2,427 patients with IBS-D (meeting Rome III criteria), average abdominal pain scores greater than 3 on a 0 to 10 scale during the week prior to randomization, and

a Bristol Stool Scale (BSS) of 5.5 or greater with at least five days of BSS of 5 or more during the week prior to randomization. Patients were randomly assigned to receive eluxadoline 75 mg, 100 mg, or placebo twice daily. The primary endpoint was defined by the simultaneous improvement in the daily worst abdominal pain score by 30% or more compared to the baseline weekly average and a reduction in the BSS to 5 or less on at least 50% of the days within a 12-week or 26-week time interval. From weeks 1 through 12, the primary endpoint was achieved by 23.9% of patients in the 75 mg group (P=0.01) and 25.1% of patients in the 100 mg group (P=0.004) versus 17.1% of patients in the placebo group. From weeks 1 through 26, 23.4% in the 75 mg group (P=0.11) and 29.3% in the 100 mg group (P<0.001) achieved the primary endpoint compared to 19% in the placebo group (Lembo et al, 2016).

- The safety and effectiveness of rifaximin for treatment of IBS-D were established in three double-blind, placebo-controlled trials.
  - In the first two trials, 1,258 patients with IBS-D (Rome II criteria) were randomly assigned to receive rifaximin 550 mg three times daily (n=624) or placebo (n=634) for 14 days, and then followed for a 10-week treatment-free period. The primary endpoint for both trials was the proportion of patients who achieved adequate relief of IBS signs and symptoms for at least two of four weeks during the month following 14 days of treatment. More rifaximin-treated patients reported improvements in abdominal pain and stool consistency than those on placebo (Trial 1: 47% vs 39%; P<0.05; Trial 2: 47% vs 36%; P<0.01 in rifaximin and placebo groups, respectively).
  - TARGET3 was the third trial, which evaluated repeat courses of rifaximin in adult patients with IBS-D (Rome III criteria) for up to 46 weeks. During a 14-day open-label phase, 1,074 patients responded to rifaximin and were evaluated over 22 weeks for continued response or recurrence of IBS symptoms. A total of 636 patients who developed recurrent signs and symptoms after a single treatment course of rifaximin were randomized to receive either rifaximin 550 mg three times daily (n=328) or placebo (n=308) for two additional 14-day courses separated by 10 weeks. More patients treated with rifaximin than placebo were responders in abdominal pain and stool consistency in this phase of the study (38% vs 31% in rifaximin and placebo groups, respectively; P<0.05) (ClinicalTrials.gov NCT01543178, 2016).

OIC

- Two randomized, double-blind, placebo-controlled trials, COMPOSE-1 and COMPOSE-2, were conducted in adult patients with chronic non-cancer pain and OIC to assess the efficacy and safety of naldemedine. The primary endpoint was the proportion of responders, where response was defined as at ≥3 SBMs per week. Patients in COMPOSE-1 and COMPOSE-2 were randomized to receive naldemedine 0.2 mg (n=274; n=277) or placebo (n=273; n=276) once daily for 12 weeks. Results from both COMPOSE-1 and COMPOSE-2 showed that participants receiving naldemedine 0.2mg experienced a significantly higher response compared to patients receiving placebo in both studies(COMPOSE-1 responders: 47.6% vs 34.6%; P=0.002 and COMPOSE-2 responders: 52.5% vs 33.6%; P<0.0001, respectively). Treatment-related adverse events due to gastrointestinal disorders were more common with naldemedine than with placebo in both studies (15% vs 7% and 16% and 7%, respectively) (Hale et al, 2017).
- A total of 1,300 patients were enrolled in three, double-blind, randomized controlled trials evaluating lubiprostone compared to placebo in patients with chronic, non-cancer related pain on stable opioid therapy and constipation. In Study 1, overall responder rate, the primary outcome, was defined as ≥1 SBM improvement over baseline for all treatment weeks and ≥3 SBMs per week for at least nine of the 12-week study period. Lubiprostone (27.1%) had a significantly higher “overall responder rate” than placebo (18.9%; P=0.03) (Jamal et al, 2015). Primary outcome parameter for Study 2 and 3 was the mean change from baseline in SBM frequency at week eight. In Study 2, lubiprostone significantly increased the mean change from baseline in SBM frequency compared to placebo (P=0.004). In Study 3, the difference was not statistically significant; however, Study 3 was the only study, which enrolled patients who received diphenylheptane opioids such as methadone. Studies 2 and 3 have not been published in a peer-reviewed journal at this time.
- A prospective, randomized, double-blind, placebo-controlled trial was conducted to evaluate the efficacy and safety of lubiprostone for relieving symptoms of OIC in adult patients with chronic non-cancer pain. OIC was defined as less than three SBMs per week. Patients were randomized to receive lubiprostone 24 mcg (n=210) or placebo (n=218) twice daily for 12 weeks. The primary endpoint was change from baseline in SBM frequency at week eight. Changes from baseline in SBM frequency rates were significantly higher at week eight (P=0.005) and overall (P=0.004) in patients treated with lubiprostone compared with placebo. The most common treatment-related adverse events with lubiprostone and placebo were nausea (16.8% vs 5.8%, respectively), diarrhea (9.6% vs 2.9%, respectively), and abdominal distention (8.2% vs 2.4%, respectively). No lubiprostone-related serious adverse events occurred (Cryer et al, 2014).
- A 2013 systematic review evaluated pharmacological therapies for the treatment of OIC. A total of 14 randomized clinical trials of mu-opioid receptor antagonists were included. All treatments including methylnaltrexone, naloxone, and

alvimopan, were superior to placebo for the treatment of OIC. Lubiprostone was included in the review; however, the reporting of data precluded meta-analysis (Ford et al, 2013).

- In 2014, another systematic review of 21 randomized clinical trials evaluated seven pharmacological treatments of OIC. Efficacy assessment was based on objective outcome measures (OOMs): BM frequency, BM within four hours, and time to first BM. Methylnatrexone showed improvements in all three OOMs. Randomized control trials in naloxone and alvimopan tended to be effective for BM frequency measures. Naloxegol (≥ 12.5 mg) improved all OOMs. Though effectiveness of lubiprostone was demonstrated for all OOMs, group differences were small to moderate. Although not FDA-approved, CB-5945 and prucalopride tended to increase BM frequency, especially for 0.1 mg twice daily and 4 mg daily, respectively. Besides nausea and diarrhea, abdominal pain was the most frequent adverse event for all drugs except for alvimopan. Treatment-related serious adverse events were slightly higher for alvimopan (cardiac events) and prucalopride (severe abdominal pain, headache) (Siemens et al, 2015).
- The efficacy of naloxegol has been established in K4 and K5, two replicate Phase 3 clinical trials with a total of 1,352 participants with OIC who had taken opioids for at least four weeks for non-cancer related pain. Participants were randomly assigned to receive oral naloxegol 12.5 mg or 25 mg or placebo once daily for 12 weeks. The trials were designed to measure a response rate, defined as ≥3 SBMs per week and an increase of ≥1 SBM from baseline.
  - Results from K4 showed that participants receiving naloxegol 25 mg or naloxegol 12.5 mg both experienced a significantly higher response rate compared to participants receiving placebo (P=0.001 and P=0.02, respectively). Results from K5 also showed significantly higher response rates in participants receiving naloxegol 25 mg vs placebo (P=0.02) but did not show a significant difference in response rate in patients receiving naloxegol 12.5 mg vs placebo (P=0.2) (Chey et al, 2014).
  - In K4, patients with an inadequate response to laxatives achieved a significantly higher response with naloxegol 25 mg vs placebo (P=0.002) and with naloxegol 12.5 mg vs placebo (P=0.03). In K5, patients receiving naloxegol 25 mg achieved a significantly higher response rate vs placebo (P=0.01); however, patients receiving naloxegol 12.5 mg did not have a significantly higher response rate.
  - Median time to first SBM was significantly shorter with both naloxegol 12.5 mg and 25 mg compared to placebo in K4 and was significantly shorter with naloxegol 25 mg in K5 (P<0.001 for all comparisons).
  - Average pain scores and opioid use remained relatively stable in both studies for patients receiving naloxegol; thus, supporting the preservation of centrally mediated analgesia.
- Clinical trials of methylnaltrexone injection in patients with advanced illness have shown response over several months with most patients reporting laxation effects similar to SBMs and predictable timing (Bull et al, 2015; Thomas et al, 2008). Similar findings have been reported in patients with OIC with chronic non-cancer pain (Michna et al, 2011, Webster et al, 2017).
- The efficacy of methylnaltrexone tablets was demonstrated in a randomized, double-blind, placebo-controlled study in patients using opioids for chronic non-cancer pain. Patients were randomized to methylnaltrexone (150 mg, 300 mg, or 450 mg) or placebo once daily for a period of four weeks followed by as-needed dosing for 8 weeks. A responder to methylnaltrexone treatment was defined as a patient with three or more SBMs per week, with an increase of one or more SBMs per week over baseline, for at least three weeks in the four-week treatment period. The percentage of patients classified as responders was 42.8%, 49.3% (P=0.03 vs placebo), 51.5% (P=0.005 vs placebo), and 38.3% in the methylnaltrexone 150 mg, 300 mg, 450 mg and placebo groups, respectively (Rauck et al, 2017).
- A systematic review and network analysis compared the efficacy and safety of agents for the treatment of OIC, including lubriprostone, naldemedine, naloxegol, subcutaneous and oral methylnaltrexone, and 2 agents, alvimopan and prucalopride, not approved for OIC in the U.S. (Sridharan & Sivaramakrishan, 2017). Observations from 16 RCTs with 4,048 patients demonstrated lubriprostone, naldemedine, naloxegol, and subcutaneous and oral methyl naltrexone to perform better vs. placebo in terms of rescue-free bowel movements (RFBM). Based on the odds ratios from direct and indirect pooled estimates, treatment with subcutaneous methyl naltrexone resulted in significantly improved RFBMs vs. lubiprostone, naloxegol, and oral methyl naltrexone. Lubiprostone and naldemedine were associated with increased risks of adverse events, while subcutaneous methylnaltrexone did not significantly affect the analgesia due to background opioid use. Of note, the quality of evidence for the comparisons was either low or very low.

IBS and CIC

- An updated systematic review on IBS and CIC was commissioned by the American College of Gastroenterology to assess the efficacy of available therapies in treating IBS and CIC compared with placebo or no treatment. The secondary objectives included assessing the efficacy of available therapies in treating IBS according to predominant stool pattern reported (IBS-C, IBS-D, and IBS-M), as well as assessing adverse events with therapies for both IBS and CIC. Parallel-group, randomized controlled trials comparing active interventions with either placebo or no therapy were evaluated. Crossover trials were eligible for inclusion if extractable data were provided at the end of the first treatment period, before crossover. The following were identified as “strong” recommendations for IBS and CIC treatments:
  - IBS
    - There is insufficient evidence to recommend loperamide for use in IBS. Quality of evidence is very low.
    - Mixed 5-HT 4 agonists/5-HT 3 antagonists are not more effective than placebo at improving symptoms of IBS-C. Quality of evidence is low.
    - Linaclotide is superior to placebo for the treatment of IBS-C. Quality of evidence is high.
    - Lubiprostone is superior to placebo for the treatment of IBS-C. Quality of evidence is moderate.
  - CIC
    - Some medicinal and dietary fiber supplements increase stool frequency in patients with CIC. Quality of evidence is low.
    - PEG is effective in improving symptoms of CIC. Quality of evidence is high.
    - Lactulose is effective in improving symptoms of CIC. Quality of evidence is low.
    - Sodium picosulfate and bisacodyl are effective in CIC. Quality of evidence is moderate.
    - Prucalopride is more effective than placebo in improving symptoms of CIC. Quality of evidence is moderate.
    - Linaclotide is effective in CIC. It is generally safe, with the main adverse event being diarrhea. Quality of evidence is high.
    - Lubiprostone is effective in the treatment of CIC. Quality of evidence is high (Ford et al, 2014).

CLINICAL GUIDELINES

- Guidelines on management of constipation suggest increased fiber intake and osmotic laxatives. Stimulant laxatives are to be used as needed or as “rescue agents”. Lubiprostone and linaclotide can be considered when symptoms of constipation do not respond to laxatives (AGA, 2013; Bharucha et al, 2013; Lindberg et al, 2010).
- The American College of Gastroenterology monograph on the management of IBS and CIC makes the following statements (reported with the strength of recommendation and quality of evidence, respectively) (Ford et al, 2014):
  - Rifaximin is effective in reducing total IBS symptoms and bloating in IBS-D (weak; moderate)
  - Alosetron is effective in females with IBS-D (weak; moderate)
  - Linaclotide is superior to placebo for the treatment of IBS-C (strong; high)
  - Linaclotide is effective in CIC (strong; high)
  - Lubiprostone is superior to placebo for the treatment of IBS-C (strong; moderate)
  - Lubiprostone is effective in the treatment of CIC (strong; high)
- The AGA guideline on management of IBS makes the following statements (reported with strength of recommendation and quality of evidence, respectively) (Weinberg et al, 2014):
  - Recommends using linaclotide (over no drug treatment) in patients with IBS-C (strong; high)
  - Suggests using lubiprostone (over no drug treatment) in patients with IBS-C (conditional; moderate)
  - Suggests using rifaximin (over no drug treatment) in patients with IBS-D (conditional; moderate)
  - Suggests using alosetron (over no drug treatment) in patients with IBS-D to improve global symptoms (conditional; moderate)
- The 2015 WGO guideline on IBS lists rifaximin and alosetron as second-line therapies for IBS-D, although it notes a risk of ischemic colitis and constipation with alosetron. Lubiprostone and linaclotide are noted to be safe and effective for the treatment of IBS-C (WGO, 2015).
- In the 2014 Technical Review of the Pharmacological Management of Irritable Bowel Syndrome, the AGA Institute reviewed and graded the evidence for pharmacological interventions (linaclotide, lubiprostone, PEG laxative, rifaximin, alosetron, loperamide, tricyclic antidepressants [TCAs], selective serotonin reuptake inhibitors (SSRIs), and antispasmodics) for treatment of IBS. Review of the evidence for these pharmacological treatments showed that across all outcomes, evidence was high for linaclotide; moderate for lubiprostone, rifaximin, and alosetron; low for TCAs, SSRIs, and PEG; and very low for loperamide and antispasmodics (Chang et al, 2014).

SAFETY SUMMARY

- AMITIZA is contraindicated with known or suspected mechanical gastrointestinal obstruction. LOTRONEX is associated with several contraindications, including history of chronic or severe constipation or sequelae from constipation; intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation, and/or adhesions; ischemic colitis; impaired intestinal circulation, thrombophlebitis, or hypercoagulable state; Crohn's disease or ulcerative colitis; diverticulitis; severe hepatic impairment. LINZESS and TRULANCE are contraindicated in patients age 6 years or younger and in patients with known or suspected mechanical obstruction. MOVANTIK is contraindicated in patients with known or suspected gastrointestinal obstruction and at increased risk of recurrent obstruction, in patients with concomitant use of strong CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole), and when there is a known serious or severe hypersensitivity reaction to the drug or any of its excipients. RELISTOR is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction and at increased risk of recurrent obstruction. SYMPROIC is contraindicated in patients with known or suspected gastrointestinal obstruction or at increased risk of recurrent obstruction, and when there is a known serious or severe hypersensitivity reaction to the drug or any of its excipients. VIBERZI has several contraindications, including use in patients with the following conditions: known or suspected biliary duct obstruction or sphincter of Oddi disease or dysfunction; alcoholism, alcohol abuse, alcohol addiction, or more than three alcoholic beverages daily; history of pancreatitis or structural diseases of the pancreas including known or suspected hepatic duct obstruction; severe hepatic impairment; severe constipation or sequelae from constipation; known or suspected mechanical gastrointestinal obstruction; or use in patients without a gallbladder. XIFAXAN is contraindicated in patients with a hypersensitivity to rifaximin, any of the rifamycin antimicrobial agents, or any of the components in XIFAXAN.
  - On March 15, 2017, an FDA Drug Safety Communication was released warning that VIBERZI should not be used in patients who do not have a gallbladder. The safety announcement was based on an FDA review that found these patients have an increased risk of developing serious pancreatitis that could result in hospitalization or death (FDA Drug Safety Communication, 2017). A contraindication was added to the prescribing label for patients without a gallbladder due to an increased risk of developing serious pancreatitis. Pancreatitis was reported in patients taking either the 75 mg or 100 mg dose with most of the cases of serious pancreatitis occurring within a week of starting treatment.
- LINZESS and TRULANCE have a Boxed Warning regarding the contraindication in pediatric patients 6 years of age and younger due to the risk of serious dehydration; use should be avoided in children 6 to 17 years of age.
- LOTRONEX has a Boxed Warning regarding serious gastrointestinal adverse reactions such as ischemic colitis and serious complications of constipation that may lead to hospitalization, blood transfusion, surgery, and/or death. If patients develop constipation or ischemic colitis, LOTRONEX should be discontinued. The agent should be used only in female patients with severe IBS-D who have not benefited from usual therapies (Lotronex – FDA MedWatch, 2016).
- LOTRONEX also has a Risk Evaluation and Mitigation Strategy (REMS) that distributes education to providers about the risks for ischemic colitis and serious complications of constipation (Drugs@FDA, 2017).
- There are no known drug interactions with LINZESS. Diphenylheptane opioids such as methadone may interfere with the efficacy of AMITIZA. Clinically significant drug interactions associated with LOTRONEX include cytochrome P450 (CYP) 1A2 moderate inhibitors, CYP3A4 inhibitors, drugs that decrease gastrointestinal motility, and fluvoxamine.
- Concomitant use of MOVANTIK should be avoided with the following drug classes: moderate CYP3A4 inhibitors (e.g., diltiazem, erythromycin, verapamil) due to increased naloxegol concentrations, strong CYP3A4 inducers (e.g., rifampin) due to decreased naloxegol concentrations, and other opioid antagonists due to potentially additive effects that may increase risk of opioid withdrawal. In the event concomitant use with moderate CYP3A4 inhibitors is unavoidable, a dose reduction of MOVANTIK is warranted.
- Concomitant use of RELISTOR with other opioid antagonists should be avoided due to potentially additive effects that may increase risk of opioid withdrawal.
- Concomitant use of SYMPROIC should be avoided with strong CYP3A inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's Wort) due to a significant decrease in naldemedine concentrations, and other opioid antagonists due to potentially additive effect of opioid receptor antagonism that may increase the risk of opioid withdrawal. Moderate CYP3A inhibitors (e.g., fluconazole, atazanavir, aprepitant, diltiazem, erythromycin), strong CYP3A inhibitors (itraconazole, ketoconazole, clarithromycin, ritonavir, saquinavir), and P-glycoprotein inhibitors (e.g., amiodarone, captopril, cyclosporine, quercetin, quinidine, verapamil) can increase SYMPROIC concentrations.
- A clinically important drug interaction with VIBERZI which potentially may result in clinically relevant interactions may occur with concomitant use of the following drug classes: OATP1B1 inhibitors (e.g., cyclosporine, gemfibrozil, antiretrovirals, rifampin, eltrombopag, etc.), strong CYP inhibitors (e.g., ciprofloxacin, fluconazole, clarithromycin,

paroxetine, bupropion, etc.), constipation-inducing drugs (e.g., alosetron, anticholinergics, opioids, etc.), OATP1Bi and BCRP substrate (rosuvastatin), and CYP3A substrates (e.g., alfentanil, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus).

- Concomitant administration of drugs that are P-glycoprotein inhibitors with XIFAXAN can substantially increase the systemic exposure to rifaximin. Caution should be exercised when concomitant use of XIFAXAN and a P-glycoprotein inhibitor such as cyclosporine is needed.
- The IBS agents are most commonly associated with gastrointestinal-related adverse events.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
AMITIZA (lubiprostone)	Capsule: 8 mcg 24 mcg	Treatment of CIC in adults and OIC: Capsule: 24 mcg twice daily by mouth Treatment of IBS-C in women ≥18 years of age: Capsule: 8 mcg twice daily Adjust dosing in moderate and severe hepatic impairment.	Take with food and water.
LINZESS (linaclotide)	Capsule: 72 mcg, 145 mcg, 290 mcg	IBS-C: 290 mcg once daily CIC: 145 mcg once daily. A dosage of 72 mcg once daily may be used based on individual presentation or tolerability.	Take on an empty stomach at least 30 minutes before the first meal of the day. Swallow capsules whole; do not crush or chew. If unable to swallow, administer contents of capsule with applesauce or water. No titration
LOTRONEX (alosetron)	Tablet: 0.5 mg 1 mg	Women with severe IBS-D: Tablet: 0.5 mg twice daily for four weeks; if dosage is well tolerated but does not adequately control IBS symptoms after four weeks, the dose may be increased to up to 1 mg twice daily	Take with or without food. Discontinue treatment in patients who have not had adequate control of IBS symptoms after four weeks of treatment with 1 mg twice daily.

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
MOVANTIK (naloxegol)	Tablets: 12.5 mg 25 mg	OIC in chronic non-cancer pain: 25 mg once daily; if not tolerated, may reduce to 12.5 mg once daily • Renal Impairment (CrCl <60 mL/min): 12.5 mg once daily; if tolerated, may increase to 25 mg once daily	Discontinue maintenance laxative therapy prior to initiating therapy with MOVANTIK. Take on an empty stomach at least one hour before or two hours after the first meal of the day. For patients who are unable to swallow the tablet whole, the tablet can be crushed to a powder, mixed with 4 ounces of water, and drunk immediately. The glass should be refilled with an additional 4 ounces of water and drunk immediately. Crushed MOVANTIK can also be administered via a nasogastric tube. Avoid ingestion of grapefruit or grapefruit juice. Discontinue MOVANTIK when opioid pain medication is discontinued.
RELISTOR (methylnaltrex-one)	Single-use vial: 12 mg/0.6 mL solution for use with a 27 gauge x 0.5 inch needle and 1 mL syringe Single-use pre-filled syringe: 8 mg/0.4 mL 12 mg/0.6 mL Tablet: 150 mg	OIC in chronic non-cancer pain: Injection: 12 mg subcutaneously once daily Tablets: 450 mg orally once daily in the morning • Moderate to severe renal impairment (CrCl <60 mL/min): reduce subcutaneous dose to 6 mg once daily (one-half usual dose); reduce oral dose to 150 mg once daily • Hepatic impairment: for RELISTOR tablets in patients with moderate or severe hepatic impairment: 150 mg once daily. When considering dose adjustment of RELISTOR injection in patients with severe hepatic impairment, follow reduced weight-based dosing: o Weight <38 kg: 0.075 mg/kg o Weight 38 kg to <62 kg: 4 mg o Weight 62 kg to 114 kg: 6 mg o >114 kg: 0.075 mg/kg OIC in advanced illness (injection; subcutaneous dosing): weight-based dosing once every other day, as needed (max of once daily):	Inject subcutaneously in the upper arm, abdomen, or thigh. Rotate injection sites. Be within close proximity to toilet facilities after administration. Discontinue maintenance laxative therapy prior to initiating therapy with RELISTOR. Discontinue RELISTOR when opioid pain medication is discontinued. Pre-filled syringes only should be used for patients taking 8 mg or 12 mg dose. Take RELISTOR tablets with water on an empty stomach at least 30 minutes before the first meal of the day.

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
		• Weight <38 kg: 0.15 mg/kg • Weight 38 kg to <62 kg: 8 mg • Weight 62 kg to 114 kg: 12 mg • >114 kg: 0.15 mg/kg • Moderate to severe renal impairment (CrCl <60 mL/min): reduce to one subcutaneous dose every other day based on weight, as needed o Weight <38 kg: 0.075 mg/kg o Weight 38 kg to <62 kg: 4 mg o Weight 62 kg to 114 kg: 6 mg o >114 kg: 0.075 mg/kg	
SYMPROIC (naldemedine)	Tablet: 0.2 mg	OIC in chronic non-cancer pain: 0.2 mg once daily	Take with or without food. Patients taking opioids < 4 weeks may be less responsive to treatment. Discontinue SYMPROIC when opioid pain medication is discontinued.
TRULANCE (plecanatide)	Tablet: 3 mg	CIC: 3 mg once daily	Take with or without food. For adult patients with swallowing difficulties, can be crushed and administered orally either in applesauce or with water or administered with water via a nasogastric or gastric feeding tube.
VIBERZI (eluxadoline)	Tablet: 75 mg 100 mg	Treatment of IBS-D in adults: 100 mg twice daily 75 mg twice daily in select patients who: • do not have a gallbladder • are unable to tolerate the 100 mg dose • are receiving concomitant OATP1B1 inhibitors • have mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment	Take with food Discontinue treatment in patients who develop severe constipation for more than four days.
XIFAXAN (rifaximin)	Tablet: 200 mg 550 mg	TD: 200 mg three times daily for three days Hepatic encephalopathy: 550 mg twice daily IBS-D: 550 mg three times daily for 14 days	Take with or without food. Patients with IBS-D who experience recurrence may be retreated up to two times with the same regimen. Do not use in patients with TD complicated by fever or blood in the stool or diarrhea due to pathogens other than *E. coli*.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
AMITIZA (lubiprostone)	The efficacy among those ≥65 years was consistent with the overall study population of CIC. Clinical trials of OIC had insufficient numbers of older patients to determine if differences exist. Safety profile among those ≥65 years was consistent with the overall study population of IBS-C.	Safety and efficacy have not been established.	No dosage adjustment required.	CIC or OIC with moderate impairment (Child-Pugh Class B): recommended dose is 16 mcg twice daily† CIC or OIC with severe impairment (Child-Pugh Class D): recommended dose is 8 mcg twice daily† IBS-C with severe impairment (Child-Pugh Class C): recommended dose is 8 mcg once daily†	Pregnancy Category C Unknown whether excreted in breast milk; use with caution.
LINZESS (linaclotide)	Clinical studies did not include sufficient numbers of patients ≥65 years to determine whether they respond differently from younger patients.	Contra-indicated in <6 years. Boxed Warning to avoid use in children ages 6 to <18 years.	No dosage adjustment required.	No dosage adjustment required.	Not categorized‡ Unknown whether excreted in breast milk; use with caution.
LOTRONEX (alosetron)	Use with caution in patients ≥65 years due to risk for constipation.	Safety and efficacy have not been established.	No dosage adjustment required.	Use with caution in mild or moderate impairment; avoid use in severe impairment.	Pregnancy category B Unknown whether excreted in breast milk; use with caution.
MOVANTIK (naloxegol)	No overall differences in effectiveness were observed between patients at least 65 years of age and younger patients. No dosage adjustments are required in older patients.	Safety and efficacy have not been established.	Reduce starting dose to 12.5 once daily in patients with CrCl <60 mL/min. No dose adjustments are required for mild renal impairment.	Avoid use in patients with severe hepatic impairment (Child-Pugh Class C). No dose adjustments are required for mild or moderate hepatic impairment.	Pregnancy Category C Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug.
RELISTOR (methylnal-	No overall differences in effectiveness were observed between patients	Safety and efficacy have	Reduce dose in patients with CrCl <60	Reduce dose in patients with OIC in chronic non-cancer	Not categorized‡

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
trexone bromide)	at least 65 years of age and younger patients. No dosage adjustments are required in older patients.	not been established.	mL/min (See Table 3). No dose adjustments are required for mild renal impairment.	pain and moderate or severe hepatic impairment (see Table 3). No dose adjustments are required for mild hepatic impairment.	Unknown whether excreted in breast milk; breastfeeding not recommended during treatment.
SYMPROIC (naldemedine)	No overall differences in safety or effectiveness between patients at least 65 years of age and younger patients were observed, but greater sensitivity of some older individuals cannot be ruled out.	Safety and efficacy have not been established.	No dosing adjustments necessary.	Avoid use in patients with severe hepatic impairment (Child-Pugh Class C). No dose adjustments are required for mild or moderate hepatic impairment.	Not categorized‡ Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug. If drug is discontinued, breastfeeding can be resumed 3 days after the final dose.
TRULANCE (plecanatide)	Clinical studies did not include sufficient numbers of patients ≥65 years to determine whether they respond differently from younger patients.	Contra-indicated in <6 years. Boxed Warning to avoid use in children ages 6 to 17 years.	No dosing adjustments necessary.	No dosing adjustments necessary.	Not categorized‡ Unknown whether excreted in breast milk; use with caution.
VIBERZI (eluxadoline)	No overall differences in effectiveness were observed between patients at least 65 years of age and younger patients.	Safety and efficacy have not been established.	No information available.	Reduce the dose to 75 mg twice daily with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment. Do not use in patients with severe hepatic impairment (Child-Pugh Class C).	No studies in pregnant women. Unknown whether excreted in breast milk; use with caution.
XIFAXAN (rifaximin)	No overall differences in effectiveness were observed between patients at least 65 years of age and younger patients.	Safety and efficacy have not been established in pediatric patients less	Studies in patients with renal impairment have not	No dose adjustment is recommended in patients with mild, moderate, or severe hepatic impairment.	No studies in pregnant women. Unknown whether

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
	Clinical studies with XIFAXAN for TD did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger subjects.	than 12 years of age with TD or in patients less than 18 years of age for HE and IBS-D.	been conducted.		excreted in breast milk, effects on breastfed infant, or effects on milk production; use with caution.

*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women. Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
†If this dose is tolerated and an adequate response has not been obtained after an appropriate interval, doses can then be escalated to full dosing with appropriate monitoring of response.
‡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

- Irritable Bowel Syndrome (IBS) is a gastrointestinal disorder with symptoms of abdominal pain, discomfort and bloating, and abnormal bowel habits with bouts of diarrhea and/or constipation (WGO, 2015; Quigley et al, 2012).
- Irritable Bowel Syndrome has four subtypes depending on the change in bowel habits – Irritable Bowel Syndrome-Diarrhea (IBS-D), Irritable Bowel Syndrome-Constipation (IBS-C), mixed type having diarrhea and constipation (IBS-M), or unspecified (IBS-U). IBS-C symptoms include abdominal pain and bloating, less than three bowel movements per week, straining, and feeling of incomplete evacuation of bowels.
- Most patients with mild disease are managed with disease state education and support, coupled with lifestyle modifications, including diet changes and stress reduction and, when possible, symptom control (Andresen et al, 2008; Ford et al, 2009).
- There are currently no head-to-head trials comparing the available agents used in the treatment of CIC, OIC, IBS-C, and IBS-D.
- Guidelines on management of constipation suggest increased fiber intake and osmotic laxatives. Stimulant laxatives are to be used as needed or as "rescue agents." Lubiprostone and linaclotide can be considered when symptoms of constipation do not respond to laxatives (AGA, 2013; Bharucha et al, 2013; Chang et al, 2014; Lindberg et al, 2010).
- The American College of Gastroenterology monograph on the management of IBS and CIC notes that rifaximin is effective in reducing IBS symptoms and bloating in IBS-D; alosetron is effective in females with IBS-D; and linaclotide and lubiprostone are each superior to placebo for the treatment of IBS-C. In addition, linaclotide and lubiprostone are each effective for the treatment of CIC (Ford et al, 2014).
- AMITIZA (lubiprostone) is currently the only chloride channel activator commercially available. It selectively activates intestinal chloride channels, increasing intestinal fluid secretion and delaying gastric emptying.
- In clinical trials, AMITIZA has demonstrated efficacy in the treatment of CIC as well as IBS-C in women, with improvement in SBMs, straining, constipation severity, stool consistency, and global assessment of constipation (Drossman et al, 2007; Drossman et al, 2009; Johanson et al, 2004; Johanson et al, 2005; Johanson et al, 2007; Johanson et al, 2008a; Johanson et al, 2008b).
- LINZESS (linaclotide) is a guanylate cyclase-C agonist. LINZESS acts locally in the intestine to accelerate intestinal transit, increase intestinal secretions and reduce intestinal pain. LINZESS has been shown in placebo-controlled studies to be effective in improving constipation related to IBS-C and CIC (Li et al, 2016; Nelson et al, 2017; Videlock et al, 2013).
- TRULANCE (plecanatide) is approved by the FDA for treatment of CIC. Similar to LINZESS, it is a guanylate cyclase-C agonist. In two randomized control trials, TRULANCE 3 mg demonstrated a significantly increased weekly CSBM frequency as measured by the overall CSBM responder rate vs placebo (Miner et al [abstract], 2016; Miner et al, 2017).
- Agents approved for use in OIC include MOVANTIK (naloxegol), SYMPROIC (naldemedine), and RELISTOR (methylnaltrexone) in patients with chronic non-cancer pain. RELISTOR is also approved in patients with advanced illness (including cancer) receiving palliative care and unresponsive to laxative therapy. SYMPROIC, RELISTOR,

MOVANTIK and AMITIZA, are also indicated in patients with chronic pain related to prior cancer or its treatment in those who do not require frequent (e.g., weekly) opioid dosage escalation.

- LOTRONEX (alosetron), a 5-HT receptor antagonist, has been shown to reduce pain, abdominal discomfort, urgency, and diarrhea in patients with IBS as demonstrated in several placebo-controlled trials (Andresen et al, 2008; Bardhan et al, 2000; Camilleri et al, 2000; Camilleri et al, 2001; Chey et al, 2004; Cremonini et al, 2003; Ford et al, 2009; Lembo et al, 2001; Lembo et al, 2004; Krause et al, 2007; Rahimi et al, 2008; Watson et al, 2001).
- Use of LOTRONEX is limited to female patients with chronic, severe IBS-D who have not responded to conventional therapy. Due to serious safety concerns, a boxed warning regarding gastrointestinal adverse events has been added to the alosetron prescribing information. The medication also has an approved REMS program.

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INTRODUCTION

- The ophthalmic antihistamines are Food and Drug Administration (FDA)-approved for the management of the signs and symptoms associated with allergic conjunctivitis and include Lastacaft (alcaftadine); Optivar (azelastine); Bepreve (bepotastine); Zerviate (cetirizine); Emadine (emedastine); Elestat (epinastine); the ketotifen-containing products Alaway and Zaditor; and the olopatadine-containing products Pataday, Patanol, and Pazeo *(Micromedex 2.0 2017)*.
- All products are available by prescription with the exception of ketotifen, which is available as an over-the-counter (OTC) product. Ketotifen is approved for the temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair, and dander.
- Conjunctivitis can be classified as noninfectious or infectious, and as acute, chronic, or recurrent. Types of noninfectious conjunctivitis are allergic, mechanical/irritative/toxic, immune-mediated, and neoplastic. Causes of infectious conjunctivitis are viruses and bacteria *(American Academy of Ophthalmology [AAO] 2013)*.
- Types of allergic conjunctivitis include atopic keratoconjunctivitis, simple allergic conjunctivitis, seasonal or perennial conjunctivitis, vernal conjunctivitis, and giant papillary conjunctivitis. Atopic keratoconjunctivitis is a severe, chronic, external ocular inflammation associated with atopic dermatitis. Vernal conjunctivitis is a severe form of allergic conjunctivitis that may involve the cornea *(American Optometric Association [AOA] 2007)*. None of the ophthalmic antihistamines are FDA-approved for the treatment of vernal conjunctivitis.
- Symptoms of allergic conjunctivitis include itching, tearing, mucoid discharge, chemosis, hyperemia, and redness. Most commonly, symptoms are present in both eyes, but they may also occur unilaterally *(AOA 2007)*.
- Most of these agents have been shown to have both histamine type 1 (H_1-antihistamine) and mast cell stabilizing properties *(AAO 2013)*. The ophthalmic antihistamines reduce itching and redness through competitive binding with histamine receptor sites and by inhibiting the degranulation of mast cells, thus limiting the release of inflammatory mediators associated with the development of allergy symptoms *(Micromedex 2.0 2017)*.
- Medispan Therapeutic Class: Ophthalmics - Miscellaneous

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Alaway† (ketotifen), Zaditor† (ketotifen)	✔
Bepreve (bepotastine besilate ophthalmic solution) 1.5%	-
Elestat (epinastine HCl ophthalmic solution) 0.05%	✔
Emadine (emedastine difumarate ophthalmic solution) 0.05%	-
Lastacaft (alcaftadine ophthalmic solution) 0.25%	-
Optivar (azelastine HCl ophthalmic solution, 0.05%)	✔
Pataday (olopatadine HCl ophthalmic solution) 0.2%, Patanol (olopatadine HCl ophthalmic solution) 0.1%, Pazeo (olopatadine HCl ophthalmic solution) 0.7%	✔ ✔ -
Zerviate (cetirizine ophthalmic solution) 0.24%‡	-

Key: HCl = hydrochloride
† Both products contain ketotifen 0.025% (equivalent to ketotifen fumarate 0.035%) and are available over-the-counter.
‡ Zerviate contains cetirizine 0.24% (equivalent to cetirizine hydrochloride 0.29%).

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Alaway, Zaditor (ketotifen)	Bepreve (bepotastine)	Elestat (epinastine)	Emadine (emedastine)	Lastacaft (alcaftadine)	Optivar (azelastine)	Pataday, Patanol, Pazeo (olopatadine)	Zerviate (cetirizine)
Prevention of ocular itching associated with allergic conjunctivitis			✔		✔			
Treatment of ocular itching associated with allergic conjunctivitis		✔				✔	✔*	✔
Treatment of signs and symptoms of allergic conjunctivitis							✔†	
Temporary relief of the signs and symptoms of allergic conjunctivitis				✔				
Temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair, and dander	✔							

* 0.2% and 0.7% strengths
† 0.1% strength

(Prescribing information: Alaway 2015, Bepreve 2016, Elestat 2011, Emadine 2009, Lastacaft 2015, Optivar 2009, Pataday 2010, Patanol 2007, Pazeo 2017, Zaditor 2015, Zerviate 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

- Due to the rapid onset of action of the ophthalmic antihistamines, most trials used the conjunctival allergen challenge model to establish the relative efficacy of these formulations compared to placebo. The results of most trials demonstrated improvements in symptoms, especially for itching, in those treated with ophthalmic antihistamines and antihistamines/mast cell stabilizers compared to placebo. Clinical data supporting the FDA approval of cetirizine ophthalmic solution were from 3 unpublished, placebo-controlled trials that showed improvement in ocular itching with cetirizine *(Nicox 2017)*.

- Several studies have been conducted to directly compare ophthalmic ketotifen and ophthalmic olopatadine. These studies have produced mixed results, generally demonstrating no difference between the agents. Results of some studies suggest that ophthalmic olopatadine may be preferred and better tolerated by patients *(Avunduk et al 2005, Berdy et al 2000, Borazan et al 2009, Ganz et al 2003, Leonardi et al 2004)*. There are limited head-to-head studies that compare the clinical efficacy of the other agents in this class to one another, and all are considered equally efficacious at improving ocular allergy symptoms. While some studies reported statistically significant differences in symptom scores, the overall clinical significance of these differences is not known, as many of these trials were conducted using single doses of study medication (in the conjunctival allergen challenge model) and generally enrolled a small number of patients. A Cochrane review of topical antihistamines for treatment of allergic conjunctivitis concluded that topical antihistamines and mast cell stabilizers reduce symptoms short-term. The data and study results lack for long-term use of topical antihistamines *(Castillo et al 2015)*.

CLINICAL GUIDELINES

- According to the AAO, mild allergic conjunctivitis may be treated with an OTC ophthalmic antihistamine/vasoconstrictor or a prescription ophthalmic antihistamine. Ophthalmic allergy preparations with dual antihistamine and mast cell stabilizing properties may be used for either acute or chronic disease, with no preference given to one agent over another. The use of ophthalmic vasoconstrictors should be limited due to their short duration of action and potential to cause rebound hyperemia and conjunctivitis medicamentosa. Ophthalmic mast cell stabilizers may be used if the condition is recurrent or persistent *(AAO 2013, AAO 2016)*.

SAFETY SUMMARY

- Contact lens use: patients should not wear a contact lens if the eye is red; remove contact lenses prior to instilling this product, as the preservative, benzalkonium chloride, may be absorbed by soft contact lenses.
- Contamination of tip and solution: do not touch eyelids or surrounding areas with the dropper tip of the bottle.
- Products are for topical use only.
- Adverse events are primarily ocular in nature with burning/stinging upon instillation, ocular irritation, ocular pruritus, and redness. Systemic adverse events include mild taste upon instillation, headache, rhinitis, and potential hypersensitivity reactions.
- Due to the topical application of the ophthalmic antihistamines, drug interactions have not been reported.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Alaway, Zaditor (ketotifen)	Both: Ophthalmic solutions	Ophthalmic	Twice daily	Instill 1 drop into affected eye(s) twice daily, every 8 to 12 hours, no more than twice per day. For children ≥ 3 years of age, refer to adult dose; safety and effectiveness in children < 3 years of age have not been established. Not studied in pregnancy.
Bepreve (bepotastine)	Ophthalmic solution	Ophthalmic	Twice daily	Instill 1 drop into affected eye(s) twice daily. For children ≥ 2 years of age, refer to adult dose; safety and effectiveness in children < 2 years of age have not been

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				established. Pregnancy Category C*
Elestat (epinastine)	Ophthalmic solution	Ophthalmic	Twice daily	Instill 1 drop in each eye twice daily. Treatment should be continued throughout the period of exposure (ie, until the pollen season is over or until exposure to the offending allergen is terminated), even when symptoms are absent. For children ≥ 2 years of age, refer to adult dose; safety and effectiveness in children < 2 years of age have not been established. Pregnancy Category C*
Emadine (emedastine)	Ophthalmic solution	Ophthalmic	Up to 4 times daily	Instill 1 drop into affected eye(s) up to 4 times daily. For children ≥ 3 years of age, refer to adult dose; safety and effectiveness in children < 3 years of age have not been established. Pregnancy Category B*
Lastacaft (alcaftadine)	Ophthalmic solution	Ophthalmic	Daily	Instill 1 drop in each eye once daily. If more than 1 topical ophthalmic medicinal product is being used, each one should be administered at least 5 minutes apart. For children ≥ 2 years of age, refer to adult dose; safety and effectiveness in children < 2 years of age have not been established. Pregnancy Category B*
Optivar (azelastine)	Ophthalmic solution	Ophthalmic	Twice daily	Instill 1 drop into affected eye(s) twice daily. For children ≥ 3 years of age, refer to adult dose; safety and effectiveness in children < 3 years of age have not been established.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Pregnancy Category C*
Pataday, Patanol, Pazeo (olopatadine)	All: Ophthalmic solutions	Ophthalmic	Once or twice daily (varies by product)	Patanol 0.1%: Instill 1 drop into affected eye(s) twice daily at an interval of 6 to 8 hours. Pataday 0.2%, Pazeo 0.7%: Instill 1 drop in affected eye(s) once daily For children ≥ 2 (0.2%, 0.7%) and ≥ 3 (0.1%) years of age, refer to adult dose; safety and effectiveness in children < 3 years (0.1%) and < 2 years (0.2%, 0.7%) of age have not been established. Pregnancy Pataday, Patanol: Pregnancy Category C* Pazeo: Unclassified†
Zerviate (cetirizine)	Ophthalmic solution	Ophthalmic	Twice daily	Instill 1 drop into affected eye(s) twice daily. For children ≥ 2 years of age, refer to adult dose; safety and effectiveness in children < 2 years of age have not been established. Pregnancy: Unclassified†

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

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

See the current prescribing information for full details

CONCLUSION

- The ophthalmic antihistamines are FDA-approved for the management of the signs and symptoms associated with allergic conjunctivitis, the most common form of ocular allergy.
- Few distinguishing characteristics exist among the available ophthalmic antihistamines, but alcaftadine and olopatadine 0.2% and 0.7% may be administered once daily, while remaining agents in this class are administered 2 to 4 times daily. In addition, ophthalmic alcaftadine and ophthalmic emedastine are classified as pregnancy category B; other agents in this class are pregnancy category C or were not studied in pregnant patients *(Micromedex 2.0 2017)*. Currently, ophthalmic formulations of azelastine, epinastine, ketotifen, and olopatadine are available generically. Ophthalmic formulations of ketotifen are also available generically in OTC formulations. Due to the ophthalmic administration of these agents, relatively few adverse reactions have been reported; the most common adverse reactions are ocular burning and stinging and headache.

- Several studies have been conducted to directly compare ophthalmic ketotifen and ophthalmic olopatadine. These studies have produced mixed results, generally demonstrating no difference between the agents. There are limited head-to-head studies that compare the clinical efficacy of the other agents in this class to one another, and all are considered equally efficacious at improving ocular allergy symptoms. While some studies reported statistically significant differences in symptom scores, the overall clinical significance of these differences is not known, as many of these trials were conducted using single doses of study medication (in the conjunctival allergen challenge model) and generally enrolled a small number of patients.

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Therapeutic Class Overview
Inhaled Steroids

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*):
  - 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 mepolizumab and reslizumab for the management of severe asthma with an eosinophilic phenotype *(Prescribing information: Cinqair 2016, 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. Omalizumab, mepolizumab, or reslizumab may be added if patients require a higher level of care. Omalizumab is used in patients with moderate to severe allergic asthma while mepolizumab or reslizumab are used for severe eosinophilic asthma. SABAs are the medication of choice for the relief of bronchospasm during acute exacerbations of asthma (*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 formulation of beclomethasone manufactured by Teva, was approved by the FDA in August 2017. It is not currently available, but is planned for launch in 2018 to replace the existing QVAR product, which will be discontinued. As QVAR RediHaler is not currently available, it is not included within this review.
- 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)	-

(*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)	✔ (age ≥5 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*)

- 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 (*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 twice daily demonstrated comparable efficacy between fluticasone propionate and mometasone for improvement in FEV_1, forced expiratory flow at 25 to 75% of FVC ($FEF_{25\ to\ 75\%}$), and PEF (*O'Connor et al 2001*).
  - A trial comparing fluticasone propionate 250 mcg twice daily to mometasone 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 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 168 mcg twice daily to mometasone 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 six to nine 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 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-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 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 twice daily, the FEV_1 was significantly improved from baseline in the mometasone 200 and 400 mcg treatment groups compared to the budesonide treatment group. In addition, morning wheezing scores were significantly improved in the mometasone 400 mcg twice daily group compared to the budesonide group, and patients treated with mometasone 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 440 mcg once daily, the mometasone 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 compared to other inhaled corticosteroids:
  - A meta-analysis comparing ciclesonide to other inhaled corticosteroids (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 was relatively higher in this study (*Kramer et al 2013*).

- A meta-analysis comparing mometasone furoate to other inhaled corticosteroids (beclomethasone dipropionate, budesonide, or fluticasone propionate) in patients with moderate to severe asthma demonstrated superior results with mometasone 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 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 2130 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.
  - The first phase 3 trial (n = 647, of which 389 were randomized to ArmonAir 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/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 55 mcg and 113 mcg as compared to placebo at the end of 12 weeks (lease squares means 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 *(ArmonAir prescribing information 2017)*.
  - The second phase 3 trial (n = 728, of which 437 were randomized to ArmonAir or placebo) was similarly designed, but evaluated different doses: 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 (lease squares mean 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 *(ArmonAir prescribing information 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*). The Institute for Clinical Systems Improvement (ICSI) endorsed the updated GINA guideline (*ICSI 2016*).

SAFETY SUMMARY

- Inhaled corticosteroids 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 inhaled corticosteroids
  - 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	Oral	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	Oral	Patients treated previously with only bronchodilators: initial, 80 mcg twice daily; maximum, 160 mcg twice daily Patients treated previously with an inhaled corticosteroid: 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	Oral	Dependent on asthma severity: 55, 113, or 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	Oral	Patients not previously on inhaled corticosteroids: initial, 100 mcg once daily; maximum, 200 mcg once daily	Not indicated for children <12 years of age.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Patients treated previously with an inhaled corticosteroid: Starting dose should be based on previous asthma drug therapy and disease severity, 100 mcg or 200 mcg once daily	
Asmanex HFA (mometasone)	Inhalation aerosol (HFA): 100 or 200 mcg per actuation	Oral	Patients previously receiving inhaled medium-dose corticosteroids: 100 mcg, 2 inhalations twice daily Patients previously receiving inhaled high-dose corticosteroids: 200 mcg, 2 inhalations twice daily Patients currently receiving oral corticosteroids: 200 mcg, 2 inhalations twice daily	Not indicated for children <12 years of age.
Asmanex Twisthaler (mometasone)	Dry powder inhaler: 110 or 220 mcg per actuation	Oral	Patients treated previously with bronchodilators alone or inhaled corticosteroids: 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	Oral	Patients who are not on an inhaled corticosteroid: 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	Oral	Patients who are not on an inhaled corticosteroid: initial, 88 mcg twice daily; maximum, 880 mcg twice daily	Children 4 to 11 years of age: 88 mcg twice daily

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			For other patients and those who do not respond adequately to the starting dose after 2 weeks, higher dosages may provide additional control.	
Pulmicort Flexhaler (budesonide)	Dry powder inhaler: 90 or 180 mcg per actuation	Oral	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	Oral	Children 12 months to eight years of age treated previously with only bronchodilators: initial, 0.5 mg total daily dose administered either once daily or divided into two doses; maximum, 0.5 mg total daily dose Children 12 months to eight years of age treated previously with an inhaled corticosteroid: 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 eight years of age treated previously with an oral corticosteroid: initial, 1 mg total daily dose administered either as 0.5 mg twice daily or 1 mg once daily; maximum, 1 mg total daily dose	Not indicated in adults.
Qvar (beclomethasone)	Inhalation aerosol (HFA): 40 or 80 mcg per actuation	Oral	Patients treated previously with only bronchodilators: initial, 40 to 80 mcg twice daily; maximum, 320 mcg twice daily Patients treated previously with an inhaled corticosteroid: initial, 40 to 160 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

See the current prescribing information for full details

CONCLUSION

- Inhaled corticosteroids are considered the cornerstone of drug therapy for long-term asthma control. Consensus guidelines emphasize the important role of inhaled corticosteroids as long-term controller medications. The NHLBI, GINA, and ICSI 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 ICSI 2016, NHLBI 2007*).
- Although individual head-to-head clinical trials have demonstrated some differences among inhaled corticosteroids 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 Inhaled Corticosteroids

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)	Inhalation aerosol	-	• Not approved in children <12 years of age • Not studied in pregnant women
Asmanex Twisthaler (mometasone)	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

Drug	Formulation	Advantages	Disadvantages/Limitations
			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)	Inhalation aerosol	• Approved in children ≥5 years	• Pregnancy Category C

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INTRODUCTION

- The hepatitis C virus (HCV) is an enveloped ribonucleic acid (RNA) virus that is transmitted through exposure to infected blood (*Centers for Disease Control and Prevention [CDC] 2016*).
  - Approximately 75 to 85% of people infected with HCV will develop chronic infection.
  - The CDC estimates that 2.7 to 3.9 million persons in the U.S. have chronic hepatitis C (CHC).
  - Chronic HCV infection can lead to the development of active liver disease, including cirrhosis and liver cancer. It is the most common indication for liver transplant (*CDC 2016*).
- There are 6 major genotypes of HCV, numbered 1 to 6. Genotypes are further divided into subtypes, designated by a letter (*Gower et al 2014*).
  - Genotype 1 is the most prevalent HCV genotype globally (~46% of cases), followed by genotype 3 (~22 to 30% of cases). Genotypes 2, 4, and 6 represent 22.8% of cases combined; genotype 5 represents less than 1% of cases worldwide (*Messina et al 2014, Gower et al 2014*).
  - In the U.S., the prevalence of genotype 1a, 1b, 2, 3, 4, and 6 is 46.2%, 26.3%, 10.7%, 8.9%, 6.3%, and 1.1%, respectively (*Gower et al 2014*).
- Due to the slow evolution of chronic infection, it is difficult to directly demonstrate whether treatment prevents complications of liver disease; therefore, response to treatment is defined by surrogate virologic parameters. The primary goal of therapy for hepatitis C is eradication of the virus. There are a number of different terms in use that are relevant to monitoring response to therapy:
  - Rapid virologic response (RVR): undetectable viral load at week 4
  - Early virologic response (EVR): at least a 2-log reduction in viral load by week 12 (partial EVR) or undetectable viral load by week 12 (complete EVR)
  - End-of-treatment response (ETR): undetectable viral load at the end of treatment
  - Sustained virologic response (SVR): undetectable viral load at the conclusion of therapy and 24 weeks after the conclusion of therapy (*Hepatitis C Support Project [HCSP] Fact Sheet 2015*).
- Obtaining an SVR is associated with a 97 to 100% chance of being HCV RNA negative during long-term follow-up. Furthermore, achieving an SVR is associated with decreased mortality, rates of hepatocellular carcinoma, liver-related complications, and the need for liver transplant. Thus, success at obtaining SVR is an important treatment goal and a common primary endpoint in the clinical trials of antiviral medications. Some trials report SVR at 12 weeks (SVR12) in addition to or instead of at 24 weeks (SVR24). There is a high degree of concordance between SVR12 and SVR24, and SVR12 is also considered an appropriate endpoint (*Chen et al 2013*).
- Over recent years, research has focused on oral HCV agents that act directly on viral targets. These direct-acting antivirals (DAAs) are stratified into 4 major categories: NS3/4A protease inhibitors, NS5B nucleoside polymerase inhibitors, NS5B nonnucleoside polymerase inhibitors, and NS5A inhibitors (*Liang et al 2013*).
  - The first direct-acting antiviral-containing regimens were single-ingredient direct-acting antivirals that needed to be used in combination with peginterferon (PegIFN)/ribavirin (RBV). However, several IFN-free combination products and regimens have been approved since 2014. Some of these regimens also remove the need for RBV in select populations.
- This review provides information on the direct-acting antivirals, including: Daklinza, Epclusa, Harvoni, Mavyret, Olysio, Sovaldi, Technivie, Viekira Pak, Viekira XR, Vosevi and Zepatier
- Medispan Class: Hepatitis C Agents

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Daklinza (daclatasvir)	--
Epclusa (sofosbuvir/velpatasvir)	--
Harvoni (ledipasvir/sofosbuvir)	--

Drug	Generic Availability
Mavyret (glecaprevir-pibrentasvir)	--
Olysio (simeprevir)	--
Sovaldi (sofosbuvir)	--
Technivie (ombitasvir/paritaprevir/ritonavir)	--
Viekira Pak (ombitasvir/paritaprevir/ritonavir and dasabuvir)	--
Viekira XR (ombitasvir/paritaprevir/ritonavir and dasabuvir)	--
Vosevi (sofosbuvir-velpatasvir-voxilaprevir)	--
Zepatier (elbasvir/grazoprevir)	--

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Daklinza (daclatasvir)	Epclusa (sofosbuvir-velpatasvir)	Harvoni* (ledipasvir/sofosbuvir)	Mavyret (glecaprevir-pibrentasvir)	Olysio (simeprevir)	Sovaldi* (sofosbuvir)	Technivie (ombitasvir/paritaprevir/ritonavir)	Viekira Pak, Viekira XR (ombitasvir/paritaprevir/ritonavir/dasabuvir)	Vosevi† (sofosbuvir-velpatasvir-voxilaprevir)	Zepatier (elbasvir/grazoprevir)
Genotype 1	✔	✔	✔	✔	✔	✔		✔	✔	✔
Genotype 2		✔		✔		✔			✔	
Genotype 3	✔	✔		✔		✔			✔	
Genotype 4		✔	✔	✔	✔	✔	✔		✔	✔
Genotype 5		✔	✔	✔					✔	
Genotype 6		✔	✔	✔					✔	

* Harvoni and Sovaldi are the only agents approved in pediatric patients; Harvoni is indicated for the treatment of pediatric patients 12 years of age and older or weighing at least 35 kg with HCV genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis; Sovaldi is indicated for the treatment of chronic HCV genotype 2 or 3 infection in pediatric patients 12 years of age and older or weighing at least 35 kg without cirrhosis or with compensated cirrhosis for use in combination with ribavirin.
† Only approved in patients with prior failure to an NS5A inhibitor- or sofosbuvir-containing regimen.
(*Prescribing information: Daklinza 2017, Epclusa 2017, Harvoni 2017, Mavyret 2017, Olysio 2017, Sovaldi 2017, Technivie 2017, Viekira Pak 2017, Viekira XR 2017, Vosevi 2017, Zepatier 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

Daklinza

- The clinical safety and efficacy of daclatasvir in combination with sofosbuvir and with or without RBV was evaluated in three pivotal phase 3 trials.
  - ALLY-1 was a multicenter (MC), open-label (OL) study in patients (genotype 1 to 6 included) with advanced cirrhosis (n = 60) or patients with HCV recurrence post-liver transplant (N = 53). Patients received daclatasvir plus sofosbuvir plus RBV for 12 weeks. In the advanced cirrhosis cohort, 82% of genotype 1 patients achieved SVR12 (SVR12 in overall cohort: 83%). In the post-transplant cohort, 95% of genotype 1 patients achieved SVR12 (SVR12 in overall cohort: 94%) (*Poordad et al 2016*).
  - ALLY-2 was a MC, OL, randomized study (n = 153) in patients (genotype 1 to 6 included) with HCV/human immunodeficiency virus (HIV) co-infection. Among patients who received 12 weeks of daclatasvir plus sofosbuvir

therapy, 96% and 97% of treatment-naïve HCV genotype 1 and treatment-experienced HCV genotype 1a patients achieved SVR12, respectively. All treatment-naïve and treatment-experienced patients with genotype 1b (23/23), genotype 2 (13/13), genotype 3 (10/10), or genotype 4 (3/3) infection achieved SVR12 (*Wyles et al 2015*).
  - ALLY-3 was a MC, OL study in genotype 3 patients (n = 152), including those with compensated cirrhosis. Patients received daclatasvir plus sofosbuvir for 12 weeks. The SVR12 rates were 90% in treatment-naïve patients and 86% in treatment-experienced patients, with an overall SVR12 rate of 89%. SVR12 rates were higher in patients without cirrhosis (96%) than in patients with cirrhosis. In cirrhotic treatment-naïve and treatment-experienced patients, the SVR12 rate was 58% and 69%, respectively (*Nelson et al 2015*).
- The ALLY-3+ was an additional phase 3, OL, MC study that compared 12 weeks (n = 24) vs 16 weeks (n = 26) of daclatasvir plus sofosbuvir plus RBV in patients with advanced fibrosis or cirrhosis. SVR12 was 88% in the 12-week treatment group and 92% in the 16-week group, giving an overall rate in all treated patients of 90%. All patients with advanced fibrosis achieved SVR12 (*Leroy et al 2016*).
- Several recent real world and observational studies have also found daclatasvir plus sofosbuvir, with or without RBV, to be highly effective and well tolerated for the treatment of genotype 1 or 3 infection (*Alonso et al 2016, Pol et al 2017, Welzel et al 2016*).

Epclusa
- The clinical safety and efficacy of Epclusa was evaluated in four pivotal phase 3 trials.
  - ASTRAL-1 was a double-blind (DB), placebo-controlled, MC, randomized trial in previously treated or untreated patients who were chronically infected with HCV genotype 1, 2, 4, 5, or 6. Overall, the rate of SVR among patients who received 12 weeks of Epclusa was 99% (618/624) (95% confidence interval [CI], 98 to > 99), which was significantly superior to the prespecified performance goal of 85% ($p < 0.001$). None of the 116 patients in the placebo group had an SVR (*Feld et al 2015*).
  - ASTRAL-2 was an OL, active-control (AC), MC, randomized trial comparing Epclusa for 12 weeks (n = 134) vs sofosbuvir plus RBV for 12 weeks (n = 132) in patients with genotype 2 infection. The rate of SVR12 was 99% (133/134) (95% CI, 96 to 100) among those who had received Epclusa as compared with 94% (124/132) (95% CI, 88 to 97) among those who had received sofosbuvir plus RBV (*Foster et al 2015*).
  - ASTRAL-3 was an OL, AC, MC, randomized trial comparing Epclusa for 12 weeks (n = 277) vs sofosbuvir plus RBV for 24 weeks (n = 275) in patients with genotype 3 infection. The rate of SVR12 was 95% (95% CI, 92 to 98) among those who had received Epclusa, as compared with 80% (95% CI, 75 to 85) among those who had received sofosbuvir plus RBV. The overall SVR rate with Epclusa was significantly superior to that with sofosbuvir plus RBV. The strata-adjusted absolute difference was 14.8% (95% CI, 9.6 to 20.0, $p < 0.001$) (*Foster et al 2015*).
  - ASTRAL-4 was an OL, MC, randomized trial comparing Epclusa with or without RBV for 12 weeks or Epclusa for 24 weeks in patients infected with HCV genotypes 1 through 6 and with decompensated cirrhosis. Rates of SVR12 were 83% (95% CI, 74 to 90) in patients who received Epclusa for 12 weeks, 94% (95% CI, 87 to 98) among those who received Epclusa plus RBV for 12 weeks, and 86% (95% CI, 77 to 92) among those who received Epclusa for 24 weeks. Post-hoc analyses did not detect any significant differences in rates of SVR among the 3 treatment groups (*Curry et al 2015*).

Harvoni

Adults
- The efficacy and safety of Harvoni were evaluated in 4 trials in genotype 1 HCV monoinfected patients, 1 trial in genotype 1 or 4 HCV/HIV-1 co-infected patients, 2 trials in genotype 4, 5, or 6 HCV monoinfected patients and 2 trials in genotype 1 or 4 HCV infected pre-transplant patients with decompensated cirrhosis (Child-Pugh B and C) or post-liver transplant.
  - ION-1 was a randomized, OL trial in treatment-naïve patients (n = 865) with genotype 1 with or without cirrhosis. Patients were randomized to receive Harvoni for 12 or 24 weeks, with or without RBV. In the trial, SVR12 rates of 97 to 99% were achieved (*Afdhal et al 2014[a]*).
  - ION-2 was a randomized, OL trial in patients (n = 440) with genotype 1 HCV with or without cirrhosis who failed prior therapy with an IFN-based regimen, with or without a protease inhibitor. Patients were randomized to receive Harvoni for 12 or 24 weeks, with or without RBV. SVR12 rates of up to 99% were achieved (*Afdhal et al 2014[b]*).

- ION-3 was a randomized, OL trial in treatment-naïve patients (n = 647) with non-cirrhotic HCV genotype 1 infection. Patients randomized to treatment with Harvoni for 8 or 12 weeks or Harvoni plus RBV for 8 weeks demonstrated SVR12 rates of 93 to 95% (*Kowdley et al 2014*).
- ION-4 was an OL, MC trial in patients (n = 335) evaluating 12 weeks of Harvoni in treatment-naïve and treatment-experienced cirrhotic or non-cirrhotic HIV/HCV co-infected patients. SVR12 rates were high overall (96%) with comparable rates to the HCV monoinfected population (*Naggie et al 2015*).
- SIRIUS was a DB, MC, French study in which patients with cirrhosis who did not respond to PegIFN and RBV plus telaprevir or boceprevir, were randomized to placebo for 12 weeks followed by Harvoni plus RBV for 12 weeks (n = 77) or Harvoni plus placebo for 24 weeks (n = 78). The overall SVR12 rates were 96% and 97% for Harvoni plus RBV for 12 weeks and Harvoni plus placebo for 24 weeks, respectively (*Bourlière et al 2015*).
- Study 1119 was an OL study evaluating Harvoni for 12 weeks in patients with genotype 4 (n = 44) or 5 infection (n = 41), with or without compensated cirrhosis. The study was conducted at 5 sites in France. There were high SVR12 rates (≥ 89%) with 12 weeks of Harvoni in all patient subgroups and similar rates for genotype 4 vs genotype 5 infection (*Abergel et al 2016*).
- ELECTRON-2 was an OL trial that enrolled patients from 2 centers in New Zealand. The trial evaluated Harvoni for 12 weeks in patients with genotype 6 infection (n = 25). The rate of SVR12 was 96%. The single patient who did not reach SVR12 was a patient who withdrew consent during week 8 of treatment and therefore did not receive the full course of treatment (*Gale et al 2015*).
- SOLAR-1 and SOLAR-2 were OL, MC trials that evaluated 12 and 24 weeks of treatment with Harvoni in combination with RBV in patients with genotype 1 and 4 infection who had undergone liver transplantation and/or who had decompensated liver disease. The 2 trials were identical in study design. The SVR12 rates observed with 24 weeks of Harvoni plus RBV were similar to the SVR12 rates observed with 12 weeks of treatment. In pre-transplant patients with decompensated cirrhosis, the SVR12 rate for Harvoni plus RBV for 12 weeks was 87% (80/92). In post-transplant patients (with or without cirrhosis), the SVR12 was 93% (194/208) (*Charlton et al 2015; Manns et al 2016*).

Pediatric

- A phase 2, OL, MC study (N = 100) evaluated Harvoni for 12 weeks in patients aged 12 to 17 years with chronic HCV genotype 1 infection. Overall, 98% of patients reached SVR12. No patient had virologic failure; 2 patients who did not achieve SVR12 were lost to follow-up either during or after treatment (*Balistreri et al 2016*).

Mavyret

- The efficacy of Mavyret in patients who were treatment-naïve or treatment-experienced to combinations of PegIFN, RBV and/or sofosbuvir (PRS) with genotype 1, 2, 4, 5, or 6 infection without cirrhosis was studied in 4 trials using 8- or 12-week durations: ENDURANCE-1, ENDURANCE-4, SURVEYOR-1 (Part 2), and SURVEYOR-2 (Part 2 and Part 4).
  - ENDURANCE-1 was a randomized, MC, OL trial comparing the efficacy of 8 and 12 weeks of treatment with Mavyret in patients with genotype 1 infection with or without HIV-1 co-infection. The SVR rate was 99% (348/351) and 99.7% (351/352) in the Mavyret 8- and 12-week arms, respectively (*Mavyret prescribing information 2017*).
  - ENDURANCE-4, SURVEYOR-1, and SURVEYOR-2 were OL, MC trials evaluating the safety and efficacy of Mavyret in treatment-naïve or PRS treatment-experienced patients. ENDURANCE-4 and SURVEYOR-1 evaluated 12 weeks of Mavyret in patients with genotypes 5 and 6. The overall SVR rate was 100% (57/57). SURVEYOR-2 evaluated 8 weeks of Mavyret in patients with genotypes 2, 4, 5, or 6; the SVR rate was 98% (193/197), 93% (43/46), 100% (2/2), and 100% (10/10), respectively (*Asselah et al 2017, Mavyret prescribing information 2017*).
- The efficacy of Mavyret in patients who were treatment-naïve or PRS treatment-experienced with genotype 1, 2, 4, 5, or 6 with compensated cirrhosis was studied in the OL, single-arm EXPEDITION-1 trial. Patients were treated with 12 weeks of Mavyret. The overall SVR rate was 99% (145/146) (*Forns et al 2017*).
- The efficacy of Mavyret in patients without cirrhosis or with compensated cirrhosis who were treatment-naïve or PRS treatment-experienced with genotype 3 infection was studied in ENDURANCE-3 and in SURVEYOR-2 (Part 3).
  - ENDURANCE-3 was a randomized, OL, AC trial in treatment-naïve patients. Patients were randomized (2:1) to either Mavyret for 12 weeks or to the combination of Sovaldi and Daklinza for 12 weeks; subsequently the trial included a third non-randomized arm with Mavyret for 8 weeks. The SVR rate for 8 weeks of Mavyret, 12 weeks of Mavyret, and 12 weeks of Sovaldi plus Daklinza was 94.9% (149/157), 95.3% (222/233), and 96.5% (111/115), respectively. The treatment difference for 12 weeks of Mavyret vs 12 weeks of sofosbuvir plus daclatasvir was -1.2% (95% CI, -5.6% to

3.1%). The treatment difference for 8 weeks vs 12 weeks of Mavyret was -0.4% (95% CI, -5.4% to 4.6%) (*Mavyret prescribing information 2017*).
    - SURVEYOR-2 (Part 3) was an OL trial randomizing PRS treatment-experienced patients with genotype 3 infection without cirrhosis to 12 or 16 weeks of treatment. In addition, the trial evaluated the efficacy of Mavyret in genotype 3 infected patients with compensated cirrhosis in 2 dedicated treatment arms using 12-week (treatment-naïve only) and 16-week (PRS treatment-experienced only) durations. The SVR rate was 98% (39/40) in treatment-naïve patients with cirrhosis who were treated with 12 weeks of Mavyret. The SVR rate was 96% (66/69) in PRS treatment-experienced patients, with or without cirrhosis, who were treated with 16 weeks of Mavyret (*Mavyret prescribing information 2017, Wyles et al 2017*).
- EXPEDITION-4 was an OL, single-arm, MC trial evaluating the safety and efficacy in patients with severe renal impairment (chronic kidney disease [CKD] Stages 4 and 5; 82% were on hemodialysis) with compensated liver disease (with and without cirrhosis). The study included patients with (19%) or without compensated cirrhosis (81%). The SVR rate was 98% (102/104). Of the 2 patients who failed, 1 discontinued the medication and the other was lost to follow-up (*Mavyret prescribing information 2017*).
- MAGELLAN-1 was a randomized, OL trial in genotype 1- or 4-infected patients who failed a previous regimen containing an NS5A inhibitor and/or NS3/4A protease inhibitor. Due to higher rates of virologic failure and treatment-emergent drug resistance, the data did not support labeling for treatment of HCV genotype 1-infected patients who are both NS3/4A protease inhibitor and NS5A inhibitor-experienced (*Mavyret prescribing information 2017, Poordad et al 2017*).
    - In protease inhibitor-experienced patients (but NS5A inhibitor-naïve), the SVR rate was 92% (23/25) for patients treated with Mavyret for 12 weeks. In NS5A-experienced patients (but protease inhibitor-naïve), the SVR rate was 94% (16/17).

Olysio

- The clinical safety and efficacy of simeprevir in combination with sofosbuvir were evaluated in two pivotal phase 3 trials (OPTIMIST-1 and OPTIMIST-2) and one phase 2 trial (COSMOS). Simeprevir is also indicated with PegIFN and RBV, however the results of these trials are not presented here since simeprevir triple therapy is no longer recommended by treatment guidelines for genotype 1 or 4 infection.
    - OPTIMIST-1 was an OL, MC, randomized study comparing a treatment regimen of 12 weeks (n = 155) or 8 weeks (n = 155) of simeprevir in combination with sofosbuvir in chronic HCV genotype 1 infected patients without cirrhosis. In the 12- and 8-week treatment arms, the overall SVR12 rate was 97% (95% CI, 93.7 to 99.9; superiority demonstrated vs historical control) and 83% (95% CI, 76.3 to 88.9; superiority was not demonstrated vs historical control) (*Kwo et al 2016*).
    - OPTIMIST-2 was an OL, MC study (n = 103) evaluating 12 weeks of simeprevir in combination with sofosbuvir in chronic HCV genotype 1 infected patients with cirrhosis. The SVR12 rate was 83% (95% CI, 75.8 to 91.1), demonstrating superiority over a historical control rate of 70%. SVR rates were numerically higher in treatment-naive vs treatment-experienced patients. SVR rates were numerically higher in patients with genotype 1a without the Q80K mutation vs with the Q80K mutation (*Lawitz et al 2016*).
    - COSMOS was an OL, randomized study comparing sofosbuvir plus simeprevir for 12 or 24 weeks, with or without RBV. Of the 167 patients in the overall intention-to-treat population, 92% achieved SVR12. The addition of RBV did not increase response rates in comparison with simeprevir in combination with sofosbuvir alone. Response rates were also similar regardless of treatment duration, though sample sizes were small (*Lawitz et al 2014*).

Sovaldi

Adults

- The clinical safety and efficacy of sofosbuvir were evaluated in six pivotal phase 3 trials.
    - NEUTRINO was a single-arm, OL study of sofosbuvir in combination with IFN and RBV in patients infected with HCV genotype 1, 4, 5, or 6. SVR was achieved in 90% of patients at 12 weeks (*Lawitz et al 2013*).
    - FISSION was a randomized, OL, AC, non-inferiority study in patients with HCV genotype 2 or 3. Patients received treatment with sofosbuvir plus RBV for 12 weeks or PegIFN plus RBV for 24 weeks. An SVR was reported in 67% of patients in both treatment groups at 12 weeks after the end of treatment (*Lawitz et al 2013*).
    - In POSITRON, HCV genotype 2 or 3 patients who had previously discontinued IFN therapy due to adverse events, who had a concurrent medical condition precluding therapy with an IFN, or who decided against treatment with an IFN-containing regimen were randomized to receive treatment with sofosbuvir and RBV or matching placebos. Rates

of SVR at 12 weeks were significantly higher in the sofosbuvir treatment group compared to placebo (78 vs 0%, respectively; p < 0.001) (*Jacobson et al 2013*).
- In FUSION, patients who did not achieve SVR with prior IFN therapy (relapsers or nonresponders) were randomized to receive treatment with sofosbuvir and RBV for 12 or 16 weeks. Rates of SVR were 50% with 12 weeks of treatment, as compared with 73% with 16 weeks of treatment (*Jacobson et al 2013*).
- The VALENCE trial evaluated sofosbuvir in combination with RBV for the treatment of genotype 2 or 3 HCV infection in treatment-naïve patients or patients who did not achieve SVR with prior IFN-based treatment, including those with compensated cirrhosis. Rates of SVR were 93% in genotype 2 patients and 84% in genotype 3 patients (*Zeuzem et al 2014[a]*).
- PHOTON-1 was an OL trial evaluating treatment with 12 or 24 weeks of sofosbuvir in combination with RBV in genotype 1, 2, or 3 CHC patients co-infected with HIV-1. Genotype 2 and 3 patients were either treatment-naïve or experienced, whereas genotype 1 patients were treatment-naïve. Rates of SVR were similar to those observed in patients with HCV mono-infection across all genotypes (*Sulkowski et al 2014*).

Pediatric
- Study 1112 was an OL trial evaluating treatment with Sovaldi in combination with RBV in pediatric patients 12 years of age and older with genotype 2 or 3 HCV infection. Patients with HCV genotype 2 or 3 infection in the trial were treated with Sovaldi and weight-based RBV for 12 or 24 weeks, respectively. The majority of patients were treatment-naïve (83%), and 73% were infected by vertical transmission; 40% were assessed as not having cirrhosis (the remainder did not have a cirrhosis determination). SVR12 rates were 100% (13/13) for patients with genotype 2 and 97% (38/39) for genotype 3. The single patient who did not achieve SVR was lost to follow-up after achieving SVR4 (*Wirth et al 2017*).

Technivie
- The efficacy of Technivie was evaluated in a single, phase 2b, OL, MC, randomized pivotal trial (PEARL-I). The trial evaluated genotype 1b (*Lawitz et al 2015*) and genotype 4 (*Hézode et al 2015*) patients; however Technivie is only FDA approved for genotype 4. Genotype 4 patients received Technivie with or without RBV, for 12 weeks. Genotype 1b patients received Technivie for 12 or 24 weeks, without RBV.
  - In genotype 4 treatment-naive patients, SVR12 rates were 100% (42/42, 95% CI, 91.6 to 100) in the RBV-containing regimen and 90.9% (40/44, 95% CI, 78.3 to 97.5) in the RBV-free regimen; there was no statistical difference in SVR12 rates between these 2 treatment groups after adjusting for IL28B genotype (p = 0.086). All treatment-experienced patients received Technivie with RBV and the SVR12 rate was 100% (49/49).
  - In genotype 1b patients, SVR12 was achieved in 95.2% (40/42, 95% CI, 83.8 to 99.4) of treatment-naïve and 90.0% (36/40, 95% CI, 76.3 to 97.2) of treatment-experienced patients without cirrhosis. Among patients with cirrhosis, SVR12 was achieved in 97.9% (46/47, 95% CI, 88.7 to 99.9) of treatment-naïve and 96.2% (50/52, 95% CI, 86.8 to 99.5) of treatment-experienced patients.

Vosevi
- The efficacy of Vosevi was evaluated in 2 pivotal trials in DAA-experienced patients.
  - POLARIS-1 was a randomized, DB, PC trial that evaluated 12 weeks of treatment with Vosevi compared with 12 weeks of placebo in DAA-experienced patients with genotype 1, 2, 3, 4, 5, or 6 HCV infection without cirrhosis or with compensated cirrhosis who previously failed a regimen containing an NS5A inhibitor. Overall, 51% of patients had been previously treated with ledipasvir (the NS5A component of Harvoni). The remaining patients were treated with other NS5A inhibitors. The overall SVR rate was 96% (253/263). The SVR rate was 99% (140/142) and 93% (113/121) in patients without cirrhosis and with cirrhosis, respectively (*Bourlière et al 2017*).
  - POLARIS-4 was a randomized, OL trial that evaluated 12 weeks of treatment with Vosevi and 12 weeks of treatment with Epclusa in patients with genotype 1, 2, 3, or 4 HCV infection without cirrhosis or with compensated cirrhosis who had previously failed an HCV DAA-containing regimen that did not include an NS5A inhibitor. In the trial, prior DAA regimens contained sofosbuvir (85%) with the following: PegIFN and RBV or just RBV (69%), HCV NS3/4A protease inhibitor (boceprevir, simeprevir, or telaprevir; 15%) and investigational DAA (< 1%). The SVR12 rate was 98% (178/182) (95% CI, 95 to 99; significantly superior to the prespecified performance goal of 85% [p < 0.001]) for patients receiving Vosevi for 12 weeks. The SVR12 rate was 90% (136/151) (95% CI, 84 to 94, not significantly superior to the prespecified performance goal of 85% [p = 0.09]) for patients receiving Epclusa for 12 weeks. One patient had viral breakthrough and 14 patients relapsed (*Bourlière et al 2017*).

Viekira Pak

- Efficacy and safety of Viekira Pak were evaluated in 7 pivotal clinical trials with chronic HCV genotype 1 infection:
  - Treatment-naïve genotype 1a and 1b (SAPPHIRE-I)
  - Treatment-experienced genotype 1a and 1b (SAPPHIRE-II)
  - Treatment-experienced genotype 1b (PEARL-II)
  - Treatment-naïve genotype 1b (PEARL-III)
  - Treatment-naïve genotype 1a (PEARL-IV)
  - Treatment-naïve and -experienced genotype 1a and 1b with cirrhosis (TURQUOISE-II)
  - Treatment-naïve and -experienced genotype 1b with cirrhosis (TURQUOISE-III).
- SAPPHIRE-I and SAPPHIRE-II were MC, randomized, DB, PC trials. Patients were randomized to Viekira Pak plus RBV for 12 weeks or placebo. Patients in the placebo treatment arm received placebo for 12 weeks, after which they received OL Viekira Pak plus RBV for 12 weeks (*Feld et al 2014, Zeuzem et al 2014[b]*).
  - In SAPPHIRE-I (n = 631), SVR12 was achieved in 96.2% (95% CI, 94.5 to 97.9) of patients receiving Viekira Pak with RBV. This rate was non-inferior and superior to the historical control rate with telaprevir plus PegIFN/RBV.
  - In SAPPHIRE-II (n = 394), SVR12 was achieved in 96.3% (95% CI, 94.2 to 98.4) of patients receiving Viekira Pak with RBV. This rate was non-inferior and superior to the historical control rate among patients who had previously been treated with PegIFN/RBV and who received retreatment with telaprevir plus PegIFN/RBV.
- In PEARL-II (n = 186), patients without cirrhosis were randomized to receive OL Viekira Pak with or without RBV for 12 weeks of treatment (*Andreone et al 2014*).
  - Rates of SVR12 were 96.6% (95% CI, 92.8 to 100) with Viekira Pak plus RBV and 100% (95% CI, 95.9 to 100) with Viekira Pak alone. Rates of SVR in both treatment groups were non-inferior and superior to the historical rate for telaprevir plus PegIFN/RBV in comparable treatment-experienced patients.
  - Non-inferiority of treatment with Viekira Pak alone compared to Viekira Pak plus RBV was met (treatment difference in SVR12 rates, 3.4% [95% CI, -0.4 to 7.2]).
- PEARL-III and PEARL-IV were MC, double-blind, placebo controlled trials. Patients without cirrhosis were randomized to receive Viekira Pak with or without RBV for 12 weeks of treatment (*Ferenci et al 2014*).
  - In PEARL-III (n = 419), treatment with Viekira Pak resulted in SVR12 rates of 99.5% (95% CI, 98.6 to 100) with RBV and 99% (95% CI, 97.7 to 100) without RBV in patients with genotype 1b infection.
  - In PEARL-IV (n = 305), treatment with Viekira Pak resulted in SVR12 rates of 97% (95% CI, 93.7 to 100) with RBV and 90.2% (95% CI, 86.2 to 94.3) without RBV in patients with genotype 1a infection.
- The OL TURQUOISE-II trial (n = 380) enrolled patients with compensated cirrhosis (Child-Pugh A) or liver scarring with few to no outward symptoms who were either treatment-naïve or PegIFN/RBV treatment-experienced. Patients were randomized to receive Viekira Pak in combination with RBV for 12 or 24 weeks of treatment. Patients who previously failed therapy with a treatment regimen that included a DAA were excluded (*Poordad et al 2014*).
  - Patients who received 12 weeks of treatment had an SVR12 response of 91.8% (97.5% CI, 87.6 to 96.1).
  - Those patients who received 24 weeks of treatment achieved an SVR12 rate of 95.9% (97.5% CI, 92.6 to 99.3).
  - Rates of SVR12 in the 12- and 24-week treatment groups were non-inferior and superior to the historical rate with telaprevir plus PegIFN/RBV among patients with HCV genotype 1 infection and cirrhosis. The difference in the rates of SVR between the 2 treatment groups was not significant.
- The OL TURQUOISE-III trial (n = 60) enrolled genotype 1b patients with compensated cirrhosis who were either treatment-naïve or PegIFN/RBV treatment-experienced. Patients were randomized to receive Viekira Pak for 12 weeks. SVR12 was achieved in all patients enrolled in the study (*Feld et al 2016*).
- Safety and efficacy of Viekira Pak were also evaluated in liver transplant patients and in patients with HCV genotype 1 co-infected with HIV-1.
  - CORAL-I was a phase 2, OL trial in HCV genotype 1 liver transplant recipients who were at least 12 months post transplantation with mild fibrosis (Metavir score < F2). Patients received treatment with Viekira Pak with RBV for 24 weeks. Of the 34 patients enrolled, 33 achieved an SVR12, for a rate of 97% (95% CI, 85 to 100) (*Kwo et al 2014*).
  - TURQUOISE-I was a phase 3, randomized, OL trial in 63 patients with treatment-naïve or -experienced HCV genotype 1 infection who were co-infected with HIV-1. Patients on a stable antiretroviral therapy regimen were treated for 12 or 24 weeks with Viekira Pak in combination with RBV. SVR12 rates were 91% for patients with HCV genotype 1a infection and 100% for those with genotype 1b infection (*Wyles et al 2014*).

Viekira XR

- The approval of Viekira XR was based on comparability of bioavailability for each of the components in Viekira XR compared to that of the previously approved formulations in Viekira Pak. A clinical trial to evaluate the efficacy and safety of Viekira XR was not required.

Zepatier

- The safety and efficacy of Zepatier were evaluated in 6 pivotal clinical trials including patients with genotype 1 or 4 infection. A small number of patients with other HCV genotypes were also included in the clinical trials; however, Zepatier is only indicated for genotypes 1 and 4.
  - C-EDGE TN was a DB, PC, MC, randomized study in treatment-naïve patients with genotype 1, 4, or 6 infection. Of the 316 patients receiving Zepatier for 12 weeks, 95% (95% CI, 92 to 97) achieved SVR12. SVR12 was achieved in 97% (95% CI, 90 to 100) of cirrhotic patients and 94% (95% CI, 90 to 97) of noncirrhotic patients (*Zeuzem et al 2015*).
  - C-EDGE CO-INFECTION was an OL, MC trial in treatment-naïve patients with genotype 1, genotype 4, and genotype 6 infection who were co-infected with HIV. All patients (n = 218) received Zepatier for 12 weeks. In the overall population, 96% achieved SVR12 (95% CI, 92.9 to 98.4), exceeding the historical reference rate of 70% (*Rockstroh et al 2015*).
  - C-SURFER was a double-blind, placebo-controlled, MC, randomized study, evaluating Zepatier for 12 weeks in patients with genotype 1 infection with CKD stage 4 to 5. Of the 122 patients receiving Zepatier, 6 were excluded from the modified full analysis set population for reasons other than virologic failure. Of the 116 remaining patients, 115 achieved SVR12, a rate better than the historical control rate of 45% ($p < 0.001$) (*Roth et al 2015*).
  - C-SCAPE was an OL, randomized study that evaluated the efficacy of Zepatier for 12 weeks, with or without RBV, in patients with genotype 4, 5, or 6 infection. In patients with genotype 4 infection, SVR12 was achieved in 100% (10/10) of patients receiving Zepatier with RBV vs 90% (9/10) in patients receiving Zepatier alone (*Brown et al 2016*).
  - C-EDGE TE was an OL, MC, randomized study evaluating 12 or 16 weeks of Zepatier, with or without RBV in patients with genotype 1, 4, or 6 HCV infection and previous treatment with Peg IFN/RBV. SVR12 was achieved in 92.4% (97/105) receiving Zepatier alone for 12 weeks, 94.2% (98/104) receiving Zepatier plus RBV for 12 weeks, 92.4% (97/105) receiving Zepatier alone for 16 weeks, and 97.2% (103/106) receiving Zepatier plus RBV (*Kwo et al 2017*).
  - C-SALVAGE was an OL, MC study evaluating Zepatier plus RBV for 12 weeks in patients (n = 79) with genotype 1 infection who failed a regimen containing PegIFN/RBV and another DAA. SVR12 was achieved in 96% (95% CI, 89.3 to 99.2) of patients. The 3 patients not achieving SVR12 had a past history of virologic failure (*Forns et al 2015*).

CLINICAL GUIDELINES

- In order to provide healthcare professionals with timely guidance, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) have developed a web-based process for the rapid formulation and dissemination of evidence-based, expert-developed recommendations for hepatitis C management (*AASLD-IDSA 2017*).
  - Recommended regimens are those that are favored for most patients in a given group, based on optimal efficacy, favorable tolerability and toxicity profiles, and duration.
  - The guidance also lists alternative regimens, which are those that are effective but, relative to recommended regimens, have potential disadvantages, limitations for use in certain patient populations, or less supporting data than recommended regimens. For a listing of alternative regimens, refer to the web-based guidance for full details.
- For the general genotype 1 population, the guidance recommends 4 different regimens considered to have comparable efficacy: Epclusa, Harvoni, Mavyret, and Zepatier. The level of evidence and treatment duration depend on the genotype 1 subtype, prior treatment status (naïve or experienced), and the presence of cirrhosis.
- The guidance recommends Epclusa and Mavyret for patients with genotype 2 or 3 infection.
- The guidance recommends Epclusa, Harvoni, Mavyret, and Zepatier for the treatment of genotype 4 infection. The guidance recommends Epclusa, Harvoni, and Mavyret for treatment of genotype 5 and 6.
- The guidance provides recommendations for several unique patient populations, including patients who have failed prior therapy with DAAs, co-infection with HIV/HCV, decompensated cirrhosis, recurrent HCV infection in the post-transplant setting, or renal impairment. Some key recommendations include:
  - Epclusa, Harvoni (listed as an alternative for patients with compensated cirrhosis), and Mavyret are recommended for genotype 1 patients with prior failure to HCV NS3/4A protease inhibitors. Epclusa (genotype 1b), Mavyret (regardless

of genotype 1 subtype), and Vosevi (genotype 1a) are recommended for patients with prior failure to sofosbuvir-containing regimens.
  - Vosevi is recommended in genotype 1, 3, 4, 5, or 6 patients with prior failure to an NS5A inhibitor-containing regimen.
  - Sovaldi-based regimens (ie, Epclusa, Harvoni, Sovaldi plus Daklinza) are recommended for patients with decompensated cirrhosis.
  - HIV/HCV-co-infected patients should be treated and re-treated the same as patients without HIV infection, after recognizing and managing interactions with antiretroviral medications.
  - For patients with stage 4 or 5 CKD (creatinine clearance below 30 mL/min), Mavyret (regardless of genotype) and Zepatier (genotypes 1 and 4 only) are recommended. For kidney transplant recipients, Harvoni (genotypes 1 and 4 only) and Mavyret are recommended.

SAFETY SUMMARY

- Due to the DAAs used in combination therapy with PegIFN and RBV, all contraindications to those 2 medications (PegIFN and RBV) also apply to the class. This includes a contraindication for use in pregnancy due to the RBV component.
- Mavyret is contraindicated in patients with severe hepatic impairment (Child-Pugh C) and coadministration with atazanavir and rifampin.
- Technivie, Viekira Pak, and Viekira XR are contraindicated in patients with:
  - Moderate to severe hepatic impairment (Child-Pugh B and C) due to the risk of potential toxicity.
  - Known hypersensitivity to ritonavir (eg, toxic epidermal necrolysis or Stevens-Johnson syndrome).
  - Concomitant use of drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events.
  - Concomitant use of drugs that are moderate or strong inducers of CYP3A.
  - Concomitant use of drugs that are strong inducers or strong inhibitors of CYP2C8 (Viekira Pak and Viekira XR only)
- Vosevi is contraindicated in patients with rifampin coadministration.
- Zepatier is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C). It is also contraindicated with organic anion transporting polypeptides 1B1/3 (OATP1B1/3) inhibitors, strong inducers of CYP3A, and efavirenz.
- Daklinza is contraindicated in combination with drugs that strongly induce CYP3A.
- Key warnings and precautions for the DAAs include:
  - Serious symptomatic bradycardia may occur in patients taking amiodarone and sofosbuvir in combination with another DAA (eg, Sovaldi plus Daklinza, Epclusa, Harvoni, Vosevi).
  - Technivie, Viekira Pak, and Viekira XR carry a risk of hepatic decompensation and hepatic failure in patients with cirrhosis.
- Overall, DAA combination therapies are well tolerated and discontinuations due to adverse events are not common.
  - The most common adverse reactions observed with each treatment regimen listed below include:
    - Daklinza in combination with Sovaldi: headache and fatigue
    - Daklinza in combination with Sovaldi and RBV: headache, anemia, fatigue, and nausea
    - Epclusa: headache and fatigue
    - Epclusa and RBV in patients with decompensated cirrhosis: fatigue, anemia, nausea, headache, insomnia, and diarrhea
    - Harvoni: fatigue, headache, and asthenia
    - Mavyret: headache and fatigue
    - Olysio with Sovaldi during 12 or 24 weeks of treatment: fatigue, headache, and nausea
    - Olysio with PegIFN and RBV during the first 12 weeks of treatment: rash (including photosensitivity), pruritus, and nausea
    - Sovaldi in combination with RBV: fatigue and headache; Sovaldi in combination with PegIFN alfa and RBV: fatigue, headache, nausea, insomnia, and anemia
    - Technivie in combination with RBV: asthenia, fatigue, nausea, and insomnia
    - Viekira Pak and Viekira XR: fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia.
    - Viekira Pak or Viekira XR without RBV: nausea, pruritus, and insomnia
    - Vosevi: headache, fatigue, diarrhea, and nausea
    - Zepatier: fatigue, headache, and nausea.

- Zepatier with RBV: anemia and headache

- On October 4, 2016, the FDA announced that a new *Boxed Warning* would be added to all DAAs for HCV infection, regarding the risk of hepatitis B virus (HBV) reactivation. The new *Boxed Warning* is based on case reports submitted to the FDA and from the published literature of HCV/HBV co-infected patients treated with DAAs from November 2013 to July 2016 (*FDA 2016*).
  - HBV can become reactivated in any patient who has a current or previous infection with HBV and is treated with direct-acting antivirals. In a few cases, HBV reactivation in patients treated with direct-acting antivirals resulted in serious liver problems or death.
  - The *Boxed Warning* was added to the labeling for all of the DAAs in February 2017. The warning directs healthcare providers to test all patients for evidence of current or prior HBV infection before initiation of HCV treatment. HCV/HBV co-infected patients should be monitored for HBV reactivation and hepatitis flare during HCV treatment and post-treatment follow-up. Appropriate patient management for HBV infection should be initiated as clinically indicated.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Route	Usual Recommended Frequency	Comments
Daklinza (daclatasvir)	Oral	One tablet once daily (60 mg dose); must be used in combination with Sovaldi	*Recommended dosage modification with CYP3A inhibitors and inducers*: • Strong CYP3A inhibitors and certain HIV antiviral agents: 30 mg once daily • Moderate CYP3A inducers and nevirapine: 90 mg once daily *Duration of therapy:* • 12 to 24 weeks (when used in combination with Sovaldi)
Epclusa (sofosbuvir/velpatasvir)	Oral	One tablet once daily	• No dosage recommendation can be given for patients with severe renal impairment or end-stage renal disease (ESRD). *Duration of therapy:* • 12 weeks
Harvoni (ledipasvir/sofosbuvir)	Oral	One tablet once daily	• No dosage recommendation can be given for patients with severe renal impairment or ESRD.
Mavyret (glecaprevir/pibrentasvir)	Oral	Three tablets daily	• Contraindicated in patients with severe hepatic impairment (Child-Pugh C). Not recommended in patients with moderate hepatic impairment (Child-Pugh B). *Duration of therapy:* • 8 to 16 weeks
Olysio (simeprevir)	Oral	One capsule once daily; must be used with PegIFN/RBV or Sovaldi	• In HCV genotype 1a-infected patients with compensated cirrhosis, screening for the

Drug	Route	Usual Recommended Frequency	Comments
			presence of virus with the NS3 Q80K polymorphism may be considered prior to initiation of treatment with Olysio with Sovaldi. • Prior to initiation of treatment with Olysio in combination with PegIFN/RBV, screening patients with HCV genotype 1a infection for the presence of virus with the NS3 Q80K polymorphism is strongly recommended. • Not recommended for use in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) due to higher simeprevir exposures. *Duration of therapy:* • 12 to 24 weeks (when used in combination with Sovaldi)
Sovaldi (sofosbuvir)	Oral	One tablet once daily; must be used in combination with RBV ± PegIFN, Sovaldi, or Daklinza	• Safety and efficacy have not been established in patients with severe renal impairment. *Duration of therapy:* • 12 to 24 weeks (when used in combination with Daklinza or Olysio)
Technivie (ombitasvir/paritaprevir/ritonavir)	Oral	Two tablets once daily	• Contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C). *Duration of therapy:* • 12 weeks
Viekira Pak (ombitasvir/paritaprevir/ritonavir and dasabuvir)	Oral	Two ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablets once daily (in the morning) and one dasabuvir 250 mg tablet twice daily (morning and evening)	• Contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C). *Duration of therapy:* • 12 to 24 weeks
Viekira XR (ombitasvir/paritaprevir/ ritonavir/dasabuvir)	Oral	Three tablets once daily	• Contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C). *Duration of therapy:* • 12 to 24 weeks

Drug	Route	Usual Recommended Frequency	Comments
Vosevi (sofosbuvir/velpatasvir/voxilaprevir)	Oral	One tablet once daily	• No dosage recommendation can be given for patients with severe renal impairment or ESRD. • Not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C). *Duration of therapy:* • 12 weeks
Zepatier (elbasvir/grazoprevir)	Oral	One tablet once daily	• Testing patients with HCV genotype 1a infection for the presence of virus with NS5A resistance-associated polymorphisms is recommended prior to initiation of treatment with Zepatier to determine dosage regimen and duration. • Contraindicated in patients with moderate hepatic impairment (Child-Pugh B) due to the lack of clinical safety and efficacy experience in HCV-infected Child-Pugh B patients, and in patients with severe hepatic impairment (Child-Pugh C) due to a 12-fold increase in grazoprevir exposure. *Duration of therapy:* • 12 to 16 weeks

See the current prescribing information for full details

CONCLUSION

- Hepatitis C is a disease affecting primarily the liver that results from infection with the hepatitis C virus. Long-term complications include cirrhosis and hepatocellular carcinoma. Hepatitis C is the leading indication for liver transplant.
- Success at obtaining an SVR is an important treatment goal and a common primary endpoint in the clinical trials of antiviral medications.
- PegIFN-free, DAA combination regimens, such as Epclusa, Harvoni, Mavyret, and Zepatier have become the standard of care for the treatment of genotype 1 infection. There is a lack of head-to-head trial data available comparing these regimens, but they are considered to have comparable efficacy and safety for treating the general genotype 1 population (*AASLD-IDSA 2017*).
- The only DAA fixed-dose combination products approved and recommended for the treatment of genotypes 2 and 3 infection are Mavyret and Epclusa (*AASLD-IDSA 2017*).
- Similar to genotype 1, several DAA combination regimens have demonstrated high SVR rates for genotype 4 infection. Epclusa, Harvoni, Mavyret, and Zepatier are recommended by the AASLD-IDSA guidance (*AASLD-IDSA 2017*).
- Data are limited for treatment of genotype 5 and 6 infection; however, Epclusa, Harvoni, and Mavyret are approved by the FDA and supported by the AASLD-IDSA guidance (*AASLD-IDSA 2017*).
- Of the combination products, Epclusa and Harvoni are the preferred treatment options in patients with decompensated cirrhosis (Child-Pugh B and C). Mavyret and Zepatier are recommended for patients with advanced kidney disease.

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Therapeutic Class Overview
Beta Agonist and Anticholinergic Combinations

INTRODUCTION

- Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities. The abnormalities are usually caused by exposure to noxious particles or gases. Airflow limitation is caused by a combination of small airway disease (eg, obstructive bronchiolitis) and parenchymal destruction (emphysema); the relative contributions of each component vary between patients. The most common symptoms of COPD include dyspnea, cough, and sputum production (Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2017).
- COPD affects 6.4% of the United States population and is the major contributor to mortality from chronic lower respiratory diseases, the third leading cause of death in the United States (Centers for Disease Control and Prevention, 2016). Globally, COPD is the fourth leading cause of death and is expected to be the third leading cause of death by 2020; the burden of COPD continues to increase due to continued exposure to risk factors and aging of the population (GOLD, 2017).
- Cigarette smoking is the main risk factor for COPD; other risk factors include biomass fuel exposure (such as from cooking and heating in poorly ventilated dwellings) and air pollution. Host factors such as genetic abnormalities, abnormal lung development, and accelerated aging can predispose individuals to COPD development (GOLD, 2017).
- Patients with COPD may experience exacerbations, which are periods of acute worsening of respiratory symptoms (GOLD, 2017).
- Pharmacologic therapy for COPD can reduce symptoms, reduce the frequency and severity of exacerbations, and improve patients' health status and exercise tolerance. There is no conclusive evidence that COPD medications modify the long-term decline in lung function characteristic of COPD (GOLD, 2017).
- Pharmacologic options for COPD treatment comprise several classes, including β_2-agonists, anticholinergics, methylxanthines, various combination products (including bronchodilators with inhaled corticosteroids [ICSs]), and the phosphodiesterase (PDE)-4 inhibitor roflumilast. Pharmacologic treatments should be individualized based on symptom severity, risk of exacerbations, side effects, comorbidities, drug availability, and cost, as well as the patient's response, preference, and ability to use various drug delivery devices (GOLD, 2017).
- Inhaled bronchodilators are central to COPD symptom management, and are usually given on a regular basis to prevent or reduce symptoms. Several long-acting inhaled bronchodilators are available, and use of short-acting bronchodilators on a regular basis is not generally recommended (GOLD, 2017).
- Available β_2-agonist/anticholinergic combinations include COMBIVENT RESPIMAT and DUONEB, which are combinations of the short-acting agents, albuterol and ipratropium, and the combination long-acting β_2-agonists (LABAs)/long-acting anticholinergics (also called long-acting muscarinic antagonists [LAMAs]) ANORO ELLIPTA (umeclidinium/vilanterol), STIOLTO RESPIMAT (tiotropium/olodaterol, UTIBRON NEOHALER (glycopyrrolate/indacaterol), and BEVESPI AEROSPHERE (glycopyrrolate/formoterol fumarate) (see Table 1).
- Updated 2017 GOLD guidelines place the use of combination LAMA/LABAs more prominently than in previous versions, recommending dual bronchodilator therapy as a first- or second-line treatment for most patients with COPD (with the exception of low-risk patients with milder symptoms) (GOLD, 2017).
- For many years, an inhalation aerosol combining ipratropium and albuterol was available as the COMBIVENT inhaler. Original COMBIVENT contained chlorofluorocarbons (CFCs) and has been discontinued due to regulations limiting the use of CFCs. It has been replaced by a newer formulation, COMBIVENT RESPIMAT inhalation spray (Food and Drug Administration, 2015). Because original COMBIVENT is unavailable, information on this product is no longer included in this review. However, data from some clinical studies using original COMBIVENT is still included as it may be relevant to evaluation of COMBIVENT RESPIMAT.
- Medispan class/subclass: sympathomimetics; adrenergic combinations.

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
ANORO ELLIPTA (umeclidinium/vilanterol)	GlaxoSmithKline	12/18/2013	-
BEVESPI AEROSPHERE (glycopyrrolate/formoterol fumarate)	AstraZeneca	04/25/2016	-
COMBIVENT RESPIMAT (ipratropium/albuterol)	Boehringer Ingelheim	10/07/2011	-
DUONEB (ipratropium/albuterol)	various	03/21/2001	✔
STIOLTO RESPIMAT (tiotropium/olodaterol)	Boehringer Ingelheim	05/21/2015	-
UTIBRON NEOHALER (glycopyrrolate/indacaterol)	Novartis	10/29/2015	-

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

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)

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

Ipratropium/albuterol

- The combination of ipratropium and albuterol is a well-established treatment that has been used for many years in the management of COPD.
- Several double-blind, randomized, controlled studies have demonstrated greater effectiveness of the combination of ipratropium and albuterol in a metered dose inhaler (MDI) compared to monotherapy with either of the individual components (Bone et al, 1994; Dorinsky et al, 1999; Friedman et al, 1999). Demonstrated improvements relative to monotherapies include the following:
    - Mean peak response in forced expiratory volume in one second (FEV_1) (Bone et al, 1994)
    - Overall forced vital capacity (FVC) response (Bone et al, 1994)
    - The percentage of patients demonstrating a 15% increase in FEV_1 after medication administration (Dorinsky et al, 1999)
    - FEV_1 area under the curve (AUC) (0 to 4 hours) (Friedman et al, 1999)
- A multicenter, randomized controlled trial evaluating ipratropium/albuterol given via MDI four times daily, via nebulizer four times daily, and via nebulizer twice daily (morning and night) and MDI twice daily (afternoon and evening) demonstrated no significant differences among groups in quality-of-life scores, peak flow measurements, or patient symptom scores (Tashkin et al, 2007).
- A double-blind, double-dummy trial comparing ipratropium/albuterol 20 mcg/100 mcg via RESPIMAT inhaler four times daily to ipratropium/albuterol 36 mcg/206 mcg via MDI four times daily demonstrated non-inferiority of the RESPIMAT inhaler to the MDI based on FEV_1 and FVC endpoints (ZuWallack et al, 2010).

Umeclidinium/vilanterol

- A multicenter, double-blind, placebo-controlled, randomized controlled trial (N=1,532) compared once-daily doses of umeclidinium/vilanterol 62.5 mcg/25 mcg (ANORO ELLIPTA) to umeclidinium 62.5 mcg alone, vilanterol 25 mcg alone, or placebo. The primary endpoint, least squares mean (LSM) change in FEV_1 from baseline, was significantly greater in the umeclidinium/vilanterol group (171 mL) compared to the placebo group (4 mL; P<0.001), as well as compared to the umeclidinium monotherapy group (119 mL; P=0.004) and the vilanterol monotherapy group (76 mL; P<0.001). Improvements were also noted for ANORO ELLIPTA in the weighted mean FEV_1 over 0 to 6 hours post-dose, rescue albuterol use, COPD exacerbations, and St. George's Respiratory Questionnaire (SGRQ) (Donohue et al, 2013).
- Two multicenter, double-blind, double-dummy, active-controlled, randomized controlled trials (N=843 and 869), reported together, evaluated umeclidinium/vilanterol 62.5 mcg/25 mcg (ANORO ELLIPTA), umeclidinium/vilanterol 125 mcg/25 mcg, and tiotropium 18 mcg (SPIRIVA HANDIHALER). One trial had an additional arm evaluating vilanterol 25 mcg monotherapy, and the other had an additional arm evaluating umeclidinium 125 mcg monotherapy (Decramer et al, 2014).
    - In the first trial, the LSM difference in trough FEV_1 was greater for umeclidinium/vilanterol 62.5 mcg/25 mcg (211 mL) compared to vilanterol 25 mcg (121 mL) and tiotropium 18 mcg (121 mL) (P=0.0006 vs either monotherapy). The weighted mean (wm) FEV_1 over 0 to 6 hours also favored combination therapy over tiotropium alone or vilanterol alone. Most patient-reported endpoints appeared comparable with combination therapy and monotherapy (Decramer et al, 2014).
    - In the second trial, the LSM difference in trough FEV_1 was greater for umeclidinium/vilanterol 62.5 mcg/25 mcg (208 mL) compared to tiotropium 18 mcg (149 mL) (P=0.0182), but was not significantly different from monotherapy with umeclidinium 125 mcg (186 mL) (P=0.38). The wm FEV_1 over 0 to 6 hours favored combination therapy over tiotropium alone or umeclidinium alone. Most patient-reported endpoints appeared comparable with combination therapy and monotherapy (Decramer et al, 2014).
- Two identical multicenter, double-blind, placebo-controlled, crossover studies (N=308 and N=349), reported together, evaluated the use of umeclidinium/vilanterol 62.5 mcg/25 mcg, umeclidinium/vilanterol 125 mcg/25 mcg, umeclidinium 125 mcg, umeclidinium 62.5 mcg, vilanterol 25 mcg, and placebo. Co-primary endpoints were exercise endurance time (EET) and FEV_1. These studies led to inconsistent results, with one study demonstrating small but statistically significant improvement in EET compared to placebo, and the other showing no significant improvement. The differences in trial results seemed to be explained by unexpected improvements observed in the placebo group in one of the trials, and a *post-hoc* integrated analysis demonstrated significant improvement for umeclidinium/vilanterol vs placebo. Both studies demonstrated improved lung function based on FEV_1 compared to placebo. Comparisons were

not presented between the combination therapies and monotherapy with umeclidinium or vilanterol (Maltais et al, 2014).

- 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). When comparing trough FEV_1 on day 85, umeclidinium/vilanterol demonstrated non-inferiority to combination treatment with tiotropium and indacaterol. Other measures, including rescue medication use, TDI focal scores, and SGRQ scores, were also similar among both treatment groups on day 85 (P values not provided) (Kalberg et al, 2016).

Tiotropium/Olodaterol

- A multicenter, double-blind, placebo-controlled, crossover trial (N=219) evaluated tiotropium/olodaterol 5 mcg/5 mcg (STIOLTO RESPIMAT) compared to placebo, olodaterol 5 mcg monotherapy, tiotropium 2.5 mcg monotherapy, tiotropium 5 mcg monotherapy, and combination tiotropium/olodaterol 2.5 mcg/5 mcg daily. Tiotropium/olodaterol 5 mcg/5 mcg demonstrated a greater change from baseline in the FEV_1 AUC (0 to 24 hours) (244 mL) compared to placebo (-37 mL) and compared to each monotherapy (117 to 133 mL) (P<0.0001). Additional lung function endpoints were also favorable for tiotropium/olodaterol compared to placebo and monotherapies (Beeh et al, 2015).
- Two multicenter, double-blind, parallel group, active controlled, randomized trials (N=2,624 and 2,539), reported together, evaluated tiotropium/olodaterol 5 mcg/5 mcg compared to olodaterol 5 mcg monotherapy, tiotropium 2.5 mcg monotherapy, tiotropium 5 mcg monotherapy, and combination tiotropium/olodaterol 2.5 mcg/5 mcg daily. In both trials, the tiotropium/olodaterol 5 mcg/5 mcg group demonstrated improvement over monotherapy with either tiotropium or olodaterol in each co-primary endpoint, including the FEV_1 AUC (0 to 3 hours), trough FEV_1, and SGRQ. Dyspnea, assessed by the change from baseline in transition dyspnea index (TDI) focal score, was also improved with combination therapy (Buhl et al, 2015).

Glycopyrrolate/Indacaterol

- Two 12-week, multicenter, randomized, double-blind, parallel group, placebo- and active-controlled studies (N=2,038) evaluated the efficacy and safety of indacaterol/glycopyrrolate. Patients were randomized (1:1:1:1) to indacaterol/glycopyrrolate (27.5/15.6 mcg twice daily), indacaterol (27.5 mcg twice daily), glycopyrrolate (15.6 mcg twice daily), or placebo. Pooled data demonstrated that the group that received combination indacaterol/glycopyrrolate had statistically superior measurements in terms of FEV_1 AUC (0 to 12 hours) compared with its monocomponents (P<0.001). When compared to placebo, the group that received combination treatment with indacaterol/glycopyrrolate also had statistically significant improvements in SGRQ, TDI scores, and use of rescue medications (P<0.001) (Mahler et al, 2015).
- A comparative trial in 1,680 patients with COPD and at least 1 exacerbation during the previous year showed a significant reduction in COPD exacerbation rate with indacaterol/glycopyrrolate compared to salmeterol/fluticasone (rate ratio, 0.89; 95% CI, 0.83 to 0.96; P=0.003) (Wedzicha et al, 2016).

Glycopyrrolate/Formoterol fumarate

- Efficacy and safety of glycopyrrolate/formoterol fumarate (18/9.6 mcg twice daily) were demonstrated in two 24-week, phase 3, multi-center, double-blind, placebo-controlled trials, PINNACLE-1 and PINNACLE-2 (total N=3,718) (Martinez et al, 2017).
    - In both trials, glycopyrrolate/formoterol fumarate demonstrated a larger increase in mean change from baseline in trough FEV_1 at week 24 relative to placebo and to either monotherapy. In PINNACLE-1, the differences for glycopyrrolate/formoterol fumarate were 150 mL vs. placebo, 59 mL vs. glycopyrrolate, and 64 mL vs. formoterol fumarate (P<0.0001 for all comparisons), and in PINNACLE-2, these differences were 103 mL, 54 mL, and 56 mL, respectively (P<0.001 for all comparisons).
    - Improvements compared to placebo were also noted in secondary endpoints including peak FEV_1 and daily rescue albuterol use. There was also a trend toward improvement in the SGRQ responder rate (improvement in score of 4 or more), with an odds ratio vs placebo of 1.49 (95% confidence interval [CI], 1.05 to 2.11) in PINNACLE-1 and 1.31 (95% CI, 0.94 to 1.84) in PINNACLE-2.

Meta-Analyses

- 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 is 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 US], 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. Safety profiles were also similar among the products (Schlueter et al, 2016).

Treatment Guidelines

- The 2017 GOLD guidelines underwent a significant update from prior guideline versions. The guidelines state that the management strategy for stable COPD should be predominantly based on an assessment of the patient's symptoms and future risk of exacerbations. The risk of exacerbations is now based solely on the exacerbation history, whereas in previous versions of the guideline, risk assessment also included consideration of airflow limitation assessed by spirometry. Key recommendations from the GOLD guidelines are as follows (GOLD, 2017):
    - Inhaled bronchodilators are recommended over oral bronchodilators.
    - LAMAs and LABAs are preferred over short-acting agents except for patients with only occasional dyspnea.
    - Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on one bronchodilator, treatment should be escalated to two.
    - Long-term monotherapy with ICSs is not recommended. Long-term treatment with ICSs may be considered in association with LABAs for patients with a history of exacerbations despite treatment with long-acting bronchodilators.
    - Treatment recommendations are given for patients with COPD based on their GOLD patient group (see Table 3 below).
        - Group A: Patients should be offered bronchodilator treatment (short- or long-acting). This should be continued if symptomatic benefit is documented.
        - Group B: Initial therapy should consist of a long-acting bronchodilator (LAMA or LABA). For patients with persistent breathlessness on monotherapy, use of two bronchodilators is recommended (LAMA + LABA). For patients with severe breathlessness, initial therapy with two bronchodilators may be considered. If the addition of a second bronchodilator does not improve symptoms, it is suggested that treatment could be stepped down to a single bronchodilator.
        - Group C: Initial therapy should be a LAMA. Patients with persistent exacerbations may benefit from adding a second long-acting bronchodilator (LAMA + LABA, preferred) or using an ICS + LABA.
        - Group D: It is recommended to start therapy with a LAMA + LABA combination. In some patients, initial therapy with an ICS + LABA may be the first choice; these patients may have a history and/or findings suggestive of asthma-COPD overlap. In patients who develop further exacerbations on LAMA + LABA therapy, alternative pathways include escalation to a LAMA + LABA + ICS (preferred) or a switch to an ICS + LABA. If patients treated with a LAMA + LABA + ICS still have exacerbations, options for selected patients may include addition of roflumilast, addition of a macrolide, or stopping the ICS.

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

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

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

- Guidelines 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

- 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 that are standard for the LABAs, which state that LABAs 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 LABAs, 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, discontinue the product and institute alternative therapy.
    - Cardiovascular effect: β_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. Use 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. Use with caution in patients with narrow-angle glaucoma. In addition, 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. Use caution when administering this medication to patients with prostatic hyperplasia or bladder-neck obstruction.
    - Do not exceed recommended dose: 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, discontinue therapy and consider alternative treatment.
    - Coexisting conditions: Due to the β_2-agonist component, use with caution 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).

  - o 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).

DOSING AND ADMINISTRATION

Table 3. Dosage and Administration

Drug	Dosage Form and Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
ANORO ELLIPTA	Disposable inhaler containing two double-foil blister strips: 62.5 mcg/25 mcg	One inhalation once daily	Do not exceed recommended dose	Opening the cover of the inhaler prepares a dose for inhalation. If the inhaler is opened and closed without inhalation, the dose is lost. The inhaler contains a dose counter.
BEVESPI AEROSPHERE	Inhalation spray; each actuation delivers 9 mcg of glycopyrrolate and 4.8 mcg of formoterol fumarate	Two inhalations twice daily	Use in the morning and in the evening	Each canister delivers 120 inhalations. The canister has an attached dose indicator, which indicates how many inhalations remain; dose indicator display will move after every tenth actuation.
COMBIVENT RESPIMAT	Inhalation spray; each actuation delivers 20 mcg ipratropium bromide and 100 mcg albuterol (equivalent to 120 mcg albuterol sulfate) from the mouthpiece.	One inhalation four times daily	Patients may take additional inhalations as needed; maximum six inhalations per 24 hours	Each cartridge delivers 120 metered actuations after preparation for use (60 actuations in the institutional pack). The inhaler has an indicator that shows approximately how much medicine is left. Once the actuations have been used, the inhaler locks so it can no longer be used.
DUONEB	3 mL sterile solution for nebulization in sterile low-density polyethylene unit-dose vials	One 3 mL vial by nebulization four times daily	Patients may take additional doses as needed; maximum six doses per 24 hours	DUONEB should be administered via a jet nebulizer connected to an air compressor with an adequate air flow, equipped with a mouthpiece or suitable face mask.
STIOLTO RESPIMAT	Inhalation spray; each actuation delivers 3.124 mcg tiotropium bromide monohydrate, equivalent to 2.5 mcg tiotropium, and 2.736	Two inhalations once daily	Take at the same time each day; do not exceed the recommended dose	Each cartridge delivers 60 metered actuations after preparation for use (28 in the institutional pack). Once the actuations have been used,

Drug	Dosage Form and Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	mcg olodaterol hydrochloride, equivalent to 2.5 mcg olodaterol			the inhaler locks so it can no longer be used.
UTIBRON NEOHALER	Inhalation powder; each capsule contains 27.5 mcg of indacaterol and 15.6 mcg of glycopyrrolate	One inhalation of capsule contents twice daily	Take at the same time each day (1 capsule in the morning, and 1 capsule in the evening); do not exceed the recommended dose	Administer via Neohaler device only.

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
ANORO ELLIPTA (umeclidinium/ vilanterol)	No dose adjustment is required.	Safety and efficacy have not been established.	No dose adjustment is required.	No dose adjustment is required for moderate impairment. Not studied in patients with severe impairment.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.
BEVESPI AEROSPHERE (glycopyrrolate/ formoterol fumarate)	No dose adjustment is required.	Safety and efficacy have not been established.	Pharmaco-kinetics have not been studied; use with caution.	Pharmacokinetics have not been studied; use with caution as formoterol is cleared hepatically.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.
COMBIVENT RESPIMAT & DUONEB (ipratropium/ albuterol)	No marked differences in adverse reactions have been observed; no dosage adjustment is necessary.	Safety and efficacy have not been established.	Pharmaco-kinetics have not been studied; use with caution.	Pharmacokinetics have not been studied; use with caution.	Pregnancy Category C* Unknown whether excreted in breast milk; a decision should be made whether to discontinue nursing or discontinue the drug.
STIOLTO RESPIMAT (tiotropium/ olodaterol)	No dose adjustment is required.	Safety and efficacy have not been established.	No dose adjustment is required. Patients with creatinine clearance ≤60 mL/min should be monitored for anticholinergic effects.	No dose adjustment is required with mild and moderate impairment. Not studied with severe impairment.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
UTIBRON NEOHALER (glycopyrrolate/ indacaterol)	No dose adjustment is required.	Safety and efficacy have not been established.	No dose adjustment is required. Patients with creatinine clearance ≤30 mL/min should be monitored for anticholinergic effects.	No dose adjustment is required for mild to moderate hepatic impairment. Not studied with severe impairment.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.

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

CONCLUSION

- Pharmacologic therapy for COPD can reduce symptoms, reduce the frequency and severity of exacerbations, and improve patients' health status and exercise tolerance. The combination of ipratropium and albuterol is a well-established treatment that has been used for many years in the management of COPD; however, it requires dosing four times per day for maintenance therapy. Newer combination products are now available, which are administered either once daily (ANORO ELLIPTA and STIOLTO RESPIMAT) or twice daily (BEVESPI AEROSPHERE and UTIBRON NEOHALER).
- Ipratropium and albuterol combination products include inhalers and vials for nebulization. Based on available information, efficacy appears to be comparable between these two products.
- With respect to lung function, each LAMA/LABA combination has been demonstrated to be more effective than use of its individual components. Data is limited on the effects of combination therapy compared to monotherapy on the rate of exacerbations and on patient-reported endpoints such as dyspnea.
- A meta-analysis of 27 trials including four LAMA/LABA fixed dose combination agents (aclidinium/formoterol [not FDA approved for use in the US], glycopyrrolate/indacaterol, tiotropium/olodaterol, and umeclidinium/vilanterol) did not show significant differences in efficacy, exacerbations, or discontinuation rates. Safety profiles were also similar among the products (Schlueter et al, 2016).
- Clinical guidelines generally favor long-acting bronchodilators over short-acting bronchodilators for maintenance therapy of COPD.
- Updated 2017 GOLD guidelines recommend the use of LAMA/LABA combination therapy as a first- or second-line treatment in most patients with COPD, with the exception of low-risk patients with milder symptoms (GOLD, 2017).

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INTRODUCTION

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

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

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

Table 1. Medications Included Within Class Review

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

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

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

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

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

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

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

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

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

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

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

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

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

CLINICAL EFFICACY SUMMARY

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

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

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

CLINICAL GUIDELINES

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

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

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

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

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

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

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

SAFETY SUMMARY

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

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

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

DOSING AND ADMINISTRATION

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

Table 3. Dosing and Administration

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

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

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

CONCLUSION

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

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

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

INTRODUCTION

- Osteoarthritis (OA) is a key area where topical formulations of nonsteroidal anti-inflammatory drugs (NSAIDs) are used. OA, the most common form of arthritis, causes signs and symptoms such as pain, tenderness, reduced range of motion, bony swelling, joint deformity, and instability. Symptoms typically appear in one or a few joints in a middle-aged or older person, and are often progressive (*Doherty et al 2016*).
- The number of U.S. adults affected by OA has increased in the last several decades due to aging of the population and the increasing prevalence of obesity. Approximately 30 million U.S. adults are affected by OA, up from 21 million in 1995 (*Centers for Disease Control and Prevention 2017, Suri et al 2012*).
- Oral NSAIDs are effective for the treatment of moderate to severe pain, but are associated with an increased risk of several gastrointestinal (GI) and cardiovascular adverse events. The NSAID products as a class, including topical products, carry a Boxed Warning regarding the risk of cardiovascular and GI adverse events associated with their use. However, the use of topical NSAIDs applied directly to the affected area reduces overall systemic absorption and minimizes the risk of severe adverse events (*Galer 2011*). The adverse events associated with the topical NSAIDs are typically dermatologic in nature and are self-limiting in most cases.
- Diclofenac is the only NSAID commercially available in topical formulations. There are currently 3 formulations available, and Food and Drug Administration (FDA)-approved indications vary among products.
- The following products are included within this review:
  - Flector (diclofenac epolamine patch, 1.3%) is indicated for the topical treatment of acute pain due to minor strains, sprains, and contusions. Flector is composed of an adhesive material containing 1.3% diclofenac epolamine applied to a polyester felt backing.
  - Pennsaid (diclofenac sodium topical solution, 1.5%) is indicated for the treatment of signs and symptoms of OA of the knee(s); and higher strength Pennsaid (diclofenac sodium topical solution, 2%) is indicated for the treatment of pain of OA of the knees. Pennsaid contains diclofenac sodium as well as the penetration enhancer dimethyl sulfoxide (DMSO) and other inactive ingredients.
  - Voltaren (diclofenac sodium topical gel, 1%) is indicated for the relief of pain of OA of joints amenable to topical treatment, such as the knees and those of the hands. Voltaren provides diclofenac sodium in a white gel base.
- Medispan class: Anti-inflammatory Agents - Topical

Table 1. Medications Included Within Class Review

Drug	Generic Availability
diclofenac sodium topical solution 1.5%*	✔
Flector (diclofenac epolamine patch) 1.3%	-
Pennsaid (diclofenac sodium topical solution) 2%	-
Voltaren (diclofenac sodium topical gel) 1%	✔

*Pennsaid 1.5% solution is no longer marketed; however, generic formulations are available.
(*Drugs@FDA 2017, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Flector (diclofenac epolamine patch)	diclofenac sodium topical solution 1.5%	Pennsaid (diclofenac sodium topical solution) 2%	Voltaren (diclofenac sodium topical gel)
Treatment of acute pain due to minor strains, sprains and contusions	✔			
Relief of the pain of OA of joints amenable to topical treatment, such as				✔

Indication	Flector (diclofenac epolamine patch)	diclofenac sodium topical solution 1.5%	Pennsaid (diclofenac sodium topical solution) 2%	Voltaren (diclofenac sodium topical gel)
the knees and those of the hands				
Treatment of signs and symptoms of OA of the knee(s)		✔		
Treatment of the pain of OA of the knee(s)			✔	

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

- Two studies evaluated the use of diclofenac patch vs placebo patch in patients with acute injuries.
  - Patients who had experienced a sports-related sprain, strain, or contusion experienced a statistically significantly improvement in scores for pain and functioning following application of the diclofenac epolamine patch over 14 days (p = 0.036 and p = 0.048, respectively) (*Galer et al 2000*).
  - Patients with a minor soft tissue injury experienced an 18.2% reduction in visual analog scale (VAS) pain scores following twice-daily application of the diclofenac epolamine patch over 14 days (p = 0.002) (*Kuehl et al 2011*).
- The efficacy and safety of diclofenac gel have been evaluated in patients with OA of the hands and knees in an 8-week study. Study results demonstrated greater pain relief, Australian/Canadian Osteoarthritis Hand Index (AUSCAN) score improvement, and global rating of disease with diclofenac sodium gel compared to placebo in patients with OA of the hand (*Altman et al 2009*). In patients with OA of the knee, treatment with diclofenac gel for 12 weeks led to greater improvement in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score, WOMAC physical function score, and global rating of disease (*Barthel et al 2009*). Additionally, a 12-month, open-label study in patients with OA of the knee demonstrated sustained long-term improvement compared to baseline for WOMAC pain scores, stiffness, and physical function (*Peniston et al 2011*).
- In a study by Simon et al, patients with OA of the knee treated with topical diclofenac sodium 1.5% solution achieved statistically significant reductions in pain scores compared to patients treated with placebo (-6 vs -4.7; p = 0.015) and dimethyl sulfoxide alone (-6 vs -4.7; p = 0.009). There was no statistically significant difference in pain scores compared to patients receiving diclofenac tablets (-6 v. -7; p = 0.429) (*Simon et al 2009*).
- The safety and efficacy of diclofenac 2% solution were evaluated in a phase 2, randomized, double-blind, parallel-group, placebo-controlled, 4-week clinical trial in patients with osteoarthritis of the knee (N = 260). A reduction of 4.5 in the WOMAC pain score was noted in the diclofenac 2% group as compared to a 3.6 reduction in the placebo vehicle group (p = 0.04) (*Wadsworth et al 2016*).
- The clinical effectiveness of the gel and solution formulations has not been compared in any head-to-head trials. However, a single-dose patient preference trial in 24 healthy volunteers demonstrated a preference for the solution formulation on several characteristics, including odor/smell, oiliness/greasiness, and stickiness/tackiness (*Galer et al 2011*).
- A systematic review of 19 trials summarized the benefits of diclofenac solution, gel, and patch based on clinical studies comparing the topical diclofenac products to placebo or oral NSAIDs. Key reported outcomes included:
  - Superiority of diclofenac patch and gel over placebo for the treatment of acute pain due to blunt impact injuries or ankle sprains
  - Superiority of diclofenac gel and solution over placebo for pain due to OA of the knee
  - Superiority of diclofenac gel over placebo for pain relief due to epicondylitis and periarthritis, and superiority of diclofenac patch over placebo for epicondylitis
  - Similar efficacy of diclofenac gel and/or diclofenac liquid with DMSO compared to oral NSAIDS for several outcomes including pain relief due to OA of the hand and knee and acute musculoskeletal injury (*Zacher et al 2008*)
- A recent meta-analysis of 9 randomized trials evaluated topical diclofenac therapy (patch, solution, or gel) compared to placebo or vehicle for the treatment of OA. The combined data demonstrated significantly improved pain scores with

topical diclofenac compared to the control group (standard mean difference, 0.4; 95% confidence interval [CI], 0.19 to 0.62; p = 0.0003). The data also suggested an improvement in function scores, but further studies on this endpoint would be required to confirm the results (*Deng et al 2016*).

- In a Cochrane review, data from an analysis of 39 double-blind, randomized controlled trials comparing topical NSAIDs to placebo, oral NSAIDs, or other topical treatments demonstrated a small benefit of topical NSAIDs compared to a placebo vehicle in patients with chronic musculoskeletal conditions. Treatment success was achieved in 60% of patients treated with topical diclofenac vs 50% of patients treated with a placebo vehicle. The analysis also demonstrated similar efficacy with topical NSAIDs and oral NSAIDs, with treatment success in in 55% and 54% of patients, respectively (*Derry et al 2016*).
- Another Cochrane review focused on the use of topical NSAIDs for acute musculoskeletal pain, including sprains, strains, contusions, tendinitis, and acute low back pain. A total of 61 double-blind, randomized controlled trials comparing topical NSAIDs to topical placebo or an oral NSAID were included. Overall, topical NSAID formulations provided good levels of pain relief in acute conditions. The majority of the recent data is for topical diclofenac, and this recent data is of higher quality than earlier data. Based on 10 studies, 74% of patients treated with topical diclofenac experienced a successful treatment outcome, compared to 47% with placebo (RR, 1.6; 95% CI, 1.5 to 1.7). Data was not sufficient to compare the efficacy of different topical NSAIDs or of oral vs topical formulations of the same NSAID.
  - Topical NSAIDs were not associated with an increase in local or systemic adverse events compared to topical placebo. There were fewer systemic adverse events with topical vs oral treatment; however, this was based on limited data (*Derry et al 2015*).

CLINICAL GUIDELINES

- According to the American College of Rheumatology (ACR) 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in OA of the hand, hip, and knee:
  - For the initial management of OA pain of the hand, topical capsaicin, oral or topical NSAIDs, or tramadol may be used. In patients > 75 years of age, topical NSAIDs are preferred over oral formulations.
  - For the initial management of OA pain of the knee, acetaminophen, NSAIDs (oral or topical), tramadol, or intraarticular corticosteroid injections may be used. In patients > 75 years of age, topical NSAIDs are preferred over oral formulations.
  - No one topical NSAID product is recommended over another within the guidelines (*Hochberg et al 2012*).
- According to the American Academy of Orthopedic Surgeons (AAOS) 2013 Guidelines for the treatment of OA of the knee:
  - Acupuncture, lateral wedge insoles, and glucosamine and chondroitin are not recommended.
  - NSAIDs (oral or topical) or tramadol are recommended.
  - There is inconclusive evidence to recommend either for or against the use of acetaminophen, opioids, pain patches, or intraarticular corticosteroids.
  - No one topical NSAID product is recommended over another within the guidelines (*AAOS 2013*).
- According to the Osteoarthritis Research Society International (OARSI) 2014 guidelines for the non-surgical management of knee OA:
  - Appropriate treatments vary based on patient-specific comorbidities and whether patients have knee-only OA or multi-joint OA.
  - Topical NSAIDs are recommended as appropriate in patients with knee-only OA, but their use in patients with multi-joint OA is uncertain and will depend on an assessment of individual patients' risks and benefits.
  - No one topical NSAID product is recommended over another within the guidelines (*McAlindon et al 2014*).
- According to the Veterans Affairs (VA)/Department of Defense (DOD) clinical practice guideline for the non-surgical management of hip and knee OA:
  - In patients with no contraindications to pharmacologic therapy, clinicians should consider acetaminophen or oral NSAIDs as first-line treatment.
  - The recommendation to use topical NSAID therapy as an alternative to oral NSAIDs is supported by evidence from studies that have compared various topical and oral NSAIDs in patients with knee OA. The results have consistently shown that the topical and oral formulations of any given NSAID are similar in terms of improvement in pain and function in patients with knee OA.

- For topical NSAIDs collectively, the reduction in the incidence of GI events has been shown to be 36% relative to the oral formulations. However, there is insufficient evidence to compare topical and oral NSAIDs in terms of serious GI adverse events (perforation, ulcers or bleeding).
- The decision to use a topical NSAID (vs oral NSAID with or without proton pump inhibitor) should be based on consideration of patient preference, adverse event potential (including GI adverse events), and resource utilization.
- No studies have directly compared the solution and gel formulations in patients with OA (*VA/DOD 2014*).

SAFETY SUMMARY

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

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
diclofenac sodium topical solution	1.5% topical solution	Topical	Four times daily	Apply to clean, dry skin; do not apply heat or occlusive dressings
Flector (diclofenac epolamine patch)	1.3% topical patch	Topical	Twice daily	Should not be applied to non-intact or damaged skin; should not be worn while bathing or showering
Pennsaid (diclofenac sodium topical	2% topical solution	Topical	Twice daily	Apply to clean, dry skin; do not apply heat or occlusive dressings

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
solution)				
Voltaren (diclofenac sodium topical gel)	1% gel	Topical	Four times daily	Use enclosed dosing card to measure dose Apply to clean, dry, intact skin; do not apply heat or occlusive dressings.

See the current prescribing information for full details.

CONCLUSION

- NSAIDs are commonly used for the treatment of pain due to OA or minor strains, sprains, and contusions. The topical application of NSAIDs may reduce the risk of severe adverse events associated with oral NSAID use. Diclofenac is currently the only NSAID available in topical formulations.
- Flector is available as a 1.3% patch and is indicated for acute pain due to minor strains, sprains, and contusions. Pennsaid is available as a 1.5% topical solution and is indicated for the treatment of signs and symptoms of OA of the knee(s). A higher strength formulation of Pennsaid (2%) has also been made available; it is indicated for the treatment of pain of OA of the knees. Voltaren is available as a 1% topical gel and is indicated for the relief of pain of OA of joints amenable to topical treatment, such as the knees and those of the hands. Of the topical NSAIDs, Pennsaid 1.5% and Voltaren 1% are available generically. Branded Pennsaid 1.5% solution is no longer marketed.
- The topical products carry many of the same warnings as their respective orally-administered products; however, systemic absorption is generally low, and the most frequent adverse events are administration site reactions.
- Guidelines from ACR, AAOS, ORSI, and VA/DOD recommend the use of topical NSAIDs for the treatment of OA (for specific joints), however, they do not recommend one topical NSAID product over another (*Hochberg et al 2012*).

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INTRODUCTION

- Immunomodulators treat a wide variety of conditions, including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), plaque psoriasis (PsO), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC), hidradenitis suppurativa (HS), and uveitis (UV), as well as several less common conditions.
- T cells, B cells, and cytokines such as tumor necrosis factor (TNF), interleukin-1 (IL-1) and interleukin-6 (IL-6) play a key role in the inflammatory and immune process (Choy et al, 2001). This has led to the development of biologic agents to target these areas. The Food and Drug Administration (FDA) has currently approved five originator TNF inhibitors: CIMZIA® (certolizumab), ENBREL® (etanercept), HUMIRA® (adalimumab), REMICADE® (infliximab), and SIMPONI®/SIMPONI® ARIA™ (golimumab), as well as three biosimilar TNF inhibitors: AMJEVITA (adalimumab-atto), ERELZI (etanercept-szzs), and INFLECTRA (infliximab-dyyb). Other agents targeting different cells and cytokines are also FDA approved for RA treatment. These include ORENCIA® (abatacept), which inhibits CD28-B7 mediated costimulation of the T-cell; RITUXAN® (rituximab), which targets CD20, a molecule that is found on the surface of B-cells; ACTEMRA® (tocilizumab), which has activity directed against the IL-6 receptor; and KINERET® (anakinra), which targets the IL-1 receptor. An oral agent on the market, XELJANZ® and XELJANZ® XR (tofacitinib), targets Janus-associated kinase (JAK) pathways. By inhibiting the JAK pathway, the ability of cytokines to produce inflammation is reduced.
- Other immunomodulators include ILARIS® (canakinumab), which binds to the IL-1ß receptor and is approved to treat JIA; and ENTYVIO™ (vedolizumab), which binds to the α4β7 integrin and is approved to treat CD and UC. OTEZLA® (apremilast), an oral, small-molecule phosphodiesterase 4 (PDE-4) inhibitor, and STELARA (ustekinumab), which targets the IL-12 and IL-23 cytokines, are each approved for the treatment of PsA and PsO; STELARA is additionally indicated for the treatment of CD. COSENTYX™ (secukinumab) and TALTZ® (ixekizumab) bind and neutralize IL-17A and are indicated for the treatment of PsO; COSENTYX is additionally indicated to treat PsA and AS. A related agent, SILIQ™ (brodalumab), is an IL-17 receptor antagonist indicated for selected patients with PsO.
- Certain rare conditions for which immunomodulators are indicated are mentioned in this review but are not discussed in detail; these include:
    - ILARIS for the treatment of 1) cryopyrin-associated periodic syndromes (CAPS), specifically the subtypes familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS); 2) TNF receptor associated periodic syndrome (TRAPS); 3) hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD); and 4) familial Mediterranean fever (FMF)
    - KINERET for the treatment of CAPS, specifically neonatal-onset multisystem inflammatory disease (NOMID)
- RITUXAN is also approved for non–Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), and granulomatosis with polyangiitis (GPA) (Wegener's granulomatosis) and microscopic polyangiitis (MPA). These indications will not be discussed in this review.
- TYSABRI® (natalizumab), an integrin receptor antagonist, is indicated for multiple sclerosis and CD for patients who have had an inadequate response to, or are unable to tolerate conventional therapies and TNF inhibitors; it is not included as a drug product in this review (TYSABRI prescribing information, 2016). ARCALYST (rilonacept), an interleukin-1 blocker indicated for CAPS, is also not included in this review (ARCALYST prescribing information, 2016).
- Although FDA approved, the launch plans for AMJEVITA (adalimumab-atto) and ERELZI (etanercept-szzs) are pending and may be delayed; thus, information on AMJEVITA and ERELZI is not currently included in this review.
- Medispan Classes: Antineoplastic-Monoclonal Antibodies, Antipsoriatics, Antirheumatic-Enzyme Inhibitors, Anti-TNF-Alpha-Monoclonal Antibodies, Integrin Receptor Antagonists, Interleukin-1 Receptor Antagonists, Interleukin-1beta Receptor Inhibitors, Interleukin-6 Receptor Inhibitors, PDE-4 Inhibitors, Selective Costimulation Modulators, Soluble Tumor Necrosis Factor Receptor Agents, Tumor Necrosis Factor Alpha Blockers

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Biosimilar or Generic Availability	Type of Agent
ACTEMRA (tocilizumab)	Genentech	01/08/2010	-	Human monoclonal antibody targeting the IL-6 receptor
CIMZIA (certolizumab)	UCB	04/22/2008	-	TNFα inhibitor
COSENTYX (secukinumab)	Novartis	01/21/2015	-	Human monoclonal antibody to IL-17A
ENBREL (etanercept)	Amgen	11/02/1998	-*	sTNFR fusion protein, TNFα inhibitor
ENTYVIO (vedolizumab)	Takeda Pharmaceuticals America, Inc.	05/20/2014	-	Human monoclonal antibody binds to the α4β7 integrin
HUMIRA (adalimumab)	Abbott	12/31/2002	-*	TNFα inhibitor
ILARIS (canakinumab)	Novartis	06/17/2009	-	Human monoclonal antibody that binds to IL-1ß
INFLECTRA (infliximab-dyyb)	Celltrion/ Hospira/Pfizer	04/05/2016	N/A†	TNFα inhibitor
KINERET (anakinra)	Swedish Orphan Biovitrum	11/14/2001	-	IL-1 receptor antagonist
ORENCIA (abatacept)	Bristol Myers Squibb	12/23/2005	-	sCTLA-4-Ig recombinant fusion protein
OTEZLA (apremilast)	Celgene Corporation	03/21/2014	-	Small-molecule phosphodiesterase 4 inhibitor
REMICADE (infliximab)	Janssen Biotech	8/24/1998	-†	TNFα inhibitor
RITUXAN (rituximab)	Genentech	11/26/1997	-	Anti-CD20 monoclonal antibody
SILIQ (brodalumab)‡	Valeant	02/15/2017	-	Human monoclonal antibody directed against the IL-17 receptor A (IL-17RA)
SIMPONI/ SIMPONI ARIA (golimumab)	Janssen Biotech	04/24/2009 and 07/18/2013	-	TNFα inhibitor
STELARA (ustekinumab)	Janssen Biotech	09/25/2009	-	Human monoclonal antibody targeting the IL-12 and IL-23 cytokines
TALTZ (ixekizumab)	Eli Lilly	03/22/2016	-	Human monoclonal antibody to IL-17A
XELJANZ / XELJANZ XR (tofacitinib)	Pfizer	11/06/2012 and 02/23/2016	-	Small molecule Janus kinase (JAK) inhibitor

*ERELZI (etanercept-szzs) and AMJEVITA (adalimumab-atto) have been FDA approved as biosimilars to ENBREL (etanercept) and HUMIRA (adalimumab), respectively. The specific launch dates for these products are pending and may be delayed. Further information on ERELZI and AMJEVITA will be included in this review closer to the time of launch.
†INFLECTRA (infliximab-dyyb) has been FDA approved as a biosimilar to REMICADE (infliximab). It is not an interchangeable biologic.
‡SILIQ is anticipated to be launched in the second half of 2017.

(Drugs@FDA, 2016; Prescribing information: ACTEMRA, 2016; CIMZIA, 2017; COSENTYX, 2016; ENBREL, 2016; ENTYVIO, 2014; HUMIRA, 2016; ILARIS, 2016; INFLECTRA, 2016; KINERET, 2016; ORENCIA, 2016; OTEZLA, 2015; REMICADE, 2015; RITUXAN, 2014; SILIQ, 2017; SIMPONI, 2017; SIMPONI ARIA, 2017; STELARA, 2016; TALTZ, 2016; XELJANZ/XELJANZ XR, 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.

INDICATIONS

Table 2. Food and Drug Administration Approved Indications (see footnotes for less common indications: CAPS, FMF, HIDS/MKD, and TRAPS)

Drug	Rheumatoid Arthritis (RA)	Crohn's Disease (CD)	Systemic Juvenile Idiopathic Arthritis (SJIA)	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Ankylosing Spondylitis (AS)	Ulcerative Colitis (UC)	Hidradenitis Suppurativa (HS)	Uveitis (UV)
ACTEMRA (tocilizumab)	✔ *		✔ **	✔ **						
CIMZIA (certolizumab)	✔	✔				✔	✔			
COSENTYX (secukinumab)					✔ ‡	✔	✔			
ENBREL (etanercept)	✔ †			✔ **	✔ ‡	✔ †	✔			
ENTYVIO (vedolizumab)		✔						✔		
HUMIRA (adalimumab)	✔ ‡‡	✔ ⌐		✔ ∫	✔ ‡	✔ ∫∫	✔	✔	✔	✔ ▼

Drug	Rheumatoid Arthritis (RA)	Crohn's Disease (CD)	Systemic Juvenile Idiopathic Arthritis (SJIA)	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Ankylosing Spondylitis (AS)	Ulcerative Colitis (UC)	Hidradenitis Suppurativa (HS)	Uveitis (UV)
ILARIS" (canakinumab)			✔ **							
INFLECTRA (infliximab-dyyb)	✔ ⊥	✔ ⌐⌐			✔ ‡‡‡	✔	✔	✔ ⊥⊥		
KINERET▼▼ (anakinra)	✔ ∞									
ORENCIA (abatacept)	✔ ∞∞			✔ ⌂						
OTEZLA (apremilast)					✔ ‡	✔				
REMICADE (infliximab)	✔ ⊥	✔ ⌐⌐			✔ ‡‡‡	✔	✔	✔ ⊥⊥		
RITUXAN‴ (rituximab)	✔ ⫩									

Drug	Rheumatoid Arthritis (RA)	Crohn's Disease (CD)	Systemic Juvenile Idiopathic Arthritis (SJIA)	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Ankylosing Spondylitis (AS)	Ulcerative Colitis (UC)	Hidradenitis Suppurativa (HS)	Uveitis (UV)
SILIQ (brodalumab)					✓‡‡					
SIMPONI (golimumab)	✓†					✓††	✓	✓~		
SIMPONI ARIA (golimumab)	✓†									
STELARA (ustekinumab)		✓⌐⌐⌐			✓‡	✓				
TALTZ (ixekizumab)					✓‡					
XELJANZ / XELJANZ XR (tofacitinib)	✓‡‡									

*Patients with moderately to severely active RA who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).
**Patients 2 years and older.
†In combination with methotrexate (MTX) or used alone.
‡Indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe PsO who are candidates for systemic therapy or phototherapy, with the exception of ENBREL, which is indicated for the treatment of patients 4 years and older with chronic moderate to severe PsO who are candidates for systemic therapy or phototherapy.
‡‡Indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA. Can be used alone or in combination with MTX or other DMARDs.

‡‡‡ Indicated for the treatment of adult patients with chronic severe (ie, extensive and/or disabling) PsO who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.
∫Indicated for reducing signs and symptoms of JIA for patients 2 years of age and older. Can be used alone or in combination with MTX.
∫∫Indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA. Can be used alone or in combination with non-biologic DMARDs.
▼Treatment of non-infectious intermediate, posterior and panuveitis in adult patients.
▼▼KINERET is also indicated for the treatment of cryopyrin-associated periodic syndromes (CAPS) including neonatal-onset multisystem inflammatory disease (NOMID).
"ILARIS also indicated for the treatment of CAPS in adults and children 4 years of age and older including: familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS); tumor necrosis factor receptor associated periodic syndrome (TRAPS) in adult and pediatric patients; hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD) in adult and pediatric patients; and familial Mediterranean fever (FMF) in adult and pediatric patients.
∞Indicated for the reduction in signs and symptoms and slowing the progression of structural damage in moderately to severely active RA, in patients 18 years of age or older who have failed one or more DMARDs. Can be used alone or in combination with DMARDs other than TNF blocking agents.
∞∞Indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA. May be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.
⌂ Indicated for reducing signs and symptoms in pediatric patients 6 years and old with moderate to severely active PJIA. May be used as monotherapy or with MTX.
⌐For all patients 6 years of age and older, indicated for reducing signs and symptoms and inducing and maintaining clinical remission in patients who have had an inadequate response to conventional therapy. For adults, also indicated for reducing signs and symptoms and inducing clinical remission if patients have also lost a response to or are intolerant of infliximab.
⌐⌐Indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy and for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing CD. And for patients 6 years of age and older for reducing signs and symptoms and inducing and maintaining clinical remission with moderately to severely active disease who have had an inadequate response to conventional therapy.
⌐⌐⌐Indicated for treatment of adult patients with moderately to severely active CD who have: 1) failed or were intolerant to treatment with immunomodulators or corticosteroids but never failed a TNF blocker, or 2) failed or were intolerant to treatment with one or more TNF blockers
┴In combination with MTX, is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active RA.
┴┴For reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy. Also for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active disease who have had an inadequate response to conventional therapy (REMICADE only). The biosimilar INFLECTRA did not receive FDA approval for pediatric UC due to existing marketing exclusivity for Remicade for this indication (not for clinical reasons).
"'RITUXAN also indicated for Non–Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), and granulomatosis with polyangiitis (GPA) (Wegener's Granulomatosis) and microscopic polyangiitis (MPA).
╪In combination with MTX is indicated for the treatment of adult patients with moderately- to severely- active RA who have had an inadequate response to one or more TNF antagonist therapies.
╪╪Treatment of moderate to severe PsO in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies.
┤ In combination with MTX, is indicated for the treatment of adult patients with moderately to severely active RA.
┤┤ Alone or in combination with MTX, is indicated for the treatment of adult patients with active PsA.
╪╪Indicated for the treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to MTX. It may be used as monotherapy or in combination with MTX or other nonbiologic DMARDs. Use in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.
˜Indicated in adult patients with moderately to severely active UC who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosalicylates, oral corticosteroids, azathioprine, or 6-mercaptopurine for: inducing and maintaining clinical response; improving endoscopic appearance of the mucosa during induction; inducing clinical remission; and achieving and sustaining clinical remission in induction responders.

CLINICAL EFFICACY SUMMARY

Rheumatoid arthritis (RA)

- The approval of the subcutaneous (SQ) formulation of ORENCIA (abatacept) was based on a double-blind, double-dummy, randomized trial demonstrating noninferiority to the intravenous (IV) formulation. The trial enrolled patients with RA who had an inadequate response to methotrexate (MTX). The proportion of patients achieving American College of Rheumatology 20% improvement (ACR 20) was not significantly different between the groups (Genovese et al, 2011).
- ORENCIA (abatacept), REMICADE (infliximab), and placebo were compared in a Phase 3, randomized, double-blind trial (N=431). Enrolled patients had had an inadequate response to MTX, and background MTX was continued during the trial. Although efficacy was comparable between abatacept and infliximab after six months of treatment, some differences in favor of abatacept were evident after one year of treatment. After one year, the mean changes from baseline in disease activity score based on erythrocyte sedimentation rate (DAS28-ESR) were -2.88 and -2.25 in the abatacept and infliximab groups, respectively (estimate of difference, -0.62; 95% confidence interval [CI], -0.96 to -0.29). Abatacept demonstrated greater efficacy vs infliximab on some (but not all) secondary endpoints, including the proportion of patients with a good European League Against Rheumatism (EULAR) response (32.0% vs 18.5%), low disease activity score (LDAS) (35.3% vs 22.4%), ACR 20 responses (72.4% vs 55.8%), and improvements in the Medical Outcomes Study short-form-36 (SF-36) physical component summary (PCS) (difference of 1.93). Overall, abatacept had a relatively more acceptable safety and tolerability profile, with fewer serious adverse events (AEs) and discontinuations due to AEs than the infliximab group (Schiff et al, 2008).
- Treatment with ORENCIA (abatacept) was directly compared to treatment with HUMIRA (adalimumab), both added to MTX, in a multicenter, investigator-blind, randomized controlled trial (N=646) of RA patients with inadequate response to MTX. After two years, the proportions of patients achieving ACR 20 responses were comparable between abatacept and adalimumab treatment groups (59.7 and 60.1%, respectively; difference 1.8%; 95% CI, -5.6 to 9.2%). ACR 50 and ACR 70 responses were also similar between the two groups after two years of treatment. Rates of AEs were similar between treatment groups (Schiff et al, 2014).
- The RAPID-1 and RAPID-2 studies compared CIMZIA (certolizumab) in combination with MTX to placebo plus MTX in adults with active RA despite MTX therapy (Keystone et al, 2008; Smolen et al, 2009a). A significantly greater proportion of patients on certolizumab 400 mg plus MTX at weeks zero, two, and four then 200 or 400 mg every two weeks attained greater ACR 20, ACR 50 and ACR 70 responses over patients on placebo and MTX, respectively, after 24 weeks (P≤0.01). The response rates were sustained with active treatment over 52 weeks (Keystone et al, 2008). The Modified Total Sharp Score (mTSS) was significantly lower with certolizumab in combination with MTX compared to MTX in combination with placebo (Keystone et al, 2008; Smolen et al, 2009a). A trial evaluated CIMZIA (certolizumab) monotherapy vs placebo in patients with active disease who had failed at least one prior DMARD. After 24 weeks, ACR 20 response rates were significantly greater with active treatment (45.5%) compared to placebo (9.3%; P<0.001). Significant improvements in secondary endpoints (ACR 50, ACR 70, individual ACR component scores, and patient reported outcomes) were also associated with certolizumab therapy (Fleischmann et al, 2009).
- ievedCIMZIA (certolizumab)-treated patients achieved clinical disease activity index (CDAI) remission than placebo-treated patients (18.8% vs 6.1%, P≤0.05) in a randomized, double-blind, placebo-controlled trial of certolizumab over 24 weeks in 194 patients with RA who were on DMARD therapy with MTX, leflunomide, sulfasalazine and/or hydroxychloroquine for at least six months (Smolen et al, 2015a).
- A randomized, double-blind, placebo-controlled trial (N=316) conducted in Japan compared CIMZIA (certolizumab) plus MTX to placebo plus MTX in MTX-naïve patients with early RA (≤12 months persistent disease) and poor prognostic factors: high anti-cyclic citrullinated peptide (anti-CCP) antibody and either positive rheumatoid factor and/or presence of bone erosions (Atsumi et al, 2016). The primary endpoint was inhibition of radiographic progression (change from baseline in mTSS at week 52). The certolizumab plus MTX group showed significantly greater inhibition of radiographic progression vs MTX alone (mTSS change, 0.36 vs 1.58; P<0.001). Clinical remission rates were higher in patients treated with certolizumab plus MTX vs MTX alone. The authors suggest that certolizumab plus MTX could be used as possible first-line treatment in this patient population.
- The FDA approval of SIMPONI (golimumab) for RA was based on three multicenter, double-blind, randomized, controlled trials in 1,542 patients greater than or equal to18 years of age with moderate to severe active disease. A greater percentage of patients from all three trials treated with the combination of golimumab and MTX achieved ACR responses at week 14 and week 24 vs patients treated with MTX alone (Emery et al, 2009; Keystone et al, 2009; Smolen et al, 2009b). Additionally, the golimumab 50 mg groups demonstrated a greater improvement compared to the control groups in the change in mean Health Assessment Questionnaire (HAQ) Disability Index (HAQ-DI) (Keystone et al, 2009; Smolen et al, 2009b). Response with golimumab + MTX was sustained for up to five years (Keystone et al, 2013a; Smolen et al, 2015b).

- SIMPONI ARIA (golimumab) was studied in patients with RA. In one trial, 643 patients could receive golimumab 2 mg/kg or 4 mg/kg intravenously (IV) every 12 weeks with or without MTX, or placebo with MTX. The proportion of patients meeting the primary endpoint of ACR 50 response was not significantly different between the golimumab with or without MTX groups and the placebo group. However, significantly more patients receiving golimumab plus MTX achieved an ACR 20 response at week 14 compared with patients receiving placebo plus MTX (53 vs 28%; P<0.001) (Kremer et al, 2010). In the GO-FURTHER trial (N=592), golimumab 2 mg/kg IV or placebo was given at weeks zero, four and then every eight weeks. An increased percentage of patients treated with golimumab + MTX achieved ACR 20 response at week 14 (58.5% [231/395] of golimumab + MTX patients vs 24.9% [49/197] of placebo + MTX patients [P<0.001]) (Weinblatt et al, 2013). In an open-label extension period, treatment was continued through week 100, with placebo-treated patients crossing over to golimumab at week 16 (early escape) or week 24. Clinical response was maintained through week 100, with an ACR 20 response of 68.1%. There was a very low rate of radiographic progression throughout the study, and patients treated with IV golimumab plus MTX from baseline had significantly less radiographic progression to week 100 compared to patients who had initially received placebo plus MTX. No unexpected AEs occurred (Bingham et al, 2015). In the GO-MORE trial, investigators treated patients with golimumab SQ for six months. If patients were not in remission, they could be randomized to receive golimumab SQ or IV. The percentages of patients who achieved DAS28-ESR remission did not differ between the combination SQ+IV group and the SQ golimumab group (Combe et al, 2014).
- The efficacy and safety of ACTEMRA (tocilizumab) were assessed in several randomized, double-blind, multicenter studies in patients ages 18 years and older with active RA. Patients were diagnosed according to ACR criteria, with at least eight tender and six swollen joints at baseline. Tocilizumab was given every four weeks as monotherapy (AMBITION), in combination with MTX (LITHE and OPTION) or other DMARDs (TOWARD) or in combination with MTX in patients with an inadequate response to tumor necrosis factor (TNF) antagonists (RADIATE). In all studies, mild to moderate AEs were reported, occurring in similar frequencies in all study groups. The most common AEs in all studies were infections and gastrointestinal symptoms (Emery et al, 2008; Genovese et al, 2008; Jones et al, 2010; Kremer et al, 2011; Smolen et al, 2008).
    - AMBITION evaluated the safety and efficacy of tocilizumab monotherapy vs MTX in patients with active RA for whom previous treatment with MTX or biological agents had not failed. A total of 673 patients were randomized to one of three treatment arms, tocilizumab 8 mg/kg every four weeks, MTX 7.5 mg/week and titrated to 20 mg/week within eight weeks, or placebo for eight weeks followed by tocilizumab 8 mg/kg. The primary endpoint was the proportion of patients achieving ACR 20 response at week 24. The results showed that tocilizumab monotherapy when compared to MTX monotherapy produced greater improvements in RA signs and symptoms, and a favorable benefit-risk ratio in patients who had not previously failed treatment with MTX or biological agents. Additionally, more patients treated with tocilizumab achieved remission at week 24 when compared to patients treated with MTX (Jones et al, 2010).
    - LITHE evaluated 1,196 patients with moderate to severe RA who had an inadequate response to MTX. Patients treated with tocilizumab had three times less progression of joint damage, measured by Total Sharp Score, when compared to patients treated with MTX alone. Significantly more patients treated with tocilizumab 8 mg/kg were also found to achieve remission at six months as compared to MTX (33% vs 4%), and these rates continued to increase over time to one year (47% vs 8%) (Kremer et al, 2011). These benefits were maintained or improved at two years with no increased side effects (Fleishmann et al, 2013).
    - OPTION evaluated tocilizumab in 623 patients with moderate to severely active RA. Patients received tocilizumab 8 mg/kg, 4 mg/kg, or placebo IV every four weeks, with MTX at stable pre-study doses (10 to 25 mg/week). Rescue therapy with tocilizumab 8 mg/kg was offered at week 16 to patients with less than 20% improvement in swollen and tender joint counts. The primary endpoint was ACR 20 at week 24. The findings showed that ACR 20 was seen in significantly more patients receiving tocilizumab than in those receiving placebo at week 24 (P<0.001). Significantly more patients treated with tocilizumab achieved ACR 50 and ACR 70 responses at week 24 as well (P<0.001). Greater improvements in physical function, as measured by the HAQ-DI, were seen with tocilizumab when compared to MTX (-0.52 vs -0.55 vs -0.34; P<0.0296 for 4 mg/kg and P<0.0082 for 8 mg/kg) (Smolen et al, 2008).
    - TOWARD examined the efficacy and safety of tocilizumab combined with conventional DMARDs in 1,220 patients with active RA. Patients remained on stable doses of DMARDs and received tocilizumab 8 mg/kg or placebo every four weeks for 24 weeks. At week 24, significantly more patients taking tocilizumab with DMARDs achieved an ACR 20 response than patients in the control group. The authors concluded that tocilizumab, combined with any of the DMARDs evaluated (MTX, chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine, and leflunomide), was safe and effective in reducing articular and systemic symptoms in patients with an inadequate response to these agents. A greater percentage of patients treated

with tocilizumab also had clinically meaningful improvements in physical function when compared to placebo (60% vs 30%; P value not reported) (Genovese et al, 2008).
    - RADIATE evaluated the safety and efficacy of tocilizumab in patients with RA refractory to TNF antagonist therapy. A total of 499 patients with inadequate response to one or more TNF antagonists was randomly assigned to 8 or 4 mg/kg tocilizumab or placebo every four weeks with stable MTX doses (10 to 25 mg/week) for 24 weeks. ACR 20 responses and safety endpoints were assessed. This study found that tocilizumab plus MTX is effective in achieving rapid and sustained improvements in signs and symptoms of RA in patients with inadequate response to TNF antagonists and has a manageable safety profile. The ACR 20 response in both tocilizumab groups was also found to be comparable to those seen in patients treated with HUMIRA (adalimumab) and REMICADE (infliximab), irrespective of the type or number of failed TNF antagonists (Emery et al, 2008). In the ADACTA trial, patients with severe arthritis who could not take MTX were randomized to monotherapy with tocilizumab or adalimumab. The patients in the tocilizumab group had a significantly greater improvement in DAS28 at week 24 than patients in the adalimumab group (Gabay et al, 2013).
- More recently, results of a randomized, double-blind trial evaluating ACTEMRA (tocilizumab) in early RA were published (Bijlsma et al, 2016). Patients (N=317) had been diagnosed with RA within one year, were DMARD-naïve, and had a DAS28 score of ≥2.6. Patients were randomized to 1 of 3 groups: tocilizumab plus MTX, tocilizumab plus placebo, or MTX plus placebo. Tocilizumab was given at a dose of 8 mg/kg every 4 weeks (maximum 800 mg per dose), and MTX was given at a dose of 10 mg orally per week, increased to a maximum of 30 mg per week as tolerated. Patients not achieving remission switched from placebo to active treatments, and patients not achieving remission in the tocilizumab plus MTX group switched to a standard of care group (usually a TNF inhibitor plus MTX). The primary endpoint was the proportion of patients achieving sustained remission (defined as DAS28 <2.6 with a swollen joint count ≤4, persisting for at least 24 weeks). The percentages of patients achieving a sustained remission on the initial regimen were 86%, 84%, and 44% in the tocilizumab plus MTX, tocilizumab monotherapy, and MTX monotherapy groups, respectively (P<0.0001 for both comparisons vs MTX). The percentages of patients achieving sustained remission during the entire study were 86%, 88%, and 77% in the tocilizumab plus MTX, tocilizumab monotherapy, and MTX monotherapy groups, respectively (P=0.06 for tocilizumab plus MTX vs MTX; P=0.0356 for tocilizumab vs MTX). The authors concluded that immediate initiation of tocilizumab is more effective compared to initiation of MTX in early RA.
- The FDA approval of the subcutaneous formulation of ACTEMRA (tocilizumab) was based on one multicenter, double-blind, randomized, controlled trial in patients (N=1,262) with RA. Weekly tocilizumab SQ 162 mg was found to be non-inferior to tocilizumab IV 8 mg/kg every four weeks through 24 weeks. A higher incidence of injection-site reactions were reported with the SQ formulation (Burmester et al, 2014a). In an open-label extension period, patients in both treatment arms were re-randomized to receive either IV or SQ tocilizumab through week 97. The proportions of patients who achieved ACR 20/50/70 responses, DAS28 remission, and improvement from baseline in HAQ-DI ≥0.3 were sustained through week 97 and comparable across arms. IV and SQ treatments had a comparable safety profile with the exception of higher injection-site reactions with the SQ formulation (Burmester et al, 2016). A placebo-controlled trial in 656 patients further confirmed the efficacy of SQ ACTEMRA administered every other week (Kivitz et al, 2014).
- In a Phase 3 trial, the percentage of patients who met criteria for RA disease remission was not significantly different in the XELJANZ (tofacitinib) groups (5 mg and 10 mg twice daily) vs placebo. However, significantly more patients in the tofacitinib groups did meet criteria for decrease of disease activity. The tofacitinib groups also had significant decreases in fatigue and pain (Fleishmann et al, 2012). In another Phase 3 study, XELJANZ (tofacitinib), when administered with background MTX, was superior to placebo with respect to all clinical outcomes. Although not directly compared to HUMIRA (adalimumab), the clinical efficacy of tofacitinib was numerically similar to that observed with adalimumab. Safety of tofacitinib continues to be monitored for long term effects (van Vollenhoven et al, 2012). The ORAL Scan trial showed the ACR 20 response rates at month six for patients receiving tofacitinib 5 mg and 10 mg twice daily were 51.5% and 61.8%, respectively, vs 25.3% for patients receiving placebo (P<0.0001 for both comparisons) (van der Heijde et al, 2013). The ORAL START trial evaluated tofacitinib and MTX in 956 patients with active RA over 24 months. The primary endpoint of mean change from baseline in modified total Sharp score was significantly less with tofacitinib (0.6 for 5 mg; 0.3 for 10 mg) compared to MTX (2.1; P<0.001) (Lee et al, 2014). No radiographic progression was defined as a change from baseline in the modified total Sharp score of <0.5 points. However, a minimal clinically important difference in modified total Sharp score is 4.6 points; this study did not meet this minimal clinical meaningful difference threshold.
- In the ORAL Step study, patients with RA who had an inadequate response to one or more TNF inhibitors were randomized to XELJANZ (tofacitinib) 5 mg or 10 mg twice daily or placebo; all patients were on MTX (Burmester et al, 2013a; Strand et al, 2015a). The primary outcome, ACR 20 response rate, was significantly higher with tofacitinib 5

mg (41.7%; 95% CI, 6.06 to 28.41; P=0.0024) and 10 mg (48.1%; 95% CI, 12.45 to 34.92; P<0.0001) compared to placebo (24.4%). Improvements in HAQ-DI was reported as -0.43 (95% CI, -0.36 to -0.157; P<0.0001) for tofacitinib 5 mg and -0.46 (95% CI, -0.38 to -0.17; P<0.0001) for tofacitinib 10 mg groups compared to -0.18 for placebo. Common AEs included diarrhea, nasopharyngitis, headache, and urinary tract infections in the tofacitinib groups.

- INFLECTRA (infliximab-dyyb) was evaluated and compared to REMICADE (infliximab; European Union formulation) in PLANETRA (N=606), a double-blind, multicenter, randomized trial (Yoo et al, 2013; Yoo et al, 2016; Yoo et al, 2017). The primary endpoint, ACR 20 at week 30, was achieved by 58.6% and 60.9% of patients in the REMICADE and INFLECTRA groups, respectively (treatment difference [TD], 2%; 95% CI, -6% to 10%) (intention-to-treat population). Corresponding results in the per-protocol population were 69.7% and 73.4%, respectively (TD, 4%; 95% CI, -4% to 12%). Equivalence was demonstrated between the two products.
    - Secondary endpoints included several other disease activity scales and a quality-of-life scale; no significant differences were noted in any of these endpoints at either the 30-week or 54-week assessments.
    - In the extension study (N=302) through 102 weeks, all patients received INFLECTRA. Response rates were maintained, with no differences between the INFLECTRA maintenance group and the group who switched from REMICADE to INFLECTRA.
- Two studies, one double-blind and one open-label, evaluated RITUXAN (rituximab) in patients who had failed treatment with a TNF blocker (Cohen et al, 2006, Haraoui et al, 2011). All patients continued to receive MTX. Both studies showed greater than 50% of patients achieving ACR 20 response. AEs were generally mild to moderate in severity.
- A Cochrane review (Lopez-Olivo et al, 2015) examined RITUXAN (rituximab) for the treatment of RA. Eight studies and a total of 2720 patients were included. Rituximab plus MTX, compared to MTX alone, resulted in more patients achieving ACR 50 at 24 weeks (29% vs 9%, respectively) and clinical remission at 52 weeks (22% vs 11%). In addition, rituximab plus MTX compared to MTX alone resulted in more patients having no radiographic progression (70% vs 59% at 24 weeks, with similar results at 52 through 56 and 104 weeks). Benefits were also shown for physical function and quality of life.
- In the open-label ORBIT study (N=295), adults with active, seropositive RA and an inadequate response to DMARDs who were biologic-naïve were randomized to either RITUXAN (rituximab) (n=144) or a TNF inhibitor (physician/patient choice of ENBREL [etanercept] or HUMIRA [adalimumab]; n=151) (Porter et al, 2016). Medication doses were generally consistent with FDA-approved recommendations. Patients were able to switch over to the alternative treatment due to side effects or lack of efficacy. The primary endpoint was the change in DAS28-ESR in the per-protocol population at 12 months.
    - The changes in DAS28-ESR were -2.6 and -2.4 in patients in the rituximab and TNF inhibitor groups, respectively. The difference of -0.19 (95% CI, -0.51 to 0.13) was within the prespecified non-inferiority margin of 0.6 units. The authors concluded that initial treatment with rituximab was non-inferior to initial TNF inhibitor treatment in this patient population. However, interpretation of these results is limited due to the open-label study design and the high percentage of patients switching to the alternative treatment (32% in the TNF inhibitor group and 19% in the rituximab group). The indication for rituximab is limited to patients with an inadequate response to TNF inhibitor(s).
- A randomized, open-label trial evaluated biologic treatments in patients with RA who had had an inadequate response to a TNF inhibitor (Gottenberg et al, 2016). Patients (N=300) were randomized to receive a second TNF inhibitor (n=150) or a non-TNF-targeted biologic (n=150) of the prescriber's choice. The second TNF inhibitors, in order of decreasing frequency, included HUMIRA (adalimumab), ENBREL (etanercept), CIMZIA (certolizumab), and REMICADE (infliximab), and the non-TNF biologics included ACTEMRA (tocilizumab), RITUXAN (rituximab), and ORENCIA (abatacept). The primary endpoint was the proportion of patients with a good or moderate EULAR response at week 24, defined as a decrease in DAS28-ESR of >1.2 points resulting in a score of ≤3.2.
    - At week 24, 52% of patients in the second anti-TNF group and 69% of patients in the non-TNF group achieved a good or moderate EULAR response (P=0.003 or P=0.004, depending on how missing data were handled). Secondary disease activity scores also generally supported better efficacy for the non-TNF biologics; however, HAQ scores did not differ significantly between groups. Among the non-TNF biologics, the proportion of EULAR good and moderate responders at week 24 did not significantly differ between abatacept, rituximab, and tocilizumab (67%, 61%, and 80%, respectively). There were 8 patients (5%) in the second TNF inhibitor group and 16 patients (11%) in the non-TNF biologic group that experienced serious AEs (P=0.10), predominantly infections and cardiovascular events. There were some limitations to this trial; notably, it had an open-label design, and adherence may have differed between groups because all non-TNF biologics were given as infusions under observation and most of the TNF inhibitor drugs were self-injected by patients. The authors concluded that among patients with RA inadequately treated with TNF inhibitors, a non-

TNF biologic was more effective in achieving a good or moderate disease activity response at 24 weeks; however, a second TNF inhibitor was also often effective in producing clinical improvement.

- Another recent randomized trial (Manders et al, 2015) evaluated the use of ORENCIA (abatacept) (n=43), RITUXAN (rituximab) (n=46), or a different TNF inhibitor (n=50) in patients (N=139) with active RA despite previous TNF inhibitor treatment. ACTEMRA (tocilizumab) was not included. In this trial, there were no significant differences with respect to DAS28, HAQ-DI, or SF-36 over the 1-year treatment period, and AEs also appeared similar. A cost-effectiveness analysis was also included in this publication, but results are not reported in this review.
- A Cochrane review examined ORENCIA (abatacept) for the treatment of RA. ACR 50 response was not significantly different at three months but was significantly higher in the abatacept group at six and 12 months compared to placebo (relative risk [RR], 2.47; 95% CI, 2 to 3.07 and RR, 2.21; 95% CI, 1.73 to 2.82). Similar results were seen in ACR 20 and ACR 70 (Maxwell et al, 2009).
- The safety and efficacy of HUMIRA (adalimumab) for the treatment of RA were assessed in a Cochrane systematic review. Treatment with adalimumab in combination with MTX was associated with a RR of 1.52 to 4.63, 4.63 (95% CI, 3.04 to 7.05) and 5.14 (95% CI, 3.14 to 8.41) for ACR 20, ACR 50, and ACR 70 responses at six months when compared to placebo in combination with MTX. Adalimumab monotherapy was also proven efficacious (Navarro-Sarabia et al, 2005). In another study, patients received adalimumab 20 mg or 40 mg every other week for one year, and then could receive 40 mg every other week for an additional nine years. At Year 10, 64.2%, 49%, and 17.6% of patients achieved ACR 50, ACR 70, and ACR 90 responses, respectively (Keystone et al, 2013b).
- A Phase 3, open-label study evaluated the long-term efficacy of HUMIRA (adalimumab) for RA. Patients receiving adalimumab in one of four early assessment studies could receive adalimumab for up to 10 years in the extension study. Of 846 enrolled patients, 286 (33.8%) completed 10 years of treatment. In patients completing 10 years, adalimumab led to sustained clinical and functional responses, with ACR 20, ACR 50, and ACR 70 responses being achieved by 78.6%, 55.5%, and 32.8% of patients, respectively. The authors stated that patients with shorter disease duration achieved better outcomes, highlighting the need for early treatment. No unexpected safety findings were observed. This study demonstrated that some patients with RA can be effectively treated with adalimumab on a long-term basis; however, the study is limited by its open-label design, lack of radiographic data, and the fact that only patients who continued in the study were followed (Furst et al, 2015).
- A Cochrane review was performed to compare KINERET (anakinra) to placebo in adult patients with RA. Significant improvements in both primary (ACR 20, 38% vs 23%; RR, 1.61; 95% CI, 1.32 to 1.98) and secondary (ACR 50 and ACR 70) outcomes were detected. The only significant difference in AEs noted with anakinra use was the rate of injection site reactions (71% vs 28% for placebo) (Mertens et al, 2009).
- In another Cochrane review, ENBREL (etanercept) was compared to MTX or placebo in adult patients with RA and found that at six months 64% of individuals on etanercept 25 mg twice weekly attained an ACR 20 vs 15% of patients on either MTX alone or placebo (RR, 3.8; number needed to treat [NNT], 2). An ACR 50 and ACR 70 were achieved by 39% and 15% in the etanercept group compared to 4% (RR, 8.89; NNT, 3) and 1% (RR, 11.31; NNT, 7) in the control groups. Etanercept 10 mg twice weekly was only associated with significant ACR 20 (51% vs 11% of controls; RR, 4.6; 95% CI, 2.4 to 8.8; NNT, 3) and ACR 50 responses (24% vs 5% of controls; RR, 4.74; 95% CI, 1.68 to 13.36; NNT, 5). Seventy-two percent of patients receiving etanercept had no increase in Sharp erosion score compared to 60% of MTX patients. Etanercept 25 mg was associated with a significantly reduced total Sharp score (weighted mean difference, -10.5; 95% CI, -13.33 to -7.67). The Sharp erosion scores and joint space narrowing were not significantly reduced by either etanercept dose (Blumenauer et al, 2003). In a trial of 353 patients with RA, patients received a triple therapy combination of sulfasalazine, hydroxychloroquine and MTX or etanercept and MTX. Triple therapy was shown to be noninferior to etanercept + MTX (O'Dell et al, 2013).
- A more recent Cochrane review (Singh et al, 2016a) evaluated the benefits and harms of 10 agents for the treatment of RA in patients failing treatment with MTX or other DMARDs. Agents included XELJANZ (tofacitinib) and 9 biologics (ORENCIA [abatacept], HUMIRA [adalimumab], KINERET [anakinra], CIMZIA [certolizumab], ENBREL [etanercept], SIMPONI [golimumab], REMICADE [infliximab], RITUXAN [rituximab], and ACTEMRA [tocilizumab]), each in combination with MTX or other DMARDS, compared to comparator agents such as DMARDs or placebo. Data from 79 randomized trials (total 32,874 participants) were included. Key results from this review are as follows:
    - ACR 50: Biologic plus MTX/DMARD was associated with a statistically significant and clinically meaningful improvement in ACR 50 vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics. Differences between treatments in individual comparisons were small.
    - HAQ: Biologic plus MTX/DMARD was associated with a clinically and statistically significant improvement in function measured by HAQ vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics.
    - Remission: Biologic plus MTX/DMARD was associated with clinically and statistically significantly greater proportion of patients achieving RA remission, defined by DAS <1.6 or DAS28 <2.6, vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics.

  - Radiographic progression: Radiographic progression was statistically significantly reduced in those on biologic plus MTX/DMARD vs comparator. The absolute reduction was small and clinical relevance is uncertain.
  - Safety: Biologic plus MTX/DMARD was associated with a clinically significantly increased risk of serious AEs; statistical significance was borderline. TNF inhibitors did not differ significantly from non-TNF biologics.
- A similar Cochrane review focused on the use of biologic or XELJANZ (tofacitinib) monotherapy for RA in patients with traditional DMARD failure (Singh et al, 2016b). A total of 41 randomized trials (N=14,049) provided data for this review. Key results are as follows:
  - Biologic monotherapy was associated with a statistically significant and clinically meaningful improvement in ACR 50 and HAQ vs placebo and vs MTX or other DMARDs.
  - Biologic monotherapy was associated with a statistically significant and clinically meaningful greater proportion of patients with disease remission vs placebo.
  - Based on a single study, the reduction in radiographic progression was statistically significant for biologic monotherapy compared to active comparators, but the absolute reduction was small and of unclear clinical relevance.
- Another Cochrane review evaluated the use of biologics or XELJANZ (tofacitinib) in patients with RA who had been unsuccessfully treated with a previous biologic (Singh et al, 2017). The review included 12 randomized trials (N=3,364). Key results are as follows:
  - Biologics, compared to placebo, were associated with statistically significant and clinically meaningful improvement in RA as assessed by ACR 50 and remission rates. Information was not available for HAQ or radiographic progression.
  - Biologics plus MTX, compared to MTX or other traditional DMARDs, were associated with statistically significant and clinically meaningful improvement in ACR 50, HAQ, and RA remission rates. Information was not available for radiographic progression.
  - There were no published data for tofacitinib monotherapy vs placebo.
  - Based on a single study, tofacitinib plus MTX, compared to MTX, was associated with a statistically significant and clinically meaningful improvement in ACR 50 and HAQ. RA remission rates were not statistically significantly different, and information was not available for radiographic progression.
- Another recent Cochrane review (Hazlewood et al, 2016) compared MTX and MTX-based DMARD combinations for RA in patients naïve to or with an inadequate response to MTX; DMARD combinations included both biologic and non-biologic agents. A total of 158 studies and over 37,000 patients were included. Evidence suggested that efficacy was similar for triple DMARD therapy (MTX plus sulfasalazine plus hydroxychloroquine) and MTX plus most biologic DMARDs or XELJANZ (tofacitinib). MTX plus some biologics were superior to MTX in preventing joint damage in MTX-naïve patients, but the magnitude of effects was small.
- A meta-analysis evaluated the efficacy of REMICADE (infliximab) in combination with MTX compared to placebo plus MTX. There was a higher proportion of patients in the infliximab group that achieved an ACR 20 at 30 weeks compared to patients in the placebo group (RR, 1.87; 95% CI, 1.43 to 2.45). These effects were similar in the proportion of patients achieving ACR 50 and ACR 70 (RR, 2.68; 95% CI, 1.79 to 3.99 and RR, 2.68; 95% CI, 1.78 to 4.03) (Wiens et al, 2009).
- Another meta-analysis of randomized controlled trials included HUMIRA (adalimumab), KINERET (anakinra), ENBREL (etanercept), and REMICADE (infliximab) with or without MTX. The odds ratio (OR) for an ACR 20 was 3.19 (95% CI, 1.97 to 5.48) with adalimumab, 1.7 (95% CI, 0.9 to 3.29) with anakinra, 3.58 (95% CI, 2.09 to 6.91) with etanercept and 3.47 (95% CI, 1.66 to 7.14) with infliximab compared to placebo. The OR to achieve an ACR 50 with adalimumab was 3.97 (95% CI, 2.73 to 6.07), 2.13 (95% CI, 1.27 to 4.22) with anakinra, 4.21 (95% CI, 2.74 to 7.43) and with etanercept 4.14 (95% CI, 2.42 to 7.46) compared to placebo. Further analysis of each agent against another was performed, and no significant difference was determined between individual agents in obtaining an ACR 20 and ACR 50. However, the TNF-blockers as a class showed a greater ACR 20 and ACR 50 response compared to anakinra (OR, 1.96; 95% CI, 1.03 to 4.01 and OR, 1.93; 95% CI,1.05 to 3.5; P<0.05) (Nixon et al, 2007).
- The Agency for Healthcare Research and Quality published a review of drug therapy to treat adults with RA (Donahue et al, 2012). They concluded that there is limited head to head data comparing the biologics. Studies that are available are generally observational in nature or mixed treatment comparison meta-analysis. At this time, there appears to be no significant differences amongst the agents. Clinical trials have shown better efficacy with combination biologics and MTX and no additional increased risk of AEs. However, combinations of two biologic agents showed increased rate of serious AEs with limited or no increase in efficacy.
- s for the FDA approval of STELARA ,927) evaluated the efficacy of withdrawing biologics from patients with RA who in sustained remission or had low disease activity (Galvao et al, 2016). The biologics in the identified trials were TNF inhibitors, most commonly ENBREL (etanercept) or HUMIRA (adalimumab). Compared to withdrawing the

medication, continuing the biologic increased the probability of having low disease activity (RR, 0.66; 95% CI, 0.51 to 0.84) and remission (RR, 0.57; 95% CI, 0.44 to 0.74). Although outcomes were worse in patients withdrawing the biologic, the investigators noted that almost half of the patients maintained a low disease activity after withdrawal. The authors suggested that further research is necessary to identify subgroups for which withdrawal may be more appropriate.

Ankylosing spondylitis (AS)

- The FDA-approval of HUMIRA (adalimumab) for the treatment of AS was based on one randomized, double-blind, placebo-controlled study (N=315) in which a significantly greater proportion of patients achieved a 20% improvement in the Assessment of SpondyloArthritis International Society criteria (ASAS 20) (primary endpoint) with adalimumab (58% vs 21% with placebo; P<0.001). A greater than 50% improvement in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score, a measure of fatigue severity, spinal and peripheral joint pain, localized tenderness, and morning stiffness which is considered clinically meaningful, was detected in 45% of adalimumab-treated patients compared to 16% of placebo-treated patients (P<0.001) at week 12. This response was sustained through week 24, with 42% in the adalimumab group achieving a greater than or equal to 50% improvement in BASDAI score compared to 15% in the placebo group (P<0.001) (van der Heijde et al, 2006).
- In two double-blind, randomized, placebo-controlled trials, the efficacy of ENBREL (etanercept) was evaluated in patients with AS (Calin et al, 2004; Gorman et al, 2002). Etanercept had a significantly greater response to treatment compared to placebo (P<0.001)(Gorman et al, 2002). More patients achieved an ASAS 20 response compared to placebo (P<0.001)(Calin et al, 2004). An open-label extension study, evaluating the long-term safety and efficacy of etanercept in patients with AS, was conducted. Safety endpoints included AEs, serious AEs, serious infection, and death while efficacy endpoints included ASAS 20 response, ASAS 5/6 response and partial remission rates. After up to 192 weeks of treatment, the most common AEs were injection site reactions, headache and diarrhea. A total of 71% of patients were ASAS 20 responders at week 96 and 81% of patients were responders at week 192. The ASAS 5/6 response rates were 61% at week 96 and 60% at week 144, and partial remission response rates were 41% at week 96 and 44% at week 192. Placebo patients who switched to etanercept in the open-label extension trial showed similar patterns of efficacy maintenance (Davis et al, 2008). A multicenter, randomized, double-blind trial compared etanercept and sulfasalazine in adult patients with active AS that failed treatment with nonsteroidal anti-inflammatory drugs (NSAIDs). A significantly greater proportion of patients treated with etanercept compared to patients treated with sulfasalazine achieved the primary outcome of ASAS 20 at week 16 (P<0.0001). There were also significantly more patients that achieved ASAS 40 and ASAS 5/6 in the etanercept group compared to the sulfasalazine group (P<0.0001 for both) (Braun et al, 2011).
- The FDA-approval of SIMPONI (golimumab) for AS was based on a multicenter, randomized, double-blind, placebo-controlled trial in adult patients with active disease for at least three months (N=356). Golimumab with or without a DMARD was compared to placebo with or without a DMARD and was found to significantly improve the signs and symptoms of AS as demonstrated by the percentage of patients achieving an ASAS 20 response at week 14 (Inman et al, 2008). Sustained improvements in ASAS 20 and ASAS 40 response rates were observed for up to five years in an open-label extension trial (Deodhar et al, 2015). Safety profile through five years was consistent with other TNF inhibitors.
- The efficacy of REMICADE (infliximab) in the treatment of AS was demonstrated in 12- and 24-week double-blind, placebo-controlled trials. There was significantly more patients that achieved a 50% BASDAI score in the infliximab group compared to the placebo group at 12 weeks (P<0.0001)(Braun et al, 2002), At 24 weeks, significantly more patients in the infliximab group achieved ASAS 20 compared to the placebo group (P<0.001)(van der Heijde et al, 2005).
- INFLECTRA (infliximab-dyyb) was evaluated alongside REMICADE (infliximab; European Union formulation) for the treatment of AS in PLANETAS (N=250), a double-blind, multicenter, randomized trial (*Park et al 2013, Park et al 2016, Park et al 2017*). The primary endpoints related to pharmacokinetic equivalence. Secondary efficacy endpoints supported similar clinical activity between INFLECTRA and REMICADE. An ASAS 20 response was achieved by 72.4% and 70.5% of patients in the REMICADE and INFLECTRA groups, respectively, at 30 weeks, and by 69.4% and 67.0% of patients at 54 weeks. Other disease activity endpoints and a quality-of-life scale were also similar between groups.
    - In the extension study (N=174) through 102 weeks, all patients received INFLECTRA. From weeks 54 to 102, the proportion of patients achieving a clinical response was maintained at a similar level to that of the main study in both the maintenance and switch groups and was comparable between groups.
- The efficacy of CIMZIA (certolizumab) for the treatment of AS was established in one randomized, double-blind, placebo-controlled study (N=325) in which a significantly greater proportion of patients achieved ASAS 20 response with certolizumab 200 mg every two weeks and certolizumab 400 mg every four weeks compared to placebo at 12

weeks (Landewe et at, 2014). Patient-reported outcomes measured by the SF-36, health-related quality of life (HRQoL), and reports of pain, fatigue and sleep were significantly improved with certolizumab in both dose groups (Sieper et al, 2015a). A Phase 3, randomized, placebo-controlled trial found that 62.5% of patients on certolizumab maintained ASAS 20 response to week 96 in a population of patients with axial spondyloarthritis which includes AS (Sieper et al, 2015b).

- The efficacy and safety of COSENTYX (secukinumab) were evaluated in the double-blind, placebo-controlled, randomized MEASURE 1 and 2 studies (Baeten et al, 2015). MEASURE 1 enrolled 371 patients and MEASURE 2 enrolled 219 patients with active AS with radiologic evidence treated with NSAIDs. Patients were treated with secukinumab 75 or 150 mg SQ every 4 weeks (following IV loading doses) or placebo. The primary outcome, ASAS 20 response at week 16, was significantly higher in the secukinumab 75 mg (60%) and 150 mg (61%) groups compared to placebo (29%, P<0.001 for each dose) for MEASURE 1. For MEASURE 2 at week 16, ASAS 20 responses were seen in 61% of the secukinumab 150 mg group, 41% of the 75 mg group, and 28% of the placebo group (P<0.001 for secukinumab 150 mg vs placebo; P=0.10 for secukinumab 75 mg vs placebo). Common AEs reported included nasopharyngitis, headache, diarrhea, and upper respiratory tract infections. Improvements were observed from week 1 and sustained through week 52.
- In two systematic reviews of TNF blockers for the treatment of AS, patients taking SIMPONI (golimumab), ENBREL (etanercept), REMICADE (infliximab), and HUMIRA (adalimumab) were more likely to achieve ASAS 20 or ASAS 40 responses compared with patients from control groups. The RR of reaching ASAS 20 after 12 or 14 weeks was 2.21 (95% CI, 1.91 to 2.56) (Machado et al, 2013). After 24 weeks, golimumab, etanercept, infliximab, and adalimumab were more likely to achieve ASAS 40 compared to placebo (Maxwell et al, 2015). A systematic review and network meta-analysis evaluated biologic agents for the treatment of AS, including adalimumab, etanercept, golimumab, infliximab, COSENTYX (secukinumab), and ACTEMRA (tocilizumab; not FDA approved for AS) (Chen et al, 2016). A total of 14 studies were included. Infliximab was ranked best and secukinumab second best for achievement of ASAS 20 response; however, differences among agents were not statistically significant with the exception of infliximab 5 mg compared to tocilizumab (OR, 4.81; 95% credible interval [CrI], 1.43 to 17.04). Safety endpoints were not included in this analysis.

Crohn's disease (CD)

- In a trial evaluating REMICADE (infliximab) for induction of remission, significantly more patients achieved remission at four weeks with infliximab compared to placebo (P<0.005)(Targan et al, 1997). In a placebo-controlled trial, significantly more patients treated with infliximab 5 and 10 mg/kg had a reduction greater than or equal to 50% in the number of fistulas compared to patients treated with placebo (P=0.002 and P=0.02, respectively)(Present et al, 1999). In an open-label trial evaluating the use of infliximab in pediatric CD patients, 88.4% responded to the initial induction regimen, and 58.6% were in clinical remission at week 10 (Hyams et al, 2007).
- The safety and efficacy of ENTYVIO (vedolizumab) was demonstrated in two trials for CD in patients who responded inadequately to immunomodulator therapy, TNF blockers, and/or corticosteroids. In one trial, a higher percentage of ENTYVIO-treated patients achieved clinical response and remission at week 52 compared to placebo. However, in the second trial, ENTYVIO did not achieve a statistically significant clinical response or clinical remission over placebo at week six (Sandborn et al, 2013; Sands et al, 2014).
- A meta-analysis evaluating CIMZIA (certolizumab) use over 12 to 26 weeks for the treatment of CD demonstrated that the agent was associated with an increased rate of induction of clinical response (RR, 1.36; P=0.004) and remission (RR, 1.95; P<0.0001) over placebo. However, risk of infection was higher with certolizumab use (Shao et al, 2009).
- Additionally, HUMIRA (adalimumab), CIMZIA (certolizumab) and REMICADE (infliximab) demonstrated the ability to achieve clinical response (RR, 2.69; P<0.00001; RR, 1.74; P<0.0001 and RR, 1.66; P=0.0046, respectively) and maintain clinical remission (RR, 1.68; P=0.000072 with certolizumab and RR, 2.5; P=0.000019 with infliximab; adalimumab, data not reported) over placebo in patients with CD. Adalimumab and infliximab also had a steroid-sparing effect (Behm et al, 2008). Other systematic reviews have further demonstrated the efficacy of these agents in CD (Singh et al, 2014).
- In a systematic review of patients with CD who had failed a trial with REMICADE (infliximab), the administration of HUMIRA (adalimumab) was associated with remission rates of 19 to 68% at one year. Serious cases of sepsis, cellulitis, and fungal pneumonia occurred in zero to 19% of patients in up to four years of treatment (Ma et al, 2009).
- A systematic review of 8 randomized clinical trials with TYSABRI (natalizumab) or ENTYVIO (vedolizumab) for the management of CD evaluated the rates of failure of remission induction (Chandar et al, 2015). Fewer failures of remission induction were reported with natalizumab and vedolizumab compared to placebo (RR 0.87; 95% CI, 0.84 to 0.91; I^2=0%). The summary effect sizes were similar for both natalizumab (RR 0.86; 95% CI, 0.80 to 0.93) and vedolizumab (RR 0.87; 95% CI, 0.79 to 0.95). No significant difference was detected between the two active treatments (P=0.95). No significant differences between natalizumab and vedolizumab were observed for rates of

serious AEs, infections (including serious infections), and treatment discontinuation. Rates of infusion reactions in induction trials were more common with natalizumab over vedolizumab (P=0.007). Progressive multifocal leukoencephalopathy (PML) has been reported with natalizumab but has not been reported with vedolizumab.

- The use of STELARA (ustekinumab) for the treatment of CD was evaluated in the UNITI-1, UNITI-2, and IM-UNITI studies (Feagan et al, 2016). All were Phase 3, double-blind, placebo-controlled trials.
    - UNITI-1 (N=741) was an 8-week induction trial that compared single IV doses of ustekinumab 130 mg IV, weight-based ustekinumab (~6 mg/kg), and placebo in patients with nonresponse or intolerance to one or more TNF inhibitors. The primary endpoint was clinical response at week 6, which was defined as a decrease from baseline in the CDAI of ≥100 points or a CDAI score of <150. A clinical response was achieved by 34.4%, 33.7%, and 21.5% of patients in the ustekinumab 130 mg, weight-based ustekinumab, and placebo groups, respectively (P=0.002 for 130 mg dose vs placebo; P=0.003 for weight-based dose vs placebo). Benefits were also demonstrated on all major secondary endpoints, which included clinical response at week 8, clinical remission (CDAI <150) at week 8, and CDAI decrease of ≥70 points at weeks 3 and 6.
    - UNITI-2 (N=628) had a similar design to UNITI-1, but was conducted in patients with treatment failure or intolerance to immunosuppressants or glucocorticoids (with no requirement for prior TNF inhibitor use). In this trial, a clinical response was achieved by 51.7%, 55.5%, and 28.7% of patients in the ustekinumab 130 mg, weight-based ustekinumab, and placebo groups, respectively (P<0.001 for both doses vs placebo). Benefits were also demonstrated on all major secondary endpoints.
    - IM-UNITI was a 44-week maintenance trial that enrolled patients completing UNITI-1 and UNITI-2. Of 1,281 enrolled patients, there were 397 randomized patients (primary population); these were patients who had had a clinical response to ustekinumab induction therapy and were subsequently randomized to ustekinumab 90 mg SC every 8 or 12 weeks or placebo. The primary endpoint, clinical remission at week 44, was achieved by 53.1%, 48.8%, and 35.9% of patients in the ustekinumab every 8 week, ustekinumab every 12 week, and placebo groups, respectively (P=0.005 for every 8 week regimen vs placebo; P=0.04 for every 12 week regimen vs placebo). Numerical and/or statistically significant differences for ustekinumab vs placebo were observed on key secondary endpoints including clinical response, maintenance of remission, and glucocorticoid-free remission.

Hidradenitis suppurativa (HS)

- Two 36-week, Phase 3, double-blind, multicenter, placebo-controlled, randomized trials, PIONEER I and II, evaluated HUMIRA (adalimumab) for the treatment of HS (Kimball et al, 2016). A total of 633 adults (307 in PIONEER I and 326 in PIONEER II) with moderate to severe HS were enrolled. The study consisted of two treatment periods; in the first period, patients were randomized to placebo or weekly adalimumab for 12 weeks; in the second period, patients initially assigned to placebo received weekly adalimumab (PIONEER I) or placebo (PIONEER II) for 24 weeks and patients initially assigned to adalimumab were re-randomized to placebo, weekly adalimumab, or every-other-week adalimumab. The adalimumab dosage regimen was 160 mg at week zero, followed by 80 mg at week 2, followed by 40 mg doses starting at week 4.
    - The primary endpoint was HS clinical response (HiSCR) at week 12, defined as at least 50% reduction in total abscess and inflammatory nodule count with no increase in abscess count and no increase in draining fistula count compared to baseline. HiSCR rates at week 12 were significantly higher for the groups receiving adalimumab than for the placebo groups: 41.8% vs 26.0% in PIONEER I (P=0.003) and 58.9% vs 27.6% in PIONEER II (P<0.001).
    - Among patients with a clinical response at week 12, response rates in all treatment groups subsequently declined over time. During period 2, there were no significant differences in clinical response rates in either trial between patients randomly assigned to adalimumab at either a weekly dose or an every-other-week dose and those assigned to placebo, regardless of whether the patients had a response at week 12. For patients who received placebo in period 1, 41.4% of those assigned to adalimumab weekly in period 2 (PIONEER I) and 15.9% of those reassigned to placebo in period 2 (PIONEER II) had a clinical response at week 36.
    - The authors noted that the magnitude of improvement with adalimumab treatment was modest compared with adalimumab treatment in other disease states, and patients were unlikely to achieve complete symptom resolution.

Juvenile idiopathic arthritis (JIA)

- In a trial of pediatric patients (six to 17 years of age) with JIA (extended oligoarticular, polyarticular, or systemic without systemic manifestations), the patients treated with placebo had significantly more flares than the patients treated with ORENCIA (abatacept) (P=0.0003). The time to flare was significantly different favoring abatacept (P=0.0002) (Ruperto et al, 2008).

- HUMIRA (adalimumab) was studied in a group of patients (four to 17 years of age) with active polyarticular JIA who had previously received treatment with NSAIDs. Patients were stratified according to MTX use and received 24 mg/m^2 (maximum of 40 mg) of adalimumab every other week for 16 weeks. The patients with an American College of Rheumatology Pediatric 30 (ACR Pedi 30) response at week 16 were randomly assigned to receive adalimumab or placebo in a double-blind method every other week for up to 32 weeks. The authors found that 74% of patients not receiving MTX and 94% of those receiving MTX had an ACR Pedi 30 at week 16. Among those not receiving MTX, flares occurred in 43% receiving adalimumab and 71% receiving placebo (P=0.03). In the patients receiving MTX, flares occurred in 37 and 65% in the adalimumab and placebo groups, respectively (P=0.02). ACR Pedi scores were significantly greater with adalimumab than placebo and were sustained after 104 weeks of treatment (Lovell et al, 2008).
- A double-blind, multicenter, randomized controlled trial compared HUMIRA (adalimumab) and placebo in 46 children ages six to 18 years with enthesitis-related arthritis (Burgos-Vargas et al, 2015). Patients were TNF inhibitor naïve. At week 12, the percentage change from baseline in the number of active joints with arthritis was significantly reduced with adalimumab compared to placebo (-62.6% vs -11.6%, P=0.039). A total of seven patients (three placebo; four adalimumab) escaped the study early during the double-blind phase and moved to open-label adalimumab therapy. Analysis excluding these patients produced similar results (adalimumab, -83.3 vs placebo -32.1; P=0.018). At week 52, adalimumab-treated patients had a mean reduction in active joint count from baseline of 88.7%. A total of 93.5% of patients achieved complete resolution of their swollen joints with a mean of 41 days of adalimumab therapy.
- In a trial involving 69 pediatric patients with active polyarticular JIA despite treatment with NSAIDs and MTX, ENBREL (etanercept) was associated with a significant reduction in flares compared to placebo (28% vs 81%; P=0.003) (Lovell et al, 2000). Ninety-four percent of patients who remained in an open-label four year extension trial met ACR Pedi 30; C-reactive protein (CRP) levels, articular severity scores, and patient pain assessment scores all decreased. There were five cases of serious AEs related to etanercept therapy after four years (Lovell et al, 2006).
- The approval of ACTEMRA (tocilizumab) for the indication of SJIA was based on a randomized, placebo-controlled trial (N=112). Children age two to 17 years of age with active SJIA and inadequate response to NSAIDs and corticosteroids were included in the study. The primary endpoint was ACR 30 and absence of fever at week 12. At week 12, the proportion of patients achieving ACR 30 and absence of fever was significantly greater in the tocilizumab-treated patients compared to the placebo treated patients (85% vs 24%; P<0.0001)(De Benedetti et al, 2012). The double-blind, randomized CHERISH study evaluated tocilizumab for JIA flares in patients ages 2 to 17 years with JIA with an inadequate response or intolerance to MTX (Brunner et al, 2015). Tocilizumab-treated patients experienced significantly fewer JIA flares at week 40 compared to patients treated with placebo (25.6% vs 48.1%; P<0.0024).
- In two trials in patients with SJIA, ILARIS (canakinumab) was more effective at reducing flares than placebo. It also allowed for glucocorticoid dose tapering or discontinuation. More patients treated with canakinumab experienced infections than patients treated with placebo (Ruperto et al, 2012).
- A meta-analysis of trials evaluating biologics for the treatment of SJIA included 5 trials; one each for KINERET (anakinra), ILARIS (canakinumab), and ACTEMRA (tocilizumab), and 2 for rilonacept (not FDA approved for JIA and not included in this review) (Tarp et al, 2016). The primary endpoint, the proportion of patients achieving a modified ACR Pedi 30 response, was superior to placebo for all agents, but did not differ significantly among anakinra, canakinumab, and tocilizumab. However, comparisons were based on low-quality, indirect evidence and no firm conclusions can be drawn on their relative efficacy. No differences among drugs for serious AEs were demonstrated.

Plaque psoriasis (PsO)

- In a randomized, double-blind, double-dummy trial, HUMIRA (adalimumab) was compared to MTX and placebo in patients with moderate to severe PsO despite treatment with topical agents. The primary outcome was the proportion of patients that achieved Psoriasis Area and Severity Index (PASI) 75 at 16 weeks. Significantly more patients in the adalimumab group achieved the primary endpoint compared to patients in the MTX (P<0.001) and placebo (P<0.001) groups, respectively (Saurat et al, 2008).
- More than 2,200 patients were enrolled in two published, pivotal, phase III trials that served as the primary basis for the FDA approval of STELARA (ustekinumab) in PsO. PHOENIX 1 and PHOENIX 2 enrolled patients with moderate to severe PsO to randomly receive ustekinumab 45 mg, 90 mg or placebo at weeks zero, four and every 12 weeks thereafter (Leonardi et al, 2008; Papp et al, 2008; Langley et al, 2015). In PHOENIX 1, patients who were initially randomized to ustekinumab at week zero and achieved long-term response (at least PASI 75 at weeks 28 and 40) were re-randomized at week 40 to maintenance ustekinumab or withdrawal from treatment. Patients in the 45 mg ustekinumab and 90 mg ustekinumab groups had higher proportion of patients achieving PASI 75 compared to patients in the placebo group at week 12 (P<0.0001 for both). PASI 75 response was better maintained to at least one year in those receiving maintenance ustekinumab than in those withdrawn from treatment at week 40 (P<0.0001)

(Leonardi et al, 2008). In PHOENIX 2, the primary endpoint (the proportion of patients achieving a PASI 75 response at week 12) was achieved in significantly more patients receiving ustekinumab 45 and 90 mg compared to patients receiving placebo (P<0.0001). Partial responders were re-randomized at week 28 to continue dosing every 12 weeks or escalate to dosing every eight weeks. More partial responders at week 28 who received 90 mg every eight weeks achieved PASI 75 at week 52 than did those who continued to receive the same dose every 12 weeks. There was no such response to changes in dosing intensity in partial responders treated with 45 mg. AEs were similar between groups (Papp et al, 2008). A total of 70% (849 of 1,212) of ustekinumab-treated patients completed therapy through week 244. At week 244, the proportions of patients initially randomized to ustekinumab 45 mg and 90 mg who achieved PASI 75 were 76.5% and 78.6%, respectively. A total of 50.0% and 55.5% of patients, respectively, achieved PASI 90 (Langley et al, 2015).

- In a study comparing ENBREL (etanercept) and STELARA (ustekinumab), a greater proportion of PsO patients achieved the primary outcome (PASI 75 at week 12) with ustekinumab 45 (67.5%) and 90 mg (73.8%) compared to etanercept 50 mg (56.8%; P=0.01 vs ustekinumab 45 mg; P<0.001 vs ustekinumab 90 mg). In this trial, etanercept therapy was associated with a greater risk of injection site erythema (14.7% vs 0.7% of all ustekinumab patients) (Griffiths et al, 2010).
- Approval of OTEZLA (apremilast) for moderate to severe PsO was based on results from the ESTEEM trials. In the trials, 1,257 patients with moderate to severe PsO were randomized 2:1 to apremilast 30 mg twice daily (with a titration period) or placebo. The primary endpoint was the number of patients with a 75% improvement on the PASI 75. In ESTEEM 1, significantly more patients receiving apremilast achieved PASI 75 compared to placebo (33.1% vs 5.3%; P<0.0001) at 16 weeks. In ESTEEM 2, significantly more patients receiving apremilast also achieved PASI 75 compared to placebo (28.8% vs 5.8%; P<0.0001) at 16 weeks (Papp et al, 2015; Paul et al, 2015a).
    - Additional analyses of the ESTEEM trials have been published. In one (Thaçi et al, 2016), the impact of apremilast on health-related quality of life, general function, and mental health was evaluated using patient-reported outcome assessments. The study demonstrated improvement with apremilast vs placebo, including improvements on the dermatology life quality index (DLQI) and SF-36 mental component summary (MCS) that exceeded minimal clinically important differences. In another analysis (Rich et al, 2016), effects of apremilast on difficult-to-treat nail and scalp psoriasis were evaluated. At baseline in ESTEEM 1 and ESTEEM 2, respectively, 66.1% and 64.7% of patients had nail psoriasis and 66.7% and 65.5% had moderate to very severe scalp psoriasis. At week 16, apremilast produced greater improvements in Nail Psoriasis Severity Index (NAPSI) score vs placebo; greater NAPSI-50 response (50% reduction from baseline in target nail NAPSI score) vs placebo; and greater response on the Scalp Physician Global Assessment (ScPGA) vs placebo. Improvements were generally maintained over 52 weeks in patients with a PASI response at week 32.
- COSENTYX (secukinumab) was evaluated in two large, phase 3, double-blind trials in patients with moderate to severe PsO. The co-primary endpoints were the proportions of patients achieving PASI 75 and the proportions of patients with clear or almost clear skin (score 0 or 1) on the modified investigator's global assessment (IGA) at 12 weeks.
    - In ERASURE (N=738), 81.6%, 71.6%, and 4.5% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 65.3%, 51.2%, and 2.4% achieved a score of 0 or 1 on the IGA (Langley et al, 2014).
    - In FIXTURE (N=1,306), 77.1%, 67%, 44%, and 4.9% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, ENBREL (etanercept) at FDA-recommended dosing, and placebo, respectively, and 62.5%, 51.1%, 27.2%, and 2.8% achieved a score of 0 or 1 on the IGA (Langley et al, 2014).
- Two smaller, phase 3, double-blind, placebo-controlled trials evaluated COSENTYX (secukinumab) given by prefilled syringe (FEATURE) or auto-injector/pen (JUNCTURE). Again, co-primary endpoints were the proportions of patients achieving PASI 75 and obtaining a score of 0 or 1 on the modified IGA at 12 weeks.
    - In FEATURE (N=177), 75.9%, 69.5%, and 0% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 69%, 52.5%, and 0% achieved a score of 0 or 1 on the IGA (Blauvelt et al, 2015).
    - In JUNCTURE (N=182), 86.7%, 71.7%, and 3.3% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 73.3%, 53.3%, and 0% achieved a score of 0 or 1 on the IGA (Paul et al, 2015b).
- Secondary endpoints, including the proportions of patients demonstrating a reduction of 90% or more on the PASI (PASI 90), a reduction of 100% (PASI 100), and change in the DLQI further support the efficacy of COSENTYX (secukinumab) (Blauvelt et al, 2015; Langley et al, 2014; Paul et al, 2015b).
- In the CLEAR study, COSENTYX (secukinumab) 300 mg SQ every four weeks and STELARA (ustekinumab) 45 mg or 90 mg SQ (based on body weight) every 12 weeks were compared for safety and efficacy in a double-blind,

randomized controlled trial in 676 patients with moderate to severe PsO (Thaçi et al, 2015). The primary endpoint, proportion of patients achieving PASI 90 at week 16, was significantly higher with secukinumab compared to ustekinumab (79% vs 57.6%; P<0.0001). Achievement of PASI 100 response at week 16 was also significantly higher with secukinumab over ustekinumab (44.3% vs 28.4%; P<0.0001). Infections and infestations were reported in 29.3% of secukinumab- and 25.3% of ustekinumab-treated patients. Most infections were not serious and were managed without discontinuation. The most commonly reported AEs included headache and nasopharyngitis. Serious AEs were reported in 3% of each group.

- A meta-analysis of seven Phase 3 clinical trials demonstrated the efficacy of COSENTYX (secukinumab) vs placebo and vs ENBREL (etanercept) in patients with PsO (Ryoo et al, 2016). The ORs for achieving PASI 75 and for achieving IGA 0 or 1 were both 3.7 for secukinumab vs etanercept. Secukinumab 300 mg was significantly more effective than 150 mg. Secukinumab was well-tolerated throughout the one-year trials.
- The use of TALTZ (ixekizumab) for the treatment of PsO was evaluated in the UNCOVER-1, UNCOVER-2, and UNCOVER-3 trials. All were Phase 3, double-blind, randomized trials.
    - UNCOVER-1 (N=1,296) compared ixekizumab 160 mg loading dose then 80 mg every 2 weeks, ixekizumab 160 mg loading dose then 80 mg every 4 weeks, and placebo (Gordon et al, 2016; Taltz product dossier, 2016). Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving a physician's global assessment (PGA) score of 0 or 1 (clear or almost clear) at week 12. In the ixekizumab every 2 week, ixekizumab every 4 week, and placebo groups, PASI 75 was achieved by 89.1%, 82.6%, and 3.9% of patients, respectively (P<0.001 for both doses vs placebo), and PGA 0 or 1 was achieved by 81.8%, 76.4%, and 3.2% of patients, respectively (P<0.001 for both doses vs placebo). Improvements for ixekizumab vs placebo were also seen in secondary endpoints including PASI 90, PASI 100, PGA 0, and change in DLQI.
    - UNCOVER-2 (N=1,224) compared ixekizumab 160 mg loading dose then 80 mg every 2 weeks, ixekizumab 160 mg then 80 mg every 4 weeks, etanercept 50 mg twice weekly, and placebo (Griffiths et al, 2015). Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving a PGA 0 or 1 at week 12. The proportions of patients achieving PASI 75 were 89.7%, 77.5%, 41.6%, and 2.4% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively (P<0.0001 for all active treatments vs placebo and for both ixekizumab arms vs etanercept). The proportions of patients achieving PGA 0 or 1 were 83.2%, 72.9%, 36%, and 2.4% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively (P<0.0001 for all active treatments vs placebo and for both ixekizumab arms vs etanercept). Improvements were also greater for ixekizumab vs placebo, etanercept vs placebo, and ixekizumab vs etanercept for all secondary endpoints including PGA 0, PASI 90, PASI 100, and DLQI.
    - UNCOVER-3 (N=1,346) had the same treatment groups and primary and secondary endpoints as UNCOVER-2 (Griffiths et al, 2015). The proportions of patients achieving PASI 75 were 87.3%, 84.2%, 53.4%, and 7.3% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively (P<0.0001 for all active treatments vs placebo and for both ixekizumab arms vs etanercept). The proportions of patients achieving PGA 0 or 1 were 80.5%, 75.4%, 41.6%, and 6.7% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively (P<0.0001 for all active treatments vs placebo and for both ixekizumab arms vs etanercept). Improvements were also greater for ixekizumab vs placebo, etanercept vs placebo, and ixekizumab vs etanercept for all secondary endpoints including PGA 0, PASI 90, PASI 100, and DLQI.
    - Results through week 60 for UNCOVER-1, UNCOVER-2, and UNCOVER-3 have been reported (Gordon et al, 2016). At week 12 in UNCOVER-1 and UNCOVER-2, patients responding to ixekizumab (PGA 0 or 1) were re-randomized to receive ixekizumab 80 mg every 4 weeks, ixekizumab 80 mg every 12 weeks, or placebo through week 60. Among the patients who were randomly reassigned at week 12 to receive 80 mg of ixekizumab every 4 weeks (the approved maintenance dosing), 80 mg of ixekizumab every 12 weeks, or placebo, a PGA score of 0 or 1 was maintained by 73.8%, 39.0%, and 7.0% of the patients, respectively, and high rates were maintained or attained for additional measures such as PASI 75, PASI 90, and PASI 100 (pooled data for UNCOVER-1 and UNCOVER-2). At week 12 in UNCOVER-3, patients entered a long-term extension period in which they received ixekizumab 80 mg every 4 weeks through week 60. At week 60, at least 73% had a PGA score of 0 or 1 and at least 80% had a PASI 75 response. In addition, most patients had maintained or attained PASI 90 or PASI 100 at week 60.
- The use of SILIQ (brodalumab) for the treatment of PsO was evaluated in the AMAGINE-1, AMAGINE-2, and AMAGINE-3 trials. All were Phase 3, double-blind, randomized trials.
    - AMAGINE-1 (N=661) compared brodalumab 210 mg, brodalumab 140 mg, and placebo; each treatment was given at weeks zero, one, and two, followed by every two weeks to week 12 (Papp et al, 2016). This 12-week

induction phase was followed by a withdrawal/retreatment phase through week 52: patients receiving brodalumab who achieved PGA 0 or 1 (PGA success) were re-randomized to the placebo or induction dose, and patients randomized to brodalumab with PGA ≥2 and those initially receiving placebo received brodalumab 210 mg every two weeks. Patients in the withdrawal phase who had disease recurrence (PGA ≥3) between weeks 16 and 52 were retreated with their induction doses of brodalumab. Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving PGA success at week 12. PASI 75 was achieved by 83% (95% CI, 78 to 88), 60% (95% CI, 54 to 67), and 3% (95% CI, 1 to 6) of patients in the brodalumab 210 mg, brodalumab 140 mg, and placebo groups, respectively; PGA success was achieved by 76% (95% CI, 70 to 81), 54% (95% CI, 47 to 61), and 1% (95% CI, 0 to 4), respectively (P<0.001 for all comparisons of brodalumab vs placebo). Differences in key secondary endpoints at week 12 also favored brodalumab vs placebo, including PASI 90, PASI 100, and PGA 0. In the randomized withdrawal phase, high response rates were maintained in those who continued brodalumab, while most patients re-randomized to placebo experienced return of disease (but were able to recapture disease control with retreatment).

- AMAGINE-2 (N=1,831) and AMAGINE-3 (N=1,881) were identical in design and compared brodalumab 210 mg, brodalumab 140 mg, STELARA (ustekinumab), and placebo (Lebwohl et al, 2015). Brodalumab was given at weeks zero, one, and two, followed by every two weeks to week 12. Ustekinumab was given in weight-based doses per its FDA-approved labeling. At week 12, patients receiving brodalumab were re-randomized to receive brodalumab at a dose of 210 mg every two weeks or 140 mg every two, four, or eight weeks; patients receiving ustekinumab continued ustekinumab; and patients receiving placebo were switched to brodalumab 210 mg every two weeks; maintenance continued though week 52. The primary endpoints included a comparison of both brodalumab doses vs placebo with regard to the proportion of patients achieving PASI 75 and the proportion of patients achieving PGA success (PGA 0 or 1) at week 12, as well as a comparison of brodalumab 210 mg vs ustekinumab with regard to the proportion of patients achieving PASI 100 at week 12.
  - In AMAGINE-2, the proportion of patients achieving PASI 75 was 86% (95% CI, 83 to 89), 67% (95% CI, 63 to 70), 70% (95% CI, 65 to 75), and 8% (95% CI, 5 to 12) in the brodalumab 210 mg, brodalumab 140 mg, ustekinumab, and placebo groups, respectively, and the proportion of patients achieving PGA success was 79% (95% CI, 75 to 82), 58% (95% CI, 54 to 62), 61% (95% CI, 55 to 67), and 4% (95% CI, 2 to 7), respectively (P<0.001 for all comparisons of brodalumab vs placebo). The proportion of patients achieving PASI 100 was 44% (95% CI, 41 to 49), 26% (95% CI, 22 to 29), 22% (95% CI, 17 to 27), and 1% (95% CI, 0 to 2), respectively (P<0.001 for both brodalumab doses vs placebo and for brodalumab 210 mg vs ustekinumab; P=0.08 for brodalumab 140 mg vs ustekinumab).
  - In AMAGINE-3, the proportion of patients achieving PASI 75 was 85% (95% CI, 82 to 88), 69% (95% CI, 65 to 73), 69% (95% CI, 64 to 74), and 6% (95% CI, 4 to 9) in the brodalumab 210 mg, brodalumab 140 mg, ustekinumab, and placebo groups, respectively, and the proportion of patients achieving PGA success was 80% (95% CI, 76 to 83), 60% (95% CI, 56 to 64), 57% (95% CI, 52 to 63), and 4% (95% CI, 2 to 7), respectively (P<0.001 for all comparisons of brodalumab vs placebo). The proportion of patients achieving PASI 100 was 37% (95% CI, 33 to 41), 27% (95% CI, 24 to 31), 19% (95% CI, 14 to 23), and 0.3% (95% CI, 0 to 2), respectively (P<0.001 for both brodalumab doses vs placebo and for brodalumab 210 mg vs ustekinumab; P=0.007 for brodalumab 140 mg vs ustekinumab).
  - In both studies, the two brodalumab doses were superior to placebo with regard to all key secondary endpoints. Patients receiving brodalumab 210 mg throughout the induction and maintenance phases demonstrated an increase in PASI response rates through week 12 and a stabilization during weeks 16 to 52. Based on PGA success rates, maintenance with brodalumab 210 mg or 140 mg every two weeks was superior to the use of the less frequent maintenance regimens, and the 210 mg regimen was superior to the 140 mg regimen.

- For most immunomodulators that are FDA approved for the treatment of PsO, the indication is limited to adults. In 2016, ENBREL (etanercept) received FDA approval for treatment of PsO in pediatric patients aged four years and older. Limited information from published trials is also available on the use of STELARA (ustekinumab) in adolescent patients (age 12 to 17 years).
  - A 48-week, double-blind, placebo-controlled trial (N=211) evaluated the use of etanercept in patients 4 to 17 years of age with moderate-to-severe PsO (Paller et al, 2008). Patients received etanercept 0.8 mg SQ once weekly or placebo for 12 weeks, followed by 24 weeks of open-label etanercept; 138 patients underwent a second randomization to placebo or etanercept at week 36 to investigate effects of withdrawal and

retreatment. The primary endpoint, PASI 75 at week 12, was achieved by 57% and 11% of patients receiving etanercept and placebo, respectively. A significantly higher proportion of patients in the etanercept group than in the placebo group achieved PASI 90 (27% vs 7%) and a PGA of 0 or 1 (53% vs 13%) at week 12 (P<0.001). During the withdrawal period from week 36 to week 48, response was lost by 29 of 69 patients (42%) assigned to placebo at the second randomization. Four serious AEs (including three infections) occurred in three patients during treatment with open-label etanercept; all resolved without sequelae. The authors concluded that etanercept significantly reduced disease severity in this population. Results of a 5-year, open-label extension study (N=182) demonstrated that etanercept was generally well tolerated and efficacy was maintained in those who remained in the study for up to 264 weeks (69 of 181 patients) (Paller et al, 2016).

  - A 52-week, double-blind, placebo-controlled trial (N=110) evaluated the use of ustekinumab in patients 12 to 17 years of age with moderate-to-severe PsO (Landells et al, 2015). Patients received a weight-based standard dose (SD), a half-strength dose (HSD), or placebo. The primary endpoint, the proportion of patients achieving a PGA 0 or 1 at week 12, was significantly greater in the SD (69.4%) and HSD (67.6%) groups vs placebo (5.4%) (P<0.001 for both doses vs placebo). The proportions of patients achieving PASI 75 at this time point were 80.6%, 78.4%, and 10.8% in the SD, HSD, and placebo groups, respectively (P<0.001 for both doses vs placebo), and the proportions of patients achieving PASI 90 were 61.1%, 54.1%, and 5.4% in the SD, HSD, and placebo groups, respectively (P<0.001 for both doses vs placebo). In both groups, the proportions of patients achieving these endpoints were maintained from week 12 through week 52. The authors concluded that ustekinumab appears to be a viable treatment option for moderate-to-severe PsO in the adolescent population. The standard dose provided a response comparable to that in adults with no unexpected AEs through 1 year of treatment.

- Combination therapy is commonly utilized, such as with different topical therapies, systemic plus topical therapies, and combinations of certain systemic therapies with phototherapy (Feldman, 2015). Combinations of different systemic therapies have not been adequately studied; however, there are some data to show that combined therapy with ENBREL (etanercept) plus MTX may be beneficial for therapy-resistant patients (Busard et al, 2014; Gottlieb et al, 2012).
- In a meta-analysis evaluating the efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate to severe PsO, HUMIRA (adalimumab) use was associated with a risk difference of 64% compared to placebo in achieving a PASI 75 response (P<0.00001) while ENBREL (etanercept) 25 and 50 mg twice weekly were associated with a risk difference of 30 and 44% compared to placebo (P<0.00001 for both strengths vs placebo). The REMICADE (infliximab) group had the greatest response with a risk difference of 77% compared to the placebo group (P<0.0001). The withdrawal rate was 0.5% with adalimumab, 0.4 to 0.5% with etanercept and 1.3% with infliximab (Schmitt et al, 2008).
- Another meta-analysis evaluated the efficacy and safety of long-term treatments (≥24 weeks) for moderate-to-severe PsO (Nast et al, 2015a). A total of 25 randomized trials (N=11,279) were included. Compared to placebo, RRs for achievement of PASI 75 were 13.07 (95% CI, 8.60 to 19.87) for REMICADE (infliximab), 11.97 (95% CI, 8.83 to 16.23) for COSENTYX (secukinumab), 11.39 (95% CI, 8.94 to 14.51) for STELARA (ustekinumab), 8.92 (95% CI, 6.33 to 12.57) for HUMIRA (adalimumab), 8.39 (95% CI, 6.74 to 10.45) for ENBREL (etanercept), and 5.83 (95% CI, 2.58 to 13.17) for OTEZLA (apremilast). Head-to-head studies demonstrated better efficacy for secukinumab and infliximab vs etanercept, and for infliximab vs MTX. The biologics and apremilast also had superior efficacy vs placebo for endpoints of PASI 90 and PGA 0 or 1. The investigators stated that based on available evidence, infliximab, secukinumab, and ustekinumab are the most efficacious long-term treatments, but noted that additional head-to-head comparisons and studies on safety and patient-related outcomes are desirable.

Psoriatic arthritis (PsA)

- In two trials, PsA patients receiving HUMIRA (adalimumab) 40 mg every other week achieved an ACR 20 at a higher rate than with placebo. Thirty-nine percent in the active treatment group vs 16% in the placebo group achieved this endpoint by week 12 (P=0.012) in a trial (N=100); while 58 and 14% of patients, respectively, achieved this endpoint in a second trial (P<0.001) (Genovese et al, 2007; Mease et al, 2005). Adalimumab use was also associated with an improvement in structural damage, as measured by the mTSS, compared to those receiving placebo (-0.2 vs 1; P<0.001) (Mease et al, 2005).
- In a 12-week trial in adult patients with PsA despite NSAID therapy, 87% of ENBREL (etanercept) treated patients met PsA response criteria, compared to 23% of those on placebo (P<0.0001). A PASI 75 improvement and ACR 20 response were detected in 26 and 73% of etanercept-treated patients vs 0 (P=0.0154) and 13% (P<0.0001) of placebo-treated patients (Mease et al, 2000). In a second trial, the mean annualized rate of change in the mTSS with ENBREL (etanercept) was -0.03 unit, compared to one unit with placebo (P<0.0001). At 24 weeks, 23% of etanercept

patients eligible for PsO evaluation achieved at least a PASI 75, compared to 3% of placebo patients (P=0.001). Additionally, HAQ scores were significantly improved with etanercept (54%) over placebo (6%; P<0.0001). Injection site reaction occurred at a greater rate with etanercept than placebo (36% vs 9%; P<0.001) (Mease et al, 2004).

- The FDA approval of SIMPONI (golimumab) for PsA was based on the GO-REVEAL study, a multicenter, randomized, double-blind, placebo-controlled trial in adult patients with moderate to severely active PsA despite NSAID or DMARD therapy (N=405). Golimumab with or without MTX compared to placebo with or without MTX, resulted in significant improvement in signs and symptoms as demonstrated by the percentage of patients achieving a ACR 20 response at week 14. The ACR responses observed in the golimumab-treated groups were similar in patients receiving and not receiving concomitant MTX therapy (Kavanaugh et al, 2009).
    - Subcutaneous golimumab for patients with active PsA demonstrated safety and efficacy over five years in the long-term extension of the GO-REVEAL study. Approximately one-half of patients took MTX concurrently. ACR 20 response rates at year five were 62.8 to 69.9% for golimumab SQ 50 or 100 mg every four weeks (Kavanaugh et al, 2014b).
    - Post-hoc analyses of the 5-year GO-REVEAL results evaluated the relationship between achieving minimal disease activity (MDA; defined as the presence of ≥5 of 7 PsA outcomes measures [(≤1 swollen joint, ≤1 tender joint, PASI ≤1, patient pain score ≤15, patient global disease activity score ≤20, HAQ disability index [HAQ DI] ≤0.5, and ≤1 tender enthesis point]) and long-term radiographic outcomes including radiographic progression. Among golimumab-treated patients, achieving long-term MDA was associated with better long-term functional improvement, patient global assessment, and radiographic outcomes. Radiographic benefit was more pronounced in patients using MTX at baseline. The authors conclude that in patients with active PsA, aiming for MDA as part of a treat-to-target strategy may provide long-term functional and radiographic benefits (Kavanaugh et al, 2016).
- In another trial, more REMICADE (infliximab) treated patients achieved ACR 20 at weeks 12 and 24 compared to placebo treated patients (P<0.001) (Antoni et al, 2005).
- The efficacy of CIMZIA (certolizumab) in the treatment of PsA was established in one multicenter, double-blind, placebo controlled trial (N=409). Patients were randomized to receive placebo, CIMZIA 200 mg every two weeks, or CIMZIA 400 mg every four weeks. At week 12, ACR 20 response was significantly greater in both active treatment groups compared to placebo (Mease et al, 2014).
- The FDA-approval of STELARA (ustekinumab) for PsA was based on the results of two randomized, double-blind, placebo-controlled trials in adult patients with active PsA despite NSAID or DMARD therapy (PSUMMIT 1 and PSUMMIT 2). In PSUMMIT 1 (N=615), a greater proportion of patients treated with ustekinumab 45 mg or 90 mg alone or in combination with MTX achieved ACR 20 response at week 24 compared to placebo (42.4% and 49.5% vs 22.8%; P<0.0001 for both comparisons); responses were maintained at week 52 (McInnes et al, 2013). Similar results were observed in the PSUMMIT 2 trial (N=312) with 43.8% of ustekinumab-treated patients and 20.2% of placebo-treated patients achieving an ACR 20 response (P<0.001) (Ritchlin et al, 2014).
    - In PSUMMIT-1, patients taking placebo or ustekinumab 45 mg could adjust therapy at week 16 if they had an inadequate response, and all remaining patients in the placebo group at week 24 were crossed over to receive treatment with ustekinumab 45 mg (McInnes et al, 2013). At week 100 (Kavanaugh et al, 2015a), the ACR 20 responses were 63.6%, 56.7%, and 62.7% in the 90 mg, 45 mg, and placebo crossover groups, respectively. ACR 50 and ACR 70 responses followed a similar pattern and ranged from 37.3% to 46% and 18.6% to 24.7%, respectively. At week 100, the proportions of patients achieving PASI 75 were 71.3%, 72.5%, and 63.9% in the 90 mg, 45 mg, and placebo crossover groups, respectively. Improvements in physical function and health-related quality of life (HRQoL) were sustained over time, with median decreases in HAQ-DI scores from baseline to week 100 of 0.38, 0.25, and 0.38 in the 90 mg, 45 mg, and placebo crossover groups, respectively.
- Cosentyx (secukinumab) gained FDA approval for the treatment of PsA based on two multicenter, double-blind, placebo-controlled randomized controlled trials – FUTURE 1 and FUTURE 2 (Mease et al, 2015; McInnes et al, 2015). The FUTURE 1 study randomized patients to secukinumab 75 mg or 150 mg every 4 weeks (following IV loading doses) or placebo and evaluated ACR 20 at week 24. In the FUTURE 2 study, patients were randomized to secukinumab 75 mg, 150 mg, or 300 mg SQ every 4 weeks (following SQ loading doses given at weeks 0, 1, 2, 3, and 4) or placebo and evaluated at week 24 for ACR 20 response.
    - In FUTURE 1 at week 24, both the secukinumab 75 mg and 150 mg doses demonstrated significantly higher ACR 20 responses vs placebo (50.5% and 50.0% vs 17.3%, respectively; P<0.0001 vs placebo).
    - All pre-specified endpoints including dactylitis, enthesitis, SF-36 PCS, HAQ-DI, DAS28-CRP, ACR 50, PASI 75, PASI 90, and mTSS score were achieved by week 24 and reached statistical significance.

  - In FUTURE 2 at week 24, ACR 20 response rates were significantly greater with secukinumab than with placebo: 54.0%, 51.0%, and 29.3% vs 15.3% with secukinumab 300 mg, 150 mg, and 75 mg vs placebo, respectively (P<0.0001 for secukinumab 300 mg and 150 mg; P<0.05 for 75 mg vs placebo).
  - Improvements were seen with secukinumab 300 mg and 150 mg with regard to PASI 75/90 scores, DAS28-CRP, SF-36 PCS, HAQ-DI, dactylitis, and enthesitis. Efficacy was observed in both TNF-naïve patients and in patients with prior TNF inadequate response or intolerance.
- The efficacy of OTEZLA (apremilast) was demonstrated in three placebo-controlled trials in patients with PsA. At week 16, significantly more patients in the OTEZLA groups had ≥20% improvement in symptoms, as defined by ACR response criteria (Cutolo et al, 2013; Edwards et al, 2016; Kavanaugh et al, 2014a). Clinical improvements observed at 16 weeks were sustained at 52 weeks (Edwards et al, 2016; Kavanaugh et al, 2015b).
- A small, single-center randomized trial (N=100) compared REMICADE (infliximab), ENBREL (etanercept), and HUMIRA (adalimumab) in patients with PsA who had had an inadequate response to DMARDs (Atteno et al, 2010). The investigators found that each of the agents effectively controlled the signs and symptoms of PsA, and ACR response rates were similar among agents. Patients receiving infliximab and adalimumab showed the greatest improvement in PASI scores, whereas patients receiving etanercept showed the greatest improvement on the tender joint count and HAQ. Limitations of this trial were lack of blinding and lack of a placebo group.
- A meta-analysis based on both direct and indirect comparisons evaluated the efficacy and safety of HUMIRA (adalimumab), ENBREL (etanercept), REMICADE (infliximab), and SIMPONI (golimumab) over 24 weeks for the treatment of PsA (Fénix et al, 2013). The investigators found no differences among products for the primary endpoint of ACR 50 or secondary endpoints of ACR 20 and ACR 70, except that etanercept was associated with a lower ACR 70 response. However, low sample sizes limited the power of the analysis.
- A meta-analysis of nine randomized controlled trials and six observational studies evaluated HUMIRA (adalimumab), ENBREL (etanercept), SIMPONI (golimumab), or placebo in the achievement of ACR 20, ACR 50, and ACR 70 endpoints in patients with moderate to severe PsA (Lemos et al, 2014). Patients who used adalimumab, etanercept and golimumab were more likely to achieve ACR 20 and ACR 50 after 12 or 24 weeks of treatment. In long-term analysis (after all participants used anti-TNF for at least 24 weeks), there was no difference in ACR 20 and ACR 50 between the anti-TNF and control groups, but patients originally randomized to anti-TNF were more likely to achieve ACR 70.
- Two indirect comparison meta-analyses sought to compare the efficacy of biologics for the treatment of PsA in patients with an inadequate response to prior therapies.
  - An analysis of 12 randomized trials compared various biologics in patients having an inadequate response to NSAIDs or traditional DMARDs (Ungprasert et al, 2016a). The investigators determined that patients receiving older TNF inhibitors (evaluated as a group: ENBREL [etanercept], REMICADE [infliximab], HUMIRA [adalimumab], and SIMPONI [golimumab]) had a statistically significantly higher chance of achieving ACR 20 compared to patients receiving CIMZIA (certolizumab), OTEZLA (apremilast), or STELARA (ustekinumab). Patients receiving COSENTYX (secukinumab) also had a higher chance of achieving ACR 20 compared to certolizumab, ustekinumab, and apremilast, but the relative risk did not always reach statistical significance. There was no statistically significant difference in this endpoint between secukinumab and the older TNF inhibitors, or between apremilast, ustekinumab, and certolizumab.
  - An analysis of 5 randomized trials compared various non-TNF inhibitor biologics (ORENCIA [abatacept], secukinumab, ustekinumab, and apremilast) in patients having an inadequate response or intolerance to TNF inhibitors (Ungprasert et al, 2016b). The investigators found no difference for any between-agent comparison in the likelihood of achieving an ACR 20 response.
  - These meta-analyses had limitations, notably being based on a small number of trials, and should be interpreted with caution.

Ulcerative colitis (UC)

- Two trials (ACT 1 and ACT 2) evaluated REMICADE (infliximab) compared to placebo for the treatment of UC. In both trials, clinical response at week eight was significantly higher in infliximab 5 and 10 mg/kg treated patients compared to placebo treated patients (all P<0.001). A significantly higher clinical response rate in both infliximab groups was maintained throughout the duration of the studies (Rutgeerts et al, 2005). A randomized open-label trial evaluated infliximab at different dosing intervals for the treatment of pediatric UC. At week eight, 73.3% of patients met the primary endpoint of clinical response (95% CI, 62.1 to 84.5%) (Hyams et al, 2012).
- In the ULTRA 2 study, significantly more patients taking HUMIRA (adalimumab) 160 mg at week zero, 80 mg at week two, and then 40 mg every other week for 52 weeks achieved clinical remission and clinical response vs patients taking placebo (Sandborn et al, 2012). These long term results confirm the findings of ULTRA 1. This eight-week induction trial demonstrated that adalimumab in same dosage as ULTRA 2 was effective for inducing clinical

remission (Reinisch et al, 2011). In ULTRA 1, significant differences between the adalimumab and placebo groups were only achieved for two of the secondary end points at week eight, i.e., rectal bleeding and PGA subscores. Conversely, in ULTRA 2, significantly greater proportions of adalimumab-treated patients achieved almost all secondary end points at week eight. This may have been because of the high placebo response rates in ULTRA 1. A meta-analysis of three randomized trials comparing adalimumab to placebo demonstrated that adalimumab increased the proportion of patients with clinical responses, clinical remission, mucosal healing, and inflammatory bowel disease questionnaire responses in the induction and maintenance phases. It also increased the proportion of patients with steroid-free remission in the maintenance phase (Zhang et al, 2016).

- SIMPONI (golimumab) was studied in 1,064 patients with moderate to severe UC. Patients receiving golimumab 200 mg then 100 mg or golimumab 400 mg then 200 mg at weeks zero and two were compared to patients receiving placebo. At week six, significantly greater proportions of patients in the golimumab 200/100 mg and golimumab 400/200 mg groups (51.8%, and 55%, respectively) were in clinical response than patients assigned to placebo (29.7%; P<0.0001 for both comparisons) (Sandborn et al, 2014b). In a study enrolling patients who responded in a prior study with golimumab, the proportion of patients who maintained a clinical response through week 54 was greater for patients treated with golimumab 100 mg and 50 mg compared to placebo (49.7 and 47 vs 31.2%; P<0.001 and P=0.01, respectively) (Sandborn et al, 2014a).
- The safety and efficacy of ENTYVIO (vedolizumab) was evaluated in a trial for UC in patients who responded inadequately to previous therapy. A higher percentage of ENTYVIO-treated patients achieved or maintained clinical response and remission over placebo at weeks six and 52, as measured by stool frequency, rectal bleeding, endoscopic findings, and PGA (Feagan et al, 2013). A systematic review and meta-analysis (N=606; 4 trials) demonstrated that vedolizumab was superior to placebo for clinical response (RR, 0.82; 95% CI, 0.75 to 0.91), induction of remission (RR, 0.86; 95% CI, 0.80 to 0.91), and endoscopic remission (RR, 0.82; 95% CI, 0.75 to 0.91) (Bickston et al, 2014; Mosli et al, 2015).

Uveitis (UV)

- The safety and efficacy of HUMIRA (adalimumab) were assessed in adult patients with non-infectious intermediate, posterior, and panuveitis in two randomized, double-masked, placebo-controlled studies, VISUAL I and VISUAL II.
    - VISUAL I (N=217) enrolled adults with active noninfectious intermediate UV, posterior UV, or panuveitis despite having received prednisone treatment for ≥2 weeks (Jaffe et al, 2016). Patients were randomized to adalimumab (80 mg loading dose then 40 mg every two weeks) or placebo; all patients also received a prednisone burst followed by tapering of prednisone over 15 weeks. The primary endpoint was the time to treatment failure (TTF) at or after week 6. TTF was a multicomponent outcome that was based on assessment of new inflammatory lesions, visual acuity, anterior chamber cell grade, and vitreous haze grade. The median TTF was 24 weeks in the adalimumab group and 13 weeks in the placebo group. Patients receiving adalimumab were less likely than those in the placebo group to have treatment failure (hazard ratio, 0.50; 95% CI, 0.36 to 0.70; P<0.001).
    - VISUAL II (N=226) had a similar design to VISUAL I; however, VISUAL II enrolled patients with inactive UV on corticosteroids rather than active disease (Nguyen et al, 2016a). Patients were randomized to adalimumab (80 mg loading dose then 40 mg every two weeks) or placebo; all patients tapered prednisone by week 19. TTF was significantly improved in the adalimumab group compared with the placebo group (median not estimable [>18 months] vs 8.3 months; hazard ratio, 0.57, 95% CI, 0.39 to 0.84; P=0.004). Treatment failure occurred in 61 (55%) of 111 patients in the placebo group compared with 45 (39%) of 115 patients in the adalimumab group.

CAPS, FMF, HIDS/MKD, and TRAPs

- The efficacy of KINERET (anakinra) for NOMID was evaluated in a prospective, open-label, uncontrolled study in 43 patients treated for up to 60 months. The study demonstrated improvements in all disease symptoms comprising the disease-specific Diary Symptom Sum Score (DSSS), as well as in serum markers of inflammation. A subset of patients (n=11) who went through a withdrawal phase experienced worsening of disease symptoms and inflammatory markers, which promptly responded to reinstitution of treatment (KINERET prescribing information, 2016). A cohort study of 26 patients followed for three to five years demonstrated sustained improvement in disease activity and inflammatory markers (Sibley et al, 2012).
- The efficacy and safety of ILARIS (canakinumab) has been evaluated for the treatment of CAPS, TRAPS, HIDS/MKD, and FMF.
    - Efficacy and safety in CAPS were evaluated in a trial in patients aged 9 to 74 years with the MWS phenotype and in a trial in patients aged 4 to 74 years with both MWS and FCAS phenotypes. Most of the trial periods were open-label. Trials demonstrated improvements based on physician's assessments of disease activity and assessments of skin disease, CRP, and serum amyloid A (ILARIS prescribing information, 2016).

Published data supports the use of canakinumab for these various CAPS phenotypes (Koné-Paut et al, 2011; Kuemmerle-Deschner et al, 2011; Lachmann et al, 2009).

- Efficacy and safety in TRAPS, HIDS/MKD, and FMF were evaluated in a study in which patients having a disease flare during a screening period were randomized into a 16-week double-blind, placebo-controlled period. For the primary efficacy endpoint, canakinumab was superior to placebo in the proportion of TRAPS, HIDS/MKD, and FMF patients who resolved their index disease flare at day 15 and had no new flare for the duration of the double-blind period. Resolution of the flare was defined as a PGA score <2 (minimal or no disease) and CRP within normal range (or reduction ≥70% from baseline) (ILARIS prescribing information, 2016).

Treatment Guidelines

- RA:
  - In patients with moderate or high disease activity despite DMARD monotherapy, the ACR recommends the use of combination DMARDs, a TNF inhibitor, or a non-TNF inhibitor biologic (tocilizumab, abatacept, or rituximab); tofacitinib is another option in patients with established RA. If disease activity remains moderate or high despite use of a TNF inhibitor, a non-TNF biologic is recommended over another TNF inhibitor or tofacitinib (Singh et al, 2016c).
  - EULAR guidelines are similar to ACR guidelines. These guidelines state that if the treatment target is not reached with a conventional DMARD strategy in a patient with poor prognostic factors, addition of a biologic DMARD or a targeted synthetic DMARD (eg, tofacitinib) should be considered, with current practice being a biologic DMARD. Biologic and targeted synthetic DMARDs should be combined with a conventional DMARD, but in patients who cannot use a conventional DMARD concomitantly, a targeted synthetic DMARD or an IL-6 inhibitor (eg, tocilizumab) may have some advantages compared with other biologic DMARDs. The guideline notes that if a TNF inhibitor has failed, patients may receive another TNF inhibitor or an agent with another mode of action. An effective biologic should not be switched to another biologic for non-medical reasons (Smolen et al, 2017).
  - The ACR released a position statement on biosimilars, which stated that the decision to substitute a biosimilar product for a reference drug should only be made by the prescriber. The ACR does not endorse switching stable patients to a different medication (including a biosimilar) of the same class for cost saving reasons without advance consent from the prescriber and knowledge of the patient (ACR, 2016).
  - EULAR has released guidelines for use of antirheumatic drugs in pregnancy, which state that etanercept and certolizumab are among possible treatment options for patients requiring therapy (Götestam Skorpen et al, 2016).
- JIA:
  - bwohl etican College of Rheumatology (ACR) published recommendations for the treatment of JIA in 2011, followed by an update in 2013 focusing on the management of SJIA (and tuberculosis screening) (Beukelman et al, 2011; Ringold et al, 2013).
    - According to the 2011 guideline, recommendations for JIA treatment vary based on factors such as disease characteristics and activity, current medication, and prognostic features. For patients with a history of arthritis in ≥5 joints (which includes extended oligoarthritis, polyarthritis, and some related subtypes), a TNF inhibitor is generally recommended in patients with continued disease activity after receiving an adequate trial of a conventional DMARD. In patients with a history of ≥5 affected joints failing a TNF inhibitor, treatment approaches may include switching to a different TNF inhibitor or abatacept (Beukelman et al, 2011).
    - According to the 2013 update, the inflammatory process in SJIA is likely different from that of other JIA categories, with IL-1 and IL-6 playing a central role. In patients with SJIA and active systemic features, recommendations vary based on the active joint count and the physician global assessment. Anakinra is one of the recommended first-line therapies; canakinumab, tocilizumab, and TNF-inhibitors are among the second-line therapies. In patients with SJIA and no active systemic features, treatments vary based on the active joint count. Abatacept, anakinra, tocilizumab, and TNF inhibitors are among the second-line treatments for these patients (Ringold et al, 2013).
- UC:
  - For the treatment of UC, sulfasalazine is recommended by the American College of Gastroenterology (ACG) as first-line treatment of active disease. Balsalazide, mesalamine, olsalazine and sulfasalazine are recommended for maintenance of remission and reduction of relapses. If these therapies fail, infliximab should be considered (Kornbluth et al, 2010). Note that other immunomodulators were not indicated for UC when these guidelines were written; an update is currently in process.

- CD:
  - The ACG states that the anti-TNF monoclonal antibodies adalimumab, certolizumab, and infliximab are effective in the treatment of moderate to severely active CD in patients who have not responded despite complete and adequate therapy with a corticosteroid or an immunosuppressive agent. These TNF inhibitors may also be used as alternatives to steroid therapy in selected patients in whom corticosteroids are contraindicated or not desired. Maintenance therapy with TNF inhibitors is effective. An update to these guidelines is currently in process (Lichtenstein et al, 2009).
  - The American Gastroenterological Association (AGA) recommends using anti-TNF drugs to induce remission in patients with moderately severe CD (Terdiman et al, 2013). The AGA supports the use of TNF inhibitors and/or thiopurines as pharmacologic prophylaxis in patients with surgically-induced CD remission (Nguyen et al, 2017).
  - An AGA Institute clinical decision tool for CD notes the importance of controlling both symptoms and the underlying inflammation, and makes recommendations for treatments (budesonide, azathioprine, 6-mercaptopurine, prednisone, MTX, a TNF inhibitor, or certain combinations) based on the patient's risk level (Sandborn, 2014).
  - The European Crohn's and Colitis Organisation (ECCO) recommends TNF inhibitors for patients with CD who have relapsed or are refractory to corticosteroids, depending on disease location and severity, and states that early TNF inhibitor therapy should be initiated in patients with high disease activity and features indicating a poor prognosis. Furthermore, the ECCO guideline states that all currently available TNF inhibitors seem to have similar efficacy in luminal CD and similar AE profiles; therefore the choice depends on availability, route of administration, patient preference, and cost. Vedolizumab is noted to be an appropriate alternative to TNF inhibitors for some patients (Gomollón et al, 2017).
- Pregnancy in inflammatory bowel disease:
  - Consensus statements for the management of inflammatory bowel disease in pregnancy, coordinated by the Canadian Association of Gastroenterology, state that TNF inhibitor treatment does not appear to be associated with unfavorable pregnancy outcomes and should generally be continued during pregnancy. Because of the low risk of transfer across the placenta, certolizumab may be preferred in women who initiate TNF inhibitor therapy during pregnancy (Nguyen et al, 2016b).
- PsO and PsA:
  - Consensus guidelines from the National Psoriasis Foundation Medical Board state that treatment of PsO includes topical agents; oral therapies such as acitretin, cyclosporine, and MTX; and biologic therapies (Hsu et al, 2012).
  - Guidelines from the American Academy of Dermatology state that for the management of PsO, topical agents including corticosteroids are used adjunctively to either ultraviolet light or systemic medications for resistant lesions in patients with more severe disease (Gottleib et al, 2008; Menter et al, 2008; Menter et al, 2009a; Menter et al, 2009b; Menter et al, 2010; Menter et al, 2011). Biologic agents are routinely used when one or more traditional systemic agents are not tolerated, fail to produce an adequate response, or are unable to be used due to patient comorbidities. First-line agents for PsO (>5% BSA) with concurrent PsA include adalimumab, etanercept, golimumab, infliximab, MTX, or a combination of a TNF blocker and MTX.
  - Guidelines for PsO from the European Dermatology Forum, European Association for Dermatology and Venereology, and International Psoriasis Council (European S3 guidelines) state that adalimumab, etanercept, infliximab, and ustekinumab are recommended as second-line medications for induction and long-term treatment if phototherapy and conventional systemic agents were inadequate, contraindicated, or not tolerated (Nast et al, 2015b). In patients with PsA and active joint involvement despite use of NSAIDs and a potential poor prognosis due to polyarthritis, increased inflammatory markers and erosive changes, it is recommended to start synthetic DMARDs early to prevent progression of disease and erosive joint destruction. For inadequately responding patients with PsA after at least one synthetic DMARD, biologic DMARDS are recommended in combination with synthetic DMARDs or as monotherapy.
  - The American Academy of Dermatology recommends that moderate to severe PsA that is more extensive or aggressive in nature or that significantly impacts quality of life should be treated with MTX, TNF-blockers, or both (Gottleib et al, 2008; Menter et al, 2009b; Menter et al, 2011).
  - EULAR 2015 PsA guidelines recommend TNF inhibitors in patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD, such as MTX. For patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD, in whom a TNF inhibitor is not appropriate, biologics targeting IL-12/23 or IL-17 pathways may be considered. Apremilast is considered a treatment option in patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD, in whom biologics are not appropriate (Gossec et al, 2016; Ramiro et al, 2016).

- The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommendations for PsA vary based on whether the arthritis is peripheral or axial and based on prior therapies, and may include DMARDS, NSAIDs, simple analgesics, a TNF inhibitor, an IL-12/23 inhibitor, or a PDE-4 inhibitor (Coates et al, 2016).

- AS:
  - Joint recommendations for the management of axial spondyloarthritis are available from ASAS and EULAR. (Ankylosing spondylitis [AS] is synonymous with radiographic axial spondyloarthritis; these guidelines also include non-radiographic axial spondyloarthritis). The guidelines state that NSAIDs should be used first-line in patients with pain and stiffness; other analgesics might be considered if NSAIDs have failed or are contraindicated or poorly tolerated. Glucocorticoid injections may be considered but patients with axial disease should not receive long-term systemic glucocorticoids. Sulfasalazine may be considered in patients with peripheral arthritis, but patients with purely axial disease should normally not be treated with conventional DMARDs. Biologic DMARDs should be considered in patients with persistently high disease activity despite conventional treatments, and current practice is to start with a TNF inhibitor. If a TNF inhibitor fails, switching to another TNF inhibitor or to an IL-17 inhibitor should be considered (van der Heijde et al, 2017).
  - The 2015 ACR, Spondylitis Association of America, and Spondyloarthritis Research and Treatment Network guidelines strongly recommend TNF inhibitors for patients who have active disease despite NSAIDs. No particular TNF inhibitor is preferred over another, except in patients with concomitant inflammatory bowel disease or recurrent iritis, in whom infliximab or adalimumab would be preferred over etanercept (Ward et al, 2016).
- Ocular inflammatory disorders:
  - Expert panel recommendations for the use of TNF inhibitors in patients with ocular inflammatory disorders are available from the American Uveitis Society (Levy-Clarke et al, 2014). Infliximab and adalimumab can be considered as first-line immunomodulatory agents for the treatment of ocular manifestations of Behçet's disease and as second-line immunomodulatory agents for the treatment of UV associated with juvenile arthritis. They also can be considered as potential second-line immunomodulatory agents for the treatment of severe ocular inflammatory conditions including posterior UV, panuveitis, severe UV associated with seronegative spondyloarthropathy, and selected patients with scleritis. Etanercept seems to be associated with lower rates of treatment success in these conditions.
- Additional indications:
  - Based upon guidelines from the European Dermatology Forum, adalimumab is recommended among first-line therapies for HS, and infliximab may be considered a second-line option (Gulliver et al, 2016; Zouboulis et al, 2015).
  - For the treatment of FMF, EULAR recommendations state that treatment with colchicine should begin as soon as FMF is diagnosed. Biologic treatment, such as anti-IL-1 therapy, is indicated in patients not responding to the maximum tolerated dose of colchicine. TNF inhibitors have also been used in colchicine-resistant patients, with good responses seen in observational studies (Ozen et al, 2016).
  - No recent guidelines were identified for CAPS, HIDS/MKD, or TRAPS.

SAFETY SUMMARY

- Contraindications:
  - ACTEMRA (tocilizumab), COSENTYX (secukinumab), ENTYVIO (vedolizumab), ILARIS (canakinumab), INFLECTRA (infliximab-dyyb), KINERET (anakinra), OTEZLA (apremilast), REMICADE (infliximab), STELARA (ustekinumab), and TALTZ (ixekixumab) use in patients with hypersensitivity to any component of the product.
  - SILIQ is contraindicated in patients with Crohn's disease because SILIQ may cause worsening of disease.
  - ENBREL (etanercept) in patients with sepsis.
  - KINERET (anakinra) in patients with hypersensitivity to *E coli*-derived proteins.
  - REMICADE (infliximab) and INFLECTRA (infliximab-dyyb) in patients with hypersensitivity to murine proteins; and doses >5 mg/kg in patients with moderate to severe heart failure.
- Boxed Warnings:
  - ACTEMRA (tocilizumab), CIMZIA (certolizumab), ENBREL (etanercept), HUMIRA (adalimumab), INFLECTRA (infliximab-dyyb), REMICADE (infliximab), SIMPONI / SIMPONI ARIA (golimumab), and XELJANZ / XELJANZ XR (tofacitinib) all have warnings for serious infections such as active tuberculosis, which may present with pulmonary or extrapulmonary disease; invasive fungal infections; and bacterial, viral, and other infections due to opportunistic pathogens.

  - In addition, CIMZIA (certolizumab), ENBREL (etanercept), HUMIRA (adalimumab), INFLECTRA (infliximab-dyyb), REMICADE (infliximab), SIMPONI / SIMPONI ARIA (golimumab), and XELJANZ (tofacitinib) all have warnings for increased risk of malignancies.
  - RITUXAN (rituximab) can cause fatal infusion reactions, hepatitis B activation, severe mucocutaneous reactions, and progressive multifocal leukoencephalopathy (PML).
  - SILIQ has a boxed warning that suicidal ideation and behavior, including completed suicides, have occurred in patients treated with SILIQ. The prescriber should weigh potential risks and benefits in patients with a history of depression and/or suicidal ideation or behavior, and patients should seek medical attention if these conditions arise or worsen during treatment.
- Warnings/Precautions (applying to some or all of the agents in the class):
  - Reactivation of HBV or other viral infections
  - Serious infections including tuberculosis
  - New onset or exacerbation of central nervous system demyelinating disease and peripheral demyelinating disease
  - Pancytopenia
  - Worsening and new onset congestive heart failure
  - Hypersensitivity reactions
  - Lupus-like syndrome
  - Increased lipid parameters and liver function tests with XELJANZ / XELJANZ XR (tofacitinib)
  - Increased incidence of CD and UC with COSENTYX (secukinumab) and TALTZ (ixekixumab); risk of new-onset CD or exacerbation of CD with SILIQ (brodalumab)
  - Consult prescribing information for other drug-specific warnings/precautions
- Adverse Reactions:
  - Infusion site reactions, diarrhea, nausea/vomiting, abdominal pain, infections, hypertension and headache.
  - Consult prescribing information for other drug-specific AEs
- Risks of Long-Term Treatment: As it becomes accepted practice to treat patients with these conditions for long-term, it is imperative to assess the long-term safety of these products. Because these agents suppress the immune system, serious infections and malignancies are a concern. Several long-term efficacy and safety studies support several agents in this class. The extension studies were performed in an open-label manner and were subject to attrition bias.
  - Rheumatoid Arthritis
    - Safety of adalimumab for RA has been supported in a five-year study in RA and a 10-year study in patients with early RA (Keystone et al, 2014a; Burmester et al, 2014b). In the five-year extension study, overall rates of serious AEs and serious infections were 13.8 events per 100 patient-years and 2.8 events per 100 patient-years, respectively. The rate of serious events was highest in the first six months and then declined. No new safety signals were reported in the 10-year study.
    - Certolizumab plus MTX had a consistent safety profile over five years in patients with RA (Keystone et al, 2014b). The most frequently reported AEs included urinary tract infections (rate of 7.9 per 100 patient-years), nasopharyngitis (rate of 7.3 per 100 patient-years), and upper respiratory infections (rate of 7.3 per 100 patient-years). Serious AE rates were 5.9 events per 100 patient-years for serious infections and 1.2 events per 100 patient-years for malignancies.
    - Abatacept has been evaluated in two long-term extension studies. Abatacept IV plus MTX demonstrated a similar safety profile between the seven year follow-up and a 52-week double-blind study (Westhovens et al, 2014). Serious AEs reported in both the double-blind and long-term follow-up studies were the following: serious infections (17.6 events per 100 patient-years), malignancies (3.2 events per100 patient-years), and autoimmune events (1.2 events per 100 patient-years). In a five-year extension trial, rates of serious infections, malignancies, and autoimmune events were 2.8, 1.5, and 0.99 events per 100 patient-years exposure, respectively. Efficacy was demonstrated by ACR 20 with response rates of 82.3% and 83.6% of patients at year one and year five, respectively.
    - Data from five RCTs of ACTEMRA (tocilizumab), their open-label extension trials, and a drug interaction study were analyzed for measures of safety. A total of 4,009 patients with moderate to severe RA received at least one dose of tocilizumab. Mean duration of tocilizumab treatment was 3.07 years (up to 4.6 years); total duration of observation was 12,293 patient-years (PY). The most common AEs and serious AEs were infections. A longer-term safety profile from this analysis matches previous observations. No new safety signals were identified (Genovese et al, 2013).
    - A Cochrane review showed no evidence of a statistically significant difference in the rate of withdrawal because of AEs in the ENBREL (etanercept) plus DMARD group and the DMARD alone group at six months, 12 months, and two years. At three years, withdrawals were significantly reduced in the

etanercept 25 mg plus DMARD group compared with the DMARD alone group (RR, 0.7; 95% CI, 0.5 to 1). There was no evidence of statistically significant differences in the rates of breast cancer at 12 months, fever at six months, flu-like syndrome at six months and two years, infection at six months and two years, malignancy at 12 months and two years, pneumonia at 12 months, and serious infection at 12 months and two years between the etanercept plus DMARD group and the DMARD group (Lethaby et al, 2013).

- A systematic review analyzed 66 randomized controlled trials and 22 long-term extension studies evaluating biologics and tofacitinib for the rate of serious infections in patients with moderate to severe active RA (Strand et al, 2015b). The estimated incidence rates (unique patients with events/100 patient-years) of serious infections were 3.04 (95% CI, 2.49 to 3.72) for abatacept, 3.72 (95% CI, 2.99 to 4.62) for rituximab, 5.45 (95% CI, 4.26 to 6.96) for tocilizumab, 4.90 (95% CI, 4.41 to 5.44) for TNF inhibitors, and 3.02 (95% CI, 2.25 to 4.05) for tofacitinib 5 mg and 3.00 (95% CI, 2.24 to 4.02) for tofacitinib 10 mg. Authors concluded that the rates of serious infections with tofacitinib in RA patients are within the range of those reported for biologic DMARDs.

o PsO

- A total of 3,117 patients treated with at least one dose of STELARA (ustekinumab) for moderate to severe PsO were evaluated for long-term safety. At least four years of ustekinumab exposure was seen in 1,482 patients (including 838 patients with greater than or equal to five years of exposure). The most commonly reported AEs were nasopharyngitis, upper respiratory tract infection, headache and arthralgia. Infections, malignancies and cardiac disorders were the most commonly reported serious AEs. Twenty deaths were reported through year five. The causes of death were considered related to cardiovascular events (n=5), malignancy (n=5), infection (n=3) and other causes (n=7). The observed mortality rate among ustekinumab-treated patients was consistent with that expected in the general U.S. population (SMR = 0.36; 95% CI, 0.22 to 0.55). From year one to year five, rates of overall AEs, and AEs leading to discontinuation generally decreased. Serious AE rates demonstrated year-to-year variability with no increasing trend. The results of this long-term study of AEs are similar to reports of shorter-term studies (Papp et al, 2013).
- In a five-year extension study, a total of 2,510 patients on etanercept for the treatment of PsO were evaluated for long-term safety and efficacy (Kimball et al, 2015). Serious AEs were reported as a cumulative incidence of the entire five-year observation period. The following incidences were reported: serious infections (6.5%, 95% CI, 5.4 to 7.7%); malignancies excluding nonmelanoma skin cancer (3.2%, 95% CI, 2.3 to 4.1%); nonmelanoma skin cancer (3.6%, 95% CI, 2.7 to 4.1%); coronary artery disease (2.8%, 95% CI, 2 to 3.6%); PsO worsening (0.7%, 95% CI, 0.3 to 1.2%); CNS demyelinating disorder (0.2%, 95%CI, 0 to 0.4%); lymphoma and tuberculosis each (0.1%, 95% CI, 0 to 0.3%); and opportunistic infection and lupus each (0.1%, 95%CI, 0 to 0.2%). A total of 51% of patients reported clear/almost clear rating at month six and remained stable through five years.
- A multicenter registry called Psoriasis Longitudinal Assessment and Registry (PSOLAR) evaluated the risk of serious infections in patients with PsO (Kalb et al, 2015). Patients were followed for up to eight years with a total of 11,466 patients with PsO enrolled, 74.3% of whom were from the U.S. A total of 22,311 patient-years of data were collected. Ustekinumab, infliximab, adalimumab, and etanercept as well as traditional DMARDs were included in the data analysis. During the follow-up period, 323 serious infections were reported. The rates of serious infections per 100 patient-years were 0.83 (secukinumab), 1.47 (etanercept), 1.97 (adalimumab), and 2.49 (infliximab). The most commonly reported serious infection was cellulitis. Risk factors for serious infections were increasing age, diabetes mellitus, smoking, and history of significant infections prior to registry entry. Exposure to infliximab (hazard ratio, 2.51; 95% CI, 1.45 to 4.33; P<0.001) and adalimumab (hazard ratio, 2.13; 95% CI, 1.33 to 3.41; P=0.002) during the registry were independently associated with the risk of serious infections whereas use of ustekinumab or etanercept were not.

o PsA

- Subcutaneous golimumab for patients with active PsA demonstrated safety and efficacy over five years in the long-term extension of the randomized, placebo-controlled GO-REVEAL study (Kavanaugh et al, 2014b). Approximately one-half of patients also took MTX concurrently. No new safety signals were observed.

o Multiple indications

- One study looked at 23,458 patients who were treated with HUMIRA (adalimumab) for RA, JIA, AS, PsA, PsO and CD. Patients received adalimumab for up to 12 years. No new safety signals were observed from this analysis. Rates of malignancies and infections were similar to the general

population and also similar to rates reported in other shorter-term trials for anti-TNF therapies (Burmester et al, 2013b).
    - Pooled data from five Phase 3 trials of SQ golimumab over at least three years demonstrated a safety profile consistent with other TNF inhibitors (Kay et al, 2015). A total of 1,179 patients with RA, PsA or AS were treated for at least 156 weeks. Rates of AEs up to week 160 for placebo, golimumab 50 mg and golimumab 100 mg, respectively, were as follows: 0.28, 0.30, 0.41 for death; 5.31, 3.03, 5.09 for serious infection; 0, 0.17, 0.35 for tuberculosis; 0, 0.13, 0.24 for opportunistic infection; 0, 0, 0.12 for demyelination; and 0, 0.04, 0.18 for lymphoma.
    - A total of 18 multicenter, placebo-controlled, randomized controlled trials evaluated the safety profile of certolizumab pegol monotherapy or in combination with DMARDs in RA, CD, AS, PsA and PsO (Capogrosso Sansone et al, 2015). All but one trial was conducted in a double-blind manner. The overall pooled risk ratios for all doses of certolizumab pegol were reported as follows: AEs (defined as AE reported but not evaluated for causality) 1.09 (95% CI, 1.04 to 1.14), serious AEs 1.50 (95% CI, 1.21 to 1.86), ADRs (defined as an AE possibly related to drug treatment by investigators) 1.20 (95% CI, 1.13 to 1.45), infectious AEs 1.28 (95% CI, 1.13 to 1.45), infectious serious AEs 2.17 (95% CI, 1.36 to 3.47), upper respiratory tract infections 1.34 (95% CI, 1.15 to 1.57), neoplasms 1.04 (95% CI, 0.49 to 2.22), and tuberculosis 2.47 (95% CI, 0.64 to 9.56). Rare AEs may not have been captured by the studies due to limiting the reporting of most AEs to those occurring in > 3 to 5%.
    - Several recent meta-analyses evaluated the safety of TNF inhibitors.
        - An analysis of TNF inhibitors in RA, PsA, and AS included data from 71 randomized trials (follow-up one to 36 months) and seven open-label extension studies (follow-up six to 48 months) (Minozzi et al, 2016). The data demonstrated that use of TNF inhibitors increases the risk of infectious AEs. Overall, there was a 20% increase of any infections, a 40% increase of serious infections, and a 250% increase of tuberculosis. The tuberculosis incidence rate was higher with infliximab and adalimumab compared to etanercept. There was little data on the incidence of opportunistic infections.
        - An analysis of TNF inhibitors in RA, PsA, and AS included data from 32 randomized trials (follow-up two to 36 months) and six open-label extension trials (follow-up six to 48 months) (Bonovas et al, 2016). Synthesis of the data did not demonstrate that the use of TNF inhibitors significantly affects cancer risk during this length of treatment. However, few malignancy events were observed and evidence may be insufficient to make definitive conclusions, particularly regarding longer-term risks.

- Drug interactions
    - Do not give with live (including attenuated) vaccines; additionally, non-live vaccines may not elicit a sufficient immune response.
    - Do not give two immunomodulators together.
    - For XELJANZ / XELJANZ XR (tofacitinib), do not give with potent inhibitors of cytochrome P450 (CYP) 3A4; medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19; potent CYP3A4 inducers; and potent immunosuppressive drugs.
- Risk Evaluation and Mitigation Strategy (REMS)
    - STELARA (ustekinumab) has a REMS program in place, which consists of a communication plan regarding potential risk of serious infections, malignancy, and reversible posterior leukoencephalopathy syndrome (RPLS).
    - SILIQ (brodalumab) is available only through the SILIQ REMS program. The goal of the program is to mitigate the risk of suicidal ideation and behavior, including completed suicides, which occurred in clinical trials. Key requirements of the REMS program include:
        - Prescribers must be certified with the program.
        - Patients must sign a patient-prescriber agreement form.
        - Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive the product.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
ACTEMRA (tocilizumab)	Vials: 80 mg/4 mL; 200 mg/10 mL; 400 mg/20 mL Prefilled syringe: 162 mg/0.9 mL	**RA:** 4 mg/kg IV every 4 weeks. May increase to 8 mg/kg IV every 4 weeks. Maximum dose=800 mg. SQ: <100 kg, administer 162 mg SQ every other week, followed by an increase to every week based on clinical response. >100 kg, 162 mg administered SQ every week. **PJIA:** <30 kg, 10 mg/kg IV every 4 weeks; ≥30 kg, 8 mg/kg IV every 4 weeks. **SJIA:** <30 kg, 12 mg/kg IV every 2 weeks; ≥30 kg, 8 mg/kg IV every 2 weeks.	**RA:** Can give with MTX or other DMARDs. **PJIA and SJIA:** Can give with MTX. Adjust dose for liver enzyme abnormalities, low platelet count and low ANC.	Give as a single 60-minute intravenous infusion. <30 kg, use a 50 mL infusion bag. ≥30 kg, use a 100 mL infusion bag. Before infusion, allow bag to come to room temperature. Do not administer with other drugs. Patients can self-inject with the prefilled syringe.
CIMZIA (certolizumab)	Powder for reconstitution: 200 mg Prefilled syringe: 200 mg/mL	**CD:** 400 mg SQ initially and at weeks 2 and 4. Maintenance dose is 400 mg every 4 weeks. **RA, PsO:** 400 mg SQ initially and at weeks 2 and 4. Then 200 mg every 2 weeks. Can consider a maintenance dose of 400 mg every 4 weeks. **AS:** 400 mg SQ initially and at weeks 2 and 4. Maintenance dose is 200 mg every 2 weeks or 400 mg every 4 weeks.	Patients can self-inject with the prefilled syringe.	When a 400 mg dose is required, give as two 200 mg SQ injections in separate sites in the thigh or abdomen.
COSENTYX (secukinumab)	Sensoready pen: 150 mg/1 mL Prefilled syringe: 150 mg/1 mL Vial: 150 mg lyophilized powder	**PsO:** 300 mg by SQ injection at weeks 0, 1, 2, 3 and 4, followed by 300 mg every 4 weeks **PsA, AS:** With a loading dose (not required): 150 mg at weeks 0, 1, 2, 3, and 4, followed by 150 mg every 4 weeks; without loading dose: 150 mg	**PsO:** For some patients, a dose of 150 mg may be acceptable. **PsA:** For PsA patients with coexistent moderate to severe PsO, dosing for PsO	Each 300 mg dose is given as two subcutaneous injections of 150 mg. Patients may self-administer with the pen or prefilled syringe. The vial is for healthcare professional use only.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		every 4 weeks	should be followed. If active PsA continues, consider 300 mg dose.	
ENBREL (etanercept)	Prefilled syringe: 25 mg and 50 mg Prefilled SureClick autoinjector: 50 mg Multiple-use vial: 25 mg	**RA, AS, PsA:** 50 mg SQ weekly **PsO (adults):** 50 mg SQ twice weekly for three months, then 50 mg weekly **PJIA and PsO (pediatrics):** ≥63 kg, 50 mg SQ weekly; <63 kg, 0.8 mg/kg SQ weekly	**RA, AS, PsA:** MTX, NSAIDs, glucocorticoids, salicylates, or analgesics may be continued **JIA:** NSAIDs glucocorticoids, or analgesics may be continued	Patients may be taught to self-inject. May bring to room temperature prior to injecting.
ENTYVIO (vedolizumab)	Lyophilized cake for injection in single dose 20 mL vials: 300 mg	**CD and UC:** 300 mg administered by intravenous infusion at time zero, two and six weeks, and then every eight weeks thereafter. Discontinue therapy if there is no evidence of therapeutic benefit by week 14.	All immunizations should be to date according to current guidelines prior to initial dose.	ENTYVIO should be reconstituted at room temperature and prepared by a trained medical professional. It should be used as soon as possible after reconstitution and dilution.
HUMIRA (adalimumab)	Prefilled syringe: 10 mg/0.2 mL 20 mg/0.4 mL 40 mg/0.4 mL 40 mg/0.8 mL Single-use pen: 40 mg/0.8 mL Single-use vial: 40 mg/0.8 mL	**RA, AS, PsA**: 40 mg SQ every other week. For RA, may increase to 40 mg every week if not on MTX. **PJIA:** 10 kg to <15 kg: 10 mg SQ every other week; 15 kg to <30 kg: 20 mg SQ every other week; ≥30 kg, 40 mg SQ every other week **CD, HS and UC:** 160 mg SQ on Day 1 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), followed by 80 mg SQ two weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose of 40 mg SQ every other week. **PsO and UV:** initial	**RA, AS, PsA:** MTX, other non-biologic DMARDS, glucocorticoids, NSAIDs, and/or analgesics may be continued. **JIA:** NSAIDs, MTX, analgesics, and/or glucocorticoids, may be continued. **CD and UC:** aminosalicylates and/or corticosteroids may be continued. Azathioprine, 6-MP or MTX may be continued if necessary. Needle cover of the syringe contains dry rubber (latex).	Patients may be taught to self-inject. Injections should occur at separate sites in the thigh or abdomen. Rotate injection sites.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		dose of 80 mg SQ, followed by 40 mg SQ every other week starting one week after the initial dose. **CD in pediatric patients ≥6 years and older:** 17 kg to <40 kg: 80 mg on day 1 (given as two 40 mg injections) and 40 mg two weeks later (on day 15); maintenance dose is 20 mg every other week starting at week 4. ≥40 kg: 160 mg on day (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days) and 80 mg two weeks later (on day 150); maintenance dose is 40 mg every other week starting at week 4.		
ILARIS (canakinumab)	Vial: 150 mg (lyophilized powder and injection solution formulations)	**SJIA:** ≥7.5 kg, 4 mg/kg SQ every 4 weeks (maximum dose of 300 mg). **CAPS**: ≥15 to ≤40 kg, 2 mg/kg SQ; >40 kg, 150 mg SQ; frequency every 8 weeks **TRAPS, HIDS/MKD, and FMF**: ≤40 kg, 2 mg/kg SQ; >40 kg, 150 mg SQ; frequency every 4 weeks	For CAPS: children 15 to 40 kg with an inadequate response can be increased to 3 mg/kg For TRAPS, HIDS/MKD, and FMF: If the clinical response is inadequate, the dose may be increased to 4 mg/kg (weight ≤40 kg) or 300 mg (weight >40 kg)	Do not inject into scar tissue.
INFLECTRA (infliximab-dyyb)	Vial: 100 mg	**CD (≥6 years old), PsA, PsO and UC**: 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. In adults with CD who lose response, can increase dose to 10	**RA:** give with MTX **CD:** If no response by week 14, consider discontinuation.	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		mg/kg. **RA:** 3 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg or give every 4 weeks. **AS:** 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks.		Infuse over 2 hours. Do not administer with other drugs.
KINERET (anakinra)	Prefilled syringe: 100 mg/0.67 mL	**RA:** 100 mg SQ once daily. **CAPS (NOMID):** 1 to 2 mg/kg SQ once daily. Maximum dose is 8 mg/kg/day.	**NOMID**: dose can be given once or twice daily.	Patients may be taught to self-inject. A new syringe must be used for each dose.
ORENCIA (abatacept)	Vial: 250 mg Prefilled syringe: 125 mg/1 mL ClickJect autoinjector: 125 mg/mL	**RA:** <60kg, 500 mg IV; 60 to 100 kg, 750 mg IV; >100 kg, 1,000 mg IV initially, then 2 and 4 weeks after the first infusion and every 4 weeks thereafter SQ: 125 mg SQ once weekly initiated with or without an IV loading dose. With IV loading dose, use single IV infusion as per body weight listed above, followed by the first 125 mg SQ injection within a day of the IV infusion and then once weekly. **PJIA:** 6 to 17 years and <75 kg: 10 mg/kg IV initially, then 2 and 4 weeks after the first infusion and every 4 weeks thereafter. >75 kg, follow adult RA IV schedule; maximum dose = 1,000 kg.		IV infusion should be over 30 minutes. Use 100 mL bag for IV infusion. Do not administer with other drugs. Patients may be taught to self-inject the SQ dose. For SQ, injection sites should be rotated.
OTEZLA (apremilast)	Tablet: 10 mg, 20 mg, and 30 mg	**PsA, PsO:** Day 1: 10 mg in the morning Day 2: 10 mg in the morning and in the evening Day 3: 10 mg in the	Titrate according to the labeling when initiating therapy to reduce gastrointestinal symptoms.	May be taken with or without food. Do not crush, split, or chew the tablets.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		morning and 20 mg in evening Day 4: 20 mg in the morning and evening Day 5: 20 mg in the morning and 30 mg in the evening Day 6 and thereafter: 30 mg twice daily	Dosage should be reduced to 30 mg once daily in patients with severe renal impairment (CrCl <30 mL/min as estimated by the Cockcroft-Gault equation). For initial dosing in these patients, use only the morning titration schedule listed above (evening doses should be excluded).	
REMICADE (infliximab)	Vial: 100 mg	**CD (≥6 years old), PsA, PsO and UC (≥6 years old)**: 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. In adults with CD who lose response, can increase dose to 10 mg/kg. **RA:** 3 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg or give every 4 weeks. **AS:** 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks.	**RA:** give with MTX **CD:** If no response by week 14, consider discontinuation.	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion. Infuse over 2 hours. Do not administer with other drugs.
RITUXAN (rituximab)	Vial: 100 mg 500 mg	**RA:** 1,000 mg IV every 2 weeks times two doses. Additional doses should be given every 24 weeks or based on clinical evaluation but no sooner than 16 weeks.	Give with MTX.	Give methyl-prednisolone 100 mg IV 30 minutes prior to each infusion to reduce the incidence and severity of infusion reactions.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
SILIQ (brodalumab)	Prefilled syringe: 210 mg/1.5 mL	**PsO:** 210 mg SQ at weeks 0, 1, and 2 followed by every 2 weeks	**PsO**: If an adequate response has not been achieved after 12 to 16 weeks, consider discontinuation	Patients may self-inject when appropriate and after proper training. The syringe should be allowed to reach room temperature before injecting.
SIMPONI/ SIMPONI ARIA (golimumab)	SmartJect® autoinjector: 50 mg and 100 mg Prefilled syringe: 50 mg and 100 mg ARIA, Vial: 50 mg/4 mL	**RA, PsA, and AS**: 50 mg SQ once monthly **UC:** 200 mg SQ at week 0; then 100 mg at week 2; then 100 mg every 4 weeks. **ARIA**: 2 mg/kg IV at weeks 0 and 4, then every 8 weeks.	**RA:** give with MTX **PsA and AS**: may give with or without MTX or other DMARDs. Needle cover of the syringe contains dry rubber (latex). **ARIA**: give with MTX Efficacy and safety of switching between IV and SQ formulations have not been established.	Patients may be taught to self-inject the SQ dose. For SQ, injection sites should be rotated. For SQ, bring to room temperature for 30 minutes prior to injecting. **ARIA**: IV infusion should be over 30 minutes. Dilute with 0.9% sodium chloride or 0.45% sodium chloride for a final volume of 100 mL. Do not administer with other drugs.
STELARA (ustekinumab)	Prefilled syringe: 45 mg and 90 mg Vial: 130 mg	**PsO, PsA**: ≤100 kg, 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. >100 kg, 90 mg SQ initially and 4 weeks later, followed by 90 mg every 12 weeks. **CD**: Initial single IV dose: ≤55 kg, 260 mg; >55 kg to ≤85 kg, 390 mg; >85 kg, 520 mg; followed by 90 mg SQ every 8 weeks (irrespective of body weight)	Needle cover of the syringe contains dry rubber (latex).	Patients may be taught to self-inject using the prefilled syringes. STELARA for IV infusion must be diluted, prepared and infused by a healthcare professional; it is diluted in 0.9% sodium chloride and infused over at least one hour. Rotate injection sites.
TALTZ (ixekizumab)	Prefilled syringe: 80 mg Autoinjector: 80 mg	**PsO:** 160 mg by SQ injection at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks		Patients may be taught to self-inject with either the prefilled syringe or the autoinjector. Bring to room temperature prior to injecting. Rotate injection sites.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
XELJANZ / XELJANZ XR (tofacitinib)	Tablet: 5 mg Extended release Tablet: 11 mg	**RA:** 5 mg PO twice daily or 11 mg PO once daily	Patients may switch from XELJANZ 5 mg twice daily to XELJANZ XR 11 mg once daily the day following the last dose of XELJANZ 5 mg. Use as monotherapy or in combination with MTX or other nonbiologic DMARDs. Use of XELJANZ in combination DMARDs or with potent immunosuppres-sants such as azathioprine and cyclosporine is not recommended. Dose interruption is recommended for management of lymphopenia (< 500 cells/mm^3), neutropenia (absolute neutrophil count [ANC] < 500 cells/mm^3) and anemia. Dose adjustment needed for hepatic and renal impairment and patients taking CYP450 inhibitors.	May take with or without food. Swallow XELJANZ XR tablets whole; do not crush, split, or chew.

ANC=absolute neutrophil count; AS=ankylosing spondylitis; DMARD=disease-modifying anti-rheumatic drug; HS=hidradenitis suppurativa; IV=intravenous infusion; JIA=juvenile idiopathic arthritis; MTX=methotrexate; NOMID= neonatal-onset multisystem inflammatory disease; NSAID=non-steroidal anti-inflammatory drug; PJIA=polyarticular juvenile idiopathic arthritis; PO=orally; PsA=psoriatic arthritis; PsO= plaque psoriasis; RA=rheumatoid arthritis; SJIA=systemic juvenile idiopathic arthritis; SQ=subcutaneously; UC=ulcerative colitis

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
ACTEMRA (tocilizumab)	Frequency of serious infection greater in ≥65 years. Use caution.	Not studied in children <2 years. Safety and efficacy only established in SJIA and PJIA.	No dose adjustment in mild impairment. Not studied in moderate to severe impair-ment.	Not studied in patients with impairment.	Uncategorized† Limited data in pregnant women not sufficient to determine risks. Unknown whether excreted in breast milk; risks and benefits should be considered.
CIMZIA (certolizumab)	The number of subjects ≥65 years in clinical trials was not sufficient to determine whether they responded differently from younger subjects. Use caution.	Safety and effectiveness have not been established.	No data	No data	Uncategorized† Limited data from ongoing pregnancy registry not sufficient to inform risks. Unknown whether excreted in breast milk, but data suggest systemic exposure to a breastfed infant is expected to be low; risks and benefits should be considered.
COSENTYX (secukinumab)	The number of subjects ≥65 years in clinical trials was not sufficient to determine whether they responded differently from younger subjects.	Safety and efficacy have not been established.	No data	No data	Pregnancy category B* Unknown whether excreted in breast milk; use with caution.
ENTYVIO (vedolizumab)	The number of patients ≥65 years in clinical trials was insufficient to determine differences.	Safety and efficacy have not been established.	Safety and efficacy have not been established.	Safety and efficacy have not been established.	Pregnancy category B* Unknown whether excreted in breast milk; use with caution.
ENBREL (etanercept)	Use caution.	Not studied in children <2 years with PJIA or <4 years with PsO.	No data	No data	Pregnancy category B* Present in low levels in breast milk; use caution.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
HUMIRA (adalimumab)	Frequency of serious infection and malignancies is greater in ≥65 years. Use caution.	Only studied in PJIA (ages 2 years and older) and CD (6 years and older).	No data	No data	Uncategorized† Present in low levels in breast milk; use caution.
ILARIS (canakinumab)	The number of patients ≥65 years in clinical trials was insufficient to determine differences.	Not studied in children <2 years (SJIA, TRAPS, HIDS/ MKD, and FMF) or <4 years (CAPS).	No data	No data	Uncategorized † Limited data from postmarketing reports not sufficient to inform risks. Unknown whether excreted in breast milk; use caution.
INFLECTRA (infliximab-dyyb)	Frequency of serious infection is greater in ≥65 years. Use caution.	Not recom-mended in <6 years in children with CD.	No data	No data	Pregnancy category B* Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug.
KINERET (anakinra)	Use caution.	For NOMID, has been used in all ages. Not possible to give a dose <20 mg.	CrCl<30 mL/min: give dose every other day	No data	Pregnancy category B* Unknown whether excreted in breast milk; use caution.
ORENCIA (abatacept)	Frequency of serious infection and malignancies is greater in ≥65 years. Use caution.	Not recom-mended in <6 years. SQ formulation has not been studied in patients <18 years.	No data	No data	Uncategorized † Data on use in pregnant women insufficient to inform risks. Unknown whether excreted in breast milk.
OTEZLA (apremilast)	No overall differences were observed in the safety profile of elderly patients.	Safety and efficacy have not been established.	The dose of OTEZLA should be reduced to 30 mg once daily in patients with severe renal impairment (CrCl<30 mL/min).	No dosage adjustment necessary.	Pregnancy category C* Unknown whether excreted in breast milk; use caution.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
REMICADE (infliximab)	Frequency of serious infection is greater in ≥65 years. Use caution.	Not recommended in <6 years in children with CD or UC.	No data	No data	Pregnancy category B* Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug.
RITUXAN (rituximab)	Rates of serious infections, malignancies, and cardiovascular events were higher in older patients.	Safety and effectiveness have not been established.	No data	No data	Pregnancy category C* Unknown whether excreted in breast milk; risks and benefits should be weighed before use.
SILIQ (brodalumab)	No differences in safety or efficacy were observed between older and younger patients, but the number of patients ≥65 years was insufficient to determine any differences in response.	Safety and effectiveness in <18 years have not been established.	No data	No data	Uncategorized † There are no human data in pregnant women to inform risks. Unknown whether excreted in breast milk; risks and benefits should be weighed before use.
SIMPONI/ SIMPONI ARIA (golimumab)	SQ: No differences in AEs observed between older and younger patients. Use caution. IV ARIA: Use caution.	Safety and effectiveness in <18 years have not been established.	No data	No data	Pregnancy category B* Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug.
STELARA (ustekinumab)	No differences observed between older and younger patients. Use caution.	Safety and effectiveness have not been established.	No data	No data	Uncategorized † Limited data in pregnant women are insufficient to inform risks. Unknown whether excreted in breast milk; systemic exposure to breasted infant expected to be low; consider risks and benefits.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
TALTZ (ixekizumab)	No differences observed between older and younger patients; however, the number of patients ≥65 years was not sufficient to determine differences.	Safety and effectiveness have not been established.	No data	No data	Uncategorized † There are no available data in pregnant women to inform risks. Unknown whether excreted in breast milk; consider risks and benefits.
XELJANZ / XELJANZ XR (tofacitinib)	Frequency of serious infection is greater in ≥65 years. Use caution.	Safety and effectiveness have not been established.	Reduce dose to 5 mg daily in moderate to severe impairment.	Reduce dose to 5 mg daily in moderate hepatic impairment. Not recom-mended in severe hepatic impairment.	Pregnancy category C* Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug.

CrCl=creatinine clearance; NOMID= Neonatal-Onset Multisystem Inflammatory Disease; PJIA=polyarticular juvenile idiopathic arthritis; SJIA=systemic juvenile idiopathic arthritis
*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
†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

- Immunomodulators for a variety of conditions associated with inflammation are available. Mechanisms of action and indications vary among the products. Products in this class have clinical trial data supporting efficacy for their FDA-approved indications.
- Limited head-to-head clinical trials between the agents have been completed.
    - In patients with RA, abatacept and infliximab showed comparable efficacy at six months, but abatacept demonstrated greater efficacy after one year on some endpoints such as DAS28-ESR, EULAR response, LDAS, and ACR 20 responses (Schiff et al, 2008).
    - In patients with RA, abatacept and adalimumab were comparable for ACR 20 and ACR 50 responses over two years in a single-blind study (Schiff et al, 2014).
    - Patients with severe arthritis who could not take MTX were randomized to monotherapy with tocilizumab or adalimumab for 24 weeks in a randomized, double-blind study (Gabay et al, 2013). The patients in the tocilizumab group had a significantly greater improvement in DAS28 at week 24 than patients in the adalimumab group.
    - In biologic-naïve patients with RA and an inadequate response to DMARDs, initial treatment with rituximab was demonstrated to have non-inferior efficacy to initial TNF inhibitor treatment (Porter et al, 2016).
    - A randomized, open-label trial evaluated biologic treatments in patients with RA who had had an inadequate response to a TNF inhibitor. In this population, a non-TNF biologic (tocilizumab, rituximab, or abatacept) was more effective in achieving a good or moderate disease activity response at 24 weeks than use of a second TNF inhibitor. However, a second TNF inhibitor was also often effective in producing clinical improvement (Gottenberg et al, 2016). Another recent randomized trial did not demonstrate clinical efficacy differences between abatacept, rituximab, and use of a second TNF inhibitor in this patient population (Manders et al, 2015).
    - Secukinumab and ustekinumab were compared for safety and efficacy in the CLEAR study, a double-blind, randomized controlled trial in 676 patients with moderate to severe PsO (Thaçi et al, 2015). The proportion of

patients achieving PASI 90 at week 16 was significantly higher with secukinumab compared to ustekinumab (79% vs 57.6%; P<0.0001).
    - A greater proportion of PsO patients achieved the primary outcome, PASI 75 at week 12, with ustekinumab 45 mg (67.5%) and 90 mg (73.8%) compared to etanercept 50 mg (56.8%; P=0.01 vs ustekinumab 45 mg; P<0.001 vs ustekinumab 90 mg). In this trial, etanercept therapy was associated with a greater risk of injection site erythema than ustekinumab (14.7% vs 0.7%) (Griffiths et al, 2010).
    - In the FIXTURE study in patient with moderate to severe PsO, 77.1%, 67%, 44%, and 4.9% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, etanercept at FDA-recommended dosing, and placebo, respectively (Langley et al, 2014).
    - In the UNCOVER-2 and UNCOVER-3 studies, the proportions of patients achieving PASI 75 and achieving PGA 0 or 1 were higher in patients treated with ixekizumab compared to those treated with etanercept.
    - In the AMAGINE-2 and AMAGINE-3 studies, the proportions of patients achieving PASI 100 were higher in patients treated with brodalumab compared to those treated with ustekinumab (Lebwohl et al, 2015).
    - No meaningful differences were shown in the treatment of RA and PsA in comparisons of infliximab and infliximab-dyyb conducted to establish biosimilarity between these agents (Park et al, 2013; Park et al, 2016; Park et al, 2017; Yoo et al, 2013; Yoo et al, 2016; Yoo et al, 2017).
    - More comparative studies are needed.
- For RA, patients not responding to initial DMARD treatment may be treated with combination DMARDs, TNF inhibitors, non-TNF inhibitor biologics, and/or tofacitinib (Singh et al, 2016c; Smolen et al, 2017). EULAR has released guidelines for use of antirheumatic drugs in pregnancy, which state that the TNF inhibitors etanercept and certolizumab are among possible treatment options for patients requiring therapy (Götestam Skorpen et al, 2016).
- For the management of PsO, biologic agents are routinely used when one or more traditional systemic agents are not tolerated, fail to product an adequate response, or are unable to be used due to patient comorbidities (Gottleib et al, 2008; Menter et al, 2008; Menter et al, 2009a; Menter et al, 2009b; Menter et al, 2010; Menter et al, 2011; Nast et al, 2015b). EULAR 2015 PsA guidelines recommend TNF inhibitors in patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD, such as MTX (Gossec et al, 2016; Ramiro et al, 2016). For patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD, in whom a TNF inhibitor is not appropriate, biologics targeting IL-12/23 or IL-17 pathways may be considered. Apremilast is considered a treatment option in patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD, in whom biologics are not appropriate. Guidelines from GRAPPA recommend various biologics for the treatment of PsO and PsA based on patient-specific factors, including TNF inhibitors, IL-17 and IL-12/23 inhibitors, and PDE-4 inhibitors (Coates et al, 2016).
- In patients with JIA and involvement of ≥5 joints, the ACR recommends the use of a TNF inhibitor after an adequate trial of a conventional DMARD (Beukelman et al, 2011). The ACR updated guideline for SJIA notes that IL-1 and IL-6 play a central role in the inflammatory process for this condition, and recommend agents such as anakinra, canakinumab, tocilizumab, abatacept, and TNF inhibitors among either first- or second-line treatments (Ringold et al, 2013).
- According to the ACG, for the treatment of UC, infliximab should be considered after failure of first-line non-biologic agents (Kornbluth et al, 2010). Other immunomodulators were not indicated for UC when these guidelines were written.
- Based on ACG guidelines, the anti-TNF monoclonal antibodies adalimumab, certolizumab, and infliximab are effective in the treatment of moderate to severely active CD in patients who have not responded despite complete and adequate therapy with a corticosteroid or an immunosuppressive agent. These TNF inhibitors may also be used as alternatives to steroid therapy in selected patients in whom corticosteroids are contraindicated or not desired (Lichtenstein et al, 2009). The AGA recommends using anti-TNF drugs to induce remission in patients with moderately severe CD (Terdiman et al, 2013). ECCO recommends TNF inhibitors for patients with CD who have relapsed or are refractory to corticosteroids, depending on disease location and severity, and states that early TNF inhibitor therapy should be initiated in patients with high disease activity and features indicating a poor prognosis; vedolizumab is an alternative for some patients (Gomollón et al, 2017).
- Consensus statements for the management of inflammatory bowel disease in pregnancy, coordinated by the Canadian Association of Gastroenterology, state that TNF inhibitor treatment does not appear to be associated with unfavorable pregnancy outcomes and should generally be continued during pregnancy (Nguyen et al, 2016b).
- Based upon guidelines from the European Dermatology Forum, adalimumab is recommended among first-line therapies for HS, with infliximab a potential second-line option (Gulliver et al, 2016; Zouboulis et al, 2015).
- Joint guidelines from ASAS and EULAR state that biologic DMARDs should be considered in patients with AS and persistently high disease activity despite conventional treatments (van der Heijde et al, 2017). The 2015 ACR, Spondylitis Association of America, and Spondyloarthritis Research and Treatment Network guidelines strongly

recommend TNF inhibitors for patients who have active disease despite NSAIDs; no TNF inhibitor is preferred over another for AS for most patients (Ward et al, 2016).

- Infliximab and adalimumab are recommended over etanercept for various ocular inflammatory disorders (Levy-Clarke et al, 2016).
- Caution is warranted with these biologic agents due to severe infections and malignancies that can occur with their use. Tocilizumab, TNF inhibitors, and tofacitinib have boxed warnings regarding a risk of serious infections. TNF inhibitors and tofacitinib also have boxed warnings regarding an increased risk of malignancies. Brodalumab has a boxed warning regarding the risk of suicidal ideation and behavior.
- Warnings, precautions, and AE profiles vary in this class.
- All of the biologic agents with the exception of apremilast and tofacitinib are given by subcutaneous injection and/or intravenous infusion. Administration schedule varies among the injectable agents in the class. Apremilast and tofacitinib are given orally.
- Selection of an agent for a patient is determined by approved indications, response, administration method, tolerability, AE profile, and cost of the agent.

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INTRODUCTION

- Atopic dermatitis, also referred to as atopic eczema, is a chronic, highly pruritic, and relapsing inflammatory skin condition. The prevalence of atopic dermatitis is estimated to be between 15% to 30% in children and 2% to 10% in adults; approximately 18 million children and adults have atopic dermatitis in the United States *(Berke et al 2012, Eichenfield et al 2014a, FDA presentation 2015)*. Atopic dermatitis is one of the most common skin disorders in children with more than 90% of cases starting before the age of five years *(Eichenfield et al 2014a)*.
- The pathogenesis of atopic dermatitis can be explained by impaired epidermal barrier function due to structural and functional abnormalities in the skin as well as a cutaneous inflammatory response to environmental factors *(Weston 2017)*. Pruritus is one of the most common symptoms of atopic dermatitis, and it is an essential feature which provokes a vicious "itch-scratch" cycle that compromises the epidermal barrier which results in water loss, xerosis, microbial colonization, and secondary infection *(Castro 2008)*. The clinical manifestations of atopic dermatitis vary according to age and disease activity; however, almost all patients with atopic dermatitis report dry skin. The infantile and childhood stages are characterized by pruritic, red, crusted lesions and generally involve the face, neck, and extensor skin surfaces *(Eichenfield et al 2014a)*. The adult stage of atopic dermatitis is more lichenified and localized to the flexural folds of the extremities *(Eichenfield et al 2014a)*.
- Diagnosis of atopic dermatitis is based on a constellation of clinical symptoms. There is no optimal long-term maintenance treatment for atopic dermatitis, and there is no known cure. The general approach for the treatment of atopic dermatitis involves elimination of exacerbating factors, restoring the skin's abnormal barrier function, hydrating the skin, and controlling active disease with topical anti-inflammatory agents *(Eichenfield et al 2014b, Schneider et al 2013, Tollefson et al 2014)*.
- Patients with atopic dermatitis should avoid exacerbating factors including excessive bathing, low humidity environments, emotional stress, xerosis, and exposure to detergents. Thick creams with low water content or ointments which have zero water content protect against xerosis and should be utilized. Antihistamines are utilized as an adjunct in patients with atopic dermatitis to control pruritus and eye irritation. Sedating antihistamines (eg, diphenhydramine, hydroxyzine) appear to be more effective than non-sedating ones (eg, fexofenadine, loratadine) *(Eichenfield et al 2014b)*. However, evidence supporting their use is weak due to lack of controlled trials.
- Topical corticosteroids are considered to be the standard of care for the treatment of atopic dermatitis *(Eichenfield et al 2014b, Schneider et al 2013, Tollefson et al 2014)*. Low- to high-potency topical corticosteroids are utilized one or more times daily for the treatment of acute flares, as well as, for intermittent use to prevent relapses. One large trial showed that twice-daily application of topical corticosteroids was no more effective than once-daily application *(Krakowski et al 2008)*. There are tolerability and safety concerns regarding the use of topical corticosteroids including skin atrophy, striae, and telangiectasia, which may limit long-term use of these agents. These adverse reactions occur more frequently when topical corticosteroids are used on sensitive areas of thin skin including skin folds and the face or neck *(Eichenfield et al 2014b, Krakowski et al 2008, Schneider et al 2013)*.
- Immunosuppressive agents for atopic dermatitis include Elidel (pimecrolimus) and Protopic (tacrolimus). The exact mechanism of action in atopic dermatitis is not known. Elidel and Protopic inhibit calcineurin, a calcium-dependent phosphatase, by binding with high affinity to immunophilin-12 (FKBP-12), which is theorized to be the primary mode of inflammation reduction in atopic dermatitis *(Clinical Pharmacology 2017)*. Protopic and Elidel provide immunosuppression via inhibition of T-cell activation.
- There are some concerns regarding the long-term safety of these agents. On January 19, 2006, the FDA approved updated labeling for the agents *(FDA press release 2006)*. This updated labeling was a result of cancer-related adverse events (AEs) with the use of these medications. The labeling includes a boxed warning about a possible risk of cancer and a medication guide for patients to ensure that they are aware of this concern. The labeling clarifies that these medications are recommended for use as second-line treatments and are not recommended in children under two years of age. A definitive causal link between the topical immunosuppressants and the incidence of malignancy has not been established.

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

Table 1. Medications Included Within Class Review

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

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

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

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

(*Prescribing information: Elidel 2017, Eucrisa 2016, Protopic 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

Elidel and Protopic

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

403). These two studies showed significant clinical response based on physician's global evaluation for Elidel-treated patients compared to patients in the vehicle group. These studies are outlined in the manufacturer product labeling.

- The FDA approval of Protopic ointment was based on three randomized, double-blind, vehicle-controlled, Phase III studies in patients with moderate to severe atopic dermatitis. One of the studies was conducted in pediatric patients (N = 351) ages two to 15 years, and the other two studies were conducted in adult patients (N = 632). The primary efficacy endpoint was met by all three studies with a significantly greater percentage of patients achieving at least 90% improvement based on the physician's global evaluation of clinical response in the Protopic group compared to the vehicle group ($p < 0.001$). There was some evidence that Protopic 0.1% ointment may provide more efficacy than the 0.03% ointment in adult patients who had severe disease at baseline. There was no difference in efficacy for the two Protopic strengths in the pediatric study. These studies are outlined in the manufacturer product labeling.
- Elidel and Protopic have been directly compared in clinical trials. One trial compared Elidel 1% to Protopic 0.03% in patients two to 17 years of age (N = 141) and found no difference in the incidence of application site reactions between the two topical immunomodulators in the six-week study *(Kempers et al 2004)*. However, itching was reported at a significantly higher rate in the Protopic group. In two other clinical trials, Protopic 0.1% was compared to Elidel in adult patients over six weeks. Patients treated with Protopic had a significantly greater improvement in the Eczema Area Severity Index (EASI) score compared to those treated with Elidel (*Abramovits et al 2008, Fleischer et al 2007*). The success in therapy based on the Investigator Global Atopic Dermatitis Assessment, improvement in percent body surface area affected, and improvement in signs and symptoms of atopic dermatitis in face and neck were all statistically significant for the Protopic group in both studies *(Abramovits et al 2008, Fleischer et al 2007)*. There were no differences in AEs between the groups.
- A meta-analysis of three randomized clinical trials showed that both adults and children in the Protopic-treated group had a significantly greater improvement in EASI score at week six as compared to the Elidel group *(Paller et al 2005)*. The most common adverse effects in all studies were local application site reactions including burning and stinging *(Paller et al 2005)*.
- A meta-analysis of 25 randomized controlled trials (N = 6,897) showed that Protopic 0.1% was equally efficacious as potent topical corticosteroids and more efficacious than mild topical corticosteroids for the treatment of atopic dermatitis *(Ashcroft et al 2005)*. Additionally, Elidel was found to be less effective than potent topical corticosteroids *(Ashcroft et al 2005)*. Individual clinical trials have reported conflicting results *(Bieber et al 2007, Doss et al 2009, Doss et al 2010)*.
- A meta-analysis and systematic review assessed the effectiveness of topical immunomodulators compared to topical corticosteroids and/or placebo (N = 7,378) *(El-Batawy et al 2009)*. In terms of overall comparison, Elidel was found to be more effective than vehicle at three and six weeks. However, a long-term study that was included in this review did not find any difference between these two groups at six and twelve months. Also, betamethasone valerate, a potent topical corticosteroid, was found to be significantly more effective in adults (three weeks) than Elidel in the treatment of moderate to severe atopic dermatitis. Although this meta-analysis showed that Elidel seems to be less effective than topical corticosteroids, Elidel would be efficacious in areas where topical corticosteroids may not be recommended such as the face and sensitive areas including skin folds. Pooled analysis of Protopic trials demonstrated that Protopic was more effective than vehicle *(El-Batawy et al 2009)*. When compared to mild potency topical corticosteroids like hydrocortisone acetate, Protopic was more efficacious. However, when compared to moderate potency topical corticosteroids, Protopic 0.03% was significantly less effective than topical corticosteroids, and Protopic 0.1% was equal in effectiveness to the topical corticosteroids. Overall, Protopic was found to be more effective than mild topical corticosteroids and equally effective as moderately potent topical corticosteroids *(El-Batawy et al 2009)*.
- A systematic review of 20 randomized controlled trials (N = 6,288) showed that Protopic was more efficacious than placebo or mild topical corticosteroids for the treatment of atopic dermatitis *(Chen et al 2010)*. Additionally, Elidel was more efficacious than placebo and equally efficacious as mild topical corticosteroids for the treatment of atopic dermatitis. In this review, three trials comparing Elidel to Protopic were identified. While two of the trials did find Protopic to be significantly more efficacious, no significant difference was found in the third trial.
- A retrospective cohort evaluated initial cancer diagnosis in patients with a diagnosis of atopic dermatitis or eczema and found that while exposure to Elidel or Protopic was not associated with an increase in overall cancer rates, exposure to these agents was associated with an increased risk of T-cell lymphoma ($p < 0.001$ and $p = 0.01$, respectively). However, after the exclusion of four cases due to physician suspected T-cell lymphoma prior to exposure, the risks were only significant for patients exposed to Protopic and not Elidel ($p < 0.001$, $p = 0.086$) *(Hui et al 2009)*.

Eucrisa

- The safety and efficacy of Eucrisa were demonstrated in two identically designed, randomized, Phase III, double-blind, vehicle-controlled trials in a total of 1,522 patients with mild to moderate atopic dermatitis and ≥ 5% treatable body surface area (BSA) *(Eucrisa formulary submission dossier 2016, Paller et al 2016)*. The primary endpoint of success was defined as the proportion of subjects at Day 29 who were clear or almost clear with a ≥ 2-grade improvement from baseline by the Investigator's Static Global Assessment (ISGA) scale. More patients receiving Eucrisa vs. vehicle achieved the primary endpoint of ISGA success (Study AD-301: 32.8% vs. 25.4%, p = 0.038; Study AD-302: 31.4% vs. 18.0%, p < 0.001), with a greater percentage achieving clear/almost clear overall (51.7% vs. 40.6%, p = 0.005; 48.5% vs. 29.7%, p < 0.001). In addition, Eucrisa-treated patients achieved greater ISGA score improvements and improvement in pruritus earlier (both p < 0.001). Unpublished data from an open-label safety extension trial of AD-301 and AD-302 (N = 517), found that the most commonly observed AEs (≥ 1% of patients) included atopic dermatitis flares (3.1%), application site pain (2.3%), and application site infection (1.2%) after 48 weeks of treatment *(Eucrisa formulary submission dossier 2016)*. Cutaneous AEs, such as application-site atrophy, telangiectasia, and hypopigmentation, did not occur during the study. Overall, 22.2% of patients used 178 concomitant medications designated as rescue medications.

CLINICAL GUIDELINES

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

SAFETY SUMMARY

Elidel and Protopic

- Boxed warning: Although a causal relationship has not been established, rare cases of malignancy (eg, skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors.
  - Avoid continuous long-term use, in any age group, and limit application to areas of involvement with atopic dermatitis.
  - Both agents are not indicated for use in children less than two years of age. Only Protopic 0.03% ointment is indicated for use in children two to 15 years of age; Elidel is indicated for children two years and older and adults.
- Key Warnings/Precautions:
  - Do not use on malignant or pre-malignant skin conditions.
  - Resolve bacterial or viral infections at the treatment site.
  - While using avoid exposure to sunlight.
  - Do not use in immunocompromised patients.
- AEs: Application site irritation and reactions such as skin burning, itching, redness, and rash. Hypersensitivity reactions can also occur.
- A five-year, open-label, multicenter study evaluated the use of Elidel in 2,418 infants compared to topical corticosteroids *(Sigurgeirsson et al 2015)*. The primary endpoint was safety; the secondary endpoint was long-term efficacy defined as a score of zero to five on the Investigator's Global Assessment (IGA). Topical corticosteroids included low potency such as hydrocortisone 1% or medium potency such as hydrocortisone butyrate 0.1%. For safety, no differences between the groups were observed for growth rate or bacterial or viral infections. More Elidel patients reported bronchitis (p = 0.02), infected eczema (p < 0.001), impetigo (p = 0.045), and nasopharyngitis (p = 0.04). Serious infections and infestations were similar between the groups. Two malignancies occurred in the corticosteroid-treated group, and one benign tumor was reported in the Elidel-treated group. Over the five-year period, 88.7% and 92.3% of the Elidel- and corticosteroid-treatment groups, respectively, reported overall IGA treatment success. Significant attrition occurred with only 69.4% and 72.1% of Elidel- and corticosteroid-treated patients completing the study.

Eucrisa

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

- Hypersensitivity reactions, including contact urticaria, have occurred in patients treated with Eucrisa. Hypersensitivity should be suspected in the event of severe pruritus, swelling, and erythema at the application site or at a distant site. If signs and symptoms of hypersensitivity occur, Eucrisa should be discontinued immediately and appropriate therapy initiated.

- AEs:
  - In pivotal studies AD-301 and AD-302, 1,012 patients (two to 79 years of age) with mild to moderate atopic dermatitis were treated with Eucrisa twice daily for four weeks. The AE reported by ≥ 1% of Eucrisa-treated patients (45/1,012 [4%] vs. 6/499 [1%] of vehicle-treated patients) was application site pain, referring to skin sensations such as burning or stinging. Less common (< 1%) AEs in patients treated with Eucrisa included contact urticaria.
  - No safety signals were identified from vital signs or laboratory assessments in the pivotal studies or in the 48-week, long-term safety extension study *(Eucrisa formulary submission dossier 2016, Paller et al 2016)*.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

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

See the current prescribing information for full details

CONCLUSION

- The two topical calcineurin inhibitors, Elidel (pimecrolimus 1% cream) and Protopic (tacrolimus 0.03% and 0.1% ointment), are indicated as second-line therapies for the short-term and non-continuous chronic treatment of atopic dermatitis (Elidel: mild to moderate atopic dermatitis; Protopic: moderate to severe atopic dermatitis) in non-immunocompromised adults and children (Elidel: ≥ 2 years of age; Protopic: 0.03% and 0.1% in adults, 0.03% in patients 2 to 15 years of age) who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable. The FDA added another agent to the atopic dermatitis armamentarium with the approval of Eucrisa (crisaborole) ointment for the topical treatment of mild to moderate atopic dermatitis in patients ≥ 2 years of age.
- The topical anti-inflammatory agents work by way of several mechanisms of action; however, the exact mechanism of action in atopic dermatitis is not known. Elidel and Protopic inhibit calcineurin, a calcium-dependent phosphatase, by binding with high affinity to immunophilin-12 (FKBP-12). Protopic and Elidel provide immunosuppression via inhibition of T-cell activation, which is theorized to be the primary mode of inflammation reduction in atopic dermatitis. Eucrisa is a non-steroidal treatment option with a novel mechanism of action. In patients with atopic dermatitis, PDE-4 activity increases circulating inflammatory cells resulting in increased cytokine production. It is believed that Eucrisa enhances cellular control of inflammation by inhibiting PDE-4 and its ability to degrade intracellular cAMP, thereby suppressing the release of cytokines *(Clinical Pharmacology 2017, Paller et al 2016)*.
- Several head-to-head studies comparing the efficacy of the two calcineurin inhibitors have been conducted. A meta-analysis of three studies directly comparing Elidel and Protopic evaluated the change from baseline in EASI score at week six of treatment *(Paller et al 2005)*. Results favored treatment with Protopic, and adverse effects between the groups were similar. Another meta-analysis evaluating Elidel, Protopic, topical corticosteroids, and vehicle preparations demonstrated a significantly greater change in EASI score in patients using Protopic compared to patients using Elidel in addition to better Investigator Global Atopic Dermatitis Assessment in patients with moderate to severe disease *(Ashcroft et al 2005)*. Protopic was found to be more effective than mild topical corticosteroids and equally effective as moderately potent topical corticosteroids *(El-Batawy et al 2009)*.
- Concerns regarding the long-term safety of the topical calcineurin inhibitors have been addressed in the guidelines and position papers outlined in this review. In 2005, the FDA released a Public Health Advisory to communicate the potential risk of cancer of these two products to healthcare providers and patients. The FDA has advised that Elidel and Protopic be used only as labeled and asked providers and patients to consider these agents only as second-line therapies; new labeling was approved in early 2006 *(FDA press release 2006)*. Topical calcineurin inhibitors may be associated with immunosuppression or malignancy.
- Eucrisa demonstrated short-term efficacy over vehicle ointment in two identically designed, 28-day, Phase III, randomized, double-blind trials; more patients receiving Eucrisa vs. vehicle achieved the primary endpoint of ISGA success, with a greater percentage of Eucrisa-treated patients achieving clear/almost clear overall. Over 28 days, application site pain was the most commonly reported AE. Unpublished data gleaned from the 48-week, long-term study revealed no significant safety signals.
- Current guidelines for the treatment of atopic dermatitis recommend the use of topical corticosteroids as first-line treatment and recommend the use of topical Elidel or Protopic in those patients intolerant or unresponsive to corticosteroids or in whom corticosteroids are contraindicated or when corticosteroid-sparing measures may be desired. Eucrisa has not yet been added to the guidelines *(Eichenfield et al 2014a, Eichenfield et al 2014b, Schneider et al 2013, Sidbury et al 2014, Tollefson et al 2014)*.

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