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NOTICE OF PUBLIC MEETING – PHARMACY AND THERAPEUTICS COMMITTEE

AGENDA

Date of Publication:	**November 9, 2016**
Date and Time of Meeting:	**Thursday, December 8, 2016 at 1:00 PM**
Name of Organization:	**The State of Nevada, Department of Health and Human Services (DHHS), Division of Health Care Financing and Policy (DHCFP)**
Place of Meeting:	**Springs Preserve** **Desert Living Center** **333 S. Valley View Blvd** **Las Vegas, NV 89107** **Phone: (702) 822-7700** **Please check with staff to verify room location**
Webinar Registration:	https://catamaranrx.webex.com/catamaranrx/onstage/g.php?MTID=e73a77f1ec5b4620666829ee57f8cb0f9 OR www.webex.com, select "Join", enter Meeting Number 749 819 716, your name and email and then select, "Join". A Password should not be necessary, but if asked, enter, "Medicaid"
Event Number:	**749 819 716** **Follow the instructions that appear on your screen to join the teleconference. Audio will be broadcast over the internet (VoIP).**

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

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

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

AGENDA

1. Call to Order and Roll Call

2. Public Comment

3. Administrative

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

b. Status Update by DHCFP
   i. Public Comment

4. Established Drug Classes

a. Musculoskeletal Agents: Antigout Agents
   i. Public Comment
   ii. Drug Class Review Presentation – OptumRx
   iii. **For Possible Action**: Committee Discussion and Action
      1. Approve Clinical/Therapeutic Equivalency of Agents in Class
      2. Identify Exclusions/Exceptions for Certain Patient Groups
   iv. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
   v. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL
b. Hematological Agents: Anticoagulants – Oral
   i. Public Comment
   ii. Drug Class Review Presentation – OptumRx
   iii. **For Possible Action**: Committee Discussion and Action
      1. Approve Clinical/Therapeutic Equivalency of Agents in Class
      2. Identify Exclusions/Exceptions for Certain Patient Groups

iv. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
v. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

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

a. Cardiovascular Agents: Antihypertensive Agents: Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors)
i. Public Comment
ii. Drug Class Review Presentation – OptumRx
iii. **For Possible Action**: Committee Discussion and Action
1. Approve Clinical/Therapeutic Equivalency of Agents in Class
2. Identify Exclusions/Exceptions for Certain Patient Groups
iv. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
v. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

b. Psychotropic Agents: Anxiolytics, Sedatives, and Hypnotics
i. Public Comment
ii. Drug Class Review Presentation – OptumRx
iii. **For Possible Action**: Committee Discussion and Action
1. Approve Clinical/Therapeutic Equivalency of Agents in Class
2. Identify Exclusions/Exceptions for Certain Patient Groups
iv. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
v. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

c. Otic Agents: Otic Antiinfectives – Otic Quinolones
i. Public Comment
ii. Drug Class Review Presentation – OptumRx
iii. **For Possible Action**: Committee Discussion and Action
1. Approve Clinical/Therapeutic Equivalency of Agents in Class
2. Identify Exclusions/Exceptions for Certain Patient Groups
iv. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
v. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

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

ii. Drug Class Review Presentation – OptumRx
iii. **For Possible Action**: Committee Discussion and Action
1. Approve Clinical/Therapeutic Equivalency of Agents in Class
2. Identify Exclusions/Exceptions for Certain Patient Groups
iv. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
v. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

e. Biologic Response Modifiers: Targeted Immunomodulators
i. Public Comment
ii. Drug Class Review Presentation – OptumRx
iii. **For Possible Action**: Committee Discussion and Action
1. Approve Clinical/Therapeutic Equivalency of Agents in Class
2. Identify Exclusions/Exceptions for Certain Patient Groups
iv. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
v. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

6. Proposed New Classes

a. Functional Gastro-intestinal Disorder Drugs
i. Public Comment
ii. Drug Class Review Presentation – OptumRx
iii. **For Possible Action**: Committee Discussion and Action
1. Approve Clinical/Therapeutic Equivalency of Agents in Class
2. Identify Exclusions/Exceptions for Certain Patient Groups
iv. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
v. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

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

8. Closing Discussion
a. Public comments on any subject
b. Date and location of the next meeting
c. Adjournment

PLEASE NOTE: Items may be taken out of order at the discretion of the chairperson. Items may be combined for consideration by the public body. Items may be pulled or removed from the agenda at any time. If an action item is not completed within the time frame that has been

allotted, that action item will be continued at a future time designated and announced at this meeting by the chairperson. All public comment may be limited to 5 minutes.

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

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

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

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

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

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

Preferred Products	PA Criteria	Non-Preferred Products
IBUPROFEN TAB		DUEXIS TAB
INDOMETHACIN CAP		ETODOLAC CAP
KETOROLAC TAB		ETODOLAC TAB
MELOXICAM TAB		ETODOLAC ER TAB
NABUMETONE TAB		INDOMETHACIN CAP ER
NAPROXEN SUSP		KETOPROFEN CAP
NAPROXEN TAB		MEFENAM CAP
NAPROXEN DR TAB		MELOXICAM SUSP
PIROXICAM CAP		NAPRELAN TAB CR
SULINDAC TAB		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®
Antiinfective Agents		
Aminoglycosides		
Inhaled Aminoglycosides		
BETHKIS® KITABIS® PAK TOBI PODHALER® TOBRAMYCIN NEBULIZER		
Antivirals		
Alpha Interferons		
PEGASYS® PEGASYS® CONVENIENT PACK PEG-INTRON® and REDIPEN		

Preferred Products	PA Criteria	Non-Preferred Products
Anti-hepatitis Agents		
Polymerase Inhibitors/Combination Products		
EPCLUSA® HARVONI® SOVALDI® ZEPATIER® ~~VIEKIRA PAK®~~	**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 ®
~~Protease Inhibitors~~		
~~INCIVEK®~~ ~~VICTRELIS®~~ ~~OLYSIO®~~	~~**PA required**~~ ~~https://www.medicaid.nv.gov/Downloads/provider/FA-75.pdf~~	- - -
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®

Preferred Products	PA Criteria	Non-Preferred Products
Macrolides		
AZITHROMYCIN TABS/SUSP CLARITHROMYCIN TABS/SUSP ERYTHROMYCIN BASE ERYTHROMYCIN ESTOLATE ERYTHROMYCIN ETHYLSUCCINATE ERYTHROMYCIN STEARATE		BIAXIN® DIFICID® ZITHROMAX® ZMAX®
Quinolones		
Quinolones - 2nd Generation		
CIPROFLOXACIN TABS CIPRO® SUSP		FLOXIN® OFLOXACIN
Quinolones - 3rd Generation		
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		
Disease-Modifying Antirheumatic Agents		
ENBREL® HUMIRA®	Prior authorization is required for all drugs in this class https://www.medicaid.nv.gov/Downloads/provider/FA-61.pdf	ACTEMRA® CIMZIA® KINERET® REMICADE® SIMPONI® ORENCIA®
Multiple Sclerosis Agents		
Injectable		
AVONEX® AVONEX® ADMIN PACK BETASERON® COPAXONE® QL EXTAVIA® REBIF® QL TYSABRI®	*Trial of only one agent is required before moving to a non-preferred agent*	GLATOPA® LEMTRADA® PLEGRIDY® ZINBRYTA®

Preferred Products	PA Criteria	Non-Preferred Products
Oral		
AUBAGIO® GILENYA® TECFIDERA®		~~GILENYA®~~
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® TRANDOLAPRIL UNIVASC®

Preferred Products	PA Criteria	Non-Preferred Products
Beta-Blockers		
ACEBUTOLOL ATENOLOL ATENOLOL/CHLORTH BETAXOLOL BISOPROLOL BISOPROLOL/HCTZ BYSTOLIC®* CARVEDILOL LABETALOL METOPROLOL (Regular Release) NADOLOL PINDOLOL PROPRANOLOL PROPRANOLOL/HCTZ SOTALOL TIMOLOL	*Restricted to ICD-10 codes J40-J48	SOTYLIZE®
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®

Preferred Products	PA Criteria	Non-Preferred Products
Vasodilators		
Inhaled		
VENTAVIS® TYVASO®		
Oral		
LETAIRIS® ORENITRAM® SILDENAFIL TRACLEER®		ADCIRCA® ADEMPAS® OPSUMIT® REVATIO ®
Antilipemics		
Bile Acid Sequestrants		
COLESTIPOL CHOLESTYRAMINE WELCHOL®		QUESTRAN®
Cholesterol Absorption Inhibitors		
ZETIA®		
Fibric Acid Derivatives		
FENOFIBRATE FENOFIBRIC GEMFIBROZIL ~~LIPOFEN®~~		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®

Preferred Products	PA Criteria	Non-Preferred Products
Omega-3 Fatty Acids		
LOVAZA® VASCEPA®		OMEGA-3-ACID OMTRYG®
Dermatological Agents		
Antipsoriatic Agents		
Topical Vitamin D Analogs		
CALCIPOTRIENE		CALCITENE® DOVONEX® CREAM SORILUX® TACLONEX® VECTICAL®
Topical Analgesics		
LIDOCAINE LIDOCAINE HC LIDOCAINE VISCOUS VOLTAREN® GEL		EMLA® FLECTOR® LIDODERM® QL LIDAMANTLE® PENNSAID®
Topical Antiinfectives		
Acne Agents: Topical, Benzoyl Peroxide, Antibiotics and Combination Products		
ACANYA® AZELEX® 20% cream BENZACLIN® BENZOYL PEROXIDE (2.5, 5 and 10% only) CLINDAMYCIN ONEXTON GEL®	PA required if over 21 years old	 ACZONE GEL® BENZOYL PER AEROSOL CLINDAMYCIN AEROSOL CLINDAMYCIN/BENZOYL PEROXIDE GEL DUAC CS® ERYTHROMYCIN ERYTHROMYCIN/BENZOYL PEROXIDE SODIUM SODIUM SULFACETAMIDE/SULFUR SULFACETAMIDE
Impetigo Agents: Topical		
MUPIROCIN OINT		ALTABAX® CENTANY® MUPIROCIN CREAM
Topical Antifungals (onychomycosis)		
CICLOPIROX SOLN TERBINAFINE TABS	PA required	JUBLIA® KERYDIN® PENLAC® ITRACONAZOLE

Preferred Products	PA Criteria	Non-Preferred Products
Topical Antivirals		
ABREVA® DENAVIR® ZOVIRAX®, OINTMENT		
Topical Scabicides		
~~NATROBA® *~~ NIX® PERMETHRIN RID® SKLICE®	* PA required	EURAX® LINDANE MALATHION NATROBA® * OVIDE® ULESFIA®
Topical Antiinflammatory 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® ~~FOSRENOL®~~ RENAGEL® RENVELA®		AURYXIA ® FOSRENOL® PHOSLO® PHOSLYRA® SEVELAMER CARBONATE VELPHORO®

Preferred Products	PA Criteria	Non-Preferred Products
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	
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®
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®

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

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

Preferred Products	PA Criteria	Non-Preferred Products
Incretin Mimetics		
BYDUREON® * BYETTA® * TANZEUM® TRULICITY® VICTOZA® *	* PA required	~~TANZEUM®~~ ~~TRULICITY®~~
Insulins (Vials, Pens and Inhaled)		
APIDRA® HUMALOG® HUMULIN® LANTUS® LEVEMIR ® NOVOLIN® NOVOLOG® TRESIBA FLEX INJ		AFREZZA® HUMALOG® U-200 TOUJEO SOLO® 300 IU/ML
Meglitinides		
NATEGLINIDE (Starlix®) PRANDIMET® PRANDIN® STARLIX®		
Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors		
FARXIGA® ~~INVOKAMET®~~ INVOKANA® JARDIANCE® ~~XIGDUO XR®~~		GLYXAMBI® INVOKAMET® ~~JARDIANCE®~~ 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®)		

Preferred Products	PA Criteria	Non-Preferred Products
GLYNASE® METAGLIP® TOLAZAMIDE TOLBUTAMIDE		
Thiazolidinediones		
ACTOPLUS MET XR® ACTOS® ACTOPLUS MET® AVANDAMET® AVANDARYL® AVANDIA® DUETACT®		
Pituitary Hormones		
Growth hormone modifiers		
GENOTROPIN® NORDITROPIN®	**PA required for entire class** https://www.medicaid.nv.gov/Downloads/provider/FA-67.pdf	HUMATROPE® NUTROPIN AQ® OMNITROPE® NUTROPIN® SAIZEN® SEROSTIM® SOMAVERT® TEV-TROPIN® ZORBTIVE®
Progestins for Cachexia		
MEGESTROL ACETATE, SUSP		MEGACE ES®
Musculoskeletal Agents		
Antigout Agents		
ALLOPURINOL		
Bone Resorption Inhibitors		
Bisphosphonates		
ALENDRONATE TABS FOSAMAX PLUS D®		ACTONEL® ALENDRONATE SOLUTION ATELVIA® BINOSTO® BONIVA® DIDRONEL® ETIDRONATE IBANDRONATE SKELID®
Nasal Calcitonins		
MIACALCIN®		FORTICAL® CALCITONIN-SALMON

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

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

Preferred Products	PA Criteria	Non-Preferred Products
PEGANONE® PHENYTEK® 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®

Preferred Products	PA Criteria	Non-Preferred Products
Ophthalmic Prostaglandins		
LATANOPROST LUMIGAN® TRAVATAN® TRAVATAN Z® ~~ZIOPTAN~~®		~~LUMIGAN~~® TRAVOPROST XALATAN® ZIOPTAN®
Ophthalmic Antihistamines		
ALAWAY® BEPREVE® KETOTIFEN PAZEO® ZADITOR OTC®		AZELASTINE ALOMIDE ALOCRIL ELESTAT® EMADINE® EPINASTINE LASTACRAFT® OPTIVAR® PATADAY® PATANOL®
Ophthalmic Antiinfectives		
Ophthalmic Macrolides		
ERYTHROMYCIN OINTMENT		
Ophthalmic Quinolones		
BESIVANCE® CIPROFLOXACIN LEVOFLOXACIN MOXEZA® ~~OFLOXACIN~~® 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 Antiinflammatory Agents		
Ophthalmic Corticosteroids		
ALREX® DEXAMETHASONE DUREZOL® FLUOROMETHOLONE LOTEMAX®		FLAREX® FML® FML FORTE® MAXIDEX® OMNIPRED®

Preferred Products	PA Criteria	Non-Preferred Products
PREDNISOLONE		PRED FORTE® PRED MILD® VEXOL®
Ophthalmic Nonsteroidal Antiinflammatory Drugs (NSAIDs)		
DICLOFENAC FLURBIPROFEN ILEVRO® KETOROLAC NEVANAC®		ACULAR® ACULAR LS® ACUVAIL® BROMDAY® BROMFENAC® PROLENSA®
Otic Agents		
Otic Antiinfectives		
Otic Quinolones		
CIPRODEX® OFLOXACIN		
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®

Preferred Products	PA Criteria	Non-Preferred Products
Antidepressants		
Other		
BUPROPION BUPROPION SR BUPROPION XL DULOXETINE * MIRTAZAPINE MIRTAZAPINE RAPID TABS PRISTIQ® TRAZODONE VENLAFAXINE (ALL FORMS)	PA required for members under 18 years old * PA required *No PA required if ICD-10 - M79.1; M60.0-M60.9, M61.1.*	APLENZIN® BRINTELLIX® CYMBALTA® * DESVENLAFAXINE FUMARATE EFFEXOR® (ALL FORMS) FETZIMA® FORFIVO XL® KHEDEZLA® VIIBRYD® WELLBUTRIN®
Selective Serotonin Reuptake Inhibitors (SSRIs)		
CITALOPRAM ESCITALOPRAM FLUOXETINE PAROXETINE PEXEVA® SERTRALINE	PA required for members under 18 years old	CELEXA® FLUVOXAMINE QL LEXAPRO® LUVOX® PAXIL® PROZAC® SARAFEM® ZOLOFT®
Antipsychotics		
Atypical Antipsychotics - Oral		
~~ABILIFY®~~ ARIPIPRAZOLE CLOZAPINE FANAPT® LATUDA® OLANZAPINE QUETIAPINE REXULTI® RISPERIDONE SAPHRIS® SEROQUEL XR® ZIPRASIDONE	**PA required for Ages under 18 years old** **PA Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-70.pdf *(No PA required Parkinson's related psychosis ICD code on claim)	~~ARIPIPRAZOLE~~ ABILIFY® CLOZARIL® FAZACLO® GEODON® INVEGA® NUPLAZID®* PALIPERIDONE ~~REXULTI®~~ RISPERDAL® SEROQUEL® VRAYLAR® ZYPREXA®

Preferred Products	PA Criteria	Non-Preferred Products
Anxiolytics, Sedatives, and Hypnotics		
ESTAZOLAM FLURAZEPAM ROZEREM® * TEMAZEPAM TRIAZOLAM ZOLPIDEM	*(PA not required for ICD-10 code G47.0 and F51.0)	AMBIEN® AMBIEN CR® BELSOMRA® DORAL® ESZOPICLONE EDLUAR® HETLIOZ® INTERMEZZO® LUNESTA® SILENOR® SOMNOTE®
	PA required for members under 18 years old	SONATA® ZALEPLON ZOLPIDEM CR ZOLPIMIST®
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 Antiinflammatory Agents		
Leukotriene Receptor Antagonists		
MONTELUKAST ZAFIRLUKAST		ACCOLATE® SINGULAIR®
Respiratory Corticosteroids		
~~AEROSPAN HFA®~~ ARNUITY ELLIPTA® ASMANEX® ~~BUDESONIDE NEBS*~~ FLOVENT DISKUS® QL FLOVENT HFA® QL PULMICORT FLEXHALER® PULMICORT RESPULES®* QVAR®	*No PA required if < 4 years old	ALVESCO® AEROSPAN HFA® ~~ARNUITY ELLIPTA®~~ BUDESONIDE NEBS* ~~PULMICORT RESPULES®*~~

Preferred Products	PA Criteria	Non-Preferred Products
Nasal Corticosteroids		
FLUTICASONE NASONEX®		BECONASE AQ® FLONASE® FLUNISOLIDE NASACORT AQ® OMNARIS® QNASL® RHINOCORT AQUA® TRIAMCINOLONE ACETONIDE VERAMYST® ZETONNA®
Phosphodiesterase Type 4 Inhibitors		
DALIRESP® QL	PA required	
Respiratory Antimuscarinics		
ATROVENT® COMBIVENT RESPIMAT® IPRATROPIUM/ALBUTEROL NEBS QL IPRATROPIUM NEBS SPIRIVA®	Only one agent per 30 days is allowed	INCRUSE ELLIPTA ® SEEBRI NEOHALER® SPIRIVA RESPIMAT® TUDORZA®
Respiratory Beta-Agonists		
Long-Acting Respiratory Beta-Agonist		
~~ARCAPTA NEOHALER®~~ FORADIL® SEREVENT DISKUS® QL STRIVERDI RESPIMAT®		ARCAPTA NEOHALER® BROVANA® PERFOROMIST NEBULIZER® ~~STRIVERDI RESPIMAT®~~
Short-Acting Respiratory Beta-Agonist		
ALBUTEROL NEB/SOLN LEVALBUTEROL NEBS PROVENTIL® HFA ~~PROAIR® HFA~~ XOPENEX® HFA* QL ~~XOPENEX® Solution* QL~~	* PA required	~~LEVALBUTEROL~~ ~~MAXAIR AUTOHALER®~~ 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 ®

	Preferred Products	PA Criteria	Non-Preferred Products
Toxicology Agents			
Antidotes			
Opiate Antagonists			
	EVZIO ® NALOXONE NARCAN® NASAL SPRAY		
Substance Abuse Agents			
Mixed Opiate Agonists/Antagonists			
	BUNAVAIL® SUBOXONE® ZUBSOLV®	PA required for class	BUPRENORPHINE/NALOXONE

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

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

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

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

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

(b) Antirejection medications for organ transplants;

(c) Antihemophilic medications; and

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

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

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

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

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

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

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

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

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

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

(b) Maintains continuous eligibility for Medicaid; and

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

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

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

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

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

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

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

(c) Anticonvulsant medications;

(d) Antirejection medications for organ transplants;

(e) Antidiabetic medications;

(f) Antihemophilic medications; and

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

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

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

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

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

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

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

Definition of "Therapeutic Alternative"

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

BRIAN SANDOVAL
Governor

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Acting Administrator

Nevada Medicaid

PHARMACY AND THERAPEUTICS COMMITTEE

DRAFT MINUTES

The Division of Health Care Financing and Policy (DHCFP) Pharmacy and Therapeutics Committee held a public meeting on September 22, 2016 beginning at **1:00 p.m.** at the following location:

Canyon Gate Country Club
2001 Canyon Gate Drive
Las Vegas, NV 89117
Phone: (702) 363-0303

Committee Members Present:
Mark Decerbo, Pharm.D.; Shamim Nagy, MD; Adam Zold, Pharm.D.; Evelyn Chu, Pharm.D.; Mike Hautekeet, Pharm.D.; Joseph Adashek, MD; Nikki Beck, Pharm.D.; Christopher Highley, MD

Committee Members Absent:
Weldon Havins, MD

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

HPES:
Beth Slamowitz, Pharm.D.

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

Others:
Christy Heiner, Viking HCS; Michelle Mui, UCB; Alan Kaska, Abbott; Rob Bigham, Shire; Brian Landberg, Arkray; Joe Gilhoudy; Scott Black, Daiichi Sankyo; Michael Sans, Daiichi Sankyo; Charlotte Polhemus,

Daiichi Sankyo; Jesse Hong, Purdue; James Kotusky, Gilead; Deron Grothe, Teva; Sandy Sierawski, Pfizer; Contessa Fincher, Teva; Bruce Smith, Glaxo Smith Kline; Tammy Rogers, Purdue; Aida Maxsaur, Purdue; Sarica Klein, Mylan; Ann Nelson, Vertex; Mark Schwartz, GSK; Efrain Alton, Merck; Krystal Joy, Otsuka; Christy Lemons, Onexo; Natalie Cardens, UCB; Jill Suad, UCB; Elaine Defelice, UCB; Kathryn Munoz, Sanofi-Genzyme; Thu-Mai Duorg, Sanofi-Genzyme; Jennifer Lauper, BMS; Chris Conner, BMS; Phil Walsh, Sunovian; Robert Jaramillo, Sunovion; Aimee Doran, United Therapeutics; Richard Arnoto, UCB; David Abraham, MRR; Samantha Sweeney, Otsuka; Colin Carey, Lilly; Kathy Moore, Otsuka; Kaysen Bala, Novo Nordisk; Lovell Robinson, Abbvie; Alyssa Nguyen, Walgreens; Laura Hill, Abbvie; Laura Litzenberger, Janssen; Charissa Anne, J&J; Danielle Marano, Epilepsy Foundation; William O'Neill, BI; Steve Fuchs, Pfizer; Dan Tubridy, BI; Nick Casale, Indiviar; Georgette Dzwileski, Indiviar; Chris Anstead, Amgen; Sally Berry, Tris; David Crosby, BMS; Leon Ravin, DPBH; Tom O'Connor, Novartis; Kat McPherson, Novartis; Jeff Rose; Lisa Wilson, Biogen

Others On-line:

Chris Stanfield; Nick Lourenco; Brent Fushimi; Dominick Vanore; Michelle Giddings; Kim Jacoby; Charlene Knutila; Connie Yuen; Lee Barron; Lisa Wilson; Rob Bigham; Scott Black; Jeanette Belz

AGENDA

1. Call to Order and Roll Call

Meeting called to order at 1:01 PM

Beth Slamowitz, Hewlett Packard Enterprises
Christopher Highley
Nikki Beck
Evelyn Chu
Gabe Lither
Shamim Nagy, Chair
Adam Zold
Mark Decerbo
Michael Hautekeet
Kevin Whittington, OptumRx
Carl Jeffery, OptumRx

2. Public Comment

Shamim Nagy, Chair: Any Public Comment?

Gabe Lither: This is the time for any public comment on any topic, otherwise we will take comment as the agenda items come up.

3. Administrative

A. **For Possible Action:** Review and Approve Meeting Minutes from March 24, 2016.

Shamim Nagy, Chair: We need a motion to approve the minutes from the March meeting.
Michael Hautekeet: Move.
Evelyn Chu: Second.
Voting: Ayes across the board, the motion carries.

B. Status Update by DHCFP

Shamim Nagy, Chair: Status update from DHCFP.

Mary Griffith: My name is Mary Griffith. State staff attended the Governor's Conference on Prescription Drug Abuse. There was a lot of good information and input presented at the meeting.

The DHCFP will be hosting our Annual Provider Workshop on October 4th in Reno and October 6 in Las Vegas. There will be speakers and break-out session so providers can talk one-on-one with HP and DHCFP staff to get any billing problems addressed or help with prior authorizations.

The DHCFP will hold a public workshop on October 20 to take public comment on prescription opioid use in Nevada. It will be held in Carson City and video-conferenced to Las Vegas and Elko.

We are also having a public workshop on the 20th for prescription opioid drug abuse.

Our next Drug Use Review Board meeting will be October 27th in Reno.

We have two new members, Dr. Chris Highley, and Dr. Nikki Beck.

Christopher Highley: I'm Chris Highley, I work for Carson Medical Group.

Nikki Beck: I'm Nikki Beck and I work in a Federally Qualified Health Center in Reno.

Mary Griffith: There are some ground rules for this meeting. This is Fee For Service only, not for MCOs. We are going to limit public comment to 5 minutes because of the long meeting agenda. Optum will display the recommendations for the PDL on the screen by drug class. If your drug is recommended to be preferred, you don't have to testify. Please check the screen before proceeding to the microphone. If testimony has already been presented on your drug, we don't need to hear it again. We'd like to hear new information. Please state your name and who you represent.

Gabe Lither: Gabe Lither from the Attorney General's office, we don't discuss cost by statute. Cost is considered behind the scenes, but your job is to decide based on your clinical knowledge of the drugs.

Shamim Nagy, Chair: Public comment?

Christian Stone: Hi my name is Christian Stone, I am a gastroenterologist, I have been practicing for 16 years, representing myself and my patients. I'm here to discuss Cimzia, an antiTNF agent. Cimzia is used for Crohn's disease. I want to remind the panel of the advantages of Cimzia. I encourage the Committee to make it preferred so it is available to all patients.

Shamim Nagy, Chair: Thank you, we will take this into consideration when we discuss the class. Do we have any other public comments? We are taking drug classes out of order.

Carl Jeffery: We are starting with the ADHD medications, it is section G under Established Drug Classes.

Shamim Nagy, Chair: We will start with G, Established Drug Classes.

Gabe Lither: We taking items out of order Section 5-G – psychotropic agents – ADHD.

Shamim Nagy, Chair: Do we have any public comment?

Christy Hiner: My name is Christy Hiner, for Viking Healthcare Solution, I represent Nelis Pharmaceuticals. Please consider adding Adzenys XR to the preferred drug list. Adzenys is a long-acting amphetamine orally disintegrating tablet. Pharmacokinetic information and the benefits of ODT in youth and adults was presented.

Shamim Nagy, Chair: Any questions?

Gabe Lither: Do you see the medication on the list on the screen?

Christy Hiner: I do, it is highlighted in yellow.

Carl Jeffery: I just want to take a minute to introduce and give an overview of the meeting. For the new people, I'm Carl Jeffery, we are responsible for getting the room and hosting this meeting. The proposed list on the screen is what Optum is recommending as preferred or non-preferred, it mirrors what is on the web. On the left is what is recommended as preferred. The right is the recommended as non-preferred. The yellow highlighted area is the new or proposed changes from the previous list. The center column is just like the published PDL, it lists any PA criteria or restrictions that we may have for the class.

Shamim Nagy, Chair: Any other public comment for ADHD? None?

Carl Jeffery: We have six new agents, we heard about the Adzenys already. The other new medications are all established drugs but with new dosage forms. An overview of the new products and the drug class is presented. Guidelines do not favor one agent over another. No

head-to-head studies showing one is better. Optum recommends the class be considered clinically and therapeutically equivalent.

Shamim Nagy, Chair: Any discussion? I need a motion.

Adam Zold: Motion they are therapeutically equivalent.

Joseph Adashek: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: We recommend keeping the class the same, making Adzenys, Dyanavel and Quilichew as preferred to offer more dosing options for children. Aptensio XR and Evekeo and Zenzedi as non-preferred.

Michael Hautekeet: I make a motion to accept the recommendations.

Evelyn Chu: Second.

Voting: Ayes across the board, the motion carries.

Shamim Nagy, Chair: Antipsychotics: Atypical. Any public comment?

Dr. Leon Ivan: I am Dr. Leon Ivan, I am the statewide Psychiatric Medical Director for the Division of Public and Behavioral Health and Clinical Professor for the Department of Psychiatry at the University of Nevada School of Medicine. I would like to talk about Rexulti, brexpiprazole. I would like to request all the atypical antipsychotics including Rexulti be available for patients diagnosed with schizophrenia and other psychotic disorders. This allows the choice for the most effective medication. Delays in treatment can lead to further impairment and several other issues. The benefits of antipsychotics and how some are different is presented. Each patient is unique and responds differently based on side effects and efficacy. First exposure to medication has an impact on further treatment. Non-adherence leads to further complications. For the School of Medicine, having access for the medical residents will allow them to learn about these agents.

Shamim Nagy, Chair: Any questions?

Christopher Highley: Can you specify the benefits of Rexulti over aripiprazole? Is the formulation the same? Any compliance difference?

Dr. Leon Ivan: Both are oral tablets. The difference comes in the receptor binding, Rexulti provides more affinity to 5HT-2 1a and D2 partial agonist. Which has been described as the most beneficial for an atypical antipsychotic, published in 2008 before this medication was introduced on the market.

Shamim Nagy, Chair: Any other questions? Next public comment?

Dr. Horne: I request to have Rexulti on the preferred list because in my experience some patients do much better on this and have failed others.

Carl Jeffery: The Statute requires a trial of one agent in this class before moving to a non-preferred agent

Dr. Horne: But it doesn't have to be that it is paid for by Medicaid?

Carl Jeffery: No, just an attestation from the prescriber that a preferred agent has been tried.

Shamim Nagy, Chair: Any other comments?

Samantha Sweeny: I am Samantha Sweeny with Managed Market Liaison with Otsuka. I'm here to talk about Rexulti or brexpiprazole. An overview and new studies of Rexulti is presented. Otsuka requests Rexulti be made preferred for Nevada Medicaid.

Shamim Nagy, Chair: Any questions? No. Any other comments?

[Inaudible Name]: I use Rexulti in a lot of patients and see improvements in the symptoms. Thank you.

Shamim Nagy, Chair: Any other comment? No, Carl.

Carl Jeffery: I wanted to call out Chapter 1200 the exception criteria. On the bottom line, antipsychotics only demonstrate therapeutic failure on one preferred agent. Just keep that in mind. I want to call out the different diagnoses for each product. Calling out the new medications, Vraylar and Nuplazid. Vraylar has an indication for bipolar and schizophrenia, the only indication for Nuplazid is Parkinson's related hallucinations and psychosis. Vraylar has lots of studies showing it is effective. Nuplazid for Parkinson's disease also has some good data showing it is effective. I threw in Rexulti even though it has been out for a while. The Committee has a packet of letters from the provider community. We heard from a few other providers. From my pharmacist point of view, on paper the Rexulti and Abilify have very similar profiles as far as what receptors they react with. There are some other minor receptors and different affinities for these and that all leads to the therapeutic effect. Shown below are some of the other agents and the receptors they hit. So on paper, these are similar drugs, but that is why we have the Committee and their clinical experience to offer guidance. Optum recommends this class be considered clinically and therapeutically equivalent. We might call out Nuplazid being a little different, it is technically an antipsychotic, but it does not have the same indications as the others, so maybe add a caveat with that product.

Joseph Adashek: I move they are all clinically and therapeutically equivalent.

Adam Zold: Second.

Christopher Highley: I have a question about the first slide, what is the definition of therapeutic failure?

Carl Jeffery: It would be clinical like side effects or lack of response or contraindication.

Voting: Voting, 7 Ayes, 1 Nay – Motion carries

Carl Jeffery: Optum recommends moving the brand Abilify to non-preferred and the generic aripiprazole to preferred and then the two new agents Nuplazid and Vraylar to non-preferred. To make it clear, Nuplazid would still be available for Parkinson's related dementia because it is a unique indication, it would not require any failure on any agent before getting it approved.

Mark Decerbo: That was one of my concerns, in terms of the unique indication, you could be potentially pushing people to clozapine or quetiapine first, but we could carve out the Nuplazid with an ICD-10 code of Parkinson's?

Carl Jeffery: Yeah, we could do that to allow a Parkinson's disease related diagnosis to override the non-preferred status.

Mark Decerbo: Would that come from us or the DUR Board?

Carl Jeffery: Yes, you would do that here.

Joseph Adashek: I would like to make a motion that we make that medication preferred for a diagnosis of Parkinson's disease.

Mark Decerbo: I second.

Carl Jeffery: Gabe, does this all need to go into one motion?

Gabe Lither: It would be easier if it was all in one motion.

Joseph Adashek: I have other discussion too. I don't use this medication in my practice, but we have lots of doctors from the community say they use Rexulti a lot with good results, I listen to that. My motion would be to also make Rexulti a preferred agent. There are psychiatrists here that know more than me on this, so maybe they can speak too.

Gabe Lither: We can put that all in one motion to see if it works.

Joseph Adashek: Ok, the motion is to make Nuplazid preferred if an ICD-10 diagnosis of Parkinson's is submitted on the claim and to make Rexulti preferred as well.

Adam Zold: Second.

Mark Decerbo: So we have two motions combined.

Carl Jeffery: And for clarification, it would also be to accept the remaining recommended changes.

Joseph Adashek: Yes, to also accept the other recommendations.

Voting: Ayes: 5, Nays: 3 – The motion carries.

4. Annual Review – Established Drug Classes

A. Analgesics: Opiate Agonists

Shamim Nagy, Chair: Going back to Annual Review, established drug classes, Analgesics, Opiate agonists.

Public comment? No comment.

Carl Jeffery: I want to discuss Butrans. With the current state of the opioid abuse in Nevada, we would like to offer some agents that are less abuseable. Butrans is a one a week patch, it is a CIII so it doesn't take the extra CII prescription. It is indicated for the management of pain like the other agents on the list. One of the reasons we have never had it preferred before is because of the dose limit, once you get to 20 micrograms per hour, you need to move to something more potent. Optum recommends these be considered clinically and therapeutically equivalent.

Joseph Adashek: I move they are all therapeutic equivalents.

Adam Zold: Second.

Voting: Ayes across the board.

Carl Jeffery: Optum recommends we move Butrans to preferred and that is our only change. The abuse deterrent opioids are in a different class and will be discussed later.

Adam Zold: I move we go with Optum's recommendations.

Mark Decerbo: Second.

Voting: Ayes across the board, the motion carries.

B. Anti-infective Agents: Antivirals: Anti-hepatitis Agents: Polymerase Inhibitors/Combination
C. Anti-infective Agents: Antivirals: Anti-hepatitis Agents: Protease

Shamim Nagy, Chair: Anti-infective agents, antivirals, anti-hepatitis agents.

Chris Conner: I am Chris Connor with BMS and I am here to talk about Daklinza. An overview, indications, and data for coinfected patients is presented. It is used with Sovaldi for genotype 3. (about 12% of all Hep C patients), they are at a higher risk of progressing to cirrhosis and carcinoma. Daklinza is available in three different doses and is not co-packaged. There are no significant drug interactions with proton pump inhibitors. I ask for you to add Daklinza as preferred on the Nevada Medicaid PDL.

Shamim Nagy, Chair: Thank you, next?

Laura Hill: I am Laura Hill with Medical affairs at Abbvie, I would like the panel to consider moving Viekira and Technivie back to preferred status. There have been updates to the labeling. Indications, contraindications, studies, renal dysfunction, and efficacy information is presented. New extended release formulation now available.

Shamim Nagy, Chair: Thank you, any questions? No, next person.

James Kotusky: I am James Kotusky with Gilead Sciences, I would like to provide a brief statement for Epclusa. Indications are presented.

Gabe Lither: Sorry to interrupt, you're here for Epclusa. Could you keep it brief since your drug is preferred.

James Kotusky: Trials, lab testing and discontinuation rates information is presented.

Shamim Nagy, Chair: Any other comments or questions? Any other public comments?

Carl Jeffery: There are a few agents in this class. We used to have a separate class for the protease inhibitors. We are combining that class with this class and making it an all-encompassing Hep C class. The list of drugs available are shown here and the genotypes they cover. A quick overview of Zepatier, SVR rates show it is very effective and tolerable. Epclusa, there are high cure rates with all the genotypes. Daklinza has good cure rates, but it has to be given with Sovaldi. Optum recommends the drugs in this class be considered clinically and therapeutically equivalent.

Michael Hautekeet: I make a motion to accept these are clinically and therapeutically equivalent.

Evelyn Chu: Second.

Voting: Ayes across the board, the motion carries.

Shamim Nagy, Chair: Do we need a motion to combine the classes.

Carl Jeffery: I don't think we would, we are recommending the Olysio being moved to this class and the other two agents Incivik and Victrelis are no longer available. Gabe, do you agree?

Gabe Lither: Historically, you guys have handled the drugs classes, so I don't think we need a separate motion.

Carl Jeffery: Optum recommends we include Epclusa and Zepatier as preferred and keep Harvoni and Sovaldi as preferred too. This would make Daklinza, Olysio, Technivie and Viekira Pak as non-preferred.

Adam Zold: I would like to make a motion to include Daklinza as preferred.

Gabe Lither: Your motion is to accept the recommendation but add Daklinza as preferred too.

Carl Jeffery: If that is the direction of the Committee, you might as well make Technivie and Viekira preferred as well.

Adam Zold: We had a good discussion a few years ago, and given the cure rates of these drugs we should make the class all inclusive. I think we should stick with that, we should make all the drugs as preferred.

Gabe Lither: So you are changing the motion to include all drugs?

Adam Zold: Yes, I rescind my previous motion and move to make all drugs preferred.

Joseph Adashek: I don't use these drugs in my practice, what is the reason you recommended these as non-preferred?

Carl Jeffery: Daklinza does have a good cure rate, but it requires the addition of Sovaldi as opposed to a single agent, adding to the complexity of the regimen. That is really the basis of our decision.

Evelyn Chu: So to be clear, the agents recommended as preferred are all single agents that can be used as is, and the ones recommended as non-preferred is that they are more complex regimens and they also require ribavirin. That is the reason you are suggesting non-preferred.

Mark Decerbo: It seems ribavirin has dropped off.

Carl Jeffery: Ribavirin is in its own class and we are not reviewing that class today. To reiterate the motion on the floor is to include all medications as preferred.

Voting: Nay – 5, Aye – 3, the motion fails to pass

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

Nikki Beck: Second.

Voting: Nay – 1, Aye – 7, the motion carries.

D. Biologic Response Modifiers: Multiple Sclerosis Agents: Oral

Shamim Nagy, Chair: The next topic is Biologic Response Modifiers, Multiple Sclerosis Agents, oral.

Comments from the floor? No comments.

Carl Jeffery: No new medications in this class, but we wanted to bring this to the Committee. The medication Gilenya has more side effects compared to the other two. But there are a lot of patients that find value in this medication. Optum recommends these be considered clinically and therapeutically equivalent.

Shamim Nagy, Chair: Any discussion?

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

Michael Hautekeet: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: Optum recommends just moving Gilenya to preferred to provide more access to patients.

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

Adam Zold: Second.

Voting: Ayes across the board, the motion carries.

E. Dermatological Agents: Topical Anti-infective: Topical Scabicides

Shamim Nagy, Chair: Dermatological Agents, Topical anti-infective, topical scabicides.

Any public comment? None.

Carl Jeffery: Natroba had clinical criteria added by the DUR Board. Optum recommends these be considered clinically and therapeutically equivalent.

Adam Zold: I motion these be considered clinically and therapeutically equivalent.

Joseph Adashek: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: Our recommendation is to move Natroba to non-preferred, simply because the DUR Board evaluated it and decided it was best to add a clinical PA.

Mark Decerbo: What is the PA criteria?

Carl Jeffery: There are some requirements to use RID or permethrin before moving to the Natroba.

Adam Zold: I motion to go with Optum's recommendation.

Michael Hautekeet: Second.

Voting: Ayes across the board, the motion carries.

F. Electrolytic and Renal Agents: Phosphate Binding Agents

Shamim Nagy, Chair: Electrolyte and renal agents, phosphate binding agents.

Any public comment? No.

Carl Jeffery: No new medications in this class, just some shift in the market. We wanted to talk about Fosrenol. Calcium acetate is the most commonly used. The evidence for depleting phosphorus shows some debate about how effective this really is. The guidelines always recommend a calcium based binder as first line. Optum recommends these be considered clinically and therapeutically equivalent.

Michael Hautekeet: I make the motion that these are clinically and therapeutically equivalent.

Adam Zold: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: Optum recommends moving Fosrenol to non-preferred because the guidelines suggest using a calcium containing binder first for most patients.

Michael Hautekeet: I make the motion to accept the recommendation.

Evelyn Chu: Second.

Voting: Ayes across the board. The motion carries.

G. Gastrointestinal Agents: Antiemetics: Miscellaneous

Shamim Nagy, Chair: Gastrointestinal Agents, antiemetic, miscellaneous.

Public comment? No.

Carl Jeffery: This class is here because the DUR Board asked the P&T Committee to review using the separate ingredients vs. the combined product Diclegis. As most are aware, these products are available over the counter, getting the dose the same is a challenge. Emend doesn't really fall in with Diclegis as far as indications, but it doesn't really fit in to any other classes currently on the PDL, so with that caveat, Optum recommends this class be considered clinically and therapeutically equivalent.

Joseph Adashek: I move that these are clinically and therapeutically equivalent for the miscellaneous class.

Michael Hautekeet: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: Our idea, and this is open to discussion, if you do get a physician to train a patient to track down the medications, then they are welcome to do that.

Joseph Adashek: We use Diclegis, it is a great medication.

Mark Decerbo: For historical perspective, are there any coverage limitations with OTCs?

Carl Jeffery: OTCs are a covered benefit, they need a prescription. So the prescriber would need to write out the separate ingredients. There is a limit to two agents per class for OTCs.

Mark Decerbo: So it is important to let the prescriber know that they need to write a prescription.

Joseph Adashek: I move we accept the recommendation.

Adam Zold: Second.

Voting: Ayes across the board, the motion carries.

H. Hormones and Hormone Modifiers: Antidiabetic Agents: Dipeptidyl Peptidase-4 Inhibitors

Shamim Nagy, Chair: Next topic is Hormones and hormone modifiers, antidiabetic agents, dipeptidyl peptidase-4 inhibitors.

Public comment? No.

Carl Jeffery: This class has some authorized generics, alogliptin and combos. Same ingredients as Nesina. They are the same medications, not changes to the therapeutics. Optum recommends these be considered clinically and therapeutically equivalent.

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

Michael Hautekeet: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: Optum recommends removing the Juvisync, it is no longer available. And then to make the authorized generics as non-preferred.

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

Adam Zold: I move to accept Optum's recommendations.

Michael Hautekeet: Second.

Voting: Ayes across the board, the motion carries.

I. Hormones and Hormone Modifiers: Antidiabetic Agents: Incretin Mimetics

Shamim Nagy, Chair: Next is antidiabetic agents, incretin mimetics.

Any public comment? No.

Carl Jeffery: This is another established class that we want to move things around a little. Tanzeum and Trulicity are the newer ones. The difference is how often they are given, weekly vs. daily. Within the class, all have been shown to decrease A1c and there is not a recommendation to prefer one over the other. Optum recommends these be considered clinically and therapeutically equivalent.

Michael Hautekeet: I move we accept Optum's recommendation that they are clinically and therapeutically equivalent.

Adam Zold: Second.

Voting: Ayes across the board.

Carl Jeffery: Optum recommends Tanzeum preferred.

Nikki Beck: I was curious why Tanzeum over Trulicity?

Carl Jeffery: Tanzeum has some good clinical information, as does Trulicity. It comes down to how we recommend the preferred drug list.

Nikki Beck: Trulicity is a much easier pen device and it much easier to administer and train than the Tanzeum.

Mark Decerbo: Along with this, would Tanzeum have the same PA criteria as the others?

Carl Jeffery: Right now, until we can get this to the DUR board, Tanzeum and Trulicity will not have clinical criteria. We will get this to the DUR Board, but I might suggest PA requirements be removed. But until then, PA criteria only apply to Bydureon, Byetta and Victoza.

Michael Hautekeet: On a personal note, I used to use Bydureon, the injection sites were very bad. Where with Trulicity it did not have the same effect. I would recommend to make Trulicity preferred with the Tanzeum.

Christopher Highley: Second.

Voting: Ayes across the board, the motion carries.

Gabe Lither: The motion was to make them all preferred.

Carl Jeffery: The PA criteria will have to be reviewed and we will get this back to the DUR Board.

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

Shamim Nagy, Chair: Antidiabetic agents, sodium-glucose co-transporter 2 inhibitors.

Public comment?

Bill O'Neil: Hi my name is Bill O'Neil, a pharmacist with Boeringer Ingleheim. I want to talk about Glyxambi, Jardiance, Synjardy. I would like to point out the cardiovascular outcome studies, it does change the class dynamics. The guidelines do suggest one agent at a time, but in practice, the combinations are really used for patients with high A1c's. There are studies showing combo agents reduce A1c quickly and there are better outcomes. Synjardy is the combination of Jardiance and metformin, we would ask consideration for access to these medications.

Mark Decerbo: With the cardiovascular data, you are referring to the New England Journal that was published about a year ago?

Bill O'Neil: That is correct.

Christopher Highley: Just clinically from my practice experience, I have noticed improved compliance with the combination, in addition to lowering A1c, and tolerability, delaying the need for insulin products.

Shamim Nagy, Chair: Thank you, any other public comments?

Carl Jeffery: The SGLT-2's and the combinations are shown on this slide. We have combos with metformin and DDP-4's. All indications are the same. This has been a pretty good class to work with, as we have seen with the cardiovascular studies. Studies show good results in combination. I will remind the Committee too that they only need to try one agent before moving to a non-preferred. Optum recommends these be considered clinically and therapeutically equivalent.

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

Christopher Highley: Second.

Voting: Ayes across the board.

Carl Jeffery: Optum recommends moving the combination agents to non-preferred. This is because clinically by the guidelines, you are supposed to stabilize medication independently before moving to a combination product. This is easy with this class because they only need to try one agent before getting a non-preferred.

Nikki Beck: With the recent cardiovascular studies, Jardiance was shown to be one that decreased cardiovascular events over Invokana. Invokana had some other guidelines as far as increased fractures. I would consider adding Jardiance to preferred. In place of the Invokana if needed.

Mark Decerbo: I would agree, the newer clinical information showing the cardiovascular outcomes with Jardiance, I would support adding Jardiance. I move accepting as is with the addition of Jardiance as preferred. This is based on new clinical data.

Michael Hautekeet: Second.

Voting: Ayes across the board, the motion carries.

K. Ophthalmic Agents: Antiglaucoma Agents: Ophthalmic Prostaglandins

Shamim Nagy, Chair: Next is ophthalmic agents, anti-glaucoma, ophthalmic prostaglandins.

Public comment?

Carl Jeffery: There is a new generic out for a couple of these agents and that is why we are reviewing these today. They all have the same indication. There is one agent formulated as preservative free, Zioptan. Bimatoprost shows the greatest IOP reduction, but the clinical significance is unknown. The guidelines do not recommend one agent over another. Based on this, Optum recommends these products be considered clinically and therapeutically equivalent.

Evelyn Chu: I motion that we accept these as clinically and therapeutically equivalent.

Michael Hautekeet: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: We want to shake things up a little bit in this class. Optum is recommending moving Zioptan to non-preferred and Lumigan to preferred, the new generic travoprost will be non-preferred.

Michael Hautekeet: I make the motion to accept the recommendations.

Joseph Adashek: Second.

Voting: Ayes across the board, the motion carries.

L. Ophthalmic Agents: Ophthalmic Anti-infective/Anti-inflammatory Combinations: Ophthalmic Quinolones

Shamim Nagy, Chair: The next topic is ophthalmic quinolones.

Public comment?

Carl Jeffery: For the ophthalmic quinolones, there are all short treatments for acute infections. The studies show equal effectiveness. There is one study showing levofloxacin showed a slight better response, but really nothing else. Optum recommends these be considered clinically and therapeutically equivalent.

Joseph Adashek: I motion we accept the recommendations.

Adam Zold: Second.

Voting: Ayes across the board.

Carl Jeffery: We are going to recommend adding ofloxacin to non-preferred and we just realized we are missing levofloxacin and we recommend adding that as preferred.

Nikki Beck: I motion that we accept the recommendations.

Evelyn Chu: Second.

Voting: Ayes across the board, the motion carries.

M. Respiratory Agents: Respiratory Anti-inflammatory Agents: Respiratory Corticosteroids

Shamim Nagy, Chair: The next topic is respiratory anti-inflammatory agents, corticosteroids.

Any public comment? None.

Carl Jeffery: Another class that we want to change around. This class has both metered dose inhalers and nebulizer solution. They are all indicated for the maintenance treatment of asthma. Many placebo controlled trials show these are effective. Guidelines recommend steroid inhalers should be used pretty early in the treatment progress. The guidelines do not call out any specific product even though they may differ in potency. Optum recommends this class be considered clinically and therapeutically equivalent.

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

Michael Hautekeet: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: At one of the last meetings we moved Pulmicort to non-preferred, we want to move that back as preferred and swap the Aerospan to non-preferred, and make Arnuity preferred. Members will still have access to budesonide through the brand name.

Evelyn Chu: I motion that we accept the recommended preferred drug list.

Adam Zold: Second.

Voting: Ayes across the board, the motion carries.

N. Respiratory Agents: Respiratory Beta-Agonists: Long-Acting Respiratory Beta-Agonist

Shamim Nagy, Chair: Long-acting respiratory beta-agonists.

Any comments?

Carl Jeffery: This is another class that has been available for a long time. The guidelines to not recommend a single agent over another. They are shown to be effective for asthma related therapies. Optum recommends these be considered clinically and therapeutically equivalent.

Michael Hautekeet: I make a motion to accept Optum's recommendation of clinically and therapeutically equivalent.

Mark Decerbo: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: We want to swap two agents in this class, similar agents, but move Striverdi to preferred and Arcapta to non-preferred.

Michael Hautekeet: I make the motion to accept the recommendation.

Evelyn Chu: Second.

Voting: Ayes across the board, the motion carries.

O. Respiratory Agents: Respiratory Beta-Agonists: Short-Acting Respiratory Beta-Agonist

Shamim Nagy, Chair: The next class is short-acting respiratory beta-agonists. Public comment?

Carl Jeffery: Another long-established class. The most common in this class is the albuterol metered dose inhalers. I don't think there is any real significance between the inhalers. Based on this information Optum recommends these be considered clinically and therapeutically equivalent.

Evelyn Chu: I motion they be considered clinically and therapeutically equivalent.

Mark Decerbo: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: A couple changes we would like to recommend. First, Maxair inhaler is no longer available, so we are going to remove that from the list. We are going to switch the levalbuterol with the brand Xopenex, this only applies to the nebulizer solution. The other is moving Proair HFA to non-preferred, that will leave Proventil HFA as the sole preferred metered dose inhaler for albuterol.

Christopher Highley: What is behind the recommendation, a couple slides back there was some difference.

Carl Jeffery: The reason with the slide was to show they are about the same, in fact Proventil has slightly faster on-set than Proair. I think it is an equivalent medication, we are just trying to push the market share to Proventil.

Adam Zold: I motion to go with Optum's recommendation.

Mark Decerbo: Second.

Voting: Ayes across the board, the motion carries.

P. Toxicology Agents: Substance Abuse Agents: Mixed Opiate Agonists/Antagonists

Shamim Nagy, Chair: Substance abuse agents, mixed opiate agonists, antagonists. Any public comment?

Carl Jeffery: Since there are no recommended changes, I don't think there is any action necessary by the Committee. We thought there was going to be some market changes. I think we just need a quick vote. Optum recommends this class is clinically and therapeutically equivalent.

Michael Hautekeet: I make the motion they are clinically and therapeutically equivalent

Mark Decerbo: Second.

Voting: Ayes across the board.

Carl Jeffery: Optum recommends the class remain the same.

Evelyn Chu: I motion we accept the recommendation.

Michael Hautekeet: Second.

Voting: Ayes across the board, the motion carries.

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

A. Analgesics: Opiate Agonists - Abuse Deterrent

Shamim Nagy, Chair: Next is established drug classes being reviewed due to the release of new drugs. First is analgesics, opiate agonists, abuse deterrent.

Any public comment?

Carl Jeffery: There is a new drug in this class, Xtampza ER, it is an oxycodone product. Indicated for the same things as the others in the class, management of pain. Administered every 12 hours with food. The capsule can be opened up and sprinkled on apple sauce or given via an NG tube. The microspheres form some kind of gum if tampered. The abuse studies show people still prefer it crushed and ingested over placebo. With this class, Optum recommends these be considered clinically and therapeutically equivalent.

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

Michael Hautekeet: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: Optum recommends moving Hysingla ER to preferred. This is based on the current political environment with opioid abuse, we wanted to provide another abuse deterrent option, a once a day hydrocodone product. And we will keep Embeda as preferred and make the new Xtampza ER as non-preferred.

Mark Decerbo: I move we accept the recommendations.

Evelyn Chu: Second.

Voting: Ayes across the board, the motion carries.

B. Biologic Response Modifiers: Multiple Sclerosis Agents: Injectable

Shamim Nagy, Chair: Next is biologic response modifiers, multiple sclerosis agents, injectable.

Any public comment?

Laura Hill: Hi, my name is Laura Hill, I am with Medical Affairs at Abbvie, and I would like to provide comments on Zinbryta. Prescribing, mechanism of action, indications, administration, black box warning and efficacy information is presented. It is available only through REMS program.

Nikki Beck: A question for you, did you say it requires failure of two agents before moving to this product?

Laura Hill: In general, because of the safety and REMS program, it is not recommended as a first-line treatment, so it would be recommended following two or more agents.

Nikki Beck: So according to the label, you have to fail two.

Laura Hill: Generally, yes, depending on how you write the PA criteria.

Carl Jeffery: We have a new drug in this category. Laura gave us some good information. I will just reiterate the risk of liver damage and why it is not generally considered first line. Optum makes the recommendation these be considered clinically and therapeutically equivalent.

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

Mark Decerbo: Second>

Voting: Ayes across the board, the motion carries.

Carl Jeffery: Optum recommends the Zinbryta be non-preferred since that is how it falls in with the label anyway. The P&T Committee made the decision a few years ago to require failure of just one drug.

Mark Decerbo: Are there any special stipulation with ID medications?

Carl Jeffery: The PA in our preferred drug list does not apply to drugs given in the physician's office. If this is billed through the physician's office, it will not hit the PDL. These medications that need to be given by a health care provider, these rules won't apply.

Evelyn Chu: I make the motion we accept the recommendations as presented.

Voting: Ayes across the board, the motion carries.

C. Cardiovascular Agents: Antilipemics: Fibric Acid Derivatives

Shamim Nagy, Chair: Cardiovascular agents, anti-lipemics, fibric acid derivatives.

Any public comment? No.

Carl Jeffery: There is a new generic, fenofibrate for the Lipofen. No clinical changes. Optum recommends these be considered clinically and therapeutically equivalent.

Michael Hautekeet: I make the motion that we accept these as clinically and therapeutically equivalent.

Adam Zold: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: Our only recommendation is to move the brand Lipofen to non-preferred, the generic is already included as preferred.

Michael Hautekeet: I make the motion to accept the list.

Adam Zold: Second.

Voting: Ayes across the board, the motion carries.

D. Genitourinary Agents: Benign Prostatic Hyperplasia (BPH) Agents:5-Alpha Reductase Inhibitors

Shamim Nagy, Chair: Genitourinary agents, benign prostatic hypertrophy.

Public comment?

Carl Jeffery: This is an easy one too, a generic for the Jalyn is available, duterasteride and tamsulosin. Optum recommends these be considered clinically and therapeutically equivalent.

Michael Hautekeet: I make the motion to accept the recommendation.

Adam Zold: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: Optum recommends the new generic dutesteride and tamsulosin be added as non-preferred.

Michael Hautekeet: I make a motion to accept the recommendation.

Adam Zold: Second.

Voting: Ayes across the board, the motion carries.

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

Shamim Nagy, Chair: Hormones and hormone modifiers, antidiabetic agents, insulins.

Any public comment? No.

Carl Jeffery: A new long-acting Tresiba, a once a day medication. There have been some studies against Lantus, It causes a slower release without regard to meals for type 1 and 2. Good results with reducing A1c. The one caveat with this one is less hypoglycemic episodes as the Lantus. The charts show how the kinetics of the different products are. All the others remain the same, they have been available for a long time. Optum recommends these be considered clinically and therapeutically equivalent.

Adam Zold: I make the motion that these be considered clinically and therapeutically equivalent.

Mark Decerbo: Second.

Voting: Ayes across the board.

Carl Jeffery: Optum recommends that because we already have a few long-acting insulins as preferred and failure of one is needed to move to a non-preferred agent, we recommend Tresiba be added as non-preferred. If for some reason they were having an issue with hypoglycemia, then they could get Tresiba.

Nikki Beck: Can I make a comment about Tresiba? Working with diabetic agents with Tresiba and we are seeing less hypoglycemia especially at night. It is working well with type 1 and type 2 diabetics which is really nice. Plus with the increase in duration, with Lantus it only lasts 8 to 12 hours in some patients, this really does last a full 24 hours. I think we have a greater chance of getting our patients to goal with Tresiba. So I would recommend moving Tresiba to preferred.

Adam Zold: I agree with Dr. Beck, I second.

Voting: Nay – 2, Aye – 5 – the motion carries.

F. Neurological Agents: Anticonvulsants

Shamim Nagy, Chair: Neurological agents, anticonvulsants. Public comment?

Danielle Moreno: Hi my name is Danielle Moreno, I am the Executive Director of the Epilepsy Foundation of Nevada. I am an advocate for the people in Nevada living with epilepsy. Limiting access is putting lives in danger, and increasing chances of death. Patient's having their medication switched may cause breakthrough seizures. Patients shouldn't be required to appeal decisions. We believe everyone should have open access to all the medications for the treatment of epilepsy.

Nikki Beck: Was there one drug you were thinking of, or just in general.

Danielle Moreno: Just in general.

Rick Arnado: My name is Rick Arnado, I am a Pharm.D. here on behalf of UCB speaking on Briviact. Indications, mechanism of action, available trials, results, adverse reactions, contraindications, and dosing recommendations information is presented. Briviact is schedule 5. Please consider adding access to this medication.

Carl Jeffery: I think we heard about the Briviact and the dosage forms available. The other medication Spritam, levetriacetam is indicated for the adjunctive therapy. It is available in an oral tablet that disintegrates in the mouth. This class has some protections in that only one preferred needs to be tried before a non-preferred. And any product on the market on June 30, 2010 needs to be listed as preferred. Optum recommends this class be considered clinically and therapeutically equivalent.

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

Michael Hautekeet: Second.

Voting: Ayes across the board.

Carl Jeffery: We recommend the two new agents Briviact and Spritam be added as non-preferred because they are both indicated for adjunctive treatment, they are not indicated alone. They are new agents and have never been preferred, so there is nobody that would have these removed. And because only one agent is necessary, having them non-preferred just assures that they are already on another agent. That is what justifies our reasoning here.

Nikki Beck: I have a question, on the comment made earlier about brand vs. generic, if a provider write brand necessary, will that be covered.

Carl Jeffery: The way the statute is, this class is excluded from the requirement,

Mary Griffith: There are no drug classes that are excluded from the generic requirement. But it would depend on which would be less costly, but we do override the generic if the brand is needed for medical necessity. It is as dispense as written PA.

Evelyn Chu: I make a motion that we accept the list as presented.

Adam Zold: Second.

Voting: Ayes across the board, the motion carries.

I. Respiratory Agents: Respiratory Antimuscarinics

Shamim Nagy, Chair: Respiratory agents, respiratory antimuscarinics.

Public comment? No.

Carl Jeffery: Another new agent in this class, Seebri, glycopyroloate, it is another long-acting anticholinergic for the treatment of COPD. It falls in with the GOLD guidelines. No head-to-head studies, no recommendation for one agent over another. Optum recommends these be considered clinically and therapeutically equivalent.

Christopher Highley: I make the motion these be considered clinically and therapeutically equivalent.

Evelyn Chu: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: Given the understanding that the Seebri doesn't offer any benefit over the Spiriva, Optum recommends Seebri be added as non-preferred.

Christopher Highley: I make the motion that we accept the recommendation

Adam Zold: Second.

Voting: Ayes across the board, the motion carries.

G. Respiratory Agents: Respiratory Long-Acting Antimuscarinic/Long-Acting Beta-Agonist Combinations

Shamim Nagy, Chair: The next is respiratory agents, long-acting antimuscarinic, long-acting beta-agonist combinations.

Public comment? No.

Carl Jeffery: Another new agent, Utibron, combo of glycopyrolate with a long-acting beta agonist. Approved for COPD. Guidelines recommend adding it as a first line. No agent has been shown to be better than another. Optum recommends these be considered clinically and therapeutically equivalent.

Michael Hautekeet: I make the motion to accept these as clinically and therapeutically equivalent.

Adam Zold: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: Optum recommends Utibron be added as non-preferred, this leaves Anoro and Stiolto as preferred.

Michael Hautekeet: I make the motion we accept the list as presented.

Adam Zold: Second.

Voting: Ayes across the board, the motion carries.

6. ANNUAL REVIEW – DRUG CLASSES WITHOUT PROPOSED CHANGES

Shamim Nagy, Chair: Annual review of drug classes without proposed changes.

David Crosby: Good afternoon, I am David Crosby, I am an MSL with Bristol Meyers Squibb here to talk briefly on Orencia for rheumatoid arthritis. Indication, dosage, side effects, new dosage delivery device, and recommendations for the treatment of patients with rheumatoid arthritis is presented. I ask you consider adding Orencia to the preferred drug list.

Michelle William: I am Michelle William with UCB, I am here to talk about Cimzia. Dr. Stone did talk about this in his clinical practice. Indication, mechanism of action, dosage forms, and administration information is presented. Cimzia is pregnancy category B. Refer to the website

for the most current contraindications. I request you consider adding Cimzia to the preferred drug list.

Shamim Nagy, Chair: Any other comments.

Carl Jeffery: I don't know if there is any discussion from the Committee on these classes. We could bring something back for the December 8th meeting.

Adam Zold: I would like to bring up the oral anticoagulants. Could we discuss today. I run a bedside delivery service and I would like to see more access to Savaysa.

Gabe Lither: Do you want to make a motion today or wait until December?

Adam Zold: I would like to make a motion to add Savaysa as preferred in the oral anticoagulant class.

Christopher Highley: Is that once daily or twice daily?

Adam Zold: Once daily.

Shamim Nagy, Chair: Do we have a second.

Christopher Highley: I would second that.

Gabe Lither: Carl, could you go over this class real quick?

Carl Jeffery: I we refer the Committee to the preferred drug list in your binder, Savaysa is the only non-preferred in the class, we have Coumadin, Eliquis, Jantoven, Pradaxa, Warfarin and Xarelto as preferred. The DUR Board just did make some changes to remove PA requirements if the appropriate diagnosis is on the claim. It is all dependent on what it is indicated for. Other than that the only reason we didn't include it was at the time it was so new.

Mark Decerbo: Was there any other PA's on Savaysa. The one thing that concerns me is the comparative less efficacy with better renal function. Is this something we could kick back to the DUR Board for discussion?

Carl Jeffery: The DUR Board wanted to make better access to these medications, and the easiest way was to add the diagnosis. The renal function point is good, but our system is not able to look at renal function measures at the time of the claim. We can take this back to the DUR Board for further review to add additional criteria.

Shamim Nagy, Chair: We have a motion and second, voting.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: The classes might be easier to see in your agenda. Optum recommends no changes to the classes listed except for the oral anticoagulants now.

Mark Decerbo: Can we revisit the two products the speakers talked about today?

Michael Hautekeet: Second.

Voting: Ayes across the board.

Carl Jeffery: I think that is it. The next thing on the agenda is the new drugs to market, but I don't have anything right now.

A. Analgesics: Analgesic/Miscellaneous: Neuropathic Pain/Fibromyalgia Agents
B. Analgesics: Analgesic/Miscellaneous: Tramadol and Related Drugs
C. Analgesics: Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) - Oral
D. Antihistamines:H1 blockers: Non-Sedating H1 Blockers
E. Antiinfective Agents: Aminoglycosides: Inhaled Aminoglycosides
F. Antiinfective Agents: Antivirals: Alpha Interferons
G. Antiinfective Agents: Antivirals: Anti-hepatitis Agents: Ribavirins
H. Antiinfective Agents: Antivirals: Anti-Herpetic Agents
I. Antiinfective Agents: Antivirals: Influenza Agents
J. Antiinfective Agents: Cephalosporins: Second-Generation Cephalosporins
K. Antiinfective Agents: Cephalosporins: Third-Generation Cephalosporins
L. Antiinfective Agents: Macrolides
M. Antiinfective Agents: Quinolones: Quinolones - 2nd Generation
N. Antiinfective Agents: Quinolones: Quinolones - 3rd Generation
O. Autonomic Agents: Sympathomimetics: Self-Injectable Epinephrine
P. Biologic Response Modifiers: Immunomodulators: Disease-Modifying Antirheumatic Agents
Q. Biologic Response Modifiers: Multiple Sclerosis Agents: Specific Symptomatic Treatment
R. Cardiovascular Agents: Antihypertensive Agents: Angiotensin II Receptor Antagonists
S. Cardiovascular Agents: Antihypertensive Agents: Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors)
T. Cardiovascular Agents: Antihypertensive Agents: Beta-Blockers
U. Cardiovascular Agents: Antihypertensive Agents: Calcium-Channel Blockers
V. Cardiovascular Agents: Antihypertensive Agents: Direct Renin Inhibitors
W. Cardiovascular Agents: Antihypertensive Agents: Vasodilators:Inhaled
X. Cardiovascular Agents: Antihypertensive Agents: Vasodilators: Oral
Y. Cardiovascular Agents: Antilipemics: Bile Acid Sequestrants
Z. Cardiovascular Agents: Antilipemics: Cholesterol Absorption Inhibitors
AA. Cardiovascular Agents: Antilipemics: HMG-CoA Reductase Inhibitors (Statins):
BB. Cardiovascular Agents: Antilipemics: Niacin Agents
CC. Cardiovascular Agents: Antilipemics:Omega-3 Fatty Acids
DD. Dermatological Agents: Antipsoriatic Agents: Topical Vitamin D Analogs
EE. Dermatological Agents: Topical Analgesics
FF. Dermatological Agents: Topical Antiinfectives: Acne Agents: Topical, Benzoyl Peroxide, Antibiotics and Combination Products
GG. Dermatological Agents: Topical Antiinfectives: Impetigo Agents: Topical

HH. Dermatological Agents: Topical Antiinfectives: Topical Antifungals (onychomycosis)
II. Dermatological Agents: Topical Antiinfectives: Topical Antivirals
JJ. Dermatological Agents: Topical Antiinflammatory Agents: Immunomodulators: Topical
KK. Dermatological Agents: Topical Antineoplastics: Topical Retinoids
LL. Gastrointestinal Agents: Antiemetics: Serotonin-receptor antagonists/Combo
MM. Gastrointestinal Agents: Antiulcer Agents:H2 blockers
NN. Gastrointestinal Agents: Antiulcer Agents: Proton Pump Inhibitors (PPIs)
OO. Gastrointestinal Agents: Gastrointestinal Anti-inflammatory Agents
PP. Gastrointestinal Agents: Gastrointestinal Enzymes
QQ. Genitourinary Agents: Benign Prostatic Hyperplasia (BPH) Agents: Alpha-Blockers
RR. Genitourinary Agents: Bladder Antispasmodics
SS. Hematological Agents: Anticoagulants: Injectable
TT. Hematological Agents: Anticoagulants: Oral
UU. Hematological Agents: Erythropoiesis-Stimulating Agents
VV. Hematological Agents: Platelet Inhibitors
WW. Hormones and Hormone Modifiers: Androgens
XX. Hormones and Hormone Modifiers:Antidiabetic Agents: Alpha-Glucosidase Inhibitors/Amylin analogs/Misc.
YY. Hormones and Hormone Modifiers: Antidiabetic Agents: Biguanides
ZZ. Hormones and Hormone Modifiers: Antidiabetic Agents: Meglitinides
AAA. Hormones and Hormone Modifiers: Antidiabetic Agents: Sulfonylureas
BBB. Hormones and Hormone Modifiers: Antidiabetic Agents: Thiazolidinediones
CCC. Hormones and Hormone Modifiers: Pituitary Hormones: Growth hormone modifiers
DDD. Hormones and Hormone Modifiers: Progestins for Cachexia
EEE. Musculoskeletal Agents: Antigout Agents
FFF. Musculoskeletal Agents: Bone Resorption Inhibitors: Bisphosphonates
GGG. Musculoskeletal Agents: Bone Resorption Inhibitors: Nasal Calcitonins
HHH. Musculoskeletal Agents: Restless Leg Syndrome Agents
III. Musculoskeletal Agents: Skeletal Muscle Relaxants
JJJ. Neurological Agents: Alzheimer's Agents
KKK. Neurological Agents: Anticonvulsants: Barbiturates
LLL. Neurological Agents: Anticonvulsants: Benzodiazepines
MMM. Neurological Agents: Anticonvulsants: Hydantoins
NNN. Neurological Agents: Anti-Migraine Agents: Serotonin-Receptor Agonists
OOO. Neurological Agents: Antiparkinsonian Agents: Non-ergot Dopamine Agonists
PPP. Ophthalmic Agents: Antiglaucoma Agents: Carbonic Anhydrase Inhibitors/Beta-Blockers
QQQ. Ophthalmic Agents: Ophthalmic Antiinfectives: Ophthalmic Macrolides
RRR. Ophthalmic Agents: Ophthalmic Antihistamines

SSS. Ophthalmic Agents: Ophthalmic Anti-inflammatory Agents: Ophthalmic Corticosteroids
TTT. Ophthalmic Agents: Ophthalmic Anti-inflammatory Agents: Ophthalmic Nonsteroidal Anti-inflammatory Drugs (NSAIDs)
UUU. Otic Agents: Otic Antiinfectives: Otic Quinolones
VVV. Psychotropic Agents: Antidepressants: Other
WWW. Psychotropic Agents: Antidepressants: Selective Serotonin Reuptake Inhibitors (SSRIs)
XXX. Psychotropic Agents: Anxiolytics, Sedatives, and Hypnotics
YYY. Psychotropic Agents: Psychostimulants: Narcolepsy Agents
ZZZ. Respiratory Agents: Nasal Antihistamines
AAAA. Respiratory Agents: Respiratory Antiinflammatory Agents: Leukotriene Receptor Antagonists
BBBB. Respiratory Agents: Respiratory Antiinflammatory Agents: Nasal Corticosteroids
CCCC. Respiratory Agents: Respiratory Antiinflammatory Agents: Phosphodiesterase Type 4 Inhibitors
DDDD. Respiratory Agents: Respiratory Corticosteriod/Long-Acting Beta-Agonist Combinations
EEEE. Toxicology Agents: Antidotes: Opiate Antagonists

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

8. **Closing Discussion**

Shamim Nagy, Chair: Closing discussion, any comments?

Audience member: When will this be effective?

Carl Jeffery: January 1, 2017.

Shamim Nagy, Chair: No other comments. The next meeting is December 8th. The meeting is adjourned.

Meeting adjourned at 4:06 PM

Therapeutic Class Overview
Agents for Gout

Therapeutic Class Overview/Summary:
Gout is a complex inflammatory disease that occurs in response to the presence of monosodium urate monohydrate crystals in the joints, bones and soft tissues.[1,2] The disease consists of four clinical phases.[3] The first phase is asymptomatic hyperuricemia. Although hyperuricemia is a necessary predisposing factor, the presence of high serum urate levels alone does not automatically lead to gout.[1,3] One study reported that 78% of the men in the trial with serum urate levels greater than 9 mg/dL did not develop gout over a five year period.[4] Hyperuricemia can be caused by impaired renal excretion or overproduction of serum urate and/or overconsumption of purine-rich foods that are metabolized to urate.[1] Humans, lack the enzyme uricase and therefore cannot convert urate to the soluble allantoin as the end product of purine metabolism.[2] The deposition of monosodium urate monohydrate crystals into the joints and other areas of the body begin when serum urate levels are greater than 6.8 mg/dL. This concentration is the saturation point of urate in biological fluids and it is at this concentration where monosodium urate monohydrate crystals begin to precipitate. As mentioned previously the presence of hyperuricemia does not automatically lead to gout. Other factors, when combined with hyperuricemia that contribute to monosodium urate monohydrate deposition and the development of gout include trauma or irritation of joins, lower temperatures which favor crystal deposition and previously diseased joints.[4]

The second phase is characterized by intermittent acute gout attacks.[3] These attacks are due to the abrupt release of monosodium urate monohydrate crystals into the joint space where they initiate an acute inflammatory reaction characterized by painful inflammatory arthritis.[4] These attacks typically resolve spontaneously over a period of seven to 10 days.[2] The time interval separating these acute attacks is the third phase of the disease and is known as the intercritical gout period.[5] The time period separating acute gout attacks during this period vary widely between a few days to several years. Overtime, if the disease is left untreated it evolves into chronic tophaceous gout. This phase of the disease is characterized by the deposition of solid monosodium urate monohydrate crystal aggregates known as tophi in a variety of locations including joints, bursae and tendons.[5] In addition deposits of monosodium urate monohydrate crystals in the renal tubules can also lead to renal calculi and nephropathy.[3]

Treatment of gout consists of rapid relief of pain and disability caused by acute gout attacks and the reduction of serum urate levels. This reduction prevents further acute attacks and the progression of the disease to tophaceous gout.[2] Although acute attacks can be treated with anti-inflammatory medications, the underlying cause of the disease can only be treated by lowering serum urate levels.[4]

In addition to the treatment of gout the agents included in this review are also indicated for a number of other indications. These include hyperuricemia due to chemotherapy, Familial Mediterranean Fever, increasing of penicillin levels, and treatment of calcium oxalate calculi. These indications will not be discussed in detail as they are outside the scope of this review.[6-13] These agents also have different mechanisms of actions by which they exert their effects. Colchicine is believed to exert a positive effect in gout by preventing the activation, degranulation and migration of neutrophils, implicated in the pathogenesis of gout symptoms. The mechanism by which colchicine acts in patients with Familial Mediterranean Fever has not been fully established; however, there is evidence suggesting that colchicine interferes with the assembly of the inflammasome complex found in neutrophils and monocytes that medicate the activation of interleukin-1β.[7,8] Allopurinol and febuxostat are both xanthine oxidase inhibitors. These agents causes a decrease in urate levels through the inhibition of xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to xanthine and then finally to uric acid.[6,9] A major difference between these two agents is that allopurinol is a purine analogue where febuxostat is not.[14] Another major difference is that febuxostat is mainly metabolized in the liver and thus does not require renal dosing in mild-moderate renally impaired patients.[6,9] Pegloticase is a recombinant uricase, a uric acid-specific enzyme, which catalyzes the oxidation of uric acid to allantoin, thereby lowering serum uric

acid. Allantoin is an inert and water soluble purine metabolite which is readily eliminated, primarily via renal excretion.[10] Probenecid is a uricosuric agent that exerts its effects on serum urate by inhibiting the reabsorption of uric acid at the proximal tubule which leads to uric acid excretion and a decrease in overall serum urate levels.[11,15] Probenecid is also available with colchicine as a combination product.[12] Lesinurad inhibits urate transporter-1 (URAT1) and organic ion transporter-4 (OAT4) thereby reducing renal reabsorption and increasing excretion of urate and thus lowering serum uric acid (sUA) concentrations.[13]

Table 1. Current Medications Available in the Therapeutic Class[6-13]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agent			
Allopurinol (Zyloprim®*)	Management of patients with signs and symptoms of primary or secondary gout (acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy); management of patients with leukemia, lymphoma and malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels; management of patients with recurrent calcium oxalate calculi whose daily uric acid excretion exceeds 800 mg/day in male patients and 750 mg/day in female patients	Tablet: 100 mg 300 mg	✔
Colchicine (Colcrys®*, Mitigare®*)	Prophylaxis of gout flares; treatment of gout flares; treatment of Familial Mediterranean Fever	Capsule: 0.6 mg Tablet: 0.6 mg	✔
Febuxostat (Uloric®)	Chronic management of hyperuricemia in patients with gout	Tablet: 40 mg 80 mg	-
Lesinurad (Zurampic®)	In combination with a xanthine oxidase inhibitor for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with a xanthine oxidase inhibitor alone	Tablet: 200 mg	-
Pegloticase (Krystexxa®)	Treatment of chronic gout in adult patients refractory to conventional therapy	Vial 8 mg/mL Must be administered in a health care facility.	-
Probenecid*	Treatment of hyperuricemia associated with gout and gouty arthritis; adjuvant therapy with penicillin or with ampicillin,	Tablet: 500 mg	✔

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
	methicillin, oxacillin, cloxacillin, or nafcillin, for elevation and prolongation of plasma levels by whatever route the antibiotic is given		
Combination Products			
Colchicine/probenecid*	Treatment of chronic gouty arthritis when complicated by frequent, recurrent acute attacks of gout	Tablet: 0.5 mg/0.5 g	✔

*Generic available in at least one dosage form or strength.

Evidence-based Medicine

- Regarding Familial Mediterranean Fever, studies that have examined the use of colchicine for this disease state are limited. It should be noted, that approval of brand colchicine for Familial Mediterranean Fever treatment was not based on new clinical studies but rather on previously published literature. These studies as well as others confirmed that the agent is efficacious in both reducing the number of attacks and in aborting acute attacks.[7,24,25,55]
- Efficacy of colchicine for the treatment and prevention of gout and increased uric acid levels is well documented.[28-30]
- The efficacy and safety of pegloticase was evaluated in two identical randomized placebo-controlled studies. The studies were six months in duration and included adult patients with symptomatic gout and at least three gout flares in the previous 18 months or the presence of at least one gout tophus or gouty arthritis. Moreover, patients were included if they had a self-reported contraindication to allopurinol or a medical history of failure to normalize uric acid with at least three months of allopurinol treatment. Patients in both studies were treated with either pegloticase 8 mg every two weeks, every four weeks or placebo. The primary endpoint in both studies was the proportion of patients who achieved plasma uric acid (PUA) levels less than 6 mg/dL for at least 80% of the time during months 3 and 6. In the first study, 47% and 20% of patients in the 8 mg every two and four weeks respectively achieved PUA<6 mg/dL for ≥80% of the time. There was a significant difference in both groups when compared to placebo (0%, P<0.001 and P=0.044, respectively). In the second study, 38% and 49% of patients in the 8 mg every 2 and 4 weeks respectively achieved PUA<6 mg/dL for ≥80% of the time. There was a significant difference in both groups when compared to placebo (0%, P<0.001 for both pegloticase groups).[10,31]
- Regarding febuxostat, the three major trials that were the basis for approval were the FACT, APEX, and CONFIRMS trials. These studies were all randomized, double-blind, controlled trials that compared the treatment of febuxostat, in doses ranging from 40 to 240 mg/day, to allopurinol or placebo in patients with gout. The FACT and APEX studies demonstrated that a significantly greater number of patients treated with febuxostat 80, 120 and 240 mg were able to reach a serum urate goal of less than six mg/dL. In the CONFIRMS trial patients in the 80 mg group had similar outcomes to the FACT and APEX studies; however the CONFIRMS trial also evaluated a 40 mg dose where the proportion of patients with serum urate level <6 mg/dL was not found to be significantly different between the febuxostat 40 mg and the allopurinol groups. These studies also reported that febuxostat was more efficacious than allopurinol in patients with mild to moderate renal impairment. However, in all three studies there were no differences between any of the groups for the number of patients who required treatment for acute gout flares. Regarding adverse events, there were generally no significant differences in the incidence of adverse events between the febuxostat and allopurinol groups and they were generally mild to moderate in severity. There was also no statistically significant difference between groups in the incidence of cardiovascular events.[36-38]
- FDA-approval of lesinurad was based on three randomized, placebo-controlled studies of lesinurad in combination with xanthine oxidase inhibitor. Combination with allopurinol was assessed in studies CLEAR 1 and CLEAR 2, and combination therapy with febuxostat was assessed in the CRYSTAL

study. For up to 12 months, a total of 511, 510 and 516 patients were treated with lesinurad 200 mg, 400 mg and placebo, respectively. Results from these trials demonstrated combination therapy significantly increased the proportion of patients achieving target serum uric acid levels in patients with inadequate response to xanthine oxidase inhibitor monotherapy (P<0.001).[46-49]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Recommend a nonsteroidal anti-inflammatory drug (NSAID), colchicine, or a corticosteroid for the treatment of an acute gout attack.[18-21]
    - According to the more recent guidelines for the management of gout, initiation of urate lowering therapy is recommended in patients with an established diagnosis of gout and tophus or tophi, frequent attacks of acute gouty arthritis (≥2 attacks/year), chronic kidney disease stage 2 or worse, and past urolithiasis.[18]
    - Agents used to lower serum urate levels include allopurinol, probenecid, and febuxostat. The main difference between these agents is that allopurinol and febuxostat inhibit urate production and probenecid promotes urate excretion.[18-22]
    - The 2012 ACR guideline recommends either allopurinol or febuxostat as the first-line urate lowering therapy approach for the management of gout, with no preference stated between the two. While the updated EULAR guidelines recommend allopurinol as first line folled by febuxostat if allopurinol is not tolerated.[18]
    - In comparison, older guidelines, published prior to approval of febuxostat, recommend allopurinol first-line and note febuxostat as a second-line option when allopurinol is not effective or not appropriate.[19-21]
    - The ACR recommends probenecid as an alternative first-line urate lowering therapy option in patients with a contraindication or intolerance to either allopurinol or febuxostat.[16]
    - During initiation of urate lowering therapy the guidelines recommend concurrent prophylaxis with either colchicine or an NSAID, although generally colchicine is the preferred, to prevent acute attacks while starting therapy.[19-21]
    - Concomitant therapy is generally recommended for up to six months at which point only the urate lowering agent is continued. Treatment with the urate lowering agent has the potential to be lifelong.[19,20]
- Other Key Facts:
    - Colchicine tablets and colchicine capsules have different FDA-approved indications and ages approved.[1,2]
    - Colchicine tablets are approved for use in children ≥4 years of age for the treatment of Familial Mediterranean Fever (tablets).[1]

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Therapeutic Class Overview
Oral Anticoagulants

Therapeutic Class

- **Overview/Summary:** Apixaban (Eliquis®), dabigatran etexilate mesylate (Pradaxa®), edoxaban tosylate (Savaysa®), rivaroxaban (Xarelto®) and warfarin (Coumadin®, Jantoven®) are oral anticoagulants that are Food and Drug Administration (FDA)-approved for various cardiovascular indications.[1-4] Warfarin, has been the principle oral anticoagulant for more than 60 years and has extensive, well established data demonstrating its safety and efficacy in all of its FDA-approved indications.[6-8] Apixaban, edoxaban tosylate and rivaroxaban are selective factor Xa inhibitors while dabigatran etexilate mesylate is a direct thrombin inhibitor (DTI). The newer novel oral anticoagulants are approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF).[1-4] Apixaban, dabigatran etexilate mesylate and rivaroxaban are also approved for the treatment and prophylaxis deep vein thrombosis (DVT) and pulmonary embolism (PE), whereas edoxaban tosylate has approval for the treatment of DVT and PE. Dabigatran etexilate is approved for DVT and PE prophylaxis after hip replacement surgery. Additionally, apixaban and rivaroxaban are indicated for DVT prophylaxis which may lead to PE in patients undergoing knee or hip replacement surgery.[1-4] Apixaban, edoxaban tosylate and rivaroxaban are selective factor Xa inhibitors while dabigatran etexilate mesylate is a direct thrombin inhibitor. The evidence demonstrating the efficacy of warfarin for FDA-approved indications, including reducing the risk of stroke and systemic embolism in patients with AF, is well established, and warfarin has been considered the standard of care in high-risk patients with AF.[10] While the data for apixaban, dabigatran etexilate mesylate, edoxaban tosylate and rivaroxaban are not as substantial as compared to warfarin, the newer oral anticoagulants are associated with several advantages. Unlike warfarin, apixaban, dabigatran etexilate mesylate, edoxaban tosylate and rivaroxaban are not associated with a narrow therapeutic window, numerous drug-drug and -food interactions, or monitoring requirements.[11,12] Apixaban and dabigatran etexilate mesylate require twice-daily dosing for all FDA-approved indications, in comparison to edoxaban tosylate and warfarin which are only administered once daily. Rivaroxaban is dosed once daily for all indications except for the treatment of DVT and PE, for which it is dosed twice daily. It is also recommended to give rivaroxaban with food, specifically with the evening meal for AF patients.[1-5] Of all the oral anticoagulants, only warfarin does not require a dosage adjustment in patients with renal impairment. Lower doses are recommended for apixaban, dabigatran etexilate mesylate, edoxaban tosylate and rivaroxaban (in AF only).[1-5] Moreover, apixaban requires a dosage adjustment when two or more of the following factors are present: age ≥80 years, weight ≤60 kg or serum creatinine ≥1.5 mg/dL.[1] In situations where a major bleed occurs, no specific antidote is currently available for the new oral anticoagulants.[12]

Table 1. Current Medications Available in the Therapeutic Class[1-4]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Apixaban (Eliquis®)	DVT/PE prophylaxis* and treatment, DVT prophylaxis following hip or knee replacement surgery, to reduce the risk of stroke and systemic embolism in nonvalvular atrial fibrillation	Tablet: 2.5 mg 5 mg	-
Dabigatran etexilate mesylate (Pradaxa®)	DVT/PE prophylaxis‡ and treatment†, to reduce the risk of stroke and systemic embolism in nonvalvular atrial fibrillation, DVT/PE prophylaxis following hip replacement surgery	Capsule: 75 mg 110 mg 150 mg	-
Enoxaban tosylate (Savaysa®)	DVT/PE treatment†, to reduce the risk of stroke and systemic embolism in	Tablet: 15 mg	-

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
	nonvalvular atrial fibrillation	30 mg 60 mg	
Rivaroxaban (Xarelto®)	DVT/PE prophylaxis* and treatment, DVT prophylaxis following hip or knee replacement surgery, to reduce the risk of stroke and systemic embolism in nonvalvular atrial fibrillation	Tablet: 10 mg 15 mg 20 mg	-
Warfarin (Coumadin®*, Jantoven®*)	DVT/PE prophylaxis and treatment, to reduce the risk of death, recurrent MI, and thromboembolic events after an MI, prophylaxis and treatment of thromboembolic complication associated with atrial fibrillation and/or cardiac valve replacement	Tablet: 1 mg 2 mg 2.5 mg 3 mg 4 mg 5 mg 6 mg 7.5 mg 10 mg	✔

DVT=Deep Vein Thrombosis, MI=myocardial infarction, PE=pulmonary embolism
*Indicated to reduce the risk of recurrent DVT or PE following initial six months of treatment for DVT/PE.
†Indicated for treatment of DVT and PE in patients who have been treated with a parenteral anticoagulant for five to 10 days.
‡Indicated to reduce the risk of recurrent DVT or PE in patients who have been previously treated.

Evidence-based Medicine

- As it has been the principle oral anticoagulant for more than 60 years, the clinical evidence derived from meta-analyses and Cochrane Reviews demonstrating the safety and efficacy of warfarin in Food and Drug Administration-approved indications is well established.[10,12-18]
- The safety and efficacy of the oral anticoagulants have been evaluated in many clinical trials.[19-64]
- The efficacy of apixaban in patients with nonvalvular atrial fibrillation (AF) was evaluated in the AVERROES and ARISTOTLE trials.[19,23]
- In ARISTOTLE (N=18,201), patients were randomized to receive apixaban 5 mg twice daily or dose-adjusted warfarin (to target an International Normalized Ratio [INR] of 2.0 to 3.0). The incidence of stroke or systemic embolism, the primary endpoint, was significantly reduced in patients treated with apixaban compared to patients treated with warfarin (1.27 vs 1.60% per year; HR, 0.79; 95% CI, 0.66 to 0.95; *P*<0.001 for non inferiority and *P*=0.01 for superiority).
    - Treatment with apixaban was associated with a significantly lower incidence of major intracranial bleeding (*P*<0.001), and major bleeding at other locations (*P*=0.004) compared to warfarin treatment. There was no difference in the rate of major gastrointestinal bleeding with apixaban compared to warfarin (*P*=0.37). The rate of myocardial infarction (MI) was similar between the apixaban and warfarin treatment groups (*P*=0.37); however, apixaban treatment significantly reduced death from any cause compared to warfarin treatment (3.52 vs 3.94% per year; HR, 0.89; 95% CI, 0.80 to 0.998; *P*=0.047).[19]
- In AVERROES (N=5,599), patients were randomized to receive apixaban 5 mg twice daily or aspirin 81 to 324 mg once daily. The incidence of stroke or systemic embolism, the primary endpoint, was significantly reduced in patients treated with apixaban compared to patients treated with aspirin (1.6 vs 3.7% per year; hazard ratio [HR], 0.45; 95% confidence interval [CI], 0.32 to 0.62; *P*<0.001).
- There was no difference in major bleeding between the apixaban and aspirin treatment groups (*P*=0.57). The incidences of intracranial bleeding (*P*=0.69), extracranial bleeding (*P*=0.42), gastrointestinal bleeding (*P*=0.71), non gastrointestinal bleeding (*P*=0.22) and fatal bleeding (*P*=0.53) were similar between the treatment groups.[23]
- Approval of apixaban for use as prophylaxis of DVT and PE in patients who have undergone hip or knee replacement surgery, was established after being compared to enoxaparin in three large, multi-

centered, double-blind, double-dummy, randomized control trials: ADVANCE-1, ADVANCE-2, and ADVANCE-3.[44-46]

- In ADVANCE-1, the statistical criterion for the noninferiority of apixaban as compared with twice-daily administration of enoxaparin was not met. DVT, non-fatal PE, and all-cause death occurred in 104 of 1157 patients (9.0%) in the apixaban group, as compared with 100 of 1130 patients (8.8%) in the enoxaparin group (relative risk [RR], 1.02; 95% CI, 0.78 to 1.32; P=0.06 for noninferiority; difference in risk, 0.1%; 95% CI, –2.2 to 2.4; P<0.001).[44]
- In ADVANCE-2, apixaban was had statistically significant reduction in risk compared to enoxaparin once-daily for prevention of all VTE and all-cause death (RR, 0.62; 95% CI, 0.51 to 0.74, one-sided P<0.0001 when tested for non-inferiority and for superiority). Absolute risk reduction was 9.3% (95% CI, 5.8% to 12.7%) in favor of apixaban (one-sided P<0.0001 for non-inferiority).[44]
- In ADVANCE-1, There was a statistically significant increase in major and non-major bleeding for twice daily enoxaparin 30 mg compared to apixaban (adjusted difference in event rates according to type of surgery, -0.81%; 95% CI, -1.49% to −0.14%; P=0.053) as opposed to ADVANCE-2, where there was no difference in major bleeding rates between enoxaparin daily and apixaban (P=0.3014).[44,45]
- In ADVANCE-3 there was a statistically significant reduction in asymptomatic or symptomatic DVT, nonfatal PE, or death from any cause with apixaban 2.5 mg twice dialy compared with enoxaparin 40 mg daily (RR with apixaban, 0.36; 95% CI, 0.22 to 0.54; one-sided P<0.001 for noninferiority and two-sided P<0.001 for superiority). The absolute risk reduction with apixaban was 2.5% (95% CI, 1.5% to 3.5%).[46]

- Approval of dabigatran etexilate mesylate for use in AF was based on the clinical evidence derived from the non inferiority, RE-LY trial (N=18,113). After a median follow-up of two years, dabigatran etexilate mesylate 110 mg twice-daily was associated with a similar rate of stroke and systemic embolism compared to warfarin (*P*=0.34), while dabigatran etexilate mesylate 150 mg twice-daily was associated with a significantly lower rate (*P*<0.001). Rates of major bleeding were similar between warfarin and dabigatran etexilate mesylate 150 mg twice-daily (*P*=0.31) but significantly less with dabigatran etexilate mesylate 110 mg twice-daily (*P*=0.003).[26]
  - No differences were observed between the two treatments with regard to death from any cause and pulmonary embolism (PE); however, the rate of MI was significantly higher (*P*=0.048 with dabigatran etexilate mesylate 150 mg vs warfarin) and the rate of hospitalization significantly lower (*P*=0.003 with dabigatran etexilate mesylate 110 mg vs warfarin) with dabigatran etexilate mesylate.[30]
  - A 2012 subgroup analysis of RE-LY demonstrated a nonsignificant increase in MI with dabigatran etexilate mesylate compared to warfarin, but other myocardial ischemic events were not increased. In addition, results revealed that treatment effects of dabigatran etexilate mesylate were consistent in patients at higher and lower risk of myocardial ischemic events.[23] In contrast, a meta-analysis published in 2012 demonstrated that dabigatran etexilate mesylate is associated with an increased risk of MI or acute coronary syndrome (ACS) in a broad spectrum of patients (e.g., stroke prophylaxis in AF, acute venous thromboembolism [VTE], ACS, short term prophylaxis of deep venous thrombosis [DVT]) compared to different controls (warfarin, enoxaparin, or placebo).[64]
- The RE-COVER study found dabigatran etexilate mesylate to be noninferior to warfarin in preventing recurrent VTE who had presented with acute symptoms of DVT or PE (P<0.001), with the RE-COVER II study also confirming the results (P<0.001).[47,48] Patients who participated in the RE-COVER or RE-COVER II study and received dabigatran etexilate mesylate and had additional risk factors could elect for long term VTE prophylaxis in two follow up studies, RE-MEDY or RE-SONATE. RE-MEDY was and active-control study whereas RE-SONATE was placebo-controlled. Dabigatran etexilate mesylate was found to be noninferior to warfarin and superior to placebo in long-term VTE prophylaxis (P=0.01 and P<0.001 respectively).[49]
- Safety and efficacy of dabigatran etexilate for the prevention of DVT and PE after hip replacement surgery was established in two clinical trials, RE-NOVATE and RE-NOVATE II. Dabigatran etexilate 220 mg once daily was compared to enoxaparin 40 mg once daily in a double-blind, double-dummy

design for 28 to 35 days.[50,51] In RE-NOVATE, the absolute difference in dabigatran etexilate when compared to enoxaparin was -0.7% (no P value reported).[50] In RE-NOVATE II, the absolute difference was -1.1% (P=0.43).[51] In both studies, dabigatran etexilate 220 mg once daily was shown to be non-inferior to enoxaparin 40 mg once daily by having an absolute difference in total VTE and all-cause mortality below the pre-established non-inferiority margin of 7.7%.

- Approval of rivaroxaban for use in AF was based on the clinical evidence for safety and efficacy derived from the non inferiority, ROCKET-AF trial (N=14,264). Results demonstrated that rivaroxaban (15 or 20 mg/day) is non inferior to warfarin for the prevention of stroke or systemic embolism (*P*<0.001 for non inferiority), with no increased risk of major bleeding (*P*=0.44). Within ROCKET-AF, intracranial and fatal bleeding were significantly less frequent with rivaroxaban (*P*=0.02).[36]
    - In a subgroup analysis of ROCKET-AF evaluating the efficacy and safety of rivaroxaban among patients with and without previous stroke or transient ischemic attack, it was revealed that the relative efficacy and safety of rivaroxaban compared to warfarin was not different between these two patient populations. Ultimately, results support the use of rivaroxaban as an alternative to warfarin for the prevention of recurrent as well as initial stroke in patients with AF.[37]
- Approval of rivaroxaban for prophylaxis of DVT was based on the clinical evidence for safety and efficacy derived from the global program of clinical trials known collectively as RECORD (1 [N=4,541], 2 [N=2,509], 3 [2,531], and 4 [N=3,148]). All four trials compared rivaroxaban to enoxaparin for thromboprophylaxis in patients undergoing total elective hip and knee replacement surgeries.[53-56]
    - In all four trials, rivaroxaban significantly reduced the risk of the primary composite endpoint of any DVT, nonfatal PE, or death from any cause compared to enoxaparin, with no increased risk of major bleeding, any bleeding, and hemorrhagic wound complications.
- The approval of rivaroxaban for the treatment of DVT and PE, and for the reduction in the risk of recurrence of DVT and PE was based on two open-label, non inferiority trials. In EINSTEIN-DVT, 3,449 patients with an acute, symptomatic, objectively confirmed proximal DVT without symptomatic PE received rivaroxaban 15 mg twice daily for three weeks followed by 20 mg once daily or enoxaparin 1 mg/kg subcutaneously twice daily plus warfarin or acenocoumarol adjusted to maintain an INR of 2.0 to 3.0. The occurrence of symptomatic, recurrent VTE was 2.1% in the rivaroxaban group and 3.0% in the standard therapy group (HR, 0.68; 95% CI, 0.44 to 1.04; *P*<0.001 for non inferiority and *P*=0.08 for superiority).[57]
    - Clinically relevant (first major or clinically relevant non major) bleeding was similar between the treatment groups (*P*=0.77). In a 12-month extension, EINSTEIN-EXT, symptomatic, recurrent VTE occurred in eight patients receiving rivaroxaban and 42 patients receiving placebo (1.3 vs 7.1%; HR, 0.18; 95% CI, 0.09 to 0.39; *P*<0.001).[57]
- In 4,832 patients with an acute, symptomatic PE, with or without symptomatic DVT (EINSTEIN-PE), there was a symptomatic recurrence of VTE in 50 patients treated with rivaroxaban compared to 44 patients treated with standard-therapy (HR, 1.12; 95% CI, 0.75 to 1.68; *P*=0.003 for non inferiority and *P*=0.57 for superiority).[58]
    - There was no difference between the rivaroxaban and standard therapy treatment groups with regard to major or clinically relevant non major bleeding (HR, 0.90; 95% CI, 0.76 to 1.07; *P*=0.23).[58]
- The FDA approval of edoxaban tosylate was based on two phase III, double-blind, multinational, randomized controlled clinical trials.
    - The second trial compared the efficacy and safety of edoxaban tosylate to warfarin in reducing the risk of stroke and systemic embolic events in adult patients with non-valvular AF. The annualized rate for occurrence of a first stroke (ischemic or hemorrhagic) or a systemic embolic event that occurred during treatment or within three days from the last dose taken was 1.50% with warfarin compared with 1.18% with high-dose edoxaban tosylate (HR, 0.79; 97.5% CI, 0.63 to 0.99; P<0.001) and 1.61% with low-dose edoxaban tosylate (HR, 1.07; 97.5% CI, 0.87 to 1.31; P=0.005). major bleeding during treatment was found to be 3.43% with warfarin compared with 2.75% with high-dose edoxaban tosylate (HR, 0.80; 95% CI, 0.71 to 0.91; P<0.001)

and 1.61% with low-dose edoxaban tosylate (HR, 0.47; 95% CI, 0.41 to 0.55; P<0.001).[35]

- The first study evaluated edoxaban tosylate was compared to warfarin in adult patients with acute venous thromboembolism. Results showed that there was a recurrence of venous thromboembolism in 3.2% of the edoxaban tosylate group as compared with 3.5% in the warfarin group (P<0.001). Edoxaban demonstrated superiority compared to warfarin for clinically relevant bleeding (8.5% compared with 10.3% for the warfarin group [P=0.004]). However, both treatment groups were similar in regards to major bleeding (P=0.35).[52]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[10-18]
  - Atrial fibrillation:
    - The 2014 American Heart Association, American College of Cardiology, and Heart Rhythm Society guideline recommends warfarin, or either apixaban, rivaroxaban or dabigatran as an alternative to warfarin for non-valvular atrial fibrillation. Patients who already have excellent INR control would likely gain little by switching to the newer agents. They recommend not using the newer agents in end-stage chronic kidney disease or on hemodialysis due to lack of evidence regarding the risk versus benefit. A specific recommendation to avoid the use of dabigatran for patients with a mechanical heart valve is also made.[10]
    - The 2012 American College of Chest Physicians recommends oral anticoagulation in patients at intermediate to high risk of stroke, with dabigatran etexilate mesylate suggested over adjusted-dose vitamin K antagonist therapy.[12]
  - Thromboprophylaxis:
    - The 2012 American College of Chest Physicians guideline recommends dabigatran etexilate mesylate, rivaroxaban, and adjusted-dose vitamin K antagonist therapy, along with low molecular weight heparin, fondaparinux, apixaban, low dose unfractionated heparin, aspirin, and an intermittent pneumatic compression device, for thromboprophylaxis in total hip and knee arthroplasty. Low molecular weight heparin is suggested in preference to other recommended agents for this indication.[12]
    - In general, other current guidelines are in line with the American College of Chest Physicians.
  - Secondary prevention in post-myocardial infarction:[12,13,16]
    - Warfarin is recommended in post-myocardial infarction patients who have an indication for anticoagulation; however, the evidence surrounding its use in these patients is still evolving.
  - A recent Science Advisory for Healthcare Professionals by the American Heart Association and American Stroke Association states that the choice of antithrombotic treatment should be individualized based on risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including time in INR therapeutic range (if taking warfarin). Apixaban, dabigatran etexilate mesylate and rivaroxaban are recommended as an alternative to warfarin in patients with atrial fibrillation and at least one additional risk factor for stroke.[18]
- Other Key Facts:
  - Rivaroxaban for use in atrial fibrillation:[4]
    - The approved package labeling for rivaroxaban acknowledges the low percentage of "time in International Normalized Ratio range" for patients randomized to warfarin within the ROCKET-AF trial as compared to other clinical trials, and states that it is unknown how rivaroxaban compares when patients are well controlled on warfarin.
    - Within the ROCKET-AF trial, an increased incidence of adverse clinical events were noted when patients were transitioned off of rivaroxaban to warfarin or to another vitamin K antagonist.

- The prescribing information for apixaban, dabigatran, edoxaban, and rivaroxaban contain a Black Box Warning regarding an increased risk of thromboembolic events following the discontinuation of treatment.[1-4]
- Apixaban has demonstrated a significant reduction in the risk of stroke and systemic embolism, major bleeding and all-cause mortality compared to warfarin in patients with atrial fibrillation.[19]
- Dabigatran etexilate mesylate 150 mg has demonstrated a significant reduction in the risk of stroke and systemic embolism compared to warfarin in patients with atrial fibrillation; the risk of major bleeding and all-cause mortality was similar between treatments.[26]
- Rivaroxaban was non inferior to warfarin with regard to the reduction in the risk of stroke and systemic embolism in patients with atrial fibrillation (per-protocol analysis) with a similar incidence of major bleeding.[36]
- Apixaban, dabigatran and rivaroxaban All three new oral anticoagulants are associated with a significant reduction in intracranial hemorrhage compared to warfarin.[19,26,36]
- Warfarin is available generically.[9]

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Therapeutic Class Overview
Angiotensin-Converting Enzyme (ACE) Inhibitors Single Entity Agents

Therapeutic Class

- **Overview/Summary:** The renin-angiotensin-aldosterone system (RAAS) is the most important component in the homeostatic regulation of blood pressure.[1,2] Excessive activity of the RAAS may lead to hypertension and disorders of fluid and electrolyte imbalance.[3] Renin catalyzes the conversion of angiotensinogen to angiotensin I. Angiotensin I is then cleaved to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II may also be generated through other pathways (angiotensin I convertase).[1] Angiotensin II can increase blood pressure by direct vasoconstriction and through actions on the brain and autonomic nervous system.[1,3] In addition, angiotensin II stimulates aldosterone synthesis from the adrenal cortex, leading to sodium and water reabsorption. Angiotensin II exerts other detrimental cardiovascular effects including ventricular hypertrophy, remodeling and myocyte apoptosis.[1,2] The ACE inhibitors block the conversion of angiotensin I to angiotensin II, and also inhibit the breakdown of bradykinin, a potent vasodilator.[4] Evidence-based guidelines recognize the important role that ACE inhibitors play in the treatment of hypertension and other cardiovascular and renal diseases. With the exception of Epaned® (enalapril solution) and Qbrelis® (lisinopril solution), all of the ACE inhibitors are available generically.

Table 1. Current Medications Available in Therapeutic Class[5-19]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Benazepril (Lotensin®*)	Hypertension	Tablet: 5 mg 10 mg 20 mg 40 mg	✔
Captopril*	Diabetic nephropathy, heart failure, hypertension, left ventricular dysfunction post-myocardial infarction	Tablet: 12.5 mg 25 mg 50 mg 100 mg	✔
Enalapril (Vasotec®*, Epaned®)	Asymptomatic left ventricular dysfunction, heart failure, hypertension	Solution: 1 mg/mL Tablet: 2.5 mg 5 mg 10 mg 20 mg	✔
Enalaprilat*	Hypertension	Injection: 1.25 mg/mL	✔
Fosinopril*	Heart failure, hypertension	Tablet: 10 mg 20 mg 40 mg	✔
Lisinopril (Prinivil®*, Qbrelis®, Zestril®*)	Acute myocardial infarction to improve survival, heart failure, hypertension	Solution: 1 mg/mL Tablet: 2.5 mg 5 mg 10 mg 20 mg	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		30 mg 40 mg	
Moexipril*	Hypertension	Tablet: 7.5 mg 15 mg	✔
Perindopril (Aceon®*)	Hypertension, stable coronary artery disease to reduce the risk of cardiovascular mortality or nonfatal myocardial infarction	Tablet: 2 mg 4 mg 8 mg	✔
Quinapril (Accupril®*)	Heart failure, hypertension	Tablet: 5 mg 10 mg 20 mg 40 mg	✔
Ramipril (Altace®*)	Heart failure post myocardial infarction, hypertension, reduce the risk of myocardial infarction, stroke and death from cardiovascular causes	Capsule: 1.25 mg 2.5 mg 5 mg 10 mg	✔
Trandolapril (Mavik®*)	Heart failure post-myocardial infarction, hypertension, left ventricular dysfunction post-myocardial infarction	Tablet: 1 mg 2 mg 4 mg	✔

*Generic available in at least one dosage form or strength.

Evidence-based Medicine

- Angiotensin-converting enzyme (ACE) inhibitors have been shown to be effective for coronary artery disease and to reduce the risk of cardiovascular mortality, myocardial infarction and stroke.[19-30]
- Clinical Trials have demonstrated the efficacy of ACE inhibitors in reducing mortally associated with congestive heart failure.[31-47]
- ACE inhibitors have demonstrated efficacy for the treatment for hypertension and for the use in diabetic nephropathy.[48-79]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[80-97]
    - Treatment guidelines for the management of stable angina recommend angiotensin-converting enzyme (ACE) inhibitors in patients with a left ventricular ejection fraction ≤40% and in those with hypertension, diabetes or chronic kidney disease. ACE inhibitors are also recommended in patients at lower risk (mildly reduced or normal left ventricular ejection fraction) in whom cardiovascular risk factors remain well controlled and revascularization has been performed.
    - Treatment guidelines for the management of unstable angina/non-ST elevation myocardial infarction recommend the use of ACE inhibitors in the first 24 hours in patients with or without pulmonary congestion or left ventricular ejection fraction of ≤40%. ACE inhibitors are recommended in patients with heart failure, left ventricular dysfunction, diabetes or hypertension. In addition, ACE inhibitors are a reasonable for patients with heart failure and left ventricular ejection fraction >40% and patients without hypertension or diabetes. The guidelines are similar for the management of ST-elevation myocardial infarction.
    - Treatment guidelines recommend ACE inhibitors in patients who are at risk for the development of heart failure. ACE inhibitors are recommended for the management of heart failure in patients who have cardiac structural abnormalities or remodeling who have not

developed heart failure symptoms, especially in patients with reduced left ventricular ejection fraction and a history of myocardial infarction.
    - Treatment guidelines for hypertension recommend the use of ACE inhibitors as a first line option in all patients as well as in hypertensive patients with certain compelling indications including heart failure, post-myocardial infarction, left ventricular dysfunction, high coronary disease risk, diabetes, chronic kidney disease, and recurrent stroke prevention.
    - Treatment guidelines for the management of hypertension in patients with diabetes recommend a regimen including an ACE inhibitor. In patients with known cardiovascular disease, a regimen including an ACE inhibitor should be used to reduce the risk of cardiovascular events. In patients with type 1 diabetes, with hypertension and any degree of albuminuria, ACE inhibitors have been shown to delay the progression of nephropathy. In patients with type 2 diabetes, hypertension and microalbuminuria, ACE inhibitors have been shown to delay the progression to macroalbuminuria.
- Other Key Facts:
    - Clinical trials have not demonstrated significant differences when ACE inhibitors were compared to angiotensin II receptor blockers.
    - With the exception of Epaned® (enalapril solution) and Qbrelis® (lisinopril solution), all of the ACE inhibitors are available generically.

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Therapeutic Class Overview
Sedative Hypnotics

Therapeutic Class

- **Overview/Summary:**
  Insomnia is the most common sleep disorder in adulthood, affecting 33 to 69% of the population. It is estimated that five to ten percent of adults experience specific insomnia disorders.[1,2] Insomnia is a disorder that results from a difficulty in initiating or maintaining sleep, waking too early, or sleep that is considered nonrestorative or poor quality.[1-3] Furthermore, individuals with insomnia must also report at least one of the following types of daytime impairment as a result of the difficulties experienced with sleep: fatigue/malaise; impairment in memory, attention, or concentration; social or work-related dysfunction; poor school performance; irritability; day time sleepiness; loss of motivation, energy, or initiative; increased tendency for work or driving related accidents/errors; tension headaches; gastrointestinal symptoms; or concerns/worries about sleep. In individuals with insomnia, these complaints occur despite having sufficient opportunity and circumstances for sleep.[1,2] According to the International Classification of Sleep Disorders, insomnia may be classified as one of the following: short-term insomnia, chronic insomnia or other insomnia (defined as patients who experience difficulty initiating or maintaining sleep but do not meet all of the criteria for either short-term or chronic insomnia).[2]

  There are several classes of medications available for the management of insomnia.[4-6] Doxepin (Silenor®) is a tricyclic antidepressant that is Food and Drug Administration (FDA)-approved for the treatment of insomnia characterized by difficulties with sleep maintenance. The exact mechanism by which doxepin exerts its therapeutic effect on insomnia has not been elucidated; however, it is most likely due to antagonism of the histamine-1 receptor.[7] Ramelteon (Rozerem®) is a melatonin agonist that binds to melatonin receptors with much higher affinity compared to melatonin.[8] Similar to ramelteon, tasimelteon (Hetlioz®) is also a melatonin agonist and it is indicated for the treatment non-24 hour sleep-wake disorder, a disorder that is characterized by the extension of the natural sleep-wake cycle beyond 24 hours.[9] Suvorexant (Belsomra®) belongs to a novel class of orexin receptor antagonists and is thought to suppress the wake-drive by blocking the binding of wake-promoting neuropeptides.[10] Doxepin, ramelteon, tasimelteon and suvorexant are not available generically; however; doxepin is available generically in higher doses that are approved for the treatment of depression and anxiety.[6] Benzodiazepines relieve insomnia by reducing sleep latency and increasing total sleep time. Benzodiazepines increase stage two sleep while decreasing rapid eye movement sleep, stage three and stage four sleep.[5] The benzodiazepines bind to γ-aminobutyric acid subtype A ($GABA_A$) receptors in the brain, thereby stimulating GABAergic transmission and hyperpolarization of neuronal membranes.[5] The benzodiazepines primarily differ in their duration of action. Triazolam (Halcion®) has a short duration of action, while estazolam and temazepam (Restoril®) are intermediate-acting agents. Flurazepam and quazepam (Doral®) are generally considered long-acting benzodiazepines.[11-15] All of the benzodiazepines sedative-hypnotics are available generically.[6] The nonbenzodiazepine sedative hypnotics are structurally distinct from the benzodiazepines resulting in more specific activity at the $GABA_A$ receptor. As a result, the nonbenzodiazepine sedative hypnotics are associated with less anxiolytic and anticonvulsant activity compared to the benzodiazepines.[4] Zaleplon (Sonata®) has a duration of approximately one hour, and thus is an effective treatment for patients with difficulty falling asleep.[16] Zolpidem has a duration of less than two and a half hours and may also be useful for patients with difficulties initiating sleep. Zolpidem is available in as an immediate-release tablet (Ambien®), oral spray (Zolpimist®), sublingual tablet (Edluar® and Intermezzo®) and extended-release tablet (Ambien CR®). The sublingual tablet (Intermezzo®) is the only zolpidem formulation that is approved for the treatment of insomnia due to middle-of-the-night awakenings.[17-21] Of the nonbenzodiazepine sedative hypnotics, eszopiclone (Lunesta®) has the longest half-life (approximately five to seven hours); therefore it is effective in treating sleep onset insomnia and sleep maintenance insomnia.[22] Currently zaleplon, eszopiclone and several zolpidem formulations are available generically.[6]

Table 1. Current Medications Available in the Therapeutic Class[7-22]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Doxepin (Silenor®)	Treatment of insomnia characterized by difficulties with sleep maintenance	Tablet: 3 mg 6 mg	-
Estazolam*	Short-term treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings	Tablet: 1 mg 2 mg	✔
Eszopiclone (Lunesta®)	Treatment of insomnia	Tablet: 1 mg 2 mg 3 mg	-
Flurazepam*	Treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings	Capsule: 15 mg 30 mg	✔
Quazepam (Doral®*)	Treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings	Tablet: 7.5 mg 15 mg	✔
Ramelteon (Rozerem®)	Treatment of insomnia characterized by difficulty with sleep onset	Tablet: 8 mg	-
Suvorexant (Belsomra®)	Treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance	Tablet: 5 mg 10 mg 15 mg 20 mg	-
Tasimelteon (Hetlioz®)	Treatment of non-24-hour sleep-wake disorder	Capsule: 20 mg	-
Temazepam (Restoril®*)	Short-term treatment of insomnia	Capsule: 7.5 mg 15 mg 22.5 mg 30 mg	✔
Triazolam (Halcion®*)	Short-term treatment of insomnia	Tablet: 0.125 mg 0.25 mg	✔
Zaleplon (Sonata®*)	Short-term treatment of insomnia	Capsule: 5 mg 10 mg	✔
Zolpidem (Ambien®*, Ambien CR®*, Edluar®, Intermezzo®*, Zolpimist®)	Short-term treatment of insomnia characterized by difficulties with sleep initiation†, treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance‡, treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep§	Extended-release tablet: 6.25 mg 12.5 mg Immediate-release tablet: 5mg 10 mg Sublingual tablet: 5 mg* 10 mg* 1.75 mg†	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		3.5 mg† Oral mist: 5 mg/ actuation	

*Generic available in at least one dosage form or strength.
†Ambien® (zolpidem), Edluar® (zolpidem sublingual), and Zolpimist® (zolpidem oral mist).
‡ Intermezzo® (zolpidem sublingual).
§ Ambien CR® (zolpidem extended-release).

Evidence-based Medicine

- The result of clinical studies consistently demonstrate that the sedative hypnotics are more effective compared to placebo in patients experiencing insomnia.[22-84]
- The result of several meta-analyses have demonstrated that the benzodiazepine significantly improve sleep latency and total sleep time in patients with insomnia.[77,78,80,81,84]
- Some studies indicate that zaleplon may result in less residual effects and rebound insomnia when compared to zolpidem.[63,65]
- Several agents have demonstrated efficacy in the presence of various comorbidities or specific subpopulations. Eszopiclone and ramelteon have been found to be beneficial across multiple symptoms, including sleep disturbances, mood disturbances, anxiety and hot flashes in peri- and postmenopausal women.[55,35] Eszopiclone has also been found to improve sleep-related symptoms in patients with depression, Parkinson disease, and post-traumatic stress disorder. [29,32,33] Ramelteon has demonstrated efficacy in patients with comorbid generalized anxiety disorder and also in patients with substance abuse.[41,57] Zolpidem extended-release has demonstrated efficacy, when coadministered with escitalopram, in patients with both major depressive disorder as well as generalized anxiety disorder.[70,71] Zolpidem and zaleplon have both demonstrated safety and efficacy in patients with nonpsychotic psychiatric disorders.[66] Efficacy has also been established in populations of elderly patients. Doxepin has demonstrated safety and efficacy in elderly patients through 12 weeks, without causing residual sedation or increasing the risk of complex sleep behaviors.[24,28] Eszopiclone has demonstrated safety and efficacy over two weeks in elderly patients and ramelteon over five weeks.[36,50]
- Furthermore, efficacy of the Furthermore, efficacy of the non-benzodiazepine hypnotics has been demonstrated to be sustained for up to one year. Eszopiclone and zolpidem extended-release have demonstrated sustained efficacy through six months while ramelteon and zolpidem immediate-release have demonstrated sustained efficacy over the course of a year.[30,37,38,56,69,76]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Guidelines do not recommend one sedative hypnotic over another.[1]
  - All agents have been shown to result in positive effects on sleep latency, total sleep time and wake time after sleep onset. Selection of an agent should take into consideration the patient's specific symptom pattern, patient preferences, any comorbid disease states and concurrent medications, as well as the individual side effect profile for each option. Zaleplon and ramelteon have short half-lives, work well to reduce sleep latency and are unlikely to result in residual sedation; however, they have little effect on waking after sleep onset.[1]
  - Eszopiclone and temazepam have longer half-lives, are more likely to improve sleep maintenance, and are more likely to produce residual sedation.[1]
  - Triazolam has been associated with rebound anxiety and is not considered a first-line treatment.[1]
  - The use of doxepin for insomnia in the absence of co-morbid depression is not addressed in clinical guidelines, as the low-dose formulation was not available when these guidelines were published.[1]

- Depending on the patient's specific complaint of sleep initiation or sleep maintenance, consideration should be given to the pharmacokinetic parameters of the available hypnotics. Agents with a longer half-life may be preferred in those with sleep maintenance issues, while agents with a shorter time to maximum concentration may be preferred in patients with sleep initiation complaints. If a patient does not respond to the initial agent, a different agent within the same class is appropriate after evaluating the patient's response to the first agent.[1]

Other Key Facts:

- Currently, generic products are available for all benzodiazepine sedative-hypnotics as well as eszopiclone, zaleplon and several zolpidem formulations.[6]
- Doxepin is available generically in higher doses that are approved for the treatment of depression and anxiety.[6]

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Therapeutic Class Overview
Otic Fluoroquinolones

Therapeutic Class

- **Overview/Summary:** This review will focus on the otic fluoroquinolone antibiotics.[1-6] Topical corticosteroids help to aid in the resolution of the inflammatory response accompanying bacterial infections. Fluoroquinolones are broad-spectrum antimicrobial agents that directly inhibit bacterial deoxyribonucleic acid (DNA) synthesis by blocking the actions of DNA gyrase and topoisomerase IV, which leads to bacterial cell death.[1-6]

  The otic antibacterials are approved for the treatment of otitis externa and otitis media. Otitis externa (also known as swimmer's ear) is an inflammatory condition of the external ear canal auditory canal or auricle, usually from infection. Common infectious pathogens include S. aureus, S. epidermidis and P. aeruginosa; however, several other gram-positive, gram-negative and anaerobic infections along with polymicrobic infections occur frequently.[8] Topical antibacterials (alone or in combination with a corticosteroid) are very effective and systemic therapy is generally not required.[9] Acute otitis media is an inflammatory condition of the middle ear with middle ear effusion and symptoms include otalgia, hearing loss and vertigo.[10] Common pathogens in children include S. pneumoniae and H. influenzae (and M. catarrhalis in children).[10,11] Oral antibacterials are generally the initial treatment option for children and adults; however, topical antibacterials with or without corticosteroids may be used in patients with perforated tympanic membranes, tympanostomy tubes or chronic suppurative otitis media.[11-14] Current clinical guidelines support these recommendations.[15-19]

  This review only includes otic dosage forms.

Table 1. Medications Included Within the Therapeutic Class Review[4-12]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Second Generation Fluoroquinolones			
Ciprofloxacin (Cetraxal®*, Otiprio®)	Treatment of acute otitis externa (Cetraxal®)#, bilateral otitis media with effusion in pediatric patients six months of age or older undergoing tympanostomy tube placement (Otiprio®)	Otic solution, single use container (Cetraxal®): 0.2% Otic suspension (Otiprio®) 6%	✔
Ofloxacin*	Treatment of acute otitis externa‖, treatment of chronic suppurative otitis media with perforated tympanic membranes†, acute otitis media in pediatric patients with tympanostomy tubes‡	Otic solution: 0.3%	✔
Third Generation Fluoroquinolones			
Ciprofloxacin/ dexamethasone (Ciprodex®)	Treatment of acute otitis externa§, acute otitis media in pediatric patients with tympanostomy tubes‡	Otic suspension: 0.3%/0.1%	-
Ciprofloxacin/ fluocinolone (Otovel®)	Acute otitis media with tympanostomy tubes**	Otic solution: 0.3%/0.025%	
Ciprofloxacin/ hydrocortisone (Cipro HC®)	Treatment of acute otitis externa¶	Otic suspension: 0.2%/1%	-

*Generic is available in at least one dosage form or strength.
‖For adult and pediatric patients, ≥6 months of age, due to susceptible strains of E. coli, P. aeruginosa and S. aureus.
†For adult and pediatric patients ≥12 years of age, due to susceptible strains of P. mirabilis, P. aeruginosa and S. aureus.

‡For pediatric patients ≥1 year of age, due to susceptible strains of H. influenzae, M. catarrhalis, P. aeruginosa, S. aureus and S. pneumoniae.
§For adult and pediatric patients ≥6 months of age, due to susceptible strains of S. aureus and P. aeruginosa.
¶For adult and pediatric patients ≥1 year of age, due to susceptible strains of P. aeruginosa, S. aureus, and P. mirabilis.
#For adult and pediatric patients ≥1 year of age, due to susceptible strains of P. aeruginosa and S. aureus.
**For pediatric patients ≥6 months of age, due to susceptible strains of six months of age or older H. influenzae, M. catarrhalis, P. aeruginosa, S. aureus and S. pneumoniae.

Evidence-based Medicine

- Clinical trials have demonstrated that otic fluoroquinolones are effective in treating and providing relief of in otitis externa, chronic suppurative otitis media with a perforated tympanic membrane, bilateral otitis media with effusion, and acute otitis media in patients with tympanostomy tubes.[20-33]
- For otitis externa, ciprofloxacin/dexamethasone has been shown to have significantly greater clinical and microbial cure (P=0.0375 and P=00375 respectively), pain relief (P=0.0013), time to cure (no P value given) and eradication of (P=0.0044) when compared to hydrocortisone/neomycin/polymyxin B.[20-23]
- The other otic quinolones, ciprofloxacin (Cetraxal®), ofloxacin, ciprofloxacin/hydrocortisone and ciprofloxacin/dexamethasone all showed non-inferiority to hydrocortisone/neomycin/polymyxin B in the treatment of otitis externa.[24-27]
- In the treatment of otitis media, ciprofloxacin and ofloxacin have both been shown to be non-inferior to other therapies.[29,30]
- Ciprofloxacin/dexamethasone has shown significantly better clinical cure rates and time to cessation of otorrhea when compared to oral amoxicillin/clavulanate, otic ciprofloxacin alone and otic ofloxacin.[31-33]
- Ciprofloxacin 6% (Otiprio®) was evaluated in two unpublished, randomized, multicenter controlled clinical trials with a total of 532 pediatric patients for the treatment of bilateral otitis media with effusion undergoing myringotomy with tympanostomy tube placement. Differences in treatment failure between the ciprofloxacin 6% group and the sham group was 20% (95% CI, 8 to 32%) and 24% (95% CI, 12 to 36%) for trials one and two, respectively (P<0.001 for both comparisons).[2]
- The safety and efficacy of ciprofloxacin/fluocinolone otic solution for the treatment of acute otitis media with tympanostomy tubes was established in two unpublished multicenter, randomized, double-blind, active-controlled, parallel group trials. In trail 1, median time to cessation of otorrhea was significantly reduced with combination ciprofloxacin/fluocinolone (3.75 days) when compared to ciprofloxacin monotherapy (7.69 days; P=<0.001) and fluocinolone monotherapy (not estimable; P<0.001). In trail 2, median time to cessation of otorrhea was significantly reduced with combination ciprofloxacin/fluocinolone (4.94 days) when compared to ciprofloxacin monotherapy (6.83 days; P=0.028) and fluocinolone monotherapy (not estimable; P<0.001).[5]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[15-19]
    - Topical therapy, without systemic antibiotics, should be used for initial management of uncomplicated acute otitis externa in otherwise healthy patient with diffuse acute otitis externa that is not complicated by osteitis, abscess formation, middle ear disease, or recurrent episodes of infection.
    - For otic antibiotics, due to lack of differences in efficacy, the cost, adherence to therapy, and adverse effects of topical antimicrobials must also be considered.
    - When the patient has a known or suspected perforation of the tympanic membrane in otitis externa, including a tympanostomy tube, the clinician should prescribe a non-ototoxic topical preparation.
    - In otitis media, otic antibiotics should be used first line in patients with tympanostomy tubes, otherwise oral antibiotics are recommended first line (amoxicillin ± clavulanic acid).
- Other Key Facts:
    - Ciprofloxacin (Cetraxal®), ofloxacin and ciprofloxacin/fluocinolone are all formulated as solutions, whereas ciprofloxacin (Otiprio®), ciprofloxacin/dexamethasone and ciprofloxacin/hydrocortisone are formulated as suspensions.. [1-6]

- Depending on type of infection and selected agent, typical administration is three to 10 drops once or twice daily for seven to 14 days. [1-6]
- Each agent can be given to pediatric patients, but the age differs for each product. [1-6]
- Currently only ciprofloxacin (Cetraxal®) and ofloxacin otic solutions are available generically.

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Therapeutic Class Overview
Sodium-glucose co-transporter 2 (SGLT2) Inhibitors

Therapeutic Class

- **Overview/Summary:** Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a class of oral antidiabetic agents approved by the Food and Drug Association (FDA) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.[1-10] The kidneys play a pivotal role in controlling plasma glucose concentration; reabsorbing nearly all plasma glucose in the proximal tubules and preventing glucose excretion in patients with normal glucose-tolerance. Approximately 90% of the filtered renal glucose is done in the early convoluted segment of the proximal tubule and is facilitated by the SGLT2 transporter. The remaining 10% of filtered glucose is reabsorbed in the distal straight segment of the proximal tube by the SGLT1 transporter. In diabetic patients, the SGLT transporter system is often overwhelmed and unable to reabsorb all filtered plasma glucose due to hyperglycemic conditions. Once this threshold capacity is reached and surpassed, excess glucose that is not reabsorbed is excreted into the urine. In addition, a chronic elevated plasma glucose concentration provides the stimulus that ultimately leads to increased SGLT2 expression by the renal proximal tubular cells, resulting in an undesirable increase in renal capacity and threshold to reabsorb filtered glucose in both type 1 and type 2 diabetic patients.[1,2] SGLT2 inhibitors improve glycemic control by producing glucosuria. This is accomplished by inhibiting SGLT2 and increasing urinary glucose excretion. The net effect is an increase excretion of glucose from the body and normalizing plasma glucose levels. At this time, it is unknown if this mechanism of action serves to reduce the kidney's threshold capacity to reabsorb glucose, thus causing glucose excretion at lower plasma concentrations, or if the mechanism of action serves to prevent reabsorption of glucose load at all plasma glucose concentrations. SGLT2 inhibitors also have beneficial nonglycemic effects, such as weight loss observed during clinical trials and small decreases in systolic and diastolic blood pressure.[1,2]

Table 1. Current Medications Available in Therapeutic Class[3-10]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single Agent Products			
Canagliflozin (Invokana®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 100 mg 300 mg	-
Dapagliflozin (Farxiga®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 5 mg 10 mg	-
Empagliflozin (Jardiance®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 10 mg 25 mg	-
Combination Products			
Canagliflozin/ metformin (Invokamet®, Invokamet XR®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes*	Tablet: 50/500 mg 50/1,000 mg 150/500 mg 150/1,000 mg Sustained-Release Tablet: 50/500 mg 50/1,000 mg 150/500 mg 150/1,000 mg	-

Dapagliflozin/ metformin ER (Xigduo XR®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes†	Tablet: 5/500 mg 5/1000 mg 10/500 mg 10/1000 mg	-
Empagliflozin/ linagliptin (Glyxambi®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes‡	Tablet: 10 mg/5 mg 25 mg/5 mg:	-
Empagliflozin/metformin (Synjardy®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes§	Tablet: 5/500 mg 5/1000 mg 12.5/500 mg 12.5/1000 mg	-

ER=extended-release
*For patients who are not adequately controlled on a regimen containing metformin or canagliflozin or in patients already being treated with both canagliflozin and metformin.
†When treatment with both dapagliflozin and metformin is appropriate.
‡When treatment with both empagliflozin and linagliptin is appropriate.
§When treatment with both empagliflozin and metformin is appropriate.

Evidence-based Medicine

- Each agent has been studied as monotherapy and dual and triple therapy compared to placebo and active controls and combinations of placebo and active controls.
- As monotherapy, patients randomized to canagliflozin 100 or 300 mg daily compared to patients randomized to placebo had a statistically significant improvement in HbA_{1c}. Both doses also resulted in a greater proportion of patients achieving an HbA_{1c} <7.0%, significant reductions in FPG and post prandial glucose (PPG), and in percent body weight reduction compared to placebo. There were also small decreases from baseline in systolic blood pressure relative to placebo (P values not reported).[11]
- As monotherapy in treatment-naïve patients, dapagliflozin was evaluated in two placebo-controlled trials. The first trial included 274 patients randomized to treatment with 2.5, 5 and 10 mg or placebo. At week 24, treatment with dapagliflozin 5 and 10 mg resulted in significant improvements in HbA_{1c} compared to placebo (-0.6, -0.8, -0.9 vs -0.2%, respectively; P<0.05 for 5 and 10 mg comparisons). Change in FPG (-24.1 and -28.8 vs -4.1 mg/dL, respectively) from baseline was also significantly greater in the 5 and 10 mg groups compared to placebo (P<0.05 for both comparisons).[13]
- There have been no clinical efficacy studies conducted with Xigduo XR® (dapagliflozin/metformin) combination tablets. FDA-approval of dapagliflozin/metformin ER was based on previous studies conducted with the bioequivalent single-entity agents.[8] Combination therapy with metformin extended-release in patients who were treatment-naïve led to significantly greater reductions in HbA_{1c} compared to either monotherapy (dapagliflozin or metformin) in the first study (-2.0 vs -1.2 and -1.4%, respectively; P<0.0001) and second study (-2.0 vs -1.5 and -1.4%, respectively; P<0.0001). In the second study, treatment with 10 mg strength (as monotherapy) was also non-inferior to metformin (as monotherapy) for reduction of HbA_{1c}.[15]
- The safety and efficacy of empagliflozin monotherapy was evaluated in a double-blind, placebo-controlled study of patients with type 2 DM (N=986). At week 24, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA_{1c} (-0.7% and -0.8% vs. 0.1%, respectively; P<0.0001 for both comparisons), FPG (-19 mg/dL and -25 mg/dL vs. 12 mg/dL, respectively; P values not reported) and body weight (-2.8 kg and -3.2 kg vs. -0.4 kg, respectively; P values not reported) compared with placebo.[16]
- There have been no clinical efficacy studies conducted with empagliflozin/metformin combination tablets. FDA-approval of empagliflozin/metformin ER was based on previous studies conducted with the bioequivalent single-entity agents.[10] The safety and efficacy of empagliflozin added to metformin was evaluated in a double-blind, placebo-controlled study of patients with type 2 DM inadequately controlled on at least 1,500 mg of metformin per day (N=637). At week 24, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA_{1c} (-0.7% and -0.8% vs. 0.1%, respectively; P<0.0001 for both comparisons), FPG (-20 mg/dL and -22 mg/dL vs. 6 mg/dL, respectively; P values

not reported) and body weight (-2.5 kg and -2.9 kg vs. -0.5 kg, respectively; P<0.001 for both comparisons) compared with placebo.[25] In addition, the safety and efficacy of empagliflozin was evaluated in an active-control study versus glimepiride (in combination with metformin). The study was a double-blind, active-controlled, non-inferiority design of patients with type 2 DM inadequately controlled on metformin monotherapy (N=1,545). At week 52, empagliflozin 25 mg daily meet the non-inferiority criteria for lowering HbA_{1c} compared to glimepiride (-0.7% vs. -0.7%). There was a greater reduction in FPG and body weight with empagliflozin 25 mg compared to glimepiride; however the significance was not reported (-19 mg/dL vs. -9 mg/dL and -3.9 kg vs. 2 kg; P values not reported).[26]

- The safety and efficacy of empagliflozin added to linagliptin was evaluated in a 52 week double-blind, active-control, randomized trial. Change from baseline in HbA_{1c} at week 24 was significantly improved in the combination groups compared with the individual component groups (P<0.001).[33] When started as initial therapy, empagliflozin/linagliptin reduced HbA_{1c} from baseline significantly greater when compared with individual linagliptin and empagliflozin 10 mg. Empagliflozin 25 mg/linagliptin 5 mg, however, did not show a statistically significant difference compared with empagliflozin alone (P=0.179).[34]
- Similar results were observed when comparing sodium glucose co-transport 2 agents in combination for the treatment of diabetes mellitus.[18-32]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[35-42]
    - Metformin remains the cornerstone of most antidiabetic treatment regimens.
    - Patients with high glycosylated hemoglobin (HbA_{1c}) will likely require combination or triple therapy in order to achieve glycemic goals.
        - Uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered.
        - The role of sodium-glucose co-transporter 2 (SGLT2) inhibitors are addressed in several available treatment guidelines and are recommended as a potential alternative to metformin in patients who cannot receive that agent or as a part of two- or three-drug regimens in combination with other antidiabetic agents in patients not achieving glycemic goals.[36,39-40]

- Other Key Facts:
    - Canagliflozin is formulated with metformin in a single tablet (Invokamet®). Empagliflozin is formulated with linagliptin in a single tablet (Glyxambi®) and with metformin in a single tablet (Synjardy®). Canagliflozin and dapagliflozin is formulated with metformin as a single extended-release tablet (Invokamet XR®, Xigduo XR®).[6-10]
    - All products are dosed once daily, with the exception of canagliflozin/metformin and empagliflozin/metformin immediate-release tablets, which are dosed twice dialy.[3-10]
    - Other effects observed in trials include weight loss and small decreases in systolic and diastolic blood pressure.
    - Common adverse side effects associated with SGLT2 inhibitor use included increased incidence of female genital mycotic infections, urinary tract infection, and increased urination.

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Therapeutic Class Overview
Immunomodulators

Therapeutic Class

- **Overview/Summary:** This review will focus on oral and injectable immunomodulators. These agents are used for a variety of inflammatory and immunologic conditions which include: rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, juvenile/systemic idiopathic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, hidradenitis suppurativa, uveitis and several cryopyrin-associated periodic syndromes. Specific Food and Drug Administration (FDA)-approved indications for each agent are summarized in Table 1. Overall, these agents achieve their therapeutic effect via several different mechanisms of action. The majority of oral and injectable immunomodulators inhibit the effect of proinflammatory cytokines, specifically interleukins or tumor necrosis factor (TNF)-α. Interleukin (IL) inhibitors include anakinra (Kineret®), canakinumab (Ilaris®), ixekizumab (Taltz®), rilonacept (Arcalyst®), secukinumab (Cosentyx®), tocilizumab (Actemra®), and ustekinumab (Stelara®) while the TNF-α inhibitors are adalimumab (Humira®), adalimumab-atto (Amjevita®), certolizumab pegol (Cimzia®), etanercept (Enbrel®), etanercept-szzs (Erelzi®), golimumab (Simponi®, Simponi ARIA®), infliximab (Remicade®), and infliximab-dyyb (Inflectra®). Abatacept (Orencia®) is a T-cell activation inhibitor, tofacitinib (Xeljanz®) is a Janus kinase inhibitor, and vedolizumab (Entyvio®) is an α4-β7 integrin receptor antagonist.[1-19]

Table 1. Current Medications Available in the Therapeutic Class[1-20]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Abatacept (Orencia®, Orencia ClickJet®)	Rheumatoid arthritis (adults only); polyarticular juvenile idiopathic arthritis/juvenile rheumatoid arthritis (age ≥six years)	Auto-injector: 125 mg/mL Prefilled syringe: 125 mg/mL Vial: 250 mg	-
Adalimumab (Humira®, Humira Pen®)	Rheumatoid arthritis (adults only); polyarticular juvenile idiopathic arthritis/juvenile rheumatoid arthritis (age ≥two years); psoriatic arthritis (adults only); ankylosing spondylitis (adults only); Crohn's disease (age ≥six years); ulcerative colitis (adults only); plaque psoriasis (adults only); uveitis (adults only); hidradenitis suppurativa (adults only)	Prefilled pen: 40 mg/0.8 mL Prefilled syringe: 10 mg/0.2 mL 20 mg/0.4 mL 40 mg/0.8 mL	-
Adalimumab-atto (Amjevita®, Amjevita SureClick®)	Rheumatoid arthritis (adults only); polyarticular juvenile idiopathic arthritis/juvenile rheumatoid arthritis (age ≥four years); psoriatic arthritis (adults only); ankylosing spondylitis (adults only); Crohn's disease (adults only); ulcerative colitis (adults only); plaque psoriasis (adults only)	Prefilled pen: 40 mg/0.8 mL Prefilled syringe: 20 mg/0.4 mL 40 mg/0.8 mL	-
Anakinra (Kineret®)	Rheumatoid arthritis (adults); cryopyrin-associated periodic syndromes – neonatal-onset multisystem inflammatory disease (no age restriction)	Prefilled syringe: 100 mg/0.67 mL	-
Canakinumab (Ilaris®)	Cryopyrin-associated periodic syndromes – familial cold autoinflammatory syndrome or Muckle-Wells syndrome (age ≥ four years); juvenile idiopathic	Vial: 180 mg (150 mg/mL)	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	arthritis (age ≥ two years)		
Certolizumab (Cimzia®)	Crohn's disease (adults only); rheumatoid arthritis (adults only); psoriatic arthritis (adults only); ankylosing spondylitis (adults only)	Prefilled syringe: 200 mg/mL Vial: 200 mg	-
Etanercept (Enbrel®, Enbrel SureClick®)	Rheumatoid arthritis (adults only); polyarticular juvenile idiopathic arthritis/juvenile rheumatoid arthritis (age ≥two years); psoriatic arthritis (adults only); ankylosing spondylitis (adults only); severe plaque psoriasis (adults only)	Auto-injector: 50 mg/mL Prefilled syringes: 25 mg/0.5 mL 50 mg/mL Vial: 25 mg	-
Etanercept-szzs (Erelzi®, Erelzi Sensoready Pen®)	Rheumatoid arthritis (adults only); polyarticular juvenile idiopathic arthritis/juvenile rheumatoid arthritis (age ≥two years); psoriatic arthritis (adults only); ankylosing spondylitis (adults only); severe plaque psoriasis (adults only)	Auto-injector: 50 mg/mL Prefilled syringes: 25 mg/0.5 mL 50 mg/mL	-
Golimumab (Simponi®, Simponi Aria®)	Rheumatoid arthritis (Simponi® and Simponi Aria® [adults only]); psoriatic arthritis (Simponi® [adults only]); ankylosing spondylitis (Simponi® [adults only]); ulcerative colitis (Simponi® [adults only])	Auto-injector (Simponi®): 50 mg/0.5 mL, 100 mg/mL Prefilled syringe (Simponi®): 50 mg/0.5 mL 100 mg/mL Vial* (Simponi Aria®): 50 mg/4 mL	-
Infliximab (Remicade®)	Crohn's disease (age ≥six years); ulcerative colitis (age ≥six years); rheumatoid arthritis (adults only); ankylosing spondylitis (adults only); psoriatic arthritis (adults only); plaque psoriasis (adults only)	Vial: 100 mg	-
Infliximab (Inflectra®)	Crohn's disease (age ≥six years); ulcerative colitis (adults only); rheumatoid arthritis (adults only); ankylosing spondylitis (adults only); psoriatic arthritis (adults only); plaque psoriasis (adults only)	Vial: 100 mg	-
Ixekizumab (Taltz®)	Plaque Psoriasis (adults)	Auto-injector: 80 mg/mL Prefilled Syringe: 80 mg/mL	-
Rilonacept	Cryopyrin-associated periodic syndromes – familial	Vial:	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
(Arcalyst®)	cold autoinflammatory syndrome or Muckle-Wells syndrome (age ≥12 years)	220 mg (80 mg/mL)	
Secukinumab (Cosentyx®, Cosentyx SensoReady Pen®)	Ankylosing Spondylitis (adults only); juvenile idiopathic arthritis/juvenile rheumatoid arthritis; plaque psoriasis (adults only)	Auto-injector: 150 mg/mL Prefilled syringe: 150 mg/mL	-
Tocilizumab (Actemra®)	Polyarticular juvenile idiopathic arthritis (age ≥ two years) ; systemic juvenile idiopathic arthritis/juvenile rheumatoid arthritis (age ≥ two years); rheumatoid arthritis (adults only)	Prefilled syringe*: 162 mg/0.9 mL Single use vial: 80 mg/4 mL 200 mg/10 mL 400 mg/20 mL	-
Tofacitinib (Xeljanz®, Xeljanz XR®)	Rheumatoid arthritis (adults only)	Extended-release tablet (Xeljanz XR®): 11 mg Tablet (Xeljanz®): 5 mg	-
Ustekinumab (Stelara®)	Plaque psoriasis (adults only); psoriatic arthritis (adults only)	Prefilled syringe: 45 mg/0.5 mL 90 mg/mL	-
Vedolizumab (Entyvio®)	Crohn's disease (adults only); ulcerative colitis (adults only)	Vial: 300 mg/20 mL	-

*Only indicated for use in patients with rheumatoid arthritis.

Evidence-based Medicine

- The immunomodulators have been shown to be effective for their respective Food and Drug Administration (FDA)-approved indications, particularly in conditions where patients were unresponsive or refractory to traditional disease modifying antirheumatic drugs (DMARDs). Most research with these agents and FDA-approved indications (with the exception of ustekinumab) are for rheumatoid arthritis. In these trials, the immunomodulator were compared directly to placebo or traditional DMARD medications, either as monotherapy or in combination with a traditional DMARD. Consistently, immunomodulators have shown greater improvement in symptoms over the respective comparators.[58-168]
- The safety and efficacy of adalimumab for the treatment of non-infectious intermediate, posterior and panuveitis was established in two randomized, double-blind, placebo-controlled clinical trials.[8] The total length of each study was not reported; however, data is reported up to 18 weeks. The primary efficacy endpoint in both studies was time to treatment failure, defined as the development of new inflammatory chorioretinal and/or inflammatory retinal vascular lesions, an increase in anterior chamber (AC) cell grade or vitreous haze (VH) grade or a decrease in best corrected visual acuity (BCVA), on or after week six (study one) or week two (study two). At week 18 in study one, 60 patients (54.5%) failed adalimumab on or after week six compared with 84 patients (78.5%) who received placebo (hazard ratio [HR], 0.50; 95% CI, 0.36 to 0.70). Median time to failure was 5.6 months (95% CI, 3.9 to 9.2) for patients who received adalimumab and 3.0 months (95% CI, 2.7 to 3.7) for patients who received placebo. At week 18 in study two, 45 patients (39.1%) failed adalimumab on or after week two compared with 61 patients (55.0%) who received placebo (HR,

0.57; 95% CI, 0.39 to 0.84). Median time to failure for the adalimumab group was not estimable as fewer than half of the at-risk subjects had an event. Median time to failure for the placebo group was 8.3 months (95% CI, 4.8 to 12.0).[8]

- The safety and efficacy of adalimumab in the treatment of hidradenitis suppurativa was established in two clinical trials PIONEER I and PIONEER II. Both were 36-week, multicenter, randomized, double-blind clinical trials with a total of 633 adult patients with moderate to severe (Hurley Stage II and III) hidradenitis suppurativa who had an inadequate response to a trial of oral antibiotics, total abscess and inflammatory nodule count of ≥3 and lesions present in ≥2 body areas. At 12 weeks, therapy was evaluated and effectiveness was defined as improvement in abscesses and inflammatory nodules at 12 weeks using the Hidradenitis Suppurativa Clinical Response (HiSCR). Treatment with adalimumab resulted in a significantly higher proportion of patients achieving clinical response compared to placebo (PIONEER I: 41.8% vs 26.0%, P=0.003; PIONEER II: 58.9% vs 27.6%, P<0.001), regardless of whether patients continued baseline antibiotic therapy or not, and regardless of their baseline Hurley stage. [58]
- The safety and efficacy of canakinumab in the treatment of systemic juvenile idiopathic arthritis was confirmed in two parallel clinical trials. At day 15 of the first trial, a total of 36 patients in the canakinumab group (84%), as compared with four in the placebo group (10%), had an adapted ACR30 response, which was sustained at day 29 (P<0.001). The second study concluded that There was a 64% relative reduction in the risk of flare for patients in the canakinumab group as compared to those in the placebo group (hazard ratio of 0.36; 95% CI: 0.17 to 0.75).[89]
- Secukinumab for the treatment of ankylosing spondylitis in patients 18 years of age or older was evaluated in two similar, double-blind, placebo controlled trials, MEASURE 1 and 2. The primary endpoint in both studies was the proportion of patients who had an Assessment of Spondyloarthritis International Society (ASAS) criteria improvement ≥20% (ASAS20) at week 16. In MEASURE 1, ASAS20 was significantly greater at week 16 in the secukinumab 150 mg group (61%) and 75 mg group (60%) than the placebo group (29%, P<0.001 for both vs placebo). In MEASURE 2, ASAS20 at week 16 was significantly greater in the secukinumab 150 mg group (61%) when compared to the placebo group (28%, P<0.001). There was no significant difference between the placebo group and the secukinumab 75 mg group (41%, P=0.10).[70]
- The safety and efficacy of secukinumab for the treatment of plaque psoriasis was evaluated in four multicenter, randomized, double-blind, placebo-controlled trials. The proportion of patients who achieved PASI 75 was statistically significantly greater in the secukinumab 300 mg group (81.6%, 77.1%, 75.9% and 86.7%) and secukinumab 150 mg group (71.6%, 67.0%, 69.5%, and 71.7%) compared with placebo (4.5%, 4.9%, 0%, 3.3%; P<0.001 for all secukinumab comparisons compared to placebo). In one of the trials, secukinumab 300 mg and 150 mg groups were compared to etanercept. Both secukinumab groups (77.1% and 67.0%) had a higher proportion of patients that achieved PASI 75 compared with etanercept (44%; P<0.001 for both secukinumab comparisons). Results were similar when IGA mod 2011 scores were compared.[5,100-0102]
- Secukinumab for the treatment of psoriatic arthritis in patients 18 years of age or older was evaluated in two similar, double-blind, placebo controlled trials, FUTURE 1 and 2. The primary endpoint for both studies was the proportion of patients who had an American College of Rheumatology (ACR) improvement ≥20% (ACR20 response) at week 24.[115,116] In FUTURE 1, ACR20 response at week 24 was significantly greater in the secukinumab 150 mg group (50%) and 75 mg group (50.5%) than the placebo group (17.3%, P<0.001 for both vs placebo).[115] In FUTURE 2, ACR20 response at week 24 was significantly greater in the secukinumab 300 mg group (54%), the secukinumab 150 mg group (51%) and the secukinumab 75 mg group (29%), when compared to placebo (15%, P<0.001 for 300 mg and 150 mg groups vs placebo and P=0.0399 for the 75 mg group vs placebo).[116]
- The safety and efficacy of ixekizumab, for the treatment of moderate-to-severe psoriasis, was established in three multicenter, randomized, double-blind, placebo-controlled trials in patients 18 years of age or older (UNCOVER-1, UNCOVER-2 and UNCOVER-3). Patients had to have body surface area (BSA) involvement ≥10%, static Physician's Global Assessment (sPGA) ≥3 and Psoriasis Area Severity Index (PASI) ≥12. The three trials evaluated two different induction phase doses of ixekizumab: 80 mg every two weeks and 80 mg every four weeks over 12 weeks. In addition, two of the trials (UNCOVER-1 and UNCOVER-2) evaluated two different maintenance phase doses of 80 mg every four weeks and 80 mg every 12 weeks over 48 weeks. Two of the trials

(UNCOVER-2 and UNCOVER-3) had etanercept as an active comparator arm during the induction phase.[93-95] In UNCOVER-1, treatment with ixekizumab, with an initial dose of 160 mg and subsequent induction period dosages of 80 mg every two weeks or 80 mg every four weeks resulted in significant improvement during the induction period. Across all efficacy end points, response rates associated with the dosage of 80 mg every two weeks were higher than those associated with the 80 mg every four weeks dose. In UNCOVER-1 and UNCOVER-2, for ixekizumab week 12 responders, efficacy was also maintained through the 60-week maintenance period.[93,94] In UNCOVER-2 and UNCOVER-3, treatment with both induction doses of ixekizumab (80 mg every two weeks and 80 mg every four weeks) demonstrated significantly greater efficacy than etanercept. Across all efficacy endpoints, response rates associated with 80 mg every two weeks was higher than those associated with 80 mg every four weeks.[93,95]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[22-48]
    - Support the use of the immunomodulators with respect to their Food and Drug Administration (FDA)-approved indications.
    - As more recent guidelines are published, the recommendations for use tumor necrosis factor-blockers earlier in therapy is becoming a more common occurance.[31,33,36] The adverse event profiles are similar across the class; however, routes of administration and dosing frequency may vary.
    - In general, no one agent is preferred over another.

- Other Key Facts:
    - The recently upheld Patient Protection and Affordable Care Act provides a legal framework for regulatory approval of biosimilar drugs.[53]
    - While none of the agents in this class are available generically, biosimilars for adalimumab, etanercept, and infliximab (i.e., Amjevita®, Erelzi®, and Inflectra®, respectively) were recently approved by the FDA and are not considered interchangeable with the reference product. In addition, none of the biosimilar agents are commercially available due to ongoing patent litigation.[9,13,16] Specifically, the manufacturer of adalimumab-atto (Amjevita®) does not expect biosimilar adalimumab to be available until at least 2018 .[169]
    - Dosing and administration varies both by drug and by dosage form.[1-19]
        - Oral: tofacitinib (tablet, extended-release tablet)
        - Intravenous Injection: abatacept, golimumab (Simponi ARIA®), infliximab, infliximab-dyyb, tocilizumab, and vedolizumab. Each is infused over 30 minutes, with the exception of infliximab and infliximab-dyyb, which are infused over two hours.
        - Most injectables require infrequent dosing, ranging from one to 12 weeks. Anakinra is the only injectable immunomodulator that requires daily dosing.
        - Tofacitinib immediate release is taken twice daily while the extended-release formulation can be taken once daily.
        - The majority of these agents have not been studied in renal or hepatic dysfunction.
        - Anakinra and tofacitinib require renal dose adjustment for creatinine clearances less than 30 mL or 40 mL, respectively.
        - Tofacitinib requires a dose adjustment in patients with moderate hepatic dysfunction, however, it has not been studied in patients with severe hepatic dysfunction and no dosing recommendations are available.
    - The safety and efficacy of these agents in pediatric patients varies based on drug and indication.[1-19]
        - Anakinra, canakinumab and rilonacept are FDA-approved for the treatment of Cryopyrin-Associated Periodic Syndromes. Anakinra does not have a minimum age associated with its use while canakinumab is approved for use in children aged four or older and rilonacept is approved for use in children 12 to 17 years old.
        - Safety and efficacy in pediatric patients to treat juvenile idiopathic arthritis has been established for abatacept (age six or older), adalimumab (age 2 to 17 years),

adalimumab-atto (age 4 to 17 years), canakinumab, etanercept (age two or older), etanercept-szzs (age two or older), and tocilizumab (all two or older).
    - Adalimumab, infliximab, and infliximab-dyyb have been FDA-approved for the treatment of pediatric Crohn's disease in pediatric patients aged six or older. Additionally, infliximab is also indicated to treat pediatric ulcerative colitis in pediatric patients 6 to 17 years of age.
- Anakinra is the only FDA-approved agent for neonatal-onset multisystem inflammatory disease. Canakinumab and rilonacept are the only FDA-approved agents for the treatment of familial cold autoinflammatory syndrome and Muckle-Wells syndrome.

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Therapeutic Class Overview
Opioid-Induced Constipation Agents

Therapeutic Class Overview/Summary:
There are currently three agents approved by the Food and Drug Administration (FDA) for the treatment of opioid-induced constipation (OIC). Lubiprostone (Amitiza®), methylnaltrexone bromide (Relistor®), naloxegol oxalate (Movantik®) are indicated for the treatment of OIC in adults with chronic non-cancer pain. Additionally, methylnaltrexone bromide is also FDA-approved for use in adults with OIC who have advanced illness and are receiving palliative care.[1-3] While lubiprostone is also indicated for the treatment of chronic idiopathic constipation, and irritable bowel syndrome with constipation, those indications will not be covered in this review. Opioids are an effective and widely used treatment option to help control many different types of pain. Constipation, which can sometimes be severe, is a common side-effect of opioid use and may limit their acceptability.[4] The cause of constipation associated with opioid use is thought to occur due to multiple etiologies. One factor is the ability of opioids to bind to the μ- and δ-opioid receptors found on smooth muscle within the gastrointestinal tract. This decreases peristalsis in the small intestine and colon by relaxing the intestinal smooth muscles and preventing normal bowel elimination functions. In addition, opioids are thought to interfere with normal fluid and electrolyte levels within the gastrointestinal lumen due to this longer gastrointestinal transit time that causes excessive water and electrolyte reabsorption from feces.[5]

Agents used for the treatment of OIC work via one of two mechanisms. Lubiprostone is a locally acting chloride channel activator that enhances a chloride-rich intestinal fluid secretion without altering sodium and potassium concentrations in the serum. Lubiprostone acts by specifically activating the chloride channel-2 (CIC-2), which is a normal constituent of the apical membrane of the human intestine. By increasing intestinal fluid secretion, lubiprostone increases motility of the intestine, thereby increasing the passage of stool and alleviating symptoms of constipation.[1] Methylnaltrexone bromide and naloxegol oxalate are selective μ-opioid antagonists that prevent the peripheral activation of μ-opioid receptors in certain tissues, such as the gastrointestinal tract, thus reducing the constipation side-effect. At therapeutic doses, neither agent interferes with the analgesic activity of opioids, which is caused by activation of μ-opioid receptors within the central nervous system (CNS).[2-3] Methylnaltrexone bromide is a quaternary amine, which increases its polarity, and helps prevents its penetration into the CNS.[2] Naloxegol oxalate is a PEGylated derivative of naloxone, and is a substrate for the P-glycoprotein transporter (P-gp). The presence of a polyethylene glycol (PEG) moiety reduces its passive permeability into the CNS while being a substrate for P-gp increases efflux of naloxegol across the blood-brain barrer.[3]

Table 1. Current Medications Available in the Therapeutic Class[1-3]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Lubiprostone (Amitiza®)	Chronic Idiopathic constipation; opioid-induced constipation in chronic non-cancer pain, Irritable Bowel Syndrome with Constipation	Capsule: 8 μg 24 μg	-
Methylnaltrexone bromide (Relistor®)	Opioid-induced constipation in chronic non-cancer pain, Opioid-induced constipation in advanced illness	Prefilled Syringe: 8 mg/0.4 mL 12 mg/0.6 mL Vial, single-use: 12 mg/0.6 mL	-
Naloxegol oxalate (Movantik®)	Opioid-induced constipation in advanced illness	Tablet: 12.5 mg 25 mg	-

Evidence-based Medicine

- The efficacy of lubiprostone for the treatment of OIC was in patients receiving opioid therapy for chronic, non-cancer-related pain was assessed in three 12-week, randomized, double-blinded, placebo-controlled studies. In all three studies, patients had documented opioid-induced constipation at baseline, defined as having less than three spontaneous bowel movements (SBMs) per week, with at least 25% of SBMs associated with one or more of the following conditions: (1) hard to very hard stool consistency; (2) moderate to very severe straining; and/or (3) having a sensation of incomplete evacuation. Use of rescue laxatives was allowed in cases where no bowel movement had occurred in a 3-day period. At baseline, mean oral morphine equivalent daily doses (MEDDs) for the three studies were 99 mg and 130 mg, 237 mg and 265 mg, and 330 mg and 373 mg for placebo-treated and lubiprostone -treated patients, respectively.[1,6,7] Studies one and two have bene published, while study three remains unpublished. The primary endpoint of study one was the "overall responder" rate, defined as ≥1 SBM improvement over baseline frequency were reported for all treatment weeks for which data were available and ≥3 SBMs/week were reported for at least 9 of 12 treatment weeks. There was a statistically significant difference in favor of lubiprostone when compared to placebo for overall responder rate (27.1% compared with 18.9%; treatment difference, 8.2%; P=0.030). The primary endpoint of studies two and three was the mean change from baseline in SBM frequency at week eight. For study two, there was a statistically significant difference in changes from baseline in SBM frequency in favor of lubiprostone when compared to placebo (3.3 compared with 2.4; treatment difference, 0.9; P=0.004). However, in the unpublished study three, there was not a statically significant difference in the mean change from baseline in SBM frequency at week eight between lubiprostone and placebo groups (2.7 compared to 2.5; treatment difference -0.2; P=0.76).[1]
- The efficacy of methylnaltrexone bromide for the treatment of OIC was established in two clinical trials in patients with advanced illness receiving palliative care and one study in patients with chronic non-cancer pain.[2,8,9] All studies were double-blind, placebo-controlled studies that compared methylnaltrexone 0.15 mg/kg and/or 0.3 mg/kg subcutaneously to placebo. The primary endpoint of the first study was the proportion of patients with a rescue-free laxation within four hours after a single dose of study medication or placebo. Methylnaltrexone bromide-treated patients had a significantly higher rate of laxation within four hours of the double-blind dose (62% for 0.15 mg/kg and 58% for 0.3 mg/kg) than did placebo-treated patients (14%); P<0.0001 for each dose compared with placebo.[2,8] The second study evaluated the same primary end-point and found similar results. In this study the proportion of patients who had rescue-free laxation within four hours after receiving the first dose of the study drug was significantly higher in the methylnaltrexone bromide group than the placebo group (48% compared with 15%, respectively; P<0.001). In addition, the proportion of patients who had rescue-free laxation within four hours after receiving two or more of the first four doses was significantly higher in the methylnaltrexone bromide group compared to placebo (52% compared with 8%, respectively; P<0.001).[2,9] The safety and efficacy of methylnaltrexone bromide for the treatment of OIC in patients with chronic non-cancer pain was evaluated in an unpublished study with results reported only in the FDA-approved package insert. The primary endpoint was the proportion of patients with greater than three spontaneous bowel movements (SBMs) per week during the four-week double-blind period. The results from this study showed that 59% of individuals in methylnaltrexone were found to have at least three SBMs per week compared to 38% in the placebo group (P<0.001).[2]
- The efficacy of naloxegol oxalate for the treatment of OIC in adults receiving opioids for chronic noncancer-related pain was evaluated in two phase III trials. Both studies were identically designed multicenter, randomized, double-blind, placebo-controlled, 12 week trials that evaluated naloxegol 12.5 mg and 25 mg compared to placebo. In both of the trials, the primary efficacy outcome was the rate of response over weeks one through 12 (defined as ≥ SBMs/week and an increase from baseline of ≥ one SBM per week for at least nine of 12 weeks and at least three out of the last four weeks). Results from these two studies revealed that naloxegol 25 mg provided a statistically significant improvement over placebo for the primary outcome (P=0.001 and P=0.02, respectively); however, naloxegol 12.5 mg showed statistical significance only in the first study (P=0.02 and P=0.2, respectively).[3,10]

Key Points within the Medication Class

- There is limited current clinical guidance that address lubiprostone or the μ-opioid antagonists' place in therapy for OIC:[5,11-14]
    - Most, existing guidelines were published prior to approval of these agents or are only briefly mentioned.[12-14]
    - Generally well-established bowel regimens are recommended for an initial case of OIC. This may include a scheduled dose of a stimulant laxative such, as bisacodyl or senna, with or without a stool-softener, such as docusate. Alternatively, daily administration of an osmatic laxative such as lactulose or polyethylene glycol may be used.[5,11,12]
    - All laxatives are potential options and there is no data to suggest that any one approach is superior to any other.
    - The limited guidance that exists regarding the newer agents suggest that they are effective treatment options, but should be reserved for refectory cases of OIC only.[5,11-14]

- Other Key Facts:
    - There are currently no generic products available.
    - Lubiprostone and naloxegol oxalate are available as oral dosage forms.

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