BRIAN SANDOVAL
Governor

RICHARD WHITLEY, MS
Director

MARTA JENSEN
Administrator

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

NOTICE OF PUBLIC MEETING – PHARMACY AND THERAPEUTICS COMMITTEE

AGENDA

Date of Publication: October 9, 2018

Date and Time of Meeting: November 15, 2018 at 1:00 PM

Name of Organization: The State of Nevada, Department of Health and Human Services (DHHS), Division of Health Care Financing and Policy (DHCFP)

Place of Meeting: Springs Preserve
333 S. Valley View Blvd.
Las Vegas, Nevada 89107

Webinar Registration: https://optum.webex.com/optum/onstage/g.php?MTID=ea21c16cb9329f314d59a9b7bb1d3a322

OR

www.webex.com, select "Join," enter Meeting Number 649 127 642, your name and email and then select, "Join."

A Password should not be necessary, but if asked, enter "Medicaid1!"

OR

Audio Only: (763) 957-6300

Event Number: 649 127 642

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

Reasonable efforts will be made to assist and accommodate physically challenged persons desiring to attend the meeting. Please call Wendy Montgomery at: (775) 684-3722 or email wmontgomery@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 five minutes per individual, organization, or agency, but may be extended at the discretion of the Chairperson.

AGENDA

1. Call to Order and Roll Call

2. Public Comment

3. Administrative

a. **For Possible Action**: Review and Approve Meeting Minutes from September 27, 2018

b. Status Update by the DHCFP

1. Public Comment

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

a. Neurological Agents – Anticonvulsants

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

b. Toxicology Agents - Substance Abuse Agents - Mixed Opiate Agonists/Antagonists

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

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

5. Established Drug Classes

a. Biologic Response Modifiers - Multiple Sclerosis Agents - Specific Symptomatic Treatment

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

b. Neurological Agents - Anticonvulsants - Benzodiazepines

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

c. Psychotropic Agents - ADHD Agents

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

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

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

7. Closing Discussion

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

Items may be taken out of order. Two or more agenda items may be combined for consideration. Items may be removed from the agenda or discussion of items may be delayed at any time.

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

If requested in writing, a copy of the proposal will be mailed to you. Requests and/or written comments on the proposed changes may be sent to the Division of Health Care Financing and Policy, 1100 E. William Street, Suite 101, Carson City, Nevada 89701 at least three days' prior the public workshop.

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

Note: We are pleased to make reasonable accommodations for members of the public who are physically challenged and wish to attend the meeting. If special arrangements for the meeting are necessary, please notify the Division of Health Care Financing and Policy, in writing, at 1100 East William Street, Suite 101, Carson City, or call Wendy Montgomery at (775) 684-3722, as soon as possible, or e-mail at wmontgomery@dhcfp.nv.gov

---

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

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

Preferred Products	PA Criteria	Non-Preferred Products
PEG-INTRON® and REDIPEN		
Anti-hepatitis Agents		
Polymerase Inhibitors/Combination Products		
EPCLUSA® HARVONI® MAVYRET® SOVALDI® ZEPATIER®	**PA required: (see below)** http://dhcfp.nv.gov/uploadedFiles/dhcfpnvgov/content/Resources/AdminSupport/Manuals/MSMCh1200Packet6-11-15(1).pdf https://www.medicaid.nv.gov/Downloads/provider/Pharmacy_Announcement_Viekira_2015-0721.pdf	DAKLINZA® OLYSIO® TECHNIVIE® VIEKIRA® PAK VOSEVI®
Ribavirins		
RIBAVIRIN		RIBASPHERE RIBAPAK® MODERIBA® REBETOL®
Anti-Herpetic Agents		
ACYCLOVIR FAMVIR® VALCYCLOVIR		
Influenza Agents		
AMANTADINE TAMIFLU® RIMANTADINE RELENZA®		OSELTAMIVIR CAP RAPIVAB
Cephalosporins		
Second-Generation Cephalosporins		
CEFACLOR CAPS and SUSP CEFACLOR ER CEFUROXIME TABS and SUSP CEFPROZIL SUSP		CEFTIN® CECLOR® CECLOR CD® CEFZIL
Third-Generation Cephalosporins		
CEFDINIR CAPS / SUSP CEFPODOXIME TABS and SUSP		CEDAX® CAPS and SUSP CEFDITOREN OMNICEF® SPECTRACEF® SUPRAX® VANTIN®
Macrolides		
AZITHROMYCIN TABS/SUSP		BIAXIN®

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

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

Preferred Products	PA Criteria	Non-Preferred Products
CARVEDILOL LABETALOL METOPROLOL (Reg Release) NADOLOL PINDOLOL PROPRANOLOL PROPRANOLOL/HCTZ SOTALOL TIMOLOL		
Calcium-Channel Blockers		
AFEDITAB CR® AMLODIPINE CARTIA XT® DILTIA XT® DILTIAZEM ER DILTIAZEM HCL DYNACIRC CR® EXFORGE® EXFORGE HCT® FELODIPINE ER ISRADIPINE LOTREL® NICARDIPINE NIFEDIAC CC NIFEDICAL XL NIFEDIPINE ER NISOLDIPINE ER TAZTIA XT® VERAPAMIL VERAPAMIL ER		
Vasodilators		
Inhaled		
VENTAVIS® TYVASO®		
Oral		
ORENITRAM® SILDENAFIL TRACLEER®		ADCIRCA® ADEMPAS® LETAIRIS® OPSUMIT® REVATIO ® UPTRAVI®
Antilipemics		
Bile Acid Sequestrants		
COLESTIPOL		QUESTRAN®

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

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

Preferred Products	PA Criteria	Non-Preferred Products
RID® SKLICE® ULESFIA®		MALATHION NATROBA® * OVIDE® SPINOSAD
Topical Anti-inflammatory Agents		
Immunomodulators: Topical		
ELIDEL® QL EUCRISA® PROTOPIC® QL	Prior authorization is required for all drugs in this class	TACROLIMUS
Topical Antineoplastics		
Topical Retinoids		
RETIN-A MICRO®(Pump and Tube) TAZORAC® ZIANA®	Payable only for recipients up to age 21.	ADAPALENE GEL AND CREAM ATRALIN® AVITA® DIFFERIN® EPIDUO® TRETINOIN TRETIN-X® VELTIN®
Electrolytic and Renal Agents		
Phosphate Binding Agents		
CALCIUM ACETATE ELIPHOS® RENAGEL® RENVELA®		AURYXIA ® FOSRENOL® PHOSLO® PHOSLYRA® SEVELAMER CARBONATE VELPHORO®
Gastrointestinal Agents		
Antiemetics		
Miscellaneous		
Diclegis® OTC Doxylamine 25mg/Pyridoxine 10mg		BONJESTA® (NEW)
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	*PA not required for < 12 years	

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

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

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

Preferred Products	PA Criteria	Non-Preferred Products
HUMALOG® HUMULIN® LANTUS® LEVEMIR ® NOVOLIN® NOVOLOG® TRESIBA FLEX INJ		AFREZZA® BASAGLAR® FIASP® (NEW) HUMALOG® U-200 TOUJEO SOLO® 300 IU/ML
Meglitinides		
NATEGLINIDE (Starlix®) PRANDIMET® PRANDIN® STARLIX®		
Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors		
FARXIGA® INVOKANA® JARDIANCE®		GLYXAMBI® INVOKAMET® INVOKAMET® XR QTERN® (NEW) SEGLUROMET® (NEW) STEGLATRO® (NEW) STEGLUJAN™ (NEW) SYNJARDY® SYNJARDY® XR XIGDUO XR®
Sulfonylureas		
AMARYL® CHLORPROPAMIDE DIABETA® GLIMEPIRIDE (Amaryl®) GLIPIZIDE (Glucotrol®) GLUCOTROL® GLUCOVANCE® GLIPIZIDE EXT-REL (Glucotrol XL®) GLIPIZIDE/METFORMIN (Metaglip®) GLYBURIDE MICRONIZED (Glynase®) GLYBURIDE/METFORMIN (Glucovance®) GLUCOTROL XL® GLYBURIDE (Diabeta®) GLYNASE® METAGLIP® TOLAZAMIDE		

Preferred Products	PA Criteria	Non-Preferred Products
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®
Monoclonal Antibodies for the treatment of Respiratory Conditions (NEW)		
NUCALA® (NEW) XOLAIR® (NEW)		CINQAIR® (NEW) FASENRA® (NEW)
Musculoskeletal Agents		
Antigout Agents		
ALLOPURINOL COLCHICINE TAB/CAP PROBENECID PROBENECID/COLCHICINE ULORIC®		COLCRYS® TAB MITIGARE® CAP ZURAMPIC® ZYLOPRIM®
Bone Resorption Inhibitors		
Bisphosphonates		
ALENDRONATE TABS FOSAMAX PLUS D®		ACTONEL® ALENDRONATE SOLUTION ATELVIA® BINOSTO® BONIVA® DIDRONEL® ETIDRONATE IBANDRONATE SKELID®

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

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

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

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

Preferred Products	PA Criteria	Non-Preferred Products
LOTEMAX® PREDNISOLONE		OMNIPRED® PRED FORTE® PRED MILD® VEXOL®
Ophthalmic Nonsteroidal Anti-inflammatory Drugs (NSAIDs)		
DICLOFENAC FLURBIPROFEN ILEVRO® KETOROLAC NEVANAC®		ACULAR® ACULAR LS® ACUVAIL® BROMDAY® BROMFENAC® PROLENSA®
Ophthalmics for Dry Eye Disease		
RESTASIS®		XIIDRA®
Otic Agents		
Otic Anti-infectives		
Otic Quinolones		
CIPRODEX® CIPRO HC® OTIC SUSP OFLOXACIN		CIPROFLOXACIN SOL 0.2% CETRAXAL® OTOVEL® SOLN
Psychotropic Agents		
ADHD Agents		
ADDERALL XR® ADZENYS® AMPHETAMINE SALT COMBO IR DEXMETHYLPHENIDATE DEXTROAMPHETAMINE SA TAB DEXTROAMPHETAMINE TAB DEXTROSTAT® DYANAVEL® FOCALIN XR® GUANFACINE ER METADATE CD® METHYLIN® METHYLIN ER® METHYLPHENIDATE METHYLPHENIDATE ER (All forms generic extended release) METHYLPHENIDATE SOL PROCENTRA®	**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® ATOMOXETINE CONCERTA® COTEMPLA XR®-ODT DAYTRANA® DESOXYN® DEXEDRINE® DEXTROAMPHETAMINE SOLUTION EVEKEO® FOCALIN® INTUNIV® KAPVAY® METADATE ER® MYDAYIS® RITALIN® ZENZEDI®

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

Preferred Products	PA Criteria	Non-Preferred Products
	https://www.medicaid.nv.gov/Downloads/provider/FA-70B.pdf (ages 6-18)	SEROQUEL®
VRAYLAR®		SEROQUEL XR®
ZIPRASIDONE	*(No PA required Parkinson's related psychosis ICD code on claim)	ZYPREXA®
Anxiolytics, Sedatives, and Hypnotics		
ESTAZOLAM FLURAZEPAM ROZEREM® TEMAZEPAM TRIAZOLAM ZALEPLON ZOLPIDEM	No PA required if approved diagnosis code transmitted on claim (All agents in this class)	AMBIEN® AMBIEN CR® BELSOMRA® DORAL® ESZOPICLONE EDLUAR® HETLIOZ® INTERMEZZO® LUNESTA® SILENOR® SOMNOTE® SONATA® ZOLPIDEM CR ZOLPIMIST®
	PA required for members under 18 years old	
Psychostimulants		
Narcolepsy Agents		
Provigil® *	* (No PA required for ICD-10 code G47.4)	MODAFINIL NUVIGIL® XYREM®
Respiratory Agents		
Nasal Antihistamines		
DYMISTA® PATANASE®		ASTEPRO® AZELASTINE OLOPATADINE
Respiratory Anti-inflammatory Agents		
Leukotriene Receptor Antagonists		
MONTELUKAST ZAFIRLUKAST ZYFLO® ZYFLO CR®		ACCOLATE® SINGULAIR® ZILEUTON ER
Respiratory Corticosteroids		
ARNUITY ELLIPTA® ASMANEX® FLOVENT DISKUS® QL FLOVENT HFA® QL PULMICORT FLEXHALER® PULMICORT RESPULES®*	*No PA required if < 4 years old	ALVESCO® AEROSPAN HFA® ARMONAIR® BUDESONIDE NEBS* QVAR® REDIHALER™ (NEW)

Preferred Products	PA Criteria	Non-Preferred Products
QVAR®		
Nasal Corticosteroids		
FLUTICASONE TRIAMCINOLONE ACETONIDE (NEW)		BECONASE AQ® FLONASE® FLUNISOLIDE NASACORT AQ® NASONEX® (NEW) OMNARIS® QNASL® RHINOCORT AQUA® VERAMYST® XHANCE™ (NEW) 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® TRELEGY ELLIPTA® (NEW) TUDORZA®
Respiratory Beta-Agonists		
Long-Acting Respiratory Beta-Agonist		
FORADIL® SEREVENT DISKUS® QL STRIVERDI RESPIMAT®		ARCAPTA NEOHALER® BROVANA® PERFOROMIST NEBULIZER®
Short-Acting Respiratory Beta-Agonist		
ALBUTEROL NEB/SOLN LEVALBUTEROL* NEBS PROVENTIL® HFA XOPENEX® HFA* QL	* PA required	LEVALBUTEROL* HFA PROAIR® HFA PROAIR RESPICLICK® VENTOLIN HFA® XOPENEX® Solution* QL
Respiratory Corticosteriod/Long-Acting Beta-Agonist Combinations		
ADVAIR DISKUS® ADVAIR HFA® DULERA® SYMBICORT®		AIRDUO® BREO ELLIPTA® FLUTICASONE PROPIONATE/SALMETEROL
Respiratory Long-Acting Antimuscarinic/Long-Acting Beta-Agonist Combinations		
ANORO ELLIPTA® BEVESPI® 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."

BRIAN SANDOVAL
Governor

RICHARD WHITLEY, MS
Director

MARTA JENSEN
Administrator

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

PHARMACY AND THERAPEUTICS COMMITTEE

DRAFT MEETING MINUTES

Date and Time of Meeting: **Thursday, September 27, 2018 at 1:00 PM**

Name of Organization: **The State of Nevada, Department of Health and Human Services (DHHS), Division of Health Care Financing and Policy (DHCFP)**

Place of Meeting: Springs Preserve
333 S Valley View Blvd
Las Vegas, NV 89107

Attendees

Board Members (Present)
Shamim Nagy, MD, Chair
Joseph Adashek, MD
Mark Decerbo, Pharm.D.
Adam Zold, Pharm.D.
Sapandeep Khurana, MD
Kate Ward, Pharm.D.
Mark Crumby, Pharm.D.

Board Members (Absent)
Michael Hautekeet, RPh
Evelyn Chu, Pharm.D.
Steven Zuchowski, MD
Brian Passalacqua, MD

DHCFP:
Holly Long, Social Services Program Specialist
Mercedes Menendez, DAG

OptumRx:

Carl Jeffery, Pharm.D.
Kevin Whittington, RPh

Public (Las Vegas):
Sibin Stephen, UCB
Chioma Ezenduka, UCB
David Crider, UCB
Sandy Sierawski, Pfizer
Mark Rueckert, Pfizer
Melissa Walsh, Novartis
Chris Stanfield, Supernus
Lee Stout, Chiesi
John Madigan, Janssen
Danny McNatty, Janssen
Stephanie Duhoux, Tris
Anthony Locke, Tris
Amy Rodenburg, Allergan
Jason Kimball, Synergy
Dawn Dynak, Gilead Sciences
Cynthia Albert, Merck
John Meyer, Roseman
Mark Schwartz, GSK
Phil Walsh, Sunovian
Ryan Bitton, Health Plan of NV
Anthony Hoovler, MD, Novo Nordisk
Laura Hill, Abbvie
Krystal Joy, Otsuka
Micah Johnson, BMS
Jennifer Lauper, BMS
Gary Okano, BMS
David Freilich, Impax/Amneal
Lee Hochner, Impax/Amneal
Rudy Eraut, UCB
Elaine Defelice, UCB

Public (On-line)
Rob Bigham, Shire
Christiana Ogunremi, DXC
Paige Barnes
Karen Meier, Novo Nordisk
Ewa Olech
Brenda Nunnally, AZ
Coleen Fong, Gilead
Kelvin Yamashita, Sanofi

AGENDA

1. Call to Order and Roll Call

Meeting called to order at 1:00 PM

Roll Call:
Joseph Adashek, MD
Adam Zold, Pharm.D.
Sapandeep Khurana, MD
Mark Decerbo, Pharm.D.
Shamim Nagy, MD, Chair
Kate Ward, Pharm.D.
Mark Crumby, Pharm.D.
Holly Long
Kevin Whittington
Carl Jeffery

2. Public Comment

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

3. Administrative

a. **For Possible Action**: Review and Approve Meeting Minutes from June 28, 2018

Motion to approve the meeting minutes as presented. Second. Voting: Ayes are unanimous, the motion caries.

b. Status Update by DHCFP

Holly Long: I'm Holly Long with DHCFP, pharmacy. I'm going to go over some updates regarding the DUR board meeting. The DUR Board met on July 26th and recommended new prior authorization criteria. I'm going to read through the changes, some is unique and some is new. If you have questions regarding these updates, please feel free to contact me. The addition of Eucrisa was added to existing prior authorization criteria for topical immunomodulators. New prior authorization criteria was added for antihemophilia agents. Revision to the existing hepatitis C criteria was approved. We took the existing criteria and reorganized it. We updated the existing criteria for Kalydeco. New criteria was added for opioid cough preparations. The addition of two new irritable bowel syndrome agents. The addition of new prior authorization for Symdeco. And existing Botox criteria was relocated to the pharmacy chapter from another chapter within Medicaid. And we have the new prior authorization for compound medications. If anybody has any questions, please feel free to contact me after the meeting. Thank you.

4. Proposed New Classes

a.Respiratory Agents – Long-acting/maintenance therapy

Shamim Nagy, MD, Chair: Is there any public comment?

Carl Jeffery: I wanted to just pause for a second and introduce our new Board Member. Dr. Mark Crumby is our new Board Member. I don't know if you want to maybe give a quick introduction of yourself and also we've got Dr. Kate Ward. I just wanted to introduce the rest of the Board so everybody knows each other, but I don't know if Dr. Crumby if you want to give a little brief intro of yourself?

Mark Crumby, Pharm.D.: My name is Mark Crumby. I'm the Pharmacy Director at Northern Nevada Hopes in Northern Nevada.

Carl Jeffery: So, I think we eluded to you at the last meeting to attempt reorganizing the classes of our respiratory agents because they were getting so complex with different combinations, single-acting agents versus the different combinations and we didn't know quite how best to organize them. So, I think Kevin and I came up with this plan to just break them out in long-acting maintenance therapy medications all into a single class here and then the next one will have just the short-acting rescue inhalers on the next one. Very few changes that we're proposing on this one. We've got a new medication that prompted us to talk about this class anyway but the Lonhala Magnair and then also the Tudorza is the one we were going to talk about a little bit, too. The Lonhala is a new long-acting antimuscarinic agent so it's a long-term treatment. It's only indicated for COPD at this time. It's got a couple good studies that show it's more effective than placebo. It has a little nebulizer machine that

comes with it and it actually nebulizes over a 2 to 3-minute period. It's actually kind of a neat technology to administer this medication. Still doing a med analysis, it didn't show any superiority over any of the other ones and none of the other ones showed superiority over this one. We look at the different class. We have them broken down in here. It has which class their in, anticholinergic versus the beta-agonist and how often they're given and here's our quantities so I know this has been popular in the past to see the number of claims we've seen in the last quarter and by far, we've got Spiriva HandiHaler is by far the most popular. When we get into the other agents, we put them on different slides to fit them all in there. So when we get into the corticosteroid inhalers, we get a lot more. Advair and Symbicort are the number one utilizations in this class here. With the Gold guidelines and how the other guidelines for treatment of asthma and COPD work is they start with the single active agents and then slowly move into the duel therapy agents and progressing onto ultimately 3 or 4 combination agents. At this time, Optum recommends the Board consider these clinically and therapeutically equivalent.

Motion to accept as clinically and therapeutically equivalent. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: Optum makes the recommendation that Tudorza, we're going to move that from non-preferred over to preferred, and the new medication, Lonhala Magnair, as non-preferred. Usually the LAMA's are not first line of therapy anyway per the Gold guidelines. It's a corticosteroid first before they're added with the long-acting antimuscarinic, so Optum recommends keeping most of the class the same except moving Tudorza to preferred and the new agent, Lonhala, as non-preferred.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

b. Respiratory Agents – Short-acting/rescue

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

Carl Jeffery: We need the Board's approval to make the changes to the class for combining it, but we're not making any changes as far as what's preferred or what's non-preferred so everything is going to remain the same. It's just we reorganized it. So, I've got the utilization numbers there. Proventil's our preferred medication, almost 10,000 units, and albuterol nebulizers are not too far behind that. Optum makes the recommendation this class be considered clinically and therapeutically equivalent.

Motion to accept as clinically and therapeutically equivalent. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: Again, no changes as far as what's preferred or what's non-preferred in this class, but we're just combining it so Optum would like to request the Board approve the class as submitted.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

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

a. Antihistamines - H1 blockers - Non-Sedating H1 Blockers

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

Carl Jeffery: We have a few of these classes here, where it's either a new generic or single new entity in here so I'll take to make these brief. The levocetirizine is the new generic for the Xyzal. All of these medications have been on the market for a long time. I think they're pretty well known. Providers use these and they have demonstrated their efficacy in the real world. The ones that were in the binder are the ones that are only by prescription. When you look at the utilization, loratadine and the cetirizine are almost tied for the first place and they are both preferred. I think they are effective agents as far as this goes and if they're not, that means they can move on to one of the non-preferred agents. We've already seen a few claims already for the levocetirizine even though it's non-preferred. It's the new one on there but it has not had a huge pickup. Optum recommends the Board consider these clinically and therapeutically equivalent.

Motion to accept as clinically and therapeutically equivalent. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: With the addition of the new generic, Optum recommends that it be considered non-preferred with the other medications and keep the rest of the list remain the same, but the cetirizine and loratadine be preferred.

Mark Decerbo, Pharm.D. : For each class, do we need at least one or two entities as preferred?

Carl Jeffery: We need at one entity to be preferred, we can't have a class without any preferred agents. Most of the classes require a trial of two preferred agents before getting a non-preferred agent, but if there is just a single agent, they would have to try just that one before getting a non-preferred.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

b. Biologic Response Modifiers - Immunomodulators - Targeted Immunomodulators

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

Christian Stone: I'm Christian Stone, one of the gastroenterologists in town. I specialize in inflammatory bowel disease. I've spoken to you before at least couple of times at prior meetings. I'm here ready to discuss Cimzia, which you've covered in the past and so I'm advocating for the coverage of Cimzia which is one of the anti-TNF agents we use for Crohn's disease and one of the big advantages, especially from patient point of view, is that it doesn't cross the placenta so patients really are in favor of using that if they're going to get pregnancy. There's a lot of patients that I meet are young and they are childbearing age so if you tell them that it's the only anti-TNF that doesn't cross

into the placenta and there's basically no risk to the fetus, they're going to usually prefer that one. So I'm just here to again reiterate that and we hope that you'll cover it for our patients.

Chioma Ezenduka: My name is Chioma Ezenduka. I'm a medical science liaison and Pharm D with UCB. Today I'm just here to provide a few updates on Cimzia. Cimzia's a unique anti-TNF biologic and that is the only pegylated and FC-free molecule. It is available as a prefilled syringe for self-administration and as a lyophilized powder for reconstitution. It is approved by the FDA for numerous inflammatory conditions including the treatment of moderate to severe Crohn's disease, rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis and as of May 2018, Cimzia received an additional indication for psoriasis. It carries along with it a class effect black box warning for increased risk of infection such as TB but please refer to the package insert for a complete list of the precautions and warnings. Studies have shown that Crohn's disease and psoriasis typically effect women in their peak reproductive years at about 50% of patients under the age of 35 at time of diagnosis. Rheumatoid arthritis is a life-long systemic autoimmune disease that effects women three times more frequently than men and often in their reproductive years. Unfortunately, due to the lack of data, placental transfer data in this patient subpopulation, women sometimes feel the need to choose between treatment and starting a family. The FDA recognized the need for robust data in this patient population by enacting the Pregnancy and Lactation Labeling Rule which requires the replacement of pregnancy category letters with scientific data by the year 2020. Given the need for scientific data in this patient population, USB made a commitment to women of childbearing potential and became the first pharmaceutical company to sponsor two pharmacokinetic studies assessing placental and breastmilk transfer in infants born to mothers taking Cimzia. The results of this study show that Cimzia levels were negligible to low in infant's blood and mother's breastmilk. There were no serious adverse events that occurred in these infants. These results are in line with Cimzia's unique structure. The FC receptor, the placenta as Dr. Stone mentioned, is necessary for active transport of nutrients from mother to baby. Thus, the absence of the FC region in the Cimzia molecule does not allow for its active transport. The FDA recognized the impact of this data and in March 2018, approved an update to Cimzia's package insert to include the results of this study. This approval provided Cimzia as an option to women between the ages of 18 to 45 who suffer from one of its indicated autoimmune diseases and have plans for family. Currently we're aware that both formulations of Cimzia is on the state of Nevada's preferred drug list in a non-restricted position. I ask that the current access remains the same for 2019. Thank you.

Mercedes Menendez, DAG: If the drug is on the approved list, let us move on and be cognizant of it because we have a long agenda.

Carl Jeffery: Couple new products on the list here that prompted us to bring this back. The Ilumya is one of the new ones. It's an IL-23 indicated for the psoriasis. A couple good studies show that it is effective. It was compared to Humira and shown to be effective. I think it's a good medication and shows some promise as far as reducing the plaques for the psoriasis. The other one is Olumiant. It's another JAK. This is one of the oral agents so it's going to be with the Taltz class so it's kind of nice to have another option available there, approved in a couple of placebo controlled trials. It has shown it is effective for the rheumatoid arthritis. This class is getting more and more complex and I think we've talked before about how to break this out but I think when you look at the indications and the drugs that are in this class, it's really hard to break down. I don't know if we want to look at just certain diagnoses but then they cross over so then we have multiple lists with different drugs in each one and then all these indications are being added all the time. The two ones we're looking at today is the Ilumya and the Olumiant. You can see how they compare with their peers. Lots of different

indications; I'm not going to go through all of them. You can see it's pretty wide coverage on those. When you look at the utilization criteria, still Humira is our number one treatment. I think that's still the go-to for a lot of providers and we'll keep that one preferred. I think number 2 here is Enbrel so if you remember back in the day, Enbrel and Humira were the 2 preferred agents we had on our formulary for a long time. The next step is for the Board to consider these clinically and therapeutically equivalent.

Mark Decerbo, Pharm.D: I would agree, we treat them like a homogenous group, but they are different, but grouping them like this makes sense.

Motion to accept as clinically and therapeutically equivalent. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: I just wanted to point out, too, that what we're trying to do is provide a couple preferred agents within each class to give a few options so with that we've got some of the preferred ones already. Our proposal is to move Inflectra which is a bio-similar to move it to non-preferred and then the Kevzara to move to preferred and then the two new agents, Olumiant would be preferred and then Ilumya would be non-preferred.

Kate Ward, Pharm.D: Can you speak to why Inflectra to non-preferred?

Carl Jeffery: When we looked at the Inflectra, it's been preferred for a while. It has no claims so I don't think it's really adopted in there and it's an infusion so it's not quite the best option I don't think for the first line of therapy. Remicade is non-preferred, as well. I know we have the Simponi listed on here, but there's a subcutaneous option, too, so I think we list all the preferred.

Kate Ward, Pharm.D: Just as long as the biologics are (indiscernible)

Joseph Adashek, MD: Just a comment, as a high-risk pregnancy specialist, I would never take a patient off one of these medications or stop breast-feeding. We don't wait for some FDA approval.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

c. Cardiovascular Agents - Antihypertensive Agents - Beta-Blockers

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

Carl Jeffery: This is kind of a dying class. We do have a new one, Kapspargo is a new sprinkle agent. It's approved down to ages of 6, approved for just the same indications; all the other beta-blockers, heart failure and hypertension. I think there's some new data showing it's not first line so it's not the drug of choice anymore, but it's metoprolol, a drug that's been out there forever but it's just in a different form. There's utilization numbers. Still not a huge number of drugs on here; the people that we have on these, but metoprolol is still our number one use and that's just the regular release, metoprolol, and the carvedilol is number 2 up there. Optum recommends the Board consider these clinically and therapeutically equivalent.

Motion to accept as clinically and therapeutically equivalent. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: Optum recommends the new agent, Kapspargo, be non-preferred. It's one of the only branded medications on the list here.

Sapandeep Khurana, MD: Are there any other forms available to kids that are not tablets?

Carl Jeffery: The other non-preferred agent is a liquid but otherwise everything else is tablet form. All of these can be crushed or compounded into another form.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

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

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

Carl Jeffery: Another new agent in here. I don't know why they made this medication; I don't think the pitavastatin has been shown to be outstanding statin already anyway but they added a little magnesium salt to it and called it different. Very similar to the Livalo and it's still indicated for the same thing, primary hyperlipidemia and mixed lipidemia. The one advantage this one has is it doesn't have the same interactions a lot of the other ones do. Again, all of them have been shown except for the pitavastatin. I just don't think it's been out on the market long enough to really show the cardiovascular advantages that the other ones do but it may get there but it doesn't have the data behind it right now. When we look at the numbers. Atorvastatin is by far the most favorite still followed by the simvastatin. Optum recommends the Board consider these clinically and therapeutically equivalent.

Motion to accept as clinically and therapeutically equivalent. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: Optum recommends the Board as a new medication, the Zypitamag, as non-preferred and keep the rest of the class the same.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

e. Hematological Agents - Erythropoiesis-Stimulating Agents

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

Carl Jeffery: We've got a new biologic in here, the Retacrit is the new bio-similar to Epogen and Procrit. Mircera has been out on the market. It has a longer duration of action as the Aranesp but it could be up to I think every 2 weeks. Same kind of indications. It's not indicated for chemotherapy-related anemia like the other ones are but there is another option. It's shown safe and effective for the treatment of anemia with chronic kidney disease. The Retacrit is bio-similar to the Epogen and Procrit

so it kind of tags on for those indications. Pretty low utilization on these because the primary place of service for these is going to be your dialysis centers and this is all bundled service for them so they don't bill for these separately. Really we don't see very many claims for these.

Kate Ward, Pharm.D: So if it was part of the dialysis center, it wouldn't go into this bucket.

Carl Jeffery: Right, they are paid a per diem rate, they get paid the same whether they give this or not.

Kate Ward, Pharm.D: They would be able to choose their preferred agent then.

Carl Jeffery: That's right.

Motion to accept as clinically and therapeutically equivalent. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: We've got a list of Mircera and Retacrit. Optum recommends they add it as non-preferred and keep the Aranesp and Procrit as preferred.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

f. Neurological Agents – Alzheimer's Agents

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

Carl Jeffery: Lots of new generics in this class. We're looking at getting some language added so the DHCFP can make changes from brands to generic back and forth without taking it to the Board so the statute currently states we have to have you guys approve it but maybe someday in the future. A couple new generics on the market. You can see pretty much everything on here has a generic except for the Namzeric now so we are just positioning things to provide adequate coverage while seeing what we can do for the state here. Utilization numbers still the donepezil is still number one. Memantine is number two. Again, I think most of these are going to fall into your med-D space so we don't see a whole lot of claim. You're seeing the used in older people who are in med-D now so I don't think these have a huge impact in our population. Optum recommendations the Board consider these clinically and therapeutically equivalent.

Motion to accept as clinically and therapeutically equivalent. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: Before we just had Memantine without any kind of distinction on there, but there is now a solution and generic XR. We have the brand Namenda-XR tablets. So I want to make that distinction that we just want the regular-release tablets is preferred and then the two new rivastigmine generics, the capsules and transdermals added as non-preferred. We still have the Exelon patch and the solution that are as preferred. Optum recommends the new generic be added as non-preferred except for the memantine tablets make that distinction and we'll cover those as preferred.

Kate Ward, Pharm.D: What is the reason to make the XR non-preferred?

Carl Jeffery: The way it falls with the coverage, it's twice a day versus a once a day. We feel that it's worth a try trying it twice a day dosage before moving to the once a day. With the way our preferred drug list is set up, it should be pretty easy to get that if that's going to be a big enough convenience for them.

Mark Decerbo, Pharm.D: The usage slide is interesting, the generic Exelon patch was higher.

Carl Jeffery: It may have been allowed to pay as preferred until it was reviewed.

Kate Ward, Pharm.D: And these are the last quarter?

Carl Jeffery: This is the last quarter. If the Board chooses to go with our recommendation, we can certainly grandfather those recipients in so they don't have to change so they can continue getting the Namenda-XR but just any new people added to this therapy then we would just ask them to try the twice-a-day therapy instead of once-a-day. We can grandfather in and we will grandfather anybody who's currently on Namenda-XR. When we make it non-preferred, we will go ahead and allow the people to be on it.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

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

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

David Freilich: My name is David Freilich. I'm here with Amneal Pharmaceuticals. I'm here to talk a little bit about zolmitriptan nasal spray. We recently had an indication for adolescents but the other thing that I think we need to keep in mind is that it turns out that you believe Silverstein's paper from 10 years ago, about 90% of the patients have nausea, about 70% have vomiting. It is believed the American Migraine Prevention Study, about 49% of patients had migraines actually had vomiting and nausea half the time so it's important to non-oral routes of administration. If you look at non-oral routes of administration, you really only have Zomig, zolmitriptan, and sumatriptan. So, the sumatriptan nasal of several varieties, injections of several varieties. Unfortunately, when you look at triptans, we typically think of them as all being therapeutically equivalent. But for reasons we don't comprehend, you never know which triptan works in what patient so typically you start with whatever the cheapest is and then you move on until you find one that works. If you want something that's non-oral, you've got some nausea and vomiting, you have two choices or you can go to an IV infusion at the ER, which is another option. I would like you to consider zolmitriptan nasal spray as preferred when it's appropriate for these folks with nausea and vomiting. Thank you.

Carl Jeffery: A lot of new generics in this one, too, and a new dosage. The one I want to point out, the other ones are just new generics. We have the generic for Axert and Zomig and Zomig-ZMT which is an ODT now. There's a new nasal spray. Last meeting we talked about a drug for nasal polyps, a corticosteroid for nasal polyps. It's kind of a similar delivery mechanism in that you blow into this device and it shoots powder into your nose deep and they say the deposit is deeper so that's the Onzetra-Xsail but the sumatriptan nasal powder, so it's a little bit different delivery mechanism. Same drug we've had out on the market for a long time with the sumatriptan. If we look at the generic availability, a lot of them are coming generic now. The newest one that was added here was the

Treximet which is the sumatriptan/naproxen combination tablet. The other ones have been generic for quite some time. The only one that's not on here is the Zembrace Syntouch. There's Zecuity transdermal that patch that had batteries and stuff in it that was used that gave an injection over 15 minutes; it's been withdrawn from the market so we're going to pull it off the list but it's not on here anyway. If we look at the utilization. Still the sumatriptan tabs are most widely used and I think that goes with what this kind of standard practice is. Optum makes the recommendation this class be considered clinically and therapeutically equivalent.

Motion to accept as clinically and therapeutically equivalent. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: Our preferred list as we presented here, we moved to nasal sprays over to non-preferred and we're proposing the Board accept this because these generally aren't first line. You're still going to try a tablet first. There are ODT tablets available so if there are some issues with nausea and vomiting, the ODT tablet is also an option there and then with the injection so we're going to move those to preferred and that's kind of our thought process to get those on there. The rest of the new medications all would be added as non-preferred so we've got the Zembrace, the zolmitriptan, all the different generics and the new one, the Onzetra-Xsail. I don't think that'd be a first line one, either, it seems like it's a little bit more intensive therapy but Optum recommends that the Board accept our recommendations.

Sapandeep Khurana, MD: The sumatriptan nasal spray is the most used product in that category.

Carl Jeffery: You guys are always well within your right to make that preferred and, we think it's usually not your first go-to product but….

Mark Decerbo, Pharm.D: It is tough because the speaker's comments resonate with me. Having an alternative route is good, but I agree that oral should be tried first. But if you have a migraine with nausea and vomiting, you're going to have to fail a couple of these options before getting a different dosage form. I'm struggling with not having at least one non-oral route as preferred.

Joseph Adashek, MD: How does it work to obtain authorization for drugs on the right side. A neurologist sees a new patient and without their history, is it difficult to be accepted or do we accept the word of the physician?

Carl Jeffery: We accept the physician's word. If the physician trusts that the patient tried those. We don't require and we understand the medical records go back 40, 50 years sometimes.

Joseph Adashek, MD: Typically if someone says they failed something on the left, I refer them to a neurologist.

Sapandeep Khurana, MD: What would be the downside keeping the nasal spray preferred?

Carl Jeffery: There really is no downside from your perspective.

Sapandeep Khurana, MD: I would like to make a motion to keep sumatriptan nasal spray as preferred.

Second. Voting: Ayes are unanimous. The motion carries.

Motion to accept the rest of the recommendations. Second. The motion carries.

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

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

Carl Jeffery: There was supposed to be a new product in this class, but the manufacture does not participate in the Federal Drug Rebate program. So we can skip this class.

i. Otic Agents - Otic Anti-infectives - Otic Quinolones

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

Carl Jeffery: I think we eluded to the Otiprio before. It's an injection, intra-tympanic injection that they administer at the time of putting tubes in the ears. This isn't something that the pharmacy is going to be dispensing. It's to be only administered at the doctor's office. Our intent was here to make it non-preferred so it doesn't cause any confusion and somebody accidentally write for it, have the pharmacy try to order it and bill for it. You see our utilization for the other agents. Ciprodex and ofloxacin are popular agents and these are all external eardrops. Optum recommends the Board consider these clinically and therapeutically equivalent.

Motion to accept as clinically and therapeutically equivalent. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: Optum recommends keep the class the same except for the addition of Otiprio is non-preferred and mostly just to avoid the risk of errors from the pharmacy side. A quick clarification, physician that administered drug claims/had claims aren't bound to our preferred drug list so this won't impact physicians administering this in their offices at all.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

6. Annual Review – Established Drug Classes

a. Anti-infective Agents - Antivirals - Anti-Herpetic Agents

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

Carl Jeffery: We're getting into the phase where we have even more new generics and that's where really these are coming for. There's a new generic for the Famvir so the famciclovir is just a generic for the Famvir. The utilization numbers actually was higher than what I was anticipated to be but Optum recommends the Board consider these clinically and therapeutically equivalent.

Motion to accept as clinically and therapeutically equivalent. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: Optum recommends that it be added as preferred and then the brand, Famvir, as non-preferred and I'll throw this out to the Board, too. I think you guys have the option now that every single one of the preferred agents is generic in this class and the only thing that's listed non-preferred is the brand. So there's really no reason to have a preferred drug list on this class anymore so I'll ask Mercedes if it's okay if the Board can vote for just abolish the class or if they need to bring it back with a different agendized?

Mercedes Menendez, DAG: I think it needs to be on an agenda at a future meeting.

Mark Decerbo, Pharm.D: Can you remind us of the implications of removing the class?

Carl Jeffery: The reason we have the class is so we can work with the manufacturers and without any brand names on here, just no manufacturers to work with and they're all generic manufacturers that would come to us. Unless there's a new brand name that's brought into this class, and we won't need to review it ever again.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

b. Anti-infective Agents - Antivirals - Influenza Agents

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

Carl Jeffery: New generic Tamiflu suspension has been added; nothing real special about it. You see our utilization numbers. These aren't going to be real big since last quarter was not flu season. Optum recommends the Board consider these clinically and therapeutically equivalent.

Motion to accept as clinically and therapeutically equivalent. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: Optum recommends the new suspension generic be added as non-preferred. On the preferred side, we still have the Tamiflu. This includes the capsules and suspension. We have the brand name that's preferred for the suspension, too, and hopefully the manufacturer's keep up with the demand and hopefully we don't have a flu season as we did last year.

Adam Zold, Pharm.D: Is there any kind of override allowed if the brand Tamiflu becomes unavailable?

Carl Jeffery: I think it would be decision from the state but I know it's in the commercial plans last year; I think there was a shortage with the generic, though, wasn't it? So we were sitting pretty good last year since we had the brand as preferred. I think that certainly the state has that ability to make that decision if it comes to it.

Mark Decerbo, Pharm.D: At some point, we might want to look at amantadine being in the anti-Parkinson's class rather than this.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

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

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

Carl Jeffery: A couple new generics. Avelox ABC packet being discontinued and then there's a new generic for the Avelox, moxifloxacin. The numbers here, still Levaquin or levofloxacin still our number one preferred agent. The other one is hardly in usage. Optum recommends this class be considered clinically and therapeutically equivalent.

Motion to accept as clinically and therapeutically equivalent. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: So, we're just going to swap the brand, Avelox, make it non-preferred and the generic moxifloxacin is preferred and then we'll remove the Avelox ABC pack from the list since it's not longer available. This might also be a good time to just get public awareness out of our initiative for antimicrobial stewardship program the state is working on that the DUR Board voted on some limitations to some of the classes. The third generation cephalosporins and fluoroquinolones are included in this so look for more information coming up on that.

Holly Long: There is a letter going out to providers either email or fax or newsletters. You will see these letters and announcements for this new antibiotic policy.

Joseph Adashek, MD: In terms of that policy. We see patients who have cold symptoms for a long time and come to us asking for antibiotics. We tell them it is viral and do not give them antibiotics. But then they go to a quick-care clinic and get an antibiotic. Is there anything you can do with those?

Holly Long: Yes, Dr. Wilson gave a great presentation to the DUR Board and the CDC says Nevada is the worst for overprescribing and resistance.

Joseph Adashek, MD: I couldn't agree more, I have more patients requesting antibiotics than opioids.

Holly Long: Yes, there will be some criteria that requires a culture and sensitivity before being approved.

Carl Jeffery: There will be some guidelines. This perfectly describes our issue and that's what we're going after.

Holly Long: The letters will be going out to prescribers and pharmacies. We will be doing workshops to get the information out.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

d. Cardiovascular Agents - Antihypertensive Agents - Vasodilators – Oral

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

Carl Jeffery: Another new generic to talk about, the generic for Adcirca, the tadalafil. Here's a breakdown of kind of where they fall within the category. I tried to get at least one from each class included in there. Here's our utilization numbers. The sildenafil the same thing as tadalafil is we have our ED agents and then we have our PAH agents. They're in different areas in our drug database; all the ones that are used for ED are excluded. They can't be used so we have all the sildenafil. These are the only ones that are only used for pulmonary arterial hypertension. We don't really know what they're being used for but I'm hoping that they're patients with pulmonary hypertension, but you can see our utilization. Sildenafil is number one, followed by Letairis and Adcirca. Optum recommends that the Board consider these clinically and therapeutically equivalent.

Motion to accept as clinically and therapeutically equivalent. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: This gave us the opportunity to review the class. Optum recommends adding Adcirca, the brand, to preferred and the generic, the tadalafil, as non-preferred and keep the rest of the class the same.

Sapandeep Khurana, MD: Are there any limitations for sildenafil? Is it approved for other indications?

Carl Jeffery: There are not any quantity limits and we don't allow for other indications.

Adam Zold, Pharm.D: Can we add a restriction for indication or is that something the DUR committee would do?

Carl Jeffery: That would be a DUR requirement.

Holly Long: Do you want the restriction just for the sildenafil?

Carl Jeffery: We would probably just look at the whole class.

Sapandeep Khurana, MD: Why would we allow these without indication?

Carl Jeffery: We've just never looked at it before and we're looking at not quite even 100 claims over the course of a quarter. Even if half of those are legitimately pulmonary hypertension, it's worth it. I don't know if it's worth our effort to really crack down on those.

Holly Long: Do you want me to report at the next meeting?

Adam Zold, Pharm.D: Yes please, at the next meeting.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

e. Dermatological Agents – Anti-psoriatic Agents - Topical Vitamin D Analogs

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

Carl Jeffery: We have one new dosage form in here that's Taclonex ointment is available now indicated for the plaque psoriasis. We have it broken down here with a different active ingredient. It's really just a couple of active ingredients for all of these agents and then they're just different dosage form so either ointment or scalp solution or foam or cream; you can see all the different ones. A lot of generic are available now in the different dosage forms. These aren't utilized so I don't want to spend a whole lot of time racking our brains over here trying to get it just perfect. This is over a quarter so if you figure if they get one a month then there's maybe four or five members in Medicaid that are on this. Optum recommends the Board consider these clinically and therapeutically equivalent.

Motion to accept as clinically and therapeutically equivalent. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: With the addition of the new ointment, it gave us an opportunity to kind of make this more specific because I think we had the Dovonex preferred as the cream in there to give a dosage form of the cream available but then the Taclonex suspension make that distinction as to suspension, it would be preferred but the Taclonex ointment would be non-preferred just because I think we've got other psoriatic ointment in that class, as well, but I think we've got all the different dosage forms covered on that one.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

f. Dermatological Agents - Topical Anti-infectives - Topical Antifungals (onychomycosis)

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

Carl Jeffery: We don't have any recommendations for this right now. After discussion, after we put it on the agenda already, we decided it's probably better to break this class down a little bit. It's a little bit confusing the way it's listed now because it's topical antifungal but some of these are oral agents so I think what our intent was, it was a topical infection so we'll bring it back next month and have some clarification around it.

Topic tabled.

g. Electrolytic and Renal Agents - Phosphate Binding Agents

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

Carl Jeffery: Calcium acetate capsules versus the tablets is what we're talking about here. The capsules is a generic for the PhosLo. The tabs are the generic for the Eliphos. There's a difference in the state so we're going to talk about the generic availability. A lot of these have the same calcium acetate as the active ingredient and then there's maybe a different dosage form. A look at the utilizations, the Renvela used. These are used for the chronic kidney patients but these are often covered separately. They're not included in the per diem rate for the dialysis centers and we talked

about with the EPO products as being covered. These are actually covered outside and unless they get the dose at the dialysis center. Optum recommends this class be considered clinically and therapeutically equivalent.

Motion to accept as clinically and therapeutically equivalent. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: The only change that we're recommending is to make a capsule, make a distinction as the capsule would be preferred and the calcium acetate tablet is non-preferred. I don't think there's a difference therapeutically between these but it makes a difference on our side.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

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

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

Carl Jeffery: There's a new generic for the Avodart, the dutasteride. The finasteride is a generic for Proscar. It's the number one utilizer for these but Avodart doesn't have a whole lot of utilization but Optum recommends this class be considered clinically and therapeutically equivalent.

Motion to accept as clinically and therapeutically equivalent. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: Optum recommends that the dutasteride be considered as preferred and the brand Avodart be added as non-preferred, and the rest of the class remain the same.

Sapandeep Khurana, MD: When these switches happen, are they automatically grandfathered or do we need to take a separate action?

Carl Jeffery: The pharmacy can interchange these at the counter so they don't need to contact the provider for a new prescription and everything so there's no reason to grandfather in, so it goes for the brand Avodart and go home with the generic. There's no reason to grandfather these in.
Sapandeep Khurana, MD: What if they have a brand medically necessary justification?

Carl Jeffery: I would probably not grandfather these unless the Board tells me specifically. These are all AB-rated generics. There's really no reason a patient could not take the generic.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

i. Hematological Agents - Anticoagulants – Injectable

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

Carl Jeffery: Another new generic, the Arixtra has a new generic, fondaparinux. It's newly available. Again, the utilization is still the generic Lovenox. It's still surprising amount of fractionated heparin being used but Optum recommends the Board consider these clinically and therapeutically equivalent.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: For Optum, we recommend just swapping out the generic Arixtra for fondaparinux. The generic Arixtra is preferred and then the non-preferred would be the brand, Arixtra.

Kate Ward, Pharm.D: Why is heparin listed in this list?

Carl Jeffery: The class, the way it's coded, it's low-molecular weight heparin, so it's not non-preferred, it's just not listed. I think it's worth listing to make sure it's available and I think if you've got a prescriber that's going through lists to see what's preferred and they see these and heparin, maybe they choose heparin, that is going to be appropriate for a lot of patients.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

j. Hematological Agents - Anticoagulants – Oral

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

Carl Jeffery: There aren't any new agents in here. We're just going to make the recommendations. The Bevyxxa, which I think we discussed last time, entered as non-preferred. The manufacturer actually pulled out of the rebate program so Medicaid can't cover this medication anyways. We're going to remove it from the list. When you look at some of the head-to-head studies, there's been a lot of new data on this class recently and a lot of TV commercials tell me which one's best. No head-to-head studies have been shown still showing one is beneficial over the other ones. When you look at the indication comparison between all of these, I think what I wanted to highlight the most because the one we're recommending is being changed is Savaysa. It's got some caveat with both of their indications so you can see this one down here, it's the same with Pradaxa here, but they have to have a 5 to 10 day prior treatment with the parental anticoagulant before starting on it and I think that kind of throws a wrench in that use. Then also it's not indicated for non-valvular a-fib with creatinine of over 95 mL/minute. I think these are a couple of the drawbacks but I think there's some better agents on the market. It seems like the other agents are really doing a good job of continuing their studies to show that these are safe and effective and expanding their indications, etc., and showing that they've got some long-term benefits. When we look at the utilization certainly shows where the provider community wants to put what they want their patients on, the Eliquis and still Warfarin is still way up there but we looked at just NOACS, Xarelto is still pretty high up there but only 2 claims for the Savaysa within the past quarter so not a whole lot of utilization. Optum recommends this class be considered clinically and therapeutically equivalent.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: Optum is making the recommendation to move Savaysa to non-preferred and then we'll just remove the Bevyxxa because it's not covered for Medicaid anyway. The one patient that's on the Savaysa we can grandfather them in.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

k. Hormones and Hormone Modifiers - Antidiabetic Agents - Alpha-Glucosidase Inhibitors/Amylin analogs/Misc.

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

Carl Jeffery: The acarbose had 22 claims and then the Precose had 0 claims and there was no other utilization with the other agents in this class so we're not going to spend a whole lot of time in here but Optum recommends the Board consider this class clinically and therapeutically equivalent.

Motion to accept as clinically and therapeutically equivalent. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: Optum recommends moving the brand Precose to non-preferred.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

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

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

Carl Jeffery: The newest agent in here is the Bydureon BCise. It's a good delivery mechanism. It's an auto-injector. It's shown to be more effective as far as the Byetta twice a day. We look at these different products up here now and none of them are generic. Tanzeum is going away. I think it was off the market as of July so whatever products are left on the pharmacy shelves is what's being used but that one is going to go away here pretty soon. We have it broken down by the usual dosage form, how often it's dosed either once weekly, once daily, in terms of the Byetta and even twice daily so certainly those aren't the most optimal doses there. The Symlin doesn't necessarily fall directly into this class with the other ones. I just wanted to highlight the clinical guidelines in here because I think this is going to be a pretty hard decision for the Board with this one that we're proposing but they still with the incretin mimetics, they're still not the first, still metformin is still number one. It is ok to add as the second line but still there's even some other ones. The SLG2's are often preferred even over the incretin sometimes. Looking at our utilization numbers. Victoza still has some of the best data out there. Victoza's still widely used. It's got the ADA recommendation. It has some of the data for weight loss, as well, but then we see that Trulicity is number 2 and then the Tanzeum again is tapering off. The Ozempic which we made preferred last time is no utilization yet but then we've got the Bydureon up at the top. Optum recommends that the Board consider these clinically and therapeutically equivalent.

Motion to accept as clinically and therapeutically equivalent. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: This is a pretty aggressive recommendation for changes and I realize that and it puts you guys in a tough situation here but from our perspective, this provides some good coverage as far as medications available, the Bydureon, and the Bydureon Pen would still be available and of course the Victoza which is our number one utilizer but it also moves the Bydureon BCise, the Ozempic, Tanzeum which doesn't matter, but then the Trulicity which is a popular agent, too, as non-preferred. Optum recommends this is your preferred drug list.

Kate Ward, Pharm.D: Can you discuss why the list was so long and now it is being restricted?

Carl Jeffery: We are getting more aggressive, I can't go into too much detail.

Mark Decerbo, Pharm.D: It is tough; Trulicity moving to non-preferred is tough with its data and utilization.

Joseph Adashek, MD: As someone that doesn't use these very often, that is a fair amount of utilization.

Carl Jeffery: This is one where we certainly grandfathered those members in that are currently on it and just going forward; it would just be a step before they got non-preferred.

Joseph Adashek, MD: There are a lot of providers that like Trulicity. I would vote for Trulicity to be preferred.

Kate Ward, Pharm.D: The numbers show they are choosing Trulicity over Victoza. This would steer them toward the others on the preferred list.

Joseph Adashek, MD: Why do you think it is used so much more than the others?

Carl Jeffery: There's some marketing behind it and also I'll give them that Trulicity as a cool device and it's an easy to use device.

Joseph Adashek, MD: And they're more likely to be compliant with an easier to use device?

Carl Jeffery: I wouldn't say it promotes compliance as much. I don't have much interaction with diabetic patients anymore. I don't think a diabetic would choose that device as it is a little bit more difficult to use. I don't know that that's a total selling point.

Joseph Adashek, MD: For discussion, I have a hard time taking something off the preferred list with so much utilization.

Kate Ward, Pharm.D: We are running in to compliance issues if they are on Victoza. You would be moving a once-weekly medication non-preferred and not having that option any more?

Carl Jeffery: Bydureon Pen would still be available.

Joseph Adashek, MD: I would like to make a motion that Trulicy remain preferred since it is used so much and if it is easier to use. For diabetics, the better compliance, the less long-term effects they are going to have.

Mark Decerbo, Pharm.D: I would second that. I think the once weekly is beneficial and there is some data with once weekly Bydrueon vs. Trulicity and I think Trulicity comes out ahead. In terms of compliance with the once-weekly.

Joseph Adashek, MD: If they are more compliant, the long-term expenses are lower in the diabetic patients.

Shamim Nagy, MD, Chair: We have a motion to keep Trulicity as preferred.

Voting: Ayes are unanimous. The motion carries.

Motion to accept Optum's remaining recommendations. Second. Voting: Ayes are unanimous. The motion carries.

m. Musculoskeletal Agents - Bone Resorption Inhibitors – Bisphosphonates

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

Carl Jeffery: Fosamax D has been preferred for a long time, even though it hardly has any utilization so there's really no benefit to having the Fosamax D. I think initially had some ideas that would provide some benefit, but we have the alendronate sodium as available and certainly the more widely used. Optum recommends this class be considered clinically and therapeutically equivalent.

Motion to accept as clinically and therapeutically equivalent. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: Optum recommends the Fosamax plus D be entered as non-preferred.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

n. Musculoskeletal Agents - Bone Resorption Inhibitors - Nasal Calcitonins

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

Carl Jeffery: These products are kind of dwindling, Fortical and I think Miacalcin is going away, too, eventually. We're trying to get ahead of it. There are 5 claims total in this class. This isn't something that's used very often. Right now, the only thing that would be available is the generic calcitonin salmon so Optum recommends the Board consider these clinically and therapeutically equivalent.

Motion to accept as clinically and therapeutically equivalent. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: Just anticipating that Miacalcin won't be available much longer, I had that as non-preferred and we'll keep the calcitonin salmon preferred.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

o.Ophthalmic Agents - Ophthalmic Antihistamines

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

Carl Jeffery: Alaway is ketotifen which is also Zaditor and the generic so we're going to remove that one as a proposal but you see the current utilization. The ketotifen, Alaway really didn't have very many claims. They can easily switch over to the ketotifen which is number two on there but the Pazeo is going to remain as preferred in our proposal, but Optum recommends these be considered clinically and therapeutically equivalent.

Motion to accept as clinically and therapeutically equivalent. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: Optum recommends just removing Alaway brand from the preferred list to make it non-preferred and like I said, the ketotifen and the Zaditor are both available as preferred which is the same ingredient.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

p. Ophthalmic Agents - Ophthalmic Anti-infectives - Ophthalmic Macrolides

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

Carl Jeffery: This is another one where we thought there was going to be some changes in the class and it didn't happen, so I don't think we need the Board to do anything on this one. We're not proposing anything.

q. Ophthalmic Agents - Ophthalmics for Dry Eye Disease

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

Carl Jeffery: Restasis has a new multidose bottle and it has all the doses instead of getting them all individually packages single-use vials for the Restasis. It comes in just a big eye drop. Has a one-way valve and an air filter so I think it's just smaller packaging but seems to me it still has the potential to get contaminated so I don't know too much about it but you can see the utilization. It's actually pretty high surprisingly for the good amount because right now we don't have a distinction, we just have Restasis listed so it's currently hitting as preferred. Artificial Tears is something we wanted to add to make physicians aware that that's another option and probably should be tried first before they try these other agents. Optum recommends this class be considered clinically and therapeutically equivalent.

Motion to accept as clinically and therapeutically equivalent. Second. Voting: Ayes are unanimous. The motion carries.

Carl Jeffery: Optum recommends the addition of Artificial Tears just to make people aware that's another option and then to make that distinction between the Restasis vials and the Restasis multidose and make the multidose non-preferred.

Mark Crumby, Pharm.D: Is artificial tears a prescription item?

Carl Jeffery: It's over the counter but if they get a prescription from their doctor, Medicaid will pay for it.

Motion to accept Optum's recommendation. Second. Voting: Ayes are unanimous. The motion carries.

7. Annual Review – Drug Classes Without Proposed Changes

Carl Jeffery: There were some letters that were delivered to me that are letters of support for the anticonvulsants and having open access to these. We didn't have it agendized so Optum doesn't have any recommended changes but it's certainly something the Board can review and have the discussion on.

a. Public Comment

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

b. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the division of Health Care Financing and Policy Without Changes

Carl Jeffery: The Board is required to review all the drug classes at least once a year so this is the time we do that. I think the list on your agenda might be the best place to reference those and also the PDL that's in the front of your binder so you can see what's preferred and what's non-preferred. I just have them all listed here in the different slides.

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

Motion to approve remaining drug classes without changes. Second. Voting: Ayes are unanimous. The motion carries.

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

Carl Jeffery: A couple new exciting agents that are coming out. The Ampyra I wanted to highlight as a new generic. We may see this one in the future and the other ones are not so much that we used. New products, new brand names that are out here. These are a little bit telling about what we'll see again in the future. The Cassipa is a new buprenorphine naloxone product so we'll be seeing the

opioid dependent agents again here in the future. Also, we've got a new Xelpros, another glaucoma agent. We have a new class of medications. This is the second agent within the class but it's for the migraine agents. They're the CGRP agents for prophylaxis migraines. You have Ajovy and Aimovig is the other one so now that we've got a couple of these in the market, we'll probably bring that one back to the Board. Up for probably the next meeting, I'll just give you guys a little time to do some homework and go home and read about these, or let me know if you do see other agents that you think could be on the PDL. We'll see the Dry Eyes again next time or maybe it might be March, but there's a new cyclosporin product for dry eyes and then the onychomycosis agent, as well. We looked for some help from the Board to see how we want to classify these because we've got a new class of medications called a RoxyBond. It's immediate-release product, oxycodone, that's abuse deterrent and so I think we need to know like kind of what the Board wants to see where those classes go and how those are best utilized.

Mark Crumby, Pharm.D: On HIV meds, are they automatically added?

Carl Jeffery: HIV is an NRS restricted class; we are unable to put any kind of restrictions on HIV medications. The same with HIV and anti-rejection medications; we cannot limit.

9. Closing Discussion

a. Public comments on any subject
b. Date and location of the next meeting: November 15
c. Adjournment

Meeting adjourned at 2:51 PM.

Therapeutic Class Overview
Anticonvulsants

INTRODUCTION

- Epilepsy is a disease of the brain defined by any of the following (*Fisher et al 2014*):
  - At least 2 unprovoked (or reflex) seizures occurring > 24 hours apart;
  - 1 unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after 2 unprovoked seizures, occurring over the next 10 years;
  - Diagnosis of an epilepsy syndrome.
- Types of seizures include generalized seizures, focal (partial) seizures, and status epilepticus (*Centers for Disease Control and Prevention [CDC] 2018, Epilepsy Foundation 2016*).
  - Generalized seizures affect both sides of the brain and include:
    - Tonic-clonic (grand mal): begin with stiffening of the limbs, followed by jerking of the limbs and face
    - Myoclonic: characterized by rapid, brief contractions of body muscles, usually on both sides of the body at the same time
    - Atonic: characterized by abrupt loss of muscle tone; they are also called drop attacks or akinetic seizures and can result in injury due to falls
    - Absence (petit mal): characterized by brief lapses of awareness, sometimes with staring, that begin and end abruptly; they are more common in children than adults and may be accompanied by brief myoclonic jerking of the eyelids or facial muscles, a loss of muscle tone, or automatisms.
  - Focal seizures are located in just 1 area of the brain and include:
    - Simple: affect a small part of the brain; can affect movement, sensations, and emotion, without a loss of consciousness
    - Complex: affect a larger area of the brain than simple focal seizures and the patient loses awareness; episodes typically begin with a blank stare, followed by chewing movements, picking at or fumbling with clothing, mumbling, and performing repeated unorganized movements or wandering; they may also be called “temporal lobe epilepsy” or “psychomotor epilepsy”
    - Secondarily generalized seizures: begin in 1 part of the brain and spread to both sides
  - Status epilepticus is characterized by prolonged, uninterrupted seizure activity.
- Seizure classifications from the International League against Epilepsy (ILAE) were updated in 2017. The ILAE classification of seizure types is based on whether the seizure has a focal, generalized, or unknown onset; has a motor or non-motor onset; and whether the patient is aware or has impaired awareness during the event (for focal seizures). Additional classification details may also be used (*Fisher et al 2017A, Fisher et al 2017B*).
  - There is variation between the ILAE classifications and many of the Food and Drug Administration (FDA)-approved indications for antiepileptic drugs (AEDs). For example, a “focal aware” seizure corresponds to the prior term “simple partial seizure,” and a “focal impaired awareness” seizure corresponds to the prior term “complex partial seizure.”
- A number of epilepsy syndromes have also been described; these are defined by groups of features that tend to occur together such as having a similar seizure type, age of onset, part of the brain involved, and electroencephalogram (EEG) pattern (*Epilepsy Foundation 2013*). An example is a childhood epilepsy syndrome called Lennox-Gastaut syndrome (LGS), which is characterized by several seizure types including tonic (stiffening) and atonic (drop) seizures. In LGS, there is a classic EEG pattern seen and intellectual development is usually impaired (*Epilepsy Foundation 2014*).
- Epilepsy management is focused on the goals of 1) controlling seizures, 2) avoiding treatment-related adverse effects (AEs), and 3) maintaining or restoring quality of life. Management options vary based on the seizure type. It is usually appropriate to refer patients to a neurologist to establish the epilepsy diagnosis and formulate the management strategy (*Schachter 2018*).
  - A correct diagnosis is essential to proper treatment selection. For example, absence seizures are commonly confused with complex partial seizures. However, drugs that reduce absence seizures are generally ineffective for complex partial seizures, and the most effective drugs for complex partial seizures may be ineffective against or even increase the frequency of absence seizures (*Epilepsy Foundation 2016*).

- When possible, monotherapy with a single AED is the preferred treatment approach. Combination therapy may be associated with decreased patient adherence to therapy and an increased incidence of AEs and drug interactions. When combination therapy is needed, it is recommended to select products with different mechanisms of action and AE profiles. There is little comparative clinical data to support the use of specific combinations (*Schachter et al 2018*).
- Several broad classes of AEDs are available, including barbiturates, benzodiazepines, hydantoins, and miscellaneous agents (see Table 1). Of these agents, mephobarbital and ezogabine are not currently marketed as either brand or generic formulations, but are included in this review for informational and historical purposes.
- Cannibidiol (Epidiolex) was FDA-approved in June 2018 for use in pediatric patients 2 years of age and older with LGS or Dravet syndrome (*FDA news release 2018*). It is the first FDA-approved drug for treatment of patients with Dravet syndrome and is the first approved drug that contains a purified substance, cannabidiol, derived from marijuana. It is pending a Drug Enforcement Administration (DEA) scheduling designation (*GW Pharmaceuticals News Release).*
- Stiripentol (Diacomit) capsules and powder for oral suspension were FDA-approved in August 2018 for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam.
- Everolimus tablets for oral suspension (Afinitor Disperz) received an expanded indication in April 2018 for use in partial-onset seizures associated with tuberous sclerosis complex (TSC). This product is a kinase inhibitor that also has several oncology indications.
- Several of the AEDs are used for additional indications beyond the management of epilepsy, including (but not limited to) bipolar disorder, migraine prophylaxis, and several types of neuropathic pain. These additional indications are listed in Table 2; however, this review primarily focuses on the use of AEDs for the management of epilepsy. Additionally, brands and formulations FDA-approved and marketed only for non-epilepsy indications are not included within this review; these include gabapentin tablets (Gralise), FDA-approved only for the management of postherpetic neuralgia, gabapentin enacarbil extended-release tablets (Horizant), FDA-approved only for management of postherpetic neuralgia and treatment of moderate-to-severe restless leg syndrome, and pregabalin extended-release tablets (Lyrica CR), FDA-approved only for the management of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia.
- Medispan class: Antianxiety agents, benzodiazepines; Anticonvulsants, AMPA glutamate receptor antagonists; Anticonvulsants, anticonvulsants – misc; Anticonvulsants, carbamates; Anticonvulsants, GABA modulators; Anticonvulsants, hydantoins; Anticonvulsants, succinimides; Anticonvulsants, valproic acid; Hypnotics/Sedatives/Sleep Disorder Agents, barbiturate hypnotics

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Barbiturates	
Mephobarbital* (Mebaral)‡	-‡
Pentobarbital (Nembutal†)	✔
Phenobarbital* (Luminal†, Solfoton†)	✔
Primidone (Mysoline)	✔
Benzodiazepines	
Clobazam (Onfi)	-
Clonazepam (Klonopin§)	✔
Clorazepate (Tranxene T-Tab§)	✔
Diazepam (Diastat¶, Valium§)	✔ ‖
Hydantoins	
Ethotoin (Peganone)	-
Fosphenytoin (Cerebyx)	✔
Phenytoin (Dilantin§, Phenytek)	✔ ‖
Miscellaneous	
Brivaracetam (Briviact)	-
Cannabidiol (Epidiolex)***	-
Carbamazepine (Carbatrol, Epitol**, Equetro, Tegretol§, Tegretol-XR)	✔
Divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)	✔
Eslicarbazepine (Aptiom)	-

Drug	Generic Availability
Ethosuximide (Zarontin)	✔
Everolimus (Afinitor Disperz)	-
Ezogabine (Potiga)‡	-
Felbamate (Felbatol)	✔
Gabapentin (Neurontin)	✔
Lacosamide (Vimpat)	-#
Lamotrigine (Lamictal, Lamictal ODT, Lamictal XR)	✔
Levetiracetam (Keppra, Keppra XR, Roweepra**, Roweepra XR**, Spritam)	✔‖
Methsuximide (Celontin)	-
Oxcarbazepine (Oxtellar XR, Trileptal)	✔‖
Perampanel (Fycompa)	-
Pregabalin (Lyrica)	-
Rufinamide (Banzel)	-#
Stiripentol (Diacomit)	-
Tiagabine (Gabitril)	✔‖
Topiramate (Topamax, Topamax Sprinkle, Topiragen††, Trokendi XR, Qudexy XR¶)	✔‖
Valproic acid (Depacon, Depakene, Stavzor DR‡)	✔‖
Vigabatrin (Sabril, Vigadrone**)	✔‖
Zonisamide (Zonegran§)	✔

* Not FDA approved
† Brand product not currently marketed; generic is available
‡ No brand or generic currently marketed
§ Brand marketing status may vary by strength and/or formulation
‖ Generic availability may vary by strength and/or formulation
¶ Authorized generic available; no A-rated generics approved via abbreviated new drug application
# Generic is FDA-approved for at least 1 strength or formulation, but not currently marketed
** Branded generic
†† Branded generic; not currently marketed
*** Cannabidiol is not yet available as DEA schedule designation is pending (anticipated by Fall 2018) (*GW Pharmaceuticals News Release 2018*)

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

INDICATIONS

- Tables 2A and 2B provide an overview of anticonvulsant indications. Except where noted, only FDA-approved products and indications are included. For items marked with an asterisk, there is additional information about the indication provided in the box following the tables.
- Acute-care indications that are not related to convulsive disorders (for example, pre-procedural use of benzodiazepines in hospital settings) are not included.

Table 2A. Indications for anticonvulsants (Part 1 of 2)

Indications	Brivaracetam	Cannabidiol	Carbamazepine	Clobazam	Clonazepam	Clorazepate	Diazepam	Divalproex Sodium	Eslicarbazepine	Ethosuximide	Ethotoin	Everolimus	Ezogabine	Felbamate	Fosphenytoin	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam
Partial seizures (simple partial, complex partial and/or secondarily generalized)	✔ *		✔ *			A		✔, A*	✔, A*		✔ *		A*	✔, A*		A*	✔ *	✔, A*	A*
Primary generalized tonic-clonic seizure (grand mal)			✔								✔				✔ *			A*	A*
Absence seizure (petit mal)					✔ *			✔, A*		✔									
Multiple seizure types that include absence seizures								A											
Seizures of Lennox-Gastaut syndrome (LGS)		✔ *		A*	✔, A									A*				A*	
Seizures of Dravet syndrome		✔ *																	
Juvenile myoclonic epilepsy (JME)																			A*
Emergency/acute/short-term use for seizure control (see notes)							✔ *								✔ *				
Akinetic and myoclonic seizures					✔, A														
Convulsive disorders (see notes)							A*												
Certain mixed seizure patterns or other partial or generalized seizures			✔ *																
Migraine prophylaxis								✔ *											
Trigeminal neuralgia			✔ *																
Postherpetic neuralgia																✔ *			
Bipolar disorder			✔ *					✔ *										✔ *	
Panic disorder, with or without agoraphobia					✔														
Anxiety disorder; short-term relief of anxiety symptoms						✔	✔												
Symptomatic relief of acute alcohol withdrawal						✔	✔												

Indications	Brivaracetam	Cannabidiol	Carbamazepine	Clobazam	Clonazepam	Clorazepate	Diazepam	Divalproex Sodium	Eslicarbazepine	Ethosuximide	Ethotoin	Everolimus	Ezogabine	Felbamate	Fosphenytoin	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam
Relief of skeletal muscle spasm, spasticity, athetosis, and stiff-man syndrome							A												
Partial-onset seizures associated with tuberous sclerosis complex (TSC)												A*							

✓ = monotherapy (or not specified); A = adjunctive therapy

Table 2B. Indications for Anticonvulsants (Part 2 of 2)

Indications	Mephobarbital†	Methsuximide	Oxcarbazepine	Pentobarbital	Perampanel	Phenobarbital†	Phenytoin	Pregabalin	Primidone	Rufinamide	Stiripentol	Tiagabine	Topiramate	Valproic acid	Vigabatrin	Zonisamide
Partial seizures (simple partial, complex partial and/or secondarily generalized)			✓, A*		✓*		✓*	A*	✓, A*			A*	✓, A*	✓, A*	A*	A*
Primary generalized tonic-clonic seizure (grand mal)	✓				A*		✓*		✓, A*				✓, A*			
Absence seizure (petit mal)	✓	✓*												✓, A*		
Multiple seizure types which include absence seizures														A*		
Seizures of LGS										A*			A*			
Seizures of Dravet syndrome											A*					
Emergency/acute/short-term use for seizure control (see notes)				✓*			✓*									
Infantile spasms															✓*	
Convulsive disorders (see notes)						✓*										
Migraine prophylaxis													✓*	✓*		

Indications	Mephobarbital†	Methsuximide	Oxcarbazepine	Pentobarbital	Perampanel	Phenobarbital†	Phenytoin	Pregabalin	Primidone	Rufinamide	Stiripentol	Tiagabine	Topiramate	Valproic acid	Vigabatrin	Zonisamide
Postherpetic neuralgia								✔								
Bipolar disorder														✔ *		
Sedative for anxiety, tension, and apprehension	✔															
Neuropathic pain associated with diabetic peripheral neuropathy								✔								
Neuropathic pain associated with spinal cord injury								✔								
Fibromyalgia								✔								

✓ = monotherapy (or not specified); A = adjunctive therapy
†Mephobarbital and phenobarbital are not approved by the FDA.

***Notes: Additional Detail on Selected Anticonvulsant Indications**

- **Brivaracetam**:
  - Treatment of partial-onset seizures in patients ≥ 4 years of age (oral formulations); ≥ 16 years of age (IV formulation)
- **Cannabidiol**
  - Treatment of seizures associated with LGS or Dravet syndrome in patients ≥ 2 years of age
- **Carbamazepine**:
  - Partial seizures with complex symptomatology (psychomotor, temporal lobe); patients with these seizures appear to show greater improvement than those with other types; generalized tonic-clonic seizures (grand mal); mixed seizure patterns which include the above, or other partial or generalized seizures
  - Absence seizures do not appear to be controlled; carbamazepine has been associated with increased frequency of generalized convulsions in these patients
  - Treatment of pain associated with true trigeminal neuralgia; beneficial results also reported in glossopharyngeal neuralgia
  - Bipolar indication is for an extended-release capsule formulation (Equetro) only: treatment of patients with acute manic or mixed episodes associated with bipolar I disorder
- **Clobazam**:
  - Seizures associated with LGS in patients aged ≥ 2 years
- **Clonazepam**:
  - In patients with absence seizures who have failed to respond to succinimides, clonazepam may be useful
- **Diazepam**:
  - Oral diazepam may be used adjunctively in convulsive disorders
  - Rectal diazepam is indicated in the management of selected, refractory patients with epilepsy on stable regimens of AEDs who require intermittent use of diazepam to control bouts of increased seizure activity
  - Injectable diazepam is a useful adjunct in status epilepticus and severe recurrent convulsive seizures
- **Divalproex sodium**:
  - Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures (age ≥ 10 years for all formulations)

- Monotherapy and adjunctive therapy in the treatment of simple and complex absence seizures (age ≥ 10 years for extended-release tablets; age not specified for tablets/sprinkle capsules)
- The tablets and extended-release tablets have indications in bipolar disorder and migraine prophylaxis; the sprinkle capsule formulation does not. For bipolar disorder, safety and effectiveness for long-term use (> 3 weeks) has not been demonstrated in controlled clinical trials. Bipolar disorder indications are as follows:
  - Treatment of the manic episodes associated with bipolar disorder (tablets)
  - Treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features (extended-release tablets)

- **Eslicarbazepine:**
  - Treatment of partial-onset seizures in patients ≥ 4 years of age
- **Ethotoin**:
  - Complex partial (psychomotor) seizures
- **Everolimus**
  - Adjunctive treatment of adult and pediatric patients ≥ 2 years of age with TSC-associated partial-onset seizures (tablets for oral suspension only)
- **Ezogabine**:
  - Adjunctive treatment of partial-onset seizures in patients ≥18 years of age who have responded inadequately to several alternative treatments and for whom the benefits outweigh the risk of retinal abnormalities and potential decline in visual acuity
- **Felbamate**:
  - Not first-line; recommended only in patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or renal failure is deemed acceptable
  - Monotherapy or adjunctive therapy in the treatment of partial seizures, with and without generalization, in adults with epilepsy
  - Adjunctive therapy of partial and generalized seizures associated with LGS in children (age not specified)
- **Fosphenytoin**:
  - Treatment of generalized tonic-clonic status epilepticus
  - Prevention and treatment of seizures occurring during neurosurgery
  - Can be substituted short-term for oral phenytoin when oral phenytoin administration is not possible
- **Gabapentin**:
  - Adjunctive therapy in the treatment of partial onset seizures, with and without secondary generalization, in adults and pediatric patients ≥ 3 years of age with epilepsy.
  - Management of postherpetic neuralgia in adults
- **Lacosamide**:
  - Treatment of partial-onset seizures in patients ≥ 4 years of age (tablet and oral solution)
  - Treatment of partial-onset seizures in patients ≥ 17 years of age (injection)
- **Lamotrigine immediate-release formulations**:
  - Age ≥ 2 years for adjunctive therapy for partial-onset seizures, primary generalized tonic-clonic seizures, and generalized seizures of LGS
  - Age ≥ 16 years for conversion to monotherapy in patients with partial-onset seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single AED
  - Maintenance treatment of bipolar disorder to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy (treatment of acute manic or mixed episodes is not recommended)
- **Lamotrigine extended-release tablets**:
  - Age ≥ 13 years for adjunctive therapy for primary generalized tonic-clonic seizures and partial onset seizures with or without secondary generalization, and age ≥13 years for conversion to monotherapy in patients with partial-onset seizures who are receiving treatment with a single AED
  - The extended-release formulation is not FDA-approved for bipolar disorder
- **Levetiracetam**:
  - Adjunctive therapy in the treatment of partial onset seizures in adults and children ≥ 1 month of age with epilepsy (age ≥ 4 years and weighing > 20 kg for the tablets for oral suspension [Spritam])
  - Adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents ≥ 12 years with JME

- Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and children ≥ 6 years of age with idiopathic generalized epilepsy
- The extended-release tablets are only indicated for adjunctive therapy in the treatment of partial-onset seizures in patients ≥ 12 years of age with epilepsy

- **Methsuximide**:
  - Control of absence (petit mal) seizures that are refractory to other drugs
- **Oxcarbazepine immediate-release formulations**:
  - Monotherapy in the treatment of partial seizures in adults and children 4 to 16 years of age
  - Adjunctive therapy in the treatment of partial seizures in adults and children 2 to 16 years of age
- **Oxcarbazepine extended-release tablets**:
  - Adjunctive therapy in the treatment of partial seizures in adults and children 6 to 17 years of age
- **Pentobarbital**:
  - In anesthetic doses in the emergency control of certain acute convulsive episodes, eg, those associated with status epilepticus, cholera, eclampsia, meningitis, tetanus, and toxic reactions to strychnine or local anesthetics
- **Perampanel**:
  - Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy ≥ 12 years of age
  - Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in patients with epilepsy ≥ 12 years of age
- **Phenobarbital (not FDA-approved)**:
  - Phenobarbital tablets are indicated for use as an anticonvulsant; the elixir is indicated for the treatment of generalized and partial seizures; the injection is indicated as an anticonvulsant for the treatment of generalized tonic-clonic and cortical focal seizures, in the emergency control of certain acute convulsive episodes, and in pediatric patients as an anticonvulsant
- **Phenytoin oral formulations**:
  - Treatment of tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery (the oral suspension does not have the neurosurgery indication)
- **Phenytoin injection**:
  - Treatment of generalized tonic-clonic status epilepticus and prevention and treatment of seizures occurring during neurosurgery
  - Can be substituted as short-term use for oral phenytoin when oral phenytoin administration is not possible
- **Pregabalin**:
  - Adjunctive therapy for treatment of partial onset seizures in patients ≥ 4 years of age
- **Primidone**:
  - Control of grand mal, psychomotor, and focal epileptic seizures; may control grand mal seizures refractory to other anticonvulsant therapy
- **Rufinamide**:
  - Adults and pediatric patients ≥ 1 year of age
- **Stiripentol**
  - Treatment of seizures associated with Dravet syndrome in patients ≥ 2 years of age taking clobazam; no clinical data to support its use as monotherapy
- **Tiagabine**:
  - Adjunctive therapy in adults and children ≥ 12 years of age in the treatment of partial seizures
- **Topiramate**:
  - Initial monotherapy in patients with partial onset or primary generalized tonic-clonic seizures (age ≥ 2 years for tablets, immediate-release sprinkle capsules, and Qudexy XR extended-release capsules; age ≥ 6 years for Trokendi XR extended-release capsules)
  - Adjunctive therapy for adults and pediatric patients with partial onset seizures or primary generalized tonic-clonic seizures and in patients with seizures associated with LGS (age ≥ 2 years for tablets, immediate-release sprinkle capsules, and Qudexy XR extended-release capsules; age ≥ 6 years for Trokendi XR extended-release capsules)
  - Prophylaxis of migraine headache in patients ≥ 12 years of age
- **Valproic acid**:

- Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures (in adults and pediatric patients down 10 years) that occur either in isolation or in association with other types of seizures; sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types which include absence seizures
- Migraine prophylaxis and bipolar disorder indications are for the delayed-release capsule formulation only (Stavzor, which is not currently marketed). For bipolar disorder:
  - Acute treatment of manic or mixed episodes associated with bipolar disorder, with or without psychotic features; safety and effectiveness for long-term use (> 3 weeks) has not been demonstrated in controlled clinical trials

- **Vigabatrin**:
  - Refractory complex partial seizures as adjunctive therapy in patients ≥ 10 years of age who have responded inadequately to several alternative treatments; not indicated as a first-line agent
  - Infantile spasms as monotherapy in infants 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss
- **Zonisamide**:
  - Adjunctive therapy in the treatment of partial seizures in adults with epilepsy

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

CLINICAL EFFICACY SUMMARY

- Overall, the anticonvulsants have demonstrated efficacy for their FDA-approved uses. Clinical trial data demonstrating efficacy of the anticonvulsants for the treatment of epilepsy is described in the prescribing information for the individual products, particularly for anticonvulsants more recently approved by the FDA. However, the prescribing information for some older, conventional products (eg, benzodiazepines, carbamazepine, ethotoin, ethosuximide, methsuximide, phenytoin, and primidone) and non-FDA approved products (eg, mephobarbital, phenobarbital) do not contain efficacy data in their prescribing information.
- No single AED is clearly the most effective. Comparative efficacy data for the management of epilepsy are limited, and trials have generally not shown significant differences among drugs in terms of efficacy. However, the quality of the data is limited and generally derived from short-term trials (*Karceski 2017*).
- When possible, monotherapy with a single AED is the preferred treatment approach. Combination therapy may be associated with decreased patient adherence to therapy and an increased incidence of AEs and drug interactions. (*Schachter et al 2018*). Most patients with epilepsy are treated with anticonvulsant monotherapy (*Nevitt et al 2017*).
- An evidence review summarized AED efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes (*Glauser et al 2013*). This publication provides conclusions based on a review of 64 randomized trials and 11 meta-analyses. Conclusions include the following:
  - As initial monotherapy for adults with newly diagnosed or untreated partial-onset seizures:
    - Carbamazepine, levetiracetam, phenytoin, and zonisamide are established as efficacious/effective.
    - Valproate is probably efficacious/effective.
    - Gabapentin, lamotrigine, oxcarbazepine, phenobarbital, topiramate, and vigabatrin are possibly efficacious/effective.
    - Clonazepam and primidone are potentially efficacious/effective.
  - As initial monotherapy for children with newly diagnosed or untreated partial-onset seizures:
    - Oxcarbazepine is established as efficacious/effective.
    - Carbamazepine, phenobarbital, phenytoin, topiramate, valproate, and vigabatrin are possibly efficacious/effective.
    - Clobazam, carbamazepine, lamotrigine, and zonisamide are potentially efficacious/effective.
  - As initial monotherapy for elderly adults with newly diagnosed or untreated partial-onset seizures:
    - Gabapentin and lamotrigine are established as efficacious/effective.
    - Carbamazepine is possibly efficacious/effective.
    - Topiramate and valproate are potentially efficacious/effective.
  - As initial monotherapy for adults with newly diagnosed or untreated generalized-onset tonic-clonic seizures:

        - Carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate, and valproate are possibly efficacious/effective.
        - Gabapentin, levetiracetam, and vigabatrin are potentially efficacious/effective.
        - Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures.
    - For children with newly diagnosed or untreated generalized-onset tonic-clonic seizures:
        - Carbamazepine, phenobarbital, phenytoin, topiramate, and valproate are possibly efficacious/effective.
        - Oxcarbazepine is potentially efficacious/effective.
        - Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures.
    - As initial monotherapy for children with newly diagnosed or untreated absence seizures:
        - Ethosuximide and valproate are established as efficacious/effective.
        - Lamotrigine is possibly efficacious/effective.
        - Gabapentin is established as inefficacious/ineffective.
        - Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, tiagabine, and vigabatrin may precipitate or aggravate absence seizures (based on scattered reports).
    - As initial monotherapy for children with benign childhood epilepsy with centrotemporal spikes (BECTS):
        - Carbamazepine and valproate are possibly efficacious/effective.
        - Gabapentin, levetiracetam, oxcarbazepine, and sulthiame (not available in the United States) are potentially efficacious/effective.
    - For patients with newly diagnosed JME:
        - Topiramate and valproate are potentially efficacious/effective.
        - Carbamazepine, gabapentin, oxcarbazepine, phenytoin, tiagabine, and vigabatrin may precipitate or aggravate absence, myoclonic, and in some cases generalized tonic-clonic seizures. There has also been a report that lamotrigine may exacerbate seizures in JME.
    - There is a lack of well-designed randomized trials in epilepsy, particularly for generalized seizures and in the pediatric population.
- A Cochrane systematic review evaluated the efficacy of AED monotherapy for epilepsy (*Nevitt et al 2017*). The review included the use of carbamazepine, phenytoin, valproate, phenobarbital, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, and zonisamide for the treatment of partial onset seizures (simple partial, complex partial or secondarily generalized) or generalized tonic-clonic seizures with or without other generalized seizure types.
    - This network meta-analysis showed that for the primary outcome, the time to withdrawal of allocated treatment:
        - For individuals with partial seizures:
            (i) Levetiracetam performed better than carbamazepine and lamotrigine.
            (ii) Lamotrigine performed better than all other treatments (aside from levetiracetam).
            (iii) Carbamazepine performed better than gabapentin and phenobarbital.
        - For individuals with generalized onset seizures, valproate performed better than carbamazepine, topiramate and phenobarbital.
        - For both partial and generalized onset seizures, phenobarbital seems to perform worse than all other treatments.
    - For the secondary outcome, time to first seizure:
        - For individuals with partial seizures, phenobarbital and phenytoin seem to perform better than most other drugs; and carbamazepine performed better than valproate, gabapentin, and lamotrigine.
        - For individuals with generalized seizures, phenytoin seems to work better than most other drugs.
        - There were few notable differences between the newer drugs (oxcarbazepine, topiramate, gabapentin, levetiracetam, and zonisamide) for either partial seizures or generalized seizures.
    - Few notable differences were shown for either partial or generalized seizure types for the secondary outcomes of time to 6-month or 12-month remission of seizures.
    - Overall, direct evidence and network meta-analysis estimates were numerically similar, and effect sizes had overlapping confidence intervals.
    - Data for individuals with generalized seizures are still limited and additional randomized trials are needed.
- The relative efficacy among valproate, lamotrigine, phenytoin, carbamazepine, ethosuximide, topiramate, levetiracetam, and phenobarbital as monotherapy for generalized (n = 7 studies) or absence seizures (n = 3 studies) was evaluated in a systematic review and network meta-analysis (*Campos et al 2018*). The outcomes analyzed were seizure freedom and withdrawal due to inefficacy. Compared to valproate, phenytoin had a lower odds of seizure freedom (OR 0.50; 95% credible Interval [CrI] 0.27 to 0.87) in patients with generalized tonic-clonic seizures. Lamotrigine had the highest

probability of seizure freedom and valproate had the highest probability of withdrawal due to inefficacy in these patients. For absence seizures, ethosuximide and valproate were found to have a higher probability of seizure freedom compared to lamotrigine.

- A meta-analysis estimated the comparative efficacy of achieving seizure freedom with 22 antiepileptic drugs and placebo in children and adolescents (*Rosati et al 2018*). For the treatment of newly diagnosed focal epilepsy (n = 4 studies), point estimates suggested superiority of carbamazepine and lamotrigine; however, this was not statistically significant. For refractory focal epilepsy (n = 9 studies), levetiracetam and perampanel were more effective than placebo in mixed comparisons. Ethosuximide and valproic acid were more effective than lamotrigine for absence seizures. The authors concluded that better designed comparative studies with appropriate length of follow-up, well-defined outcomes, and reliable inclusion criteria are needed to validate these results.
- Approximately 20% to 40% of patients with epilepsy can be considered refractory to drug treatment, referred to as drug-resistant epilepsy. Treatment of drug-resistant epilepsy may include additional anticonvulsant drug trials, epilepsy surgery, vagal nerve stimulation, and dietary changes (the ketogenic diet) (*Sirven 2017*).
  - Combination AED regimens are an option for the treatment of drug-resistant epilepsy. However, robust clinical evidence of suitable combinations of AEDs has been difficult to generate due to the large number of possible combinations of drugs and doses. Examples of combinations for which there is some evidence of efficacy include valproate plus lamotrigine for partial-onset and generalized seizures, valproate plus ethosuximide for absence seizures, and lamotrigine plus topiramate for various seizure types; however, even this evidence is fairly limited. In general, when considering combination therapy, it is recommended to combine medications with different mechanisms of action, and to be mindful of the overall drug load to minimize AEs. Two-drug therapy should be attempted before considering addition of a third drug, and higher numbers of drugs should be avoided as they are associated with a very low likelihood of additional seizure reduction (*Kwan et al 2011*).
  - A meta-analysis examined the efficacy of newer AEDs (eslicarbazepine, brivaracetam, perampanel, and lacosamide) versus levetiracetam as adjunctive therapy for uncontrolled partial-onset seizures. Most patients in this meta-analysis were on at least 2 other AEDs at the time of treatment. In this analysis, eslicarbazepine, lacosamide, and brivaracetam were non-inferior to levetiracetam in terms of efficacy, but all newer AEDs except brivaracetam had worse tolerability profiles than levetiracetam at high doses (*Zhu et al 2017*).
  - A network meta-analysis examined the efficacy of AEDs (including brivaracetam, eslicarbazepine acetate, gabapentin, lacosamide, levetiracetam, lamotrigine, oxcarbazepine, pregabalin, perampanel, rufinamide, tiagabine, topiramate, vigabatrin, and zonisamide) for adjunctive use in patients with refractory partial-onset seizures while using monotherapy (*Zhao et al 2017*). The efficacy outcomes studied were 50% responder rate and state of seizure freedom. The authors concluded that topiramate, levetiracetam, pregabalin, and oxcarbazepine were preferable for their relatively high efficacy and low risk of AEs. Rufinamide was the least preferable medication due to its low efficacy and high risk of AEs.
  - A network meta-analysis was conducted to evaluate the efficacy of 17 newer AEDs for treatment of refractory partial-onset epilepsy with or without secondary generalization (*Hu et al 2018*). The primary outcome was seizure freedom, which was defined as a 100% seizure reduction in the maintenance or double-blind treatment period of the trial. Safety was assessed by the withdrawal rate due to treatment-emergent AEs. Based on results of 54 studies that evaluated the efficacy outcome, the most effective agents included tiagabine, brivaracetam, and valproic acid, and the least effective agents included rufinamide, lamotrigine, and zonisamide. Products with favorable safety included levetiracetam, brivaracetam, and perampanel, while those with the least favorable safety included retigabine, oxcarbazepine, and rufinamide. The authors stated that agents with the best outcomes in terms of efficacy and safety included levetiracetam, vigabatrin, valproic acid, and brivaracetam.
  - Cannibidiol (Epidiolex) was approved in June 2018 for use in pediatric patients 2 years of age and older with LGS or Dravet syndrome (*FDA news release 2018*). It is the first FDA-approved drug for treatment of patients with Dravet syndrome and is the first approved drug that contains a purified substance, cannabidiol, derived from marijuana. Its approval for these 2 indications was based on 3 placebo-controlled trials in patients refractory to other treatments. Epidiolex, along with use of other agents, demonstrated a significant reduction in seizure frequency compared to placebo. To date, no comparative trials have been published.
  - Everolimus tablets for oral suspension (Afinitor Disperz) received an expanded indication for adjunctive use in TSC-associated partial-onset seizures in April 2018. Results of a randomized, double-blind, placebo-controlled study of 366 patients with inadequately controlled seizures on 2 or more AEDs demonstrated a significant reduction in seizure frequency compared to placebo (*French et al 2016*).

- In August 2018, the FDA approved a second drug, stiripentol (Diacomit), for use in the treatment of seizures associated with Dravet syndrome. Two multicenter placebo-controlled studies evaluated the addition of stiripentol to clobazam and valproate therapy in patients 3 years to less than 18 years of age with Dravet syndrome. Responder rates (seizure frequency reduced by 50%) with respect to generalized tonic-clonic seizures were significantly lower with stiripentol compared to placebo (*Diacomit prescribing information 2018).*

CLINICAL GUIDELINES

- **Efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy**. American Academy of Neurology and American Epilepsy Society (*French et al 2004A, Kanner et al, 2018A*).
  - A 2018 update to the 2004 guideline focuses on treatment of new-onset epilepsy with second and third generation AEDs. The 2004 publication summarizes the efficacy, tolerability, and safety of gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide for the treatment of children and adults with newly diagnosed partial and generalized epilepsies.
  - The recommendations from the 2004 guideline include the following:
    - Patients with newly diagnosed epilepsy who require treatment can be initially treated with standard AEDs such as carbamazepine, phenytoin, valproic acid, or phenobarbital, or on the newer AEDs lamotrigine, gabapentin, oxcarbazepine, or topiramate. Choice will depend on individual patient characteristics.
    - Lamotrigine can be included in the options for children with newly diagnosed absence seizures.
  - The 2018 recommendations include the following :
    - As monotherapy in adult patients with new-onset focal epilepsy or unclassified generalized tonic-clonic seizures:
      - Lamotrigine use should be considered to decrease seizure frequency.
      - Lamotrigine use should be considered and gabapentin use may be considered to decrease seizure frequency in patients aged ≥ 60 years.
      - Levetiracetam use and zonisamide use may be considered to decrease seizure frequency.
      - Vigabatrin appears to be less efficacious than carbamazepine immediate-release and may not be offered; furthermore, the toxicity profile precludes vigabatrin use as first-line therapy.
      - Pregabalin 150 mg per day is possibly less efficacious than lamotrigine 100 mg per day.
      - There is insufficient evidence to consider use of gabapentin, oxcarbazepine, or topiramate over carbamazepine.
      - There is insufficient evidence to consider use of topiramate instead of phenytoin in urgent treatment of new-onset or recurrent focal epilepsy, unclassified generalized tonic-clonic seizures, or generalized epilepsy presenting with generalized tonic-clonic seizures.
      - Data are lacking to support or refute use of third-generation AEDs (eslicarbazepine, ezogabine, lacosamide, perampanel, pregabalin, and rufunamide), clobazam, felbamate, or vigabatrin for new-onset epilepsy.
      - Data are lacking to support or refute use of newer AEDs in treating unclassified generalized tonic-clonic seizures.
    - Ethosuximide or valproic acid should be considered before lamotrigine to decrease seizure frequency in children with absence epilepsy. An exception would be if there are compelling AE-related concerns with use of ethosuximide or valproic acid.
    - The guideline does not address newly approved agents including cannabidiol, everolimus, or stiripentol.
- **Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy**. American Academy of Neurology and American Epilepsy Society (*Kanner et al 2018B*, *French et al 2004B*).
  - A 2018 update to the 2004 guideline focuses on management of treatment-resistant epilepsy with second and third generation AEDs. The 2004 publication summarizes the efficacy, tolerability, and safety of gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide for the treatment of children and adults with refractory partial and generalized epilepsies.
  - Recommendations from the 2004 guideline include the following:
    - It is appropriate to use gabapentin, lamotrigine, tiagabine, topiramate, oxcarbazepine, levetiracetam, and zonisamide as add-on therapy in patients with refractory epilepsy.
    - Oxcarbazepine, topiramate, and lamotrigine can be used as monotherapy in patients with refractory partial epilepsy.
    - Topiramate may be used for the treatment of refractory generalized tonic-clonic seizures in adults and children.

- Gabapentin, lamotrigine, oxcarbazepine, and topiramate may be used as adjunctive treatment of children with refractory partial seizures.
- Topiramate and lamotrigine may be used to treat drop attacks associated with LGS in adults and children.

○ Recommendations from the 2018 guideline include the following:

- As adjunctive therapy in patients with treatment-resistant adult focal epilepsy (TRAFE):
  - Immediate-release pregabalin and perampanel are established as effective to reduce seizure frequency.
  - Lacosamide, eslicarbazepine, and extended-release topiramate should be considered to decrease seizure frequency.
  - Vigabatrin and rufinamide are effective for decreasing seizure frequency, but are not first-line agents.
  - Ezogabine use should be considered to reduce seizure frequency, but carries a serious risk of skin and retinal discoloration.
  - Clobazam and extended-release oxcarbazepine may be considered to decrease seizure frequency.
- As monotherapy in patients with TRAFE:
  - Eslicarbazepine use may be considered to decrease seizure frequency.
  - Data are insufficient to recommend use of second- and the other third-generation AEDs.
- For add-on therapy for generalized epilepsy, immediate-release and extended-release lamotrigine should be considered as add-on therapy to decrease seizure frequency in adults with treatment-resistant generalized tonic-clonic seizures secondary to generalized epilepsy. Levetiracetam use should be considered to decrease seizure frequency as add-on therapy for treatment-resistant generalized tonic-clonic seizures and for treatment-resistant juvenile myoclonic epilepsy.
- Rufinamide is effective to reduce seizure frequency as add-on therapy for LGS. Clobazam use should be considered as add-on therapy for LGS.
- For add-on therapy in pediatric patients with treatment-resistant focal epilepsy:
  - Levetiracetam use should be considered to decrease seizure frequency (ages 1 month to 16 years).
  - Zonisamide use should be considered to decrease seizure frequency (age 6 to 17 years).
  - Oxcarbazepine use should be considered to decrease seizure frequency (age 1 month to 4 years).
  - Data are unavailable on the efficacy of clobazam, eslicarbazepine, lacosamide, perampanel, rufinamide, tiagabine, or vigabatrin.
- The guideline does not address newly approved agents including cannabidiol, everolimus, or stiripentol.

- **Evidence-based guideline: management of an unprovoked first seizure in adults.** Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society (*Krumholz et al 2015*).
  - This practice guideline makes recommendations based on a consideration of the evidence for prognosis and treatment of adults with an unprovoked first seizure.
  - Recommendations include the following:
    - Adults presenting with an unprovoked first seizure should be informed that the chance for a recurrent seizure is greatest within the first 2 years after a first seizure (21% to 45%).
    - Clinicians should also advise such patients that clinical factors associated with an increased risk of seizure recurrence include a prior brain insult such as a stroke or trauma, an EEG with epileptiform abnormalities, a significant brain-imaging abnormality, or a nocturnal seizure.
    - Clinicians should advise patients that, although immediate AED therapy, as compared with delay of treatment pending a second seizure, is likely to reduce the risk of a seizure recurrence in the 2 years subsequent to a first seizure, it may not improve quality of life.
    - Clinicians should advise patients that over the longer term (> 3 years), immediate AED treatment is unlikely to improve the prognosis for sustained seizure remission.
    - Patients should be advised that their risk for AED AEs ranges from 7% to 31% and that these AEs are predominantly mild and reversible.
  - Immediate AED therapy after an unprovoked first seizure is likely to reduce seizure recurrence risk. A reduction in risk may be important, particularly for adults, for whom seizure recurrences may cause serious psychological and social consequences such as loss of driving privileges and limitations on employment. However, immediate AED treatment is not well accepted and is debated. Decisions should be based on weighing the risk of recurrence against the AEs of AED therapy, and should take patient preferences into account.
  - It is accepted that when a patient has a second or additional seizures, an AED should be initiated because the risk of subsequent seizures is very high.

- **Evidence-based guideline: treatment of convulsive status epilepticus in children and adults.** Guideline Committee of the American Epilepsy Society (*Glauser et al 2016*).
  - This publication provides conclusions and a treatment algorithm based on a structured literature review of randomized trials of anticonvulsant treatments for seizures lasting longer than 5 minutes. A total of 38 trials were included.
  - For treatment in the adult population, conclusions included the following:
    - Intramuscular (IM) midazolam, intravenous (IV) lorazepam, IV diazepam (with or without phenytoin), and IV phenobarbital are established as efficacious at stopping seizures lasting at least 5 minutes.
    - IV lorazepam is more effective than IV phenytoin in stopping seizures lasting at least 10 minutes.
    - There is no difference in efficacy between IV lorazepam followed by IV phenytoin, IV diazepam plus phenytoin followed by IV lorazepam, and IV phenobarbital followed by IV phenytoin.
    - IV valproic acid has similar efficacy to IV phenytoin or continuous IV diazepam as second therapy after failure of a benzodiazepine.
    - Insufficient data exist in adults about the efficacy of levetiracetam as either initial or second therapy.
    - In adults with status epilepticus without established IV access, IM midazolam is established as more effective compared with IV lorazepam.
    - No significant difference in effectiveness has been demonstrated between lorazepam and diazepam in adults with status epilepticus.
  - For treatment in the pediatric population, conclusions included the following:
    - IV lorazepam and IV diazepam are established as efficacious at stopping seizures lasting at least 5 minutes.
    - Rectal diazepam, IM midazolam, intranasal midazolam, and buccal midazolam are probably effective at stopping seizures lasting at least 5 minutes.
    - Insufficient data exist in children about the efficacy of intranasal lorazepam, sublingual lorazepam, rectal lorazepam, valproic acid, levetiracetam, phenobarbital, and phenytoin as initial therapy.
    - IV valproic acid has similar efficacy but better tolerability than IV phenobarbital as second therapy after failure of a benzodiazepine.
    - Insufficient data exist in children regarding the efficacy of phenytoin or levetiracetam as second therapy after failure of a benzodiazepine.
    - In children with status epilepticus, no significant difference in effectiveness has been established between IV lorazepam and IV diazepam.
    - In children with status epilepticus, non-IV midazolam (IM/intranasal/buccal) is probably more effective than diazepam (IV/rectal).
  - Conclusions included the following (age not specified):
    - Insufficient data exist about the comparative efficacy of phenytoin and fosphenytoin. Fosphenytoin is better tolerated compared with phenytoin. When both are available, fosphenytoin is preferred based on tolerability, but phenytoin is an acceptable alternative.
  - The overall treatment algorithm directs that:
    - A benzodiazepine (IM midazolam, IV lorazepam, or IV diazepam) is recommended as the initial therapy of choice in the first phase of treatment (5 to 20 minutes after the beginning of the seizure). Although IV phenobarbital is established as efficacious and well tolerated as initial therapy, its slower rate of administration positions it as an alternative initial therapy. For prehospital settings or where first-line benzodiazepine options are not available, rectal diazepam, intranasal midazolam, and buccal midazolam are reasonable initial therapy alternatives.
    - In the second phase of treatment (from 20 to 40 minutes after the beginning of the seizure), reasonable options include fosphenytoin, valproic acid, and levetiracetam. There is no clear evidence that any of these options is better than the others. Because of AEs, IV phenobarbital is a reasonable second-therapy alternative if none of the 3 recommended therapies are available.
    - There is no clear evidence to guide therapy in the third phase of therapy (≥ 40 minutes after the beginning of the seizure).
- **Evidence-based guideline update: medical treatment of infantile spasms.** Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (*Go et al 2012*). (Reaffirmed July 18, 2015)
  - This publication provides updated recommendations for the treatment of infantile spasms. The literature review included an evaluation of 26 published articles on this topic.
  - Recommendations include the following:

        - Evidence is insufficient to recommend the use of prednisolone, dexamethasone, and methylprednisolone as being as effective as adrenocorticotropic hormone (ACTH) for short-term treatment of infantile spasms.
        - Low-dose ACTH should be considered as an alternative to high-dose ACTH for treatment of infantile spasms.
        - ACTH or vigabatrin may be offered for short-term treatment of infantile spasms; evidence suggests that ACTH may be offered over vigabatrin.
        - Evidence is insufficient to recommend other therapies (valproic acid, vitamin B6, nitrazepam [not available in the United States], levetiracetam, zonisamide, topiramate, the ketogenic diet, or novel/combination therapies) for treatment of infantile spasms.
        - Hormonal therapy (ACTH or prednisolone) may be considered for use in preference to vigabatrin in infants with cryptogenic infantile spasms, to possibly improve developmental outcome.
        - A shorter lag time to treatment of infantile spasms with either hormonal therapy or vigabatrin may be considered to improve long-term cognitive outcomes.
    - There is a lack of sufficient randomized trials to provide definitive answers to key questions related to treatment of infantile spams.
- **Practice parameter: treatment of the child with a first unprovoked seizure.** Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (*Hirtz et al 2003*). (Reaffirmed January 23, 2016)
    - This parameter reviews published literature relevant to the decision to begin treatment after a child or adolescent experiences a first unprovoked seizure and presents evidence-based practice recommendations. Treatment during the neonatal period is not addressed.
    - Recommendations include the following:
        - Treatment with AEDs is not indicated for the prevention of the development of epilepsy.
        - Treatment with AEDs may be considered in circumstances where the benefits of reducing the risk of a second seizure outweigh the risks of pharmacologic and psychosocial AEs.
    - The majority of children who experience a first unprovoked seizure will have few or no recurrences. Treatment with AEDs after a first seizure as opposed to after a second seizure has not been shown to improve prognosis for long-term seizure remission.
    - Treatment has been shown in several studies combining both children and adults to reduce the risk of seizure recurrence; however, there is a relative paucity of data from studies involving only children after a first seizure.
- **Summary of recommendations for the management of infantile seizures**. Task force report for the ILAE Commission of Pediatrics (*Wilmshurst et al 2015*).
    - This publication recommends an approach to the standard and optimal management of infants with seizures. When possible, recommendations are evidence-based; however, when no evidence was available, recommendations are based on expert opinion and standard practice.
    - Recommendations/findings include the following:
        - There is no indication for initiation of chronic AEDs for simple febrile seizures. However, in the acute treatment of febrile seizures, it is important to treat seizures lasting 10 minutes or longer.
        - In an otherwise healthy infant, a policy of “wait and see” is reasonable after the first afebrile seizure. However, this is a rare event and close monitoring is essential.
        - Treatment options with established or probable efficacy include the following:
            - Focal seizures: levetiracetam
            - Epileptic spasms: High-dose or low-dose ACTH
            - Dravet syndrome: stiripentol (not available in the United States)
        - Treatment options with possible efficacy include the following:
            - Generalized seizures: levetiracetam, valproate, lamotrigine, topiramate, clobazam
            - Epileptic spasms: prednisone, vigabatrin
            - Benign infantile convulsions: carbamazepine, phenobarbital, valproate
            - Dravet syndrome: topiramate, zonisamide, valproate
            - Benign myoclonic epilepsy of infancy: valproate, topiramate, lamotrigine, clonazepam
            - Provoked or situational seizures: carbamazepine
        - There is no clear evidence supporting an optimal duration of treatment; this is dependent on seizure type.

- **Guidelines on neonatal seizures**. World Health Organization (WHO) (*WHO 2011*).
  - This document was prepared based on a systematic review of the literature and involved cooperation between the WHO, the ILAE, and the International Bureau of Epilepsy (IBE).
  - Recommendations include the following:
    - Phenobarbital should be used as the first-line agent for treatment of neonatal seizures and should be made readily available in all settings.
    - In neonates who continue to have seizures despite administering the maximum tolerated dose of phenobarbital, either a benzodiazepine, phenytoin, or lidocaine may be used as the second-line agent for control of seizures (use of phenytoin or lidocaine requires cardiac monitoring).
    - In neonates with a normal neurological examination and/or normal EEG, stopping AEDs may be considered if the neonate has been seizure-free for > 72 hours; the drug(s) should be reinstituted if seizures recur.
    - In neonates in whom seizure control is achieved with a single AED, the drug can be discontinued abruptly without tapering the dose. In neonates requiring > 1 AED for seizure control, the drugs may be stopped one at a time, with phenobarbital being the last drug to be withdrawn.
- **Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes.** Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society (*Harden et al 2009A*). (Reaffirmed July 13, 2013)
  - This publication summarizes evidence for selected issues regarding the clinical management of women with epilepsy (WWE) who are pregnant or planning to be pregnant.
  - Recommendations include the following:
    - If possible, avoidance of the use of valproate as part of polytherapy during the first trimester of pregnancy should be considered to decrease the risk of major congenital malformations (MCMs).
    - If possible, avoidance of the use of valproate monotherapy during the first trimester of pregnancy may be considered to decrease the risk of MCMs.
    - To reduce the risk of MCMs, the use of valproate during the first trimester of pregnancy should be avoided, if possible, compared to the use of carbamazepine.
    - To reduce the risk of MCMs, avoidance of the use of polytherapy with valproate during the first trimester of pregnancy, if possible, should be considered, compared to polytherapy without valproate.
    - To reduce the risk of MCMs, avoidance of the use of valproate during the first trimester of pregnancy, if possible, may be considered, compared to the use of phenytoin or lamotrigine.
    - To reduce the risk of MCMs, avoidance of the use of AED polytherapy during the first trimester of pregnancy, if possible, compared to monotherapy should be considered.
    - Limiting the dosage of valproate or lamotrigine during the first trimester, if possible, should be considered to lessen the risk of MCMs.
    - Avoidance of the use of valproate, if possible, should be considered to reduce the risk of neural tube defects and facial clefts, and may be considered to reduce the risk of hypospadias.
    - Avoidance of phenytoin, carbamazepine, and phenobarbital, if possible, may be considered to reduce the risk of specific MCMs: cleft palate for phenytoin use, posterior cleft palate for carbamazepine use, and cardiac malformations for phenobarbital use.
    - Carbamazepine exposure probably does not produce cognitive impairment in offspring of WWE.
    - Avoiding valproate in WWE during pregnancy, if possible, should be considered to reduce the risk of poor cognitive outcomes.
    - Avoiding phenytoin and phenobarbital in WWE during pregnancy, if possible, may be considered to reduce the risk of poor cognitive outcomes.
    - Monotherapy should be considered in place of polytherapy, if possible, for WWE who take AEDs during pregnancy to reduce the risk of poor cognitive outcomes.
    - For WWE who are pregnant, avoidance of valproate, if possible, should be considered compared to carbamazepine to reduce the risk of poor cognitive outcomes.
    - For WWE who are pregnant, avoidance of valproate, if possible, may be considered compared to phenytoin to reduce the risk of poor cognitive outcomes.
  - Valproate has the most data showing an association with risk from in utero exposure. If a change from valproate to another AED is planned, it is prudent to make this change well before pregnancy.

- Although many of the recommendations in this parameter suggest minimizing AED exposure during pregnancy, for most WWE, discontinuing AEDs is not a reasonable or safe option. Discontinuing AEDs may expose the mother and fetus to physical injury from accidents due to seizure activity.

- **Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding.** Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society (*Harden et al 2009B*). (Reaffirmed July 13, 2013)
  - This publication summarizes evidence for selected issues regarding the clinical management of WWE who are pregnant or planning to be pregnant.
  - Recommendations include the following:
    - The fact that phenobarbital, primidone, phenytoin, carbamazepine, levetiracetam, valproate, gabapentin, lamotrigine, oxcarbazepine, and topiramate cross the placenta may be factored into the clinical decision regarding the necessity of AED treatment for a woman with epilepsy.
    - Monitoring of lamotrigine, carbamazepine, and phenytoin levels during pregnancy should be considered.
    - Monitoring of levetiracetam and oxcarbazepine (as monohydroxy derivative) levels during pregnancy may be considered.
    - There is insufficient evidence to support or refute a change in phenobarbital, valproate, primidone, or ethosuximide levels related to pregnancy, but this lack of evidence should not discourage monitoring levels of these AEDs during pregnancy.
    - Valproate, phenobarbital, phenytoin, and carbamazepine may not transfer into breast milk to as great an extent as primidone, levetiracetam, gabapentin, lamotrigine, and topiramate.
  - Although many of the AEDs were shown to cross the placenta or enter breast milk, studies were limited in duration and did not systematically evaluate neonatal symptoms.

- Guidelines also support the use of AEDs for several common non-epilepsy indications:
  - The American Academy of Neurology and American Headache Society state that AEDs with established efficacy for migraine prevention include valproate, divalproex sodium, and topiramate; carbamazepine is noted to be possibly effective (*Silberstein et al 2012*).
  - The American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation state that, for relief of painful diabetic neuropathy, pregabalin is established as effective, and gabapentin and valproate are probably effective (*Bril et al 2011*).
  - The American Academy of Neurology states that gabapentin and pregabalin are of benefit in reducing pain from postherpetic neuralgia (*Dubinsky et al 2004*).
  - American Psychiatric Association guidelines describe the key role of AEDs in the management of bipolar disorder, including the following (*Hirschfeld et al 2002*):
    - First-line pharmacological treatment for more severe manic or mixed episodes is either lithium plus an antipsychotic or valproate plus an antipsychotic; for less ill patients, monotherapy with lithium, valproate, or an antipsychotic may be sufficient. For mixed episodes, valproate may be preferred over lithium. Carbamazepine and oxcarbazepine are alternatives.
    - First-line pharmacological treatment for bipolar depression is either lithium or lamotrigine. When an acute depressive episode of bipolar disorder does not respond to first-line medication treatment, the next steps include adding lamotrigine, bupropion, or paroxetine.
    - The initial treatment for patients who experience rapid cycling should include lithium or valproate; an alternative is lamotrigine.
    - The medications with the best empirical evidence to support their use in maintenance treatment include lithium and valproate; possible alternatives include lamotrigine, carbamazepine, or oxcarbazepine.
    - Note: This guideline was published in 2002 and cannot be assumed to be current; however, AEDs continue to be recommended for both acute (mania or hypomania) and maintenance phases of bipolar disorder *(Post 2017, Stovall 2018).*

SAFETY SUMMARY

- Tolerability and safety are as important as efficacy in determining the overall effectiveness of epilepsy treatment (*Schachter 2018*).

- Common AEs among AEDs include the following (*Schachter 2018*).
  - Systemic AEs:
    - nausea, vomiting, constipation, diarrhea, abdominal pain, anorexia
    - rash, pruritus
    - hyponatremia (carbamazepine, oxcarbazepine)
    - weight gain (ezogabine, pregabalin, valproate), weight loss (felbamate, topiramate, stiripentol)
  - Neurologic AEs:
    - headache
    - somnolence, sedation, drowsiness, lethargy, fatigue
    - dizziness, vertigo
    - tremor, anxiety, nervousness, insomnia
    - aggression, irritability, behavioral changes, hyperactivity
    - attention disturbance, inattention
    - depression, mood alteration
    - confusion, memory impairment
    - ataxia, abnormal coordination, falls
    - blurred or double vision
- Examples of rare but serious AEs include the following (*Schachter 2018*):
  - suicidal ideation and behavior (AEDs as a class, except everolimus)
  - neutropenia, leukopenia, pancytopenia, agranulocytosis, thrombocytopenia, and/or aplastic anemia (brivaracetam, carbamazepine, ethosuximide, felbamate, lacosamide, levetiracetam, oxcarbazepine, phenytoin, phenobarbital, stiripentol, valproate, zonisamide)
  - anaphylaxis or angioedema (brivaracetam, levetiracetam, pregabalin)
  - severe skin rashes, Stevens-Johnson syndrome (SJS), and/or toxic epidermal necrolysis (TEN) (carbamazepine, clobazam, eslicarbazepine, ethosuximide, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, primidone, phenobarbital, rufinamide, tiagabine, valproate, zonisamide)
  - hepatic failure (carbamazepine, ethosuximide, felbamate, phenytoin, primidone, phenobarbital, valproate)
  - hepatocellular injury (cannabidiol)
  - prolonged PR interval, atrioventricular block, and/or changes in QT interval (eslicarbazepine, ezogabine, lacosamide, rufinamide)
  - serum sickness (carbamazepine, ethosuximide, phenytoin, primidone, phenobarbital, valproate)
  - multiorgan hypersensitivity (gabapentin, lacosamide, lamotrigine, oxcarbazepine)
  - severe neuropsychiatric effects/hostility/aggression (perampanel)
  - vision loss (ezogabine)
  - hyponatremia (eslicarbazepine)
  - hemophagocytic lymphohistiocytosis (HLH) (lamotrigine)
- A number of AEDs carry boxed warnings related to potentially serious AEs; these include the following:
  - Carbamazepine:
    - Serious and sometimes fatal dermatologic reactions, including TEN and SJS, have been reported. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. Patients with ancestry in genetically at-risk populations (across broad areas of Asia) should be screened for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine.
    - Aplastic anemia and agranulocytosis have been reported. If a patient exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely, and discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.
  - Clobazam, clonazepam, clorazepate, and diazepam:
    - Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Concomitant prescribing should be reserved for use in patients for whom alternative treatment options are inadequate, and patients should be followed for signs and symptoms of respiratory depression and sedation.
  - Ezogabine:
    - Ezogabine can cause retinal and macular abnormalities and may be associated with vision loss. Ezogabine should only be used in patients who have responded inadequately to several alternative treatments and for

whom the benefits outweigh the potential risk of vision loss. Ezogabine should be discontinued in patients who fail to show substantial clinical benefit after adequate titration. All patients taking ezogabine should have baseline and periodic (every 6 months) systematic visual monitoring by an ophthalmic professional. If retinal pigmentary abnormalities or vision changes are detected, ezogabine should be discontinued unless no other suitable treatment options are available and the benefits of treatment outweigh the potential risk of vision loss.

- Felbamate:
  - Use is associated with a marked increase in the incidence of aplastic anemia. Felbamate should only be used in patients whose epilepsy is so severe that the risk of aplastic anemia is deemed acceptable. Routine blood testing cannot be reliably used to reduce the incidence of aplastic anemia, but it will in some cases allow detection of hematologic changes before the syndrome declares itself clinically. Felbamate should be discontinued if any evidence of bone marrow depression occurs.
  - Cases of acute liver failure have been reported. Felbamate should not be prescribed for anyone with a history of hepatic dysfunction. Treatment should be initiated only in individuals without active liver disease and with normal baseline serum transaminases. It has not been proven that periodic serum transaminase testing will prevent serious injury, but it is generally believed that early detection of drug-induced hepatic injury along with immediate withdrawal of the suspect drug enhances the likelihood for recovery. Serum transaminases should be monitored at baseline and periodically thereafter. Felbamate should be discontinued if either AST or ALT become increased to ≥ 2 times the upper limit of normal, or if clinical signs and symptoms suggest liver failure, and should not be considered for retreatment.
- Fosphenytoin and phenytoin:
  - There is a cardiovascular risk associated with rapid IV infusion rates. The rate of administration should not exceed recommendations, and careful cardiac monitoring is required.
- Lamotrigine:
  - Cases of life-threatening serious skin rashes, including SJS and TEN, and/or rash-related death have been caused by lamotrigine. Benign rashes are also caused by lamotrigine; however, it is not possible to predict which rashes will prove to be serious. Lamotrigine should be discontinued at the first sign of a rash, unless the rash is clearly not drug related.
- Perampanel:
  - Serious or life-threatening psychiatric and behavioral AEs including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported. Patients should be monitored for these reactions and for changes in mood, behavior, or personality. The dose should be reduced if these symptoms occur, and it should be discontinued if symptoms are severe or worsening.
- Valproic acid and divalproex sodium:
  - Hepatoxicity, including fatalities, have been reported, usually during the first 6 months of treatment. Serum liver tests are required and patients should be monitored closely.
  - There is a risk to fetuses exposed in utero, particularly neural tube defects, other major malformations, and decreased intelligence quotient (IQ). Valproate should not be given to a woman of childbearing potential unless the drug is essential to the management of her medical condition, and women should use effective contraception while using valproate.
  - Pancreatitis, including fatal hemorrhagic cases, has occurred. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation.
- Vigabatrin:
  - Vigabatrin can cause permanent bilateral concentric visual field constriction, including tunnel vision that can result in disability. In some cases, vigabatrin may also damage the central retina and may decrease visual acuity. Baseline and periodic vision assessment is recommended. However, this assessment cannot always prevent vision damage, and once detected, vision loss due to vigabatrin is not reversible. Vigabatrin should be withdrawn from patients who fail to show substantial clinical benefit.
  - Due to the risks of vision loss, vigabatrin is available only through a risk evaluation and mitigation strategy (REMS) program (*Vigabatrin REMS 2017*). Healthcare providers who prescribe vigabatrin and pharmacies that dispense the product must be specially certified. Each patient must be enrolled in the REMS program. Prescribers must ensure that periodic visual monitoring is performed and report any AE suggestive of vision loss to the vigabatrin REMS program.

- Everolimus is an antineoplastic, immunosuppressant agent associated with several adverse reactions.

- The most common AE that occurred in trials for TSC-associated partial-onset seizures was stomatitis.
- More serious AEs include:
  - non-infectious pneumonitis
  - infections
  - hypersensitivity reactions
  - angioedema (when taken with an angiotensin converting enzyme inhibitor)
  - renal failure
  - impaired wound healing
  - myelosuppression
  - reduced immune response with vaccination
  - hyperglycemia
  - hyperlipidemia
  - embryo-fetal toxicity

DOSING AND ADMINISTRATION

- General dosing information is provided in Table 3. Dosing may vary based on the specific indication, interacting medications, and the patient's age and renal and hepatic function. Additionally, some medications are recommended to be titrated during initial treatment. Please refer to the prescribing information of the individual products for more detailed information.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Barbiturates				
Mephobarbital* (Mebaral)‡	tablets	oral	Once daily or divided 3 to 4 times per day	
Pentobarbital (Nembutal†)	injection	IV, IM	Single dose	Acute use only. If needed, additional small increments may be given after the initial dose.
Phenobarbital* (Luminal†, Solfotyn†)	tablets, elixir, injection	oral, IV, IM	2 to 3 times per day	
Primidone (Mysoline)	tablets	oral	3 to 4 times per day	
Benzodiazepines				
Clobazam (Onfi)	tablets, oral suspension	oral	1 or 2 times per day	Daily doses > 5 mg should be given in divided doses 2 times per day.
Clonazepam (Klonopin)	tablets, orally disintegrating tablets (wafers)	oral	3 times per day	
Clorazepate (Tranxene T-Tab)	tablets	oral	2 to 3 times per day	
Diazepam (Diastat, Valium)	tablets, oral solution, oral concentrate, rectal gel, injection	oral, rectal, IV, IM	2 to 4 times per day	For the rectal gel (for acute use), a second dose may be given 4 to 12 hours after the initial dose when required. The injection is also for short-term acute use.
Hydantoins				
Ethotoin (Peganone)	tablets	oral	4 to 6 times per day	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Fosphenytoin (Cerebyx)	injection	IV, IM	2 times per day or other divided doses based on drug levels	Generally used in acute situations as a loading dose; may be given in divided doses when substituted for oral phenytoin.
Phenytoin (Dilantin, Phenytek)	extended-release capsules, chewable tablets, oral suspension, injection	oral, IV, IM	2 to 4 times per day	Capsules are extended-release and may be suitable for once-daily dosing in some adults.
Miscellaneous				
Brivaracetam (Briviact)	tablets, oral solution, injection	oral, IV	2 times per day	The injection may be used when oral administration is temporarily not feasible.
Cannabidiol	Oral solution	Oral	2 times per day	The provided oral syringe should be used to measure an accurate dose.
Carbamazepine (Carbatrol, Epitol, Equetro, Tegretol, Tegretol-XR)	tablets, chewable tablets, oral suspension, extended-release tablets, extended-release capsules	oral	2 to 4 times per day	Immediate-release tablets are given 2 to 3 times per day and the suspension is given 4 times per day. Carbatrol and Equetro are twice-daily extended-release capsule formulations; these capsules may be opened and sprinkled on soft food. Tegretol-XR is a twice-daily extended-release tablet formulation; these tablets must be swallowed whole.
Divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)	delayed-release tablets, delayed-release sprinkle capsules, extended-release tablets	oral	2 to 3 times per day (once daily for extended-release tablets)	Delayed-release tablets and extended-release tablets should be swallowed whole. Sprinkle capsules may be opened and sprinkled on soft food. Delayed-release tablet and capsule doses > 250 mg per day should be given in divided doses.
Eslicarbazepine (Aptiom)	tablets	oral	once daily	Tablets may be crushed.
Ethosuximide (Zarontin)	capsules, oral solution/syrup	oral	once daily or in divided doses	
Everolimus (Afinitor Disperz)	tablets for oral suspension	oral	once daily	Should be taken at the same time each day with or without food. Suspension should be prepared using water only and administered immediately after preparation. The suspension should be discarded if not

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				taken within 60 minutes of preparation. Dose adjustments are made based on trough drug concentration.
Ezogabine (Potiga)‡	tablets	oral	3 times per day	Tablets should be swallowed whole.
Felbamate (Felbatol)	tablets, oral suspension	oral	3 or 4 times per day	
Gabapentin (Neurontin)	tablets, capsules, oral solution	oral	3 times per day	Capsules should be swallowed whole.
Lacosamide (Vimpat)	tablets, oral solution, injection	oral, IV	2 times per day	
Lamotrigine (Lamictal, Lamictal ODT, Lamictal XR)	tablets, chewable dispersible tablets, orally disintegrating tablets, extended-release tablets	oral	2 times per day (once daily for extended-release tablets)	Only whole tablets should be administered. Extended-release tablets must not be chewed or crushed.
Levetiracetam (Keppra, Keppra XR, Roweepra, Roweepra XR, Spritam)	tablets, tablets for oral suspension, oral solution, extended-release tablets, injection	oral, IV	2 times per day (once daily for extended-release tablets)	Tablets and extended-release tablets should not be chewed or crushed. Tablets for oral suspension (Spritam) can be dissolved in liquid and swallowed or allowed to disintegrate in the mouth.
Methsuximide (Celontin)	capsules	oral	1 to 4 times per day (*Lexicomp 2017*)	
Oxcarbazepine (Oxtellar XR, Trileptal)	tablets, oral suspension, extended-release tablets	oral	2 times per day (once daily for extended-release tablets)	In conversion of oxcarbazepine immediate-release to Oxtellar XR, higher doses of Oxtellar XR may be necessary. Extended-release tablets must not be chewed or crushed.
Perampanel (Fycompa)	tablets, oral suspension	oral	once daily at bedtime	
Pregabalin (Lyrica)	capsules, oral solution	oral	2 to 3 times per day	
Rufinamide (Banzel)	tablets, oral suspension	oral	2 times per day	Tablets can be administered whole, as half tablets, or crushed.
Stiripentol (Diacomit)	capsules, powder for oral suspension	oral	2 to 3 times per day	Capsules must be swallowed whole with a glass of water during a meal. Powder should be mixed with water and taken immediately after mixing during a meal.
Tiagabine (Gabitril)	tablets	oral	2 to 4 times per day	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Topiramate (Topamax, Topamax Sprinkle, Topiragen, Trokendi XR, Qudexy XR)	tablets, sprinkle capsules, extended-release capsules, extended-release sprinkle capsules	oral	2 times per day (once daily for extended-release capsule formulations)	Sprinkle capsules may be opened and sprinkled on soft food. Extended-release capsules (Trokendi XR) must not be chewed or crushed, but extended release sprinkle capsules (Qudexy XR) may be sprinkled on soft food.
Valproic acid (Depakene, Stavzor DR‡, Depacon)	capsules, delayed-release capsules, oral solution/ syrup, injection	oral, IV	2 to 4 times per day (*Lexicomp 2017*)	Capsules should be swallowed whole without chewing to avoid local irritation of the mouth and throat. If the total dose exceeds 250 mg, it should be given in divided doses.
Vigabatrin (Sabril)	tablets, powder for oral solution	oral	2 times per day	Powder for oral solution is supplied in individual dose packets to be mixed with water before administration.
Zonisamide (Zonegran)	capsules	oral	1 or 2 times per day	Capsules must be swallowed whole.

* Not FDA approved
† Brand product not currently marketed; generic is available
‡ No brand or generic currently marketed

CONCLUSION

- Several classes of AEDs are available, including barbiturates, benzodiazepines, hydantoins, and miscellaneous agents. These products vary in terms of their indications for specific seizure types and indications other than epilepsy.
- Overall, the anticonvulsants have demonstrated efficacy for their FDA-approved uses. When possible, monotherapy with a single AED is the preferred treatment approach.
- Patients who are refractory to monotherapy may be treated with combination therapy. When considering combination therapy, it is recommended to combine medications with different mechanisms of action and AE profiles.
- Comparative efficacy data for the management of epilepsy are limited.
- Tolerability and safety are as important as efficacy in determining the overall effectiveness of epilepsy treatment. Both systemic AEs and neurologic AEs commonly occur. Some AEDs are associated with rare but serious AEs, and careful patient selection and monitoring are required.
- Epilepsy management can be complex and it is often treated by neurologists. A variety of AEDs should be available to allow clinicians to select the most clinically appropriate agent for individual patients.
- Anticonvulsants are also established as effective for several non-epilepsy indications, including (but not limited to) bipolar disorder, migraine prophylaxis, and neuropathic pain.

REFERENCES

- Afinitor Disperz [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Inc.; April 2018.
- Aptiom [package insert], Marlborough, MA: Sunovion Pharmaceuticals Inc.; October 2017.
- Banzel [package insert], Woodcliff Lake, NJ: Eisai Inc.; June 2015.
- Bril V, England J, Franklin GM, et al. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology*. 2011;76:1758-1765.
- Briviact [package insert], Smyrna, GA: UCB Inc.; May 2018.
- Campos MSA, Ayres LR, Morelo MRS, Carizio FAM, Pereira LRL. Comparative efficacy of antiepileptic drugs for patients with generalized epileptic seizures: systematic review and network meta-analyses. *Int J Clin Pharm*. 2018 May 9. doi: 10.1007/s11096-018-0641-9.
- Carbatrol [package insert], Wayne, PA: Shire US Inc.; February 2018.
- Celontin [package insert], New York, NY: Pfizer Inc.; November 2013.

- Centers for Disease Control and Prevention (CDC). Epilepsy: Types of Seizures. CDC Web Site. https://www.cdc.gov/epilepsy/basics/types-of-seizures.htm. Updated April 25, 2018. Accessed August 16, 2018.
- Cerebyx [package insert], New York, NY: Pfizer Inc.; April 2018.
- Depacon [package insert], North Chicago, IL: AbbVie Inc.; October 2017.
- Depakene [package insert], North Chicago, IL: AbbVie Inc.; October 2017.
- Depakote (tablets) [package insert], North Chicago, IL: AbbVie Inc.; October 2017.
- Depakote ER [package insert], North Chicago, IL: AbbVie Inc.; October 2017.
- Depakote Sprinkle Capsules [package insert], North Chicago, IL: AbbVie Inc.; October 2017.
- Diacomit [package insert]. Beauvais, France: Biocodex; August 2018.
- Diastat & Diastat AcuDial [package insert], Bridgewater, NJ: Valeant Pharmaceuticals; December 2016.
- Diazepam (injection) [package insert], Lake Forest, IL: Hospira Inc.; September 2016.
- Diazepam (oral solution) and Diazepam Intensol (oral concentrate) [package insert], Eatontown, NJ: West-Ward Pharmaceuticals; May 2016.
- Dilantin-125 (oral suspension) [package insert], New York, NY: Pfizer Inc.; October 2017.
- Dilantin (capsules) [package insert], New York, NY: Pfizer Inc.; October 2017.
- Dilantin Infatabs (chewable tablets) [package insert], New York, NY: Pfizer Inc.; October 2017.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Website. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed August 16, 2018.
- Dubinsky RM, Kabbani H, El-Chami Z, Boutwell C, Ali H. Practice Parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2004; 63:959-965 (guideline reaffirmed February 8, 2008).
- Epidiolex [package insert]. Carslbad, CA: Greenwich Biosciences, Inc.; June 2018.
- Epilepsy Foundation. Lennox-Gastaut Syndrome. Epilepsy Foundation Web site. http://www.epilepsy.com/learn/types-epilepsy-syndromes/lennox-gastaut-syndrome-lgs. Reviewed March 2014. Accessed August 16, 2018.
- Epilepsy Foundation. Seizure Types. Epilepsy Foundation Web site. https://epilepsychicago.org/epilepsy/seizure-types/generalized-seizures/. 2016. Accessed August 16, 2018.
- Epilepsy Foundation. Types of Epilepsy Syndromes. Epilepsy Foundation Web site. http://www.epilepsy.com/learn/types-epilepsy-syndromes. September 2013. Accessed August 16, 2018.
- Equetro [package insert], Parsippany, NJ: Validus Pharmaceuticals LLC; October 2016.
- FDA News Release. FDA approves first drug comprised of an active ingredient derived from marijuana to treat rare, severe forms of epilepsy. Food and Drug Administration website: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm611046.htm, Accessed August 21, 2018.
- Felbatol [package insert], Somerset, NJ: Meda Pharmaceuticals Inc.; August 2012.
- Fisher RS, Acevedo C, Arzimanoglou A, et al. A practical clinical definition of epilepsy. *Epilepsia*. 2014;55(4):475-482.
- Fisher RS, Cross JH, D'Souza C, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. *Epilepsia*. 2017(A);58(4):531-542.
- Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017(B);58(4):522-530.
- French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy. Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2004(A);62:1252-1260.
- French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy. Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2004(B);62:1261-1273.
- French JA, Lawson JA, Yapici Z, et al. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomized, double-blind, placebo-controlled study. *Lancet.* 2016;388(10056):2153-2163. doi: 10.1016/S0140-6736(16)31419-2.
- Fycompa [package insert], Woodcliff Lake, NJ: Eisai Inc.; July 2017.
- Gabitril [package insert], North Wales, PA: Teva Pharmaceuticals USA Inc.; August 2016.
- Glauser T, Ben-Menachem E, Bourgeois B, et al; for the ILAE subcommission of AED Guidelines. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia*. 2013;54(3):551-563.
- Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Curr*. 2016;16(1):48-61.
- Go CY, Mackay MT, Weiss SK, et al. Evidence-based guideline update: medical treatment of infantile spasms. Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2012;78:1974-1980 (guideline reaffirmed July 18, 2015).
- Gralise [package insert], Newark, CA: Depomed Inc.; September 2015.
- GW Pharmaceuticals News Release. Biosciences announce FDA approval of Epidiolex (cannabidiol) oral solution- the first plant-derived cannabinoid prescription medicine. GW Pharmaceuticals Website. http://ir.gwpharm.com/news-releases/news-release-details/gw-pharmaceuticals-plc-and-its-us-subsidiary-greenwich. Accessed August 21, 2018.
- Harden CL, Meador KJ, Pennell PB, et al. Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes. Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. *Neurology*. 2009(A);73:133-141 (guideline reaffirmed July 13, 2013).
- Harden CL, Pennell PB, Koppel BS, et al. Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding. Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. *Neurology*. 2009(B);73:142-149 (guideline reaffirmed July 13, 2013).

- Hirschfeld RM, Bowden CL, Gitlin MJ, et al. Practice guideline for the treatment of patients with bipolar disorder; second edition. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/bipolar.pdf. Originally published April 2002. Accessed August 20, 2018.
- Hirtz D, Berg A, Bettis D, et al. Practice Parameter: treatment of the child with a first unprovoked seizure. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2003;60:166-175 (guideline reaffirmed January 23, 2016).
- Horizant [package insert], Atlanta, GA: Arbor Pharmaceuticals LLC; October 2016.
- Hu Q, Zhang F, Teng W, et al. Efficacy and safety of antiepileptic drugs for refractory partial-onset epilepsy: a network meta-analysis. *J Neurol.* 2018;265(1):1-11. doi: 10.1007/s00415-017-8621-x.
- Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2018(A);91(2):82-90. doi: 10.1212/WNL.0000000000005756.
- Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs II: treatment-resistant epilepsy. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology.* 2018(B);91(2):74-81. doi: 10.1212/WNL.0000000000005755.
- Karceski S. Initial treatment of epilepsy in adults. UpToDate Web site. www.uptodate.com. Updated December 20, 2017. Accessed August 16, 2018.
- Keppra (injection) [package insert], Smyrna, GA: UCB Inc.; October 2017.
- Keppra (tablets & oral solution) [package insert], Smyrna, GA: UCB Inc.; October 2017.
- Keppra XR [package insert], Smyrna, GA: UCB Inc.; October 2017.
- Klonopin [package insert], South San Francisco, CA: Genentech Inc.; October 2017.
- Krumholz A, Wiebe S, Gronseth GS, et al. Evidence-based guideline: management of an unprovoked first seizure in adults: report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2015;84:1705-1713.
- Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. *N Engl J Med*. 2011;365:919-926.
- Lamictal (tablets, chewable dispersible tablets & orally disintegrating tablets) [package insert], Research Triangle Park, NC: GlaxoSmithKline; July 2018.
- Lamictal XR [package insert], Research Triangle Park, NC: GlaxoSmithKline; July 2018.
- LexiComp Web site. http://online.lexi.com/lco/action/home/switch. Accessed August 20, 2018.
- Lyrica [package insert], New York, NY: Pfizer Inc.; May 2018.
- Lyrica CR [package insert], New York, NY: Pfizer Inc.; October 2017.
- Mebaral [package insert], Deerfield, IL: Lundbeck Inc.; May 2009 (archived label available at https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=76283. Accessed August 20, 2018.
- Mysoline [package insert], Bridgewater, NJ: Valeant Pharmaceuticals; January 2018.
- Nembutal [package insert], Lake Forest, IL: Akorn, Inc.; December 2016.
- Neurontin [package insert], New York, NY: Pfizer Inc.; October 2017.
- Nevitt SJ, Sudell M, Weston J, Tudur Smith C, Marson AG. Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. Cochrane Database of Systematic Reviews 2017, Issue 6. Art. No.: CD011412. DOI: 10.1002/14651858.CD011412.pub2.
- Onfi [package insert], Deerfield, IL: Lundbeck Inc.; June 2018.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed August 16, 2018.
- Oxtellar XR [package insert], Rockville, MD: Supernus Pharmaceuticals Inc.; December 2015.
- Peganone [package insert], Lebanon, NJ: Recordati Rare Diseases; July 2016.
- Phenobarbital (elixir) [package insert], Huntsville, AL: Qualitest Pharmaceuticals; February 2015.
- Phenobarbital (injection) [package insert], Eatontown, NJ: West-Ward Pharmaceuticals; June 2011.
- Phenobarbital (tablet) [package insert], Eatontown, NJ: West-Ward Pharmaceuticals; May 2018.
- Phenytoin (injection) [package insert], Eatontown, NJ: West-Ward Pharmaceuticals; December 2017.
- Post RM. Bipolar disorder in adults: choosing maintenance treatment. UpToDate Web site. www.uptodate.com. Updated November 2, 2017. Accessed August 16, 2018.
- Potiga [package insert], Research Triangle Park, NC: GlaxoSmithKline; May 2016.
- Qudexy XR [package insert], Maple Grove, MN: Upsher-Smith Laboratories Inc.; March 2017.
- Rosati A, Ilvento L, Lucenteforte E, et al. Comparative efficacy of antiepileptic drugs in children and adolescents: a network meta-analysis. *Epilepsia.* 2018;59(2):297-314. doi: 10.1111/epi.13981.
- Sabril [package insert], Deerfield, IL: Lundbeck Inc.; April 2017.
- Schachter SC. Overview of the management of epilepsy in adults. UpToDate Web site. www.uptodate.com. Updated July 9, 2018. Accessed August 16, 2018.
- Silberstein SD, Holland S, Freitag F, et al. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2012;78:1337-1345 (guideline reaffirmed July 18, 2015).
- Sirven JI. Evaluation and management of drug-resistant epilepsy. UpToDate Web site. www.uptodate.com. Updated March 2, 2018. Accessed August 16, 2018.
- Spritam [package insert], East Windsor, NJ: Aprecia Pharmaceuticals Company; February 2018.
- Stavzor [package insert], Miami, FL: Noven Therapeutics LLC; August 2014.
- Stovall J. Bipolar disorder in adults: Choosing pharmacotherapy for acute mania and hypomania. UpToDate Web site. www.uptodate.com. Updated February 06, 2018. Accessed August 20, 2018.
- Tegretol and Tegretol-XR [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corp.; March 2018.
- Topamax [package insert], Titusville, NJ: Janssen Pharmaceuticals Inc.; June 2018.

- Tranxene T-TAB [package insert], Lebanon, NJ: Recordati Rare Diseases Inc.; May 2018.
- Trileptal [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corporation; March 2018.
- Trokendi XR [package insert], Rockville, MD: Supernus Pharmaceuticals Inc.; January 2018.
- Valium [package insert], South San Francisco, CA: Genentech Inc.; June 2017.
- Vigabatrin risk evaluation and mitigation strategy (REMS) document. Food and Drug Administration Web site. https://www.accessdata.fda.gov/drugsatfda_docs/rems/Vigabatrin_SSS_2017-10-23_Full.pdf. Updated October 2017. Accessed August 20, 2018.
- Vimpat [package insert], Smyrna, GA: UCB Inc.; November 2017.
- Wilmshurst JM, Gaillard WD, Vinayan KP, et al. Summary of recommendations for the management of infantile seizures: task force report for the ILAE Commission of Pediatrics. *Epilepsia*. 2015;56(8):1185-1197.
- World Health Organization. Guidelines on neonatal seizures. World Health Organization Web site. http://www.who.int/mental_health/publications/guidelines_neonatal_seizures/en/. 2011. Accessed August 20, 2018.
- Zarontin (capsules) [package insert], New York, NY: Pfizer Inc.; May 2016.
- Zarontin (oral solution) [package insert], New York, NY: Pfizer Inc.; May 2016.
- Zhu LN, Chen D, Xu D, Tan G, Wang HJ, Liu L. Newer antiepileptic drugs compared to levetiracetam as adjunctive treatments for uncontrolled focal epilepsy: an indirect comparison. *Seizure*. 2017 Aug 16;51:121-132 (Epub).
- Zhao T, Feng X, Liu J, et al. Evaluate the efficacy and safety of anti-epileptic medications for partial seizures of epilepsy: A network meta-analysis. *J Cell Biochem*. 2017;118(9):2850-2864. doi: 10.1002/jcb.25936.
- Zonegran [package insert], St. Michael, Barbados: Concordia Pharmaceuticals Inc.; April 2016.

Publication Date: September 4, 2018

Therapeutic Class Overview
Opioid Use Disorder Agents

INTRODUCTION

Products for Treatment of Opioid Dependence

- The American Psychiatric Association (APA) defines opioid use disorder as a syndrome characterized by a problematic pattern of opioid use, leading to clinically significant impairment or distress (*APA 2013*).
  - In 2015, approximately 2 million Americans had a substance use disorder involving prescription pain relievers and 591,000 had a substance use disorder involving heroin (*American Society of Addiction Medicine [ASAM] 2016*).
- Methadone, buprenorphine (with or without naloxone), and naltrexone are Food and Drug Administration (FDA)-approved for the detoxification and maintenance treatment of opioid dependence (*Micromedex 2.0 2018*).
  - Methadone products, when used for the treatment of opioid addiction in detoxification or maintenance programs, may be dispensed only by opioid treatment programs (and agencies, practitioners or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority. Certified treatment programs may dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (Code of Federal Regulations, Title 42, Sec 8).
  - The Drug Addiction Treatment Act of 2000 expanded the clinical context of medication-assisted opioid addiction treatment by allowing qualified physicians to dispense or prescribe specifically approved medications, like buprenorphine, for the treatment of opioid addiction in treatment settings other than the traditional Opioid Treatment Program. In addition, DATA reduced the regulatory burden on physicians who choose to practice opioid addiction therapy by permitting qualified physicians to apply for and receive waivers of the special registration requirements defined in the Controlled Substances Act (*Center for Substance Abuse Treatment 2004*).
  - Naltrexone, an opioid antagonist, is only indicated for the prevention of relapse after opioid detoxification; patients must be opioid-free for at least 7 to 10 days prior to initiation of naltrexone therapy in order to avoid precipitation of withdrawal.
- All buprenorphine products are Schedule III controlled substances (*Drugs@FDA 2018*).
- In 2012, Reckitt Benckiser Pharmaceuticals notified the FDA that they were voluntarily discontinuing production of Suboxone (buprenorphine/naloxone) sublingual tablets as a result of increasing concerns over accidental pediatric exposure with the tablets. The unique child-resistant, unit-dose packaging of the film formulation is believed to be a contributing factor to reduce exposure rates in children. Generic formulations of the sublingual tablets remain available.
- In November 2017, the FDA approved Sublocade (buprenorphine ER) subcutaneous injection for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days.
  - Sublocade is injected as a liquid and the subsequent precipitation of the polymer creates a solid depot which contains buprenorphine. Buprenorphine is released via diffusion from, and the biodegradation of, the depot.
- Lofexidine, an oral central alpha-2 agonist, was approved in May 2018 for the mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults. This product is indicated for short-term use, up to 14 days, during the period of peak opioid withdrawal symptoms.
- Included in this review are the products that are FDA-approved to be used in the treatment of opioid dependence; however, methadone products are not included since they must be dispensed in an opioid treatment program when used for the treatment of opioid addiction in detoxification.
- Medispan Class: Opioid Use Disorder Agents

Table 1. Medications for Treatment of Opioid Dependence Included Within Class Review

Drug	Generic Availability
Single Entity Agents	
Lucemyra (lofexidine) tablet	-
naltrexone hydrochloride* tablet	✔

Drug	Generic Availability
Sublocade (buprenorphine) subcutaneous injection	-
Subutex (buprenorphine)* sublingual tablet	✔
Vivitrol (naltrexone) intramuscular injection	-
Combination Products	
Bunavail (buprenorphine/naloxone) buccal film	-
Suboxone‡ (buprenorphine/naloxone) sublingual tablets	✔
Suboxone (buprenorphine/naloxone) sublingual film	✔ †
Zubsolv (buprenorphine/naloxone) sublingual tablets	-

*Brand name product was discontinued; however, generic formulations are available.
‡Suboxone tablets were discontinued; however, generic formulations are available and brand name Suboxone is available as a film.
†Dr. Reddy and Mylan received FDA approval for AB-rated generic versions of the Suboxone sublingual film. Mylan has not yet launched their generic version. The manufacturer (Indivior) of brand Suboxone also announced it will pursue an immediate injunction against Dr. Reddy's "at-risk" launch.

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

Products for Emergency Treatment of Opioid Overdose

- Opiate overdose continues to be a major public health problem in the United States (U.S.). It has contributed significantly to accidental deaths among those who use or abuse illicit and prescription opioids. The number of opioid overdoses has risen in recent years, partly due to a nearly 4-fold increase in the use of prescribed opioids for the treatment of pain. Overdose deaths involving prescription opioid analgesics increased to about 19,000 deaths in 2014, more than 3 times the number in 2001 (*Substance Abuse and Mental Health Services Administration [SAMHSA] 2016)*.
- Death following opioid overdose can be averted by emergency basic life support and/or the timely administration of an opioid antagonist such as naloxone. As a narcotic antagonist, naloxone displaces opiates from receptor sites in the brain and reverses respiratory depression, which usually is the cause of overdose deaths *(SAMHSA 2016, World Health Organization [WHO] 2014)*.
- Naloxone is provided to patients through the regular course of medical care, by pharmacist-initiated collaborative practice agreements, or through community-based opioid overdose prevention programs (*Doe-Simkins 2014*).
- Recognizing the potential value of providing naloxone to laypersons, some states have passed laws and changed regulations authorizing prescribers to provide naloxone through standing orders and/or to potential overdose witnesses as well as protecting those who administer naloxone from penalties for practicing medicine without a license (*MMWR 2012, Coffin 2018*).
- In patients with opioid overdose, naloxone begins to reverse sedation, respiratory depression, and hypotension within 1 to 2 minutes after intravenous (IV) administration, 2 to 5 minutes after intramuscular (IM) or subcutaneous (SC) administration, and 8 to 13 minutes after intranasal (IN) administration. Since the half-life of naloxone is much shorter than that of most opioids, repeated administration may be necessary (*Lexicomp 2018)*.
- Naloxone was first approved by the FDA in 1971. In April 2014, an auto-injector formulation of naloxone was approved (Evzio) which incorporates both audio and visual instructions to guide the person administering the drug during a medical emergency. In November 2015, the FDA approved the first IN formulation of naloxone (Narcan nasal spray). Prior to the approval of these products, naloxone was only available in glass vials and ampules, which were distributed with syringes and needles for manual injection or with syringes and atomizers for off-label IN administration (*Evzio FDA Summary Review 2014*).
- Included in this review are the naloxone products that are FDA-approved for opioid overdose.
- Medispan Class: Opioid Antagonists

Table 2. Medications for Emergency Treatment of Opioid Overdose Included Within Class Review

Drug	Generic Availability
Evzio (naloxone hydrochloride [HCl]) auto-injector	-
Narcan (naloxone HCl)* injection	✔
Narcan (naloxone HCl) nasal spray	-

*Narcan injection was discontinued; however, generic formulations are available

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

INDICATIONS

Table 3. Food and Drug Administration Approved Indications for Buprenorphine and Buprenorphine/Naloxone Products

Indication	Single Entity Agent		Combination Products			
	Sublocade (buprenorphine) subcutaneous injection	Subutex (buprenorphine) sublingual tablets	Bunavail (buprenorphine/ naloxone) film	Suboxone (buprenorphine /naloxone) sublingual tablets	Suboxone (buprenorphine/ naloxone) film	Zubsolv (buprenorphine /naloxone) sublingual tablets
Treatment of opioid dependence			✔		✔	✔
Treatment of opioid dependence and is preferred for induction		✔				
Maintenance treatment of opioid dependence				✔		
Treatment of moderate to severe opioid use disorder†	✔					

†For use in patients who initiated treatment with transmucosal buprenorphine-containing product, followed by dose adjustment for at least 7 days.

(*Prescribing information: buprenorphine sublingual tablets 2018, buprenorphine/naloxone sublingual tablets 2018, Bunavail 2018, Sublocade 2018, Suboxone film 2018, Zubsolv 2018*)

Table 4. Food and Drug Administration Approved Indications for Other Medications Used in Opioid Dependence

Indication	Lucemyra (lofexidine) tablets	naltrexone hydrochloride tablets	Vivitrol (naltrexone HCl) injection
Mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation	✔		
Blockade of the effects of exogenously administered opioids		✔	
Treatment of alcohol dependence		✔	✔
Prevention of relapse to opioid dependence following opioid detoxification			✔

(*Prescribing information: Lucemyra 2018, naltrexone tablets 2017, Vivitrol 2015*)

Table 5. Food and Drug Administration Approved Indications for Naloxone Products

Indication	Evzio (naloxone HCl) auto-injector	Narcan (naloxone HCl) injection	Narcan (naloxone HCl) nasal spray
Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system (CNS) depression	✔		✔
Complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids, including propoxyphene, methadone, and certain mixed agonist-antagonist analgesics: nalbuphine, pentazocine, butorphanol, and cyclazocine		✔	
Diagnosis of suspected or acute opioid overdosage		✔	
Adjunctive agent to increase blood pressure in the management of septic shock		✔	

(*Prescribing information: Evzio 2016, naloxone injection 2015, Narcan nasal spray 2017*)

Limitations of use

- Prescription of Narcan nasal spray 2 mg should be restricted to opioid-dependent patients expected to be at risk for severe opioid withdrawal in situations where there is a low risk for accidental or intentional opioid exposure by household contacts.

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

CLINICAL EFFICACY SUMMARY

Products for Treatment of Opioid Dependence

- Clinical trials have demonstrated that buprenorphine/naloxone is practical and safe for use in diverse community treatment settings including primary care offices (*Amass et al 2004, Fiellin et al 2008*).
- Studies have shown that in adult patients with opioid dependence, the percentage of opioid negative urine tests was significantly higher for both buprenorphine and buprenorphine/naloxone compared to placebo, while no significant difference was seen between the 2 active treatment groups (*Daulouede et al 2010, Fudala et al 2003*). In addition, a small randomized controlled trial (N=32) also showed no significant difference in withdrawal symptoms between buprenorphine and buprenorphine/naloxone (*Strain et al 2011*).
- Several studies have compared the effectiveness of short-term detoxification to medium- or long-term maintenance treatment with buprenorphine monotherapy or buprenorphine/naloxone. Three studies have shown higher treatment retention rate or self-reported drug use with longer treatment duration compared to detoxification; however, 1 of the studies showed no significant difference in the percentage of positive urine tests between the 2 treatment groups at 12 weeks (*Kakko et al 2003, Woody et al 2008, Weiss 2011*).
- In a meta-analysis of 21 randomized controlled trials, patients receiving buprenorphine at doses ≥16 mg/day were more likely to continue treatment compared to patients receiving doses <16 mg/day; however, no significant difference was seen in the percentage of opioid positive urine tests between the high- and low-dose groups (*Fareed et al 2012*).

- Studies that compared different dosing regimens of buprenorphine showed no difference in rate of treatment retention, percentage of urine tests positive for opioids, or withdrawal symptoms (*Bickel et al 1999, Gibson et al 2008, Petry et al 1999, Schottenfeld et al 2000*).
- One study found that buprenorphine/naloxone sublingual film was comparable to the sublingual tablet form in dose equivalence and clinical outcomes (*Lintzeris et al 2013*).
- A randomized, parallel-group, noninferiority trial (N=758) found that for the treatment of patients with opioid dependence, Zubsolv (buprenorphine/naloxone) sublingual tablets was noninferior to generic buprenorphine sublingual tablets during induction and was noninferior to buprenorphine/naloxone sublingual film during early stabilization (*Gunderson et al 2015*).
- Buprenorphine has been compared to methadone in several clinical studies and reviewed in multiple meta-analyses. Overall, studies have demonstrated that buprenorphine-based therapy was as effective as methadone in the management of opioid dependence (*Farre et al 2002, Gibson et al 2008, Gowing et al 2017, Johnson et al 1992, Kamien et al 2008, Law et al 2017, Meader et al 2010, Perry et al 2013, Petitjean et al 2001, Soyka et al 2008, Strain et al 2011).* However, when low doses of buprenorphine were studied (≤8 mg/day), high doses of methadone (≥50 mg/day) proved to be more efficacious *(Farre et al 2002, Ling et al 1996, Mattick et al 2014, Schottenfeld et al 1997*).
- In a 24-week, Phase 3, double blind, placebo-controlled, randomized controlled trial (N=504), the efficacy and safety of multiple subcutaneous injections of buprenorphine (100 mg and 300 mg) over 24 weeks were assessed in treatment-seeking patients with opioid use disorder. Buprenorphine injection was shown to be superior vs placebo in achieving more illicit opioid-free weeks ($p < 0.0001$). The proportion of patients achieving treatment success (defined as any patient with at least 80% of urine samples negative for opioids combined with self-reports negative for illicit opioid use from week 5 through week 24) was statistically significantly higher in both groups receiving buprenorphine compared to the placebo group (28.4% [300 mg/100 mg], 29.1% [300 mg/300mg], and 2% [placebo]) ($p < 0.0001$) *(FDA Advisory Committee Briefing Document, Sublocade Prescribing Information)*.
- Extended-release intramuscular naltrexone was compared to buprenorphine/naloxone sublingual film in a 24-week, open-label, randomized controlled trial (N=570). More induction failures were seen with extended-release intramuscular naltrexone; as a result, in the intention-to-treat analysis, relapse-free survival was lower with extended-release intramuscular naltrexone compared to sublingual buprenorphine/naloxone. However, among patients who were able to successfully initiate treatment, extended-release intramuscular naltrexone had similar efficacy to buprenorphine/naloxone in terms of relapse prevention (*Lee et al 2018*). A 12-week, randomized, open-label, noninferiority trial (N=159) similarly found that extended-release intramuscular naltrexone was noninferior to oral buprenorphine/naloxone in terms of negative urine drug tests and days of opioid use (*Tanum et al 2017).*
- In a meta-analysis examining the efficacy of oral naltrexone for maintenance treatment of opioid dependence, oral naltrexone was no better than placebo or no pharmacologic treatment in terms of treatment retention or use of the primary substance of abuse. Based on the results of 1 study, it was also not significantly different from buprenorphine for retention, abstinence, and side effects (*Minozzi et al 2011*).
- The safety and efficacy of lofexidine for inpatient treatment of opioid withdrawal symptoms was examined in an 8-day, randomized, double-blind, placebo-controlled trial (N=264). In this study, patients treated with lofexidine had lower scores on the Short Opioid Withdrawal Scale (SOWS) Gossop scale on day 3 compared to placebo. More patients in the placebo group terminated study participation early (*Gorodetzky et al 2017).* Similar resulted were found in another, unpublished trial *(Lucemyra prescribing information 2018)*. Meta-analyses have found that although lofexidine reduces withdrawal symptoms compared to placebo, it is less effective than buprenorphine for managing opioid withdrawal in terms of withdrawal severity, withdrawal duration, and likelihood of treatment completion *(Gowing et al 2016, Gowing et al 2017)*. It is likely to be less effective than buprenorphine or methadone for opioid detoxification (*Meader 2010*).

Products for Emergency Treatment of Opioid Overdose

- The approval of Evzio auto-injector and Narcan nasal spray were based on pharmacokinetic bioequivalence studies comparing these products to a generic naloxone product, delivered SC or IM. No clinical studies were required by the FDA (*Prescribing information: Evzio 2016, Narcan 2017*).
  - The manufacturers also conducted a human factors validation study in which participants were asked to deliver a simulated dose of the drug to a mannequin without training and most demonstrated appropriate use of the device (*FDA Summary Review: Evzio 2014, Narcan nasal spray 2015*).
- Studies have suggested that IN naloxone is an effective option in the treatment of opioid overdose (*Kelly et al 2005, Kerr et al 2009, Merlin et al 2010, Robertson et al 2009, Sabzghabaee et al 2014*).

- A meta-analysis of naloxone studies found that lay administration of naloxone was associated with significantly increased odds of recovery compared with no naloxone administration (odds ratio: 8.58, 95% confidence interval [CI], 3.90 to 13.25) (*Giglio et al 2015*).
- A 2-year, non-randomized intervention study found that prescription of naloxone to patients who were prescribed long-term opioids for chronic pain was associated with a 47% decrease in opioid-related emergency visits per month after 6 months and a 63% decrease after 1 year compared to those who did not receive naloxone (*Coffin et al 2016*).

CLINICAL GUIDELINES

- The American Academy of Pediatrics (AAP), APA, American Society of Addiction Medicine (ASAM), Center for Substance Abuse Treatment (CSAT)/United States Substance Abuse and Mental Health Services Administration (SAMHSA), and the Veterans Health Administration (VHA) have published guidelines for the treatment of opioid dependence. In general, these guidelines support access to pharmacological therapy for the management of opioid dependence. Buprenorphine/naloxone combination products may be used for induction and maintenance. In pregnant women for whom buprenorphine therapy is selected, buprenorphine alone (ie, without naloxone) is recommended. Naltrexone may be considered for the prevention of relapse, although outcomes with this medication are often adversely affected by poor adherence. Extended-release injectable naltrexone may reduce, but not eliminate, some of the problems with oral naltrexone adherence. The VHA guideline recommends extended-release injectable naltrexone if opioid agonist treatment is not feasible; it does not recommend for or against oral naltrexone (*CSAT 2004, CSUP 2016, Kampman 2015, Kleber et al 2006, Kraus et al 2011, VHA 2015*).
- Clinical practice guidelines from ASAM and VHA recommend against withdrawal management alone due to the high risk of relapse compared with treatment with maintenance therapy. However, opioid withdrawal can be managed with either gradually tapering doses of opioid agonists or use of alpha-2 adrenergic agonists (eg, clonidine) along with other non-narcotic medications *(Kampman 2015, VHA 2015).*
  - Using tapering doses of opioid agonists has been shown to be superior to alpha-2 adrenergic agonists in terms of retention and opioid abstinence. However, the use of non-opioid medications may be the only option available to clinicians in some healthcare settings and may also facilitate the transition of patients to opioid antagonist medications (eg, naltrexone) and help prevent subsequent relapse.
- Various organizations including the World Health Organization (WHO) and the ASAM have endorsed the availability of naloxone for patients, bystanders, and first responders for the emergency management of suspected opioid overdose. It is recommended that people who are likely to witness an overdose should have access to and be trained in the use of naloxone (*WHO 2014, Kampman 2015*).
  - According to the WHO guidelines for community management of opioid overdose, naloxone is effective when delivered by IV, IM, SC, and IN routes of administration. Persons using naloxone should select a route of administration based on the formulation available, their skills in administration, the setting, and local context.

SAFETY SUMMARY

Products for Treatment of Opioid Dependence

- Buprenorphine and buprenorphine/naloxone products are contraindicated in patients with known hypersensitivity to the active ingredients.
- Buprenorphine products have several warnings and precautions, including: Abuse potential; respiratory depression; CNS depression; unintentional pediatric exposure; neonatal opioid withdrawal; adrenal insufficiency; risk of opioid withdrawal with abrupt discontinuation of treatment; hepatitis and hepatic events; hypersensitivity reactions; precipitation of opioid withdrawal signs and symptoms; use in patients with impaired hepatic function; impairment of ability to drive or operate machinery; orthostatic hypotension; elevation of cerebrospinal fluid pressure; elevation of intracholedochal pressure; and effects in acute abdominal conditions
- Concomitant use of buprenorphine and benzodiazepines or other CNS depressants increases the risk for adverse events, including overdose, respiratory depression, and death. Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use. This additional warning was added to opioid products in February 2018 after data demonstrated an increased risk of mortality in patients receiving benzodiazepines while on opioid maintenance treatment (*Abrahamsson et al 2017, FDA Drug Safety Communication 2017*).

- The buprenorphine subcutaneous injection also has several unique warnings and precautions, including: serious harm or death could result if administered IV (boxed warning); risks associated with treatment of emergent acute pain; use in patients at risk for arrhythmia.
- In the treatment of addiction involving opioid use in pregnant women, the buprenorphine/naloxone combination product is not recommended for use (insufficient evidence); however, the buprenorphine monoproduct is a reasonable and recommended option for use.
- Similar to other opiate products, these products may increase intracholedochal pressure, increase cerebrospinal fluid pressure, and obscure diagnosis or exacerbate acute abdominal symptoms.
- These products should not be used as analgesics.
- The most common adverse reactions observed with buprenorphine and buprenorphine/naloxone products include headache, insomnia, nausea, pain, sweating, and withdrawal syndrome.
- All of the buprenorphine-containing products have an associated risk evaluation and mitigation strategy (REMS) program (*REMS@FDA 2018*).
- Lofexidine has several warnings and precautions, including: risk of hypotension, bradycardia, and syncope; risk of QT prolongation; increased risk of CNS depression with concomitant use of CNS depressant drugs; and increased risk of opioid overdose in patients who complete opioid discontinuation and resume opioid use.
- Sudden discontinuation of lofexidine can cause a marked rise in blood pressure and symptoms that include diarrhea, insomnia, anxiety, chills, hyperhidrosis, and extremity pain. Lofexidine should be discontinued by gradually reducing the dose.
- The most common adverse reactions observed with lofexidine include orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth.
- The safety of lofexidine in pregnancy has not been established.
- Naltrexone products are contraindicated in: patients receiving opioid analgesics; patients currently dependent on opioids (including those currently maintained on opioid agonists); patients in acute opioid withdrawal; individuals who have failed a naloxone challenge test or have a positive urine screen for opioids; individuals with a history of sensitivity to naltrexone or other components of the product; and individuals with acute hepatitis or liver failure (oral naltrexone only). Extended-release injectable naltrexone is contraindicated in patients with hypersensitivity to polylactide-co-glycolide (PLG), carboxymethylcellulose, or any other component of the diluent.
- Naltrexone can precipitate withdrawal if given to an opioid-dependent patient. Prior to initiating naltrexone, an opioid-free interval of 7 to 10 days is recommended for patients previously dependent on short-acting opioids; patients transitioning from buprenorphine or methadone may be vulnerable to precipitation of withdrawal symptoms for up to 2 weeks. A naloxone challenge test may be helpful to determine whether or not the patient has had a sufficient opioid-free period prior to initiating naltrexone.
- Patients may be more vulnerable to opioid overdose after discontinuation of naltrexone due to decreased opioid tolerance.
- Monitor patients on naltrexone for the development of depression or suicidality.
- Warnings unique to extended-release intramuscular naltrexone include: injection site reactions, which may be severe; eosinophilic pneumonia; hypersensitivity reactions, including anaphylaxis; use in patients with thrombocytopenia or any coagulation disorder; and interference with certain immunoassay methods of urine opioid detection.
- The most common adverse reactions observed with oral naltrexone include difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea/vomiting, low energy, joint and muscle pain, and headache. The most common adverse reactions observed with extended-release intramuscular naltrexone include hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache.
- There are no adequate and well-controlled studies of naltrexone in pregnant women; it should be used only if the potential benefit justifies the potential risk to the fetus.
- Extended-release intramuscular naltrexone has a REMS program due to the risk of severe injection site reactions (*REMS@FDA 2018*).

Products for Emergency Treatment of Opioid Overdose

- These products are contraindicated in patients with hypersensitivity to naloxone or to any of the other ingredients.
- These products carry warnings and precautions for risks of recurrent respiratory and CNS depression, limited efficacy with partial agonists or mixed agonists/antagonists (eg, buprenorphine, pentazocine), and precipitation of severe opioid withdrawal.

- Naloxone may precipitate acute withdrawal symptoms in opioid-dependent patients including anxiety, tachycardia, sweating, piloerection, yawning, sneezing, rhinorrhea, nausea, vomiting, diarrhea, increased blood pressure, and abdominal or muscle cramps. Opioid withdrawal signs and symptoms in neonates also include convulsions, excessive crying, and hyperactive reflexes.

DOSING AND ADMINISTRATION

Table 6a. Dosing and Administration for Products for Treatment of Opioid Dependence

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single Entity Agents				
Lucemyra (lofexidine)	Tablet	Oral	4 times daily at 5- to 6-hour intervals	• May be continued for up to 14 days with dosing guided by symptoms • Adjust dose for patients with hepatic or renal impairment
Naltrexone hydrochloride	Tablet	Oral	Single daily dose May also be dosed every other day or every 3 days	• Contraindicated in patients with acute hepatitis or liver failure • Use caution in patients with hepatic or renal impairment
Sublocade (buprenorphine)	Subcutaneous injection	SC	Monthly (minimum 26 days between doses)	• Can only be administered by a healthcare provider • Patients with moderate or severe hepatic impairment are not candidates for this product
Subutex (buprenorphine)	Sublingual tablets	Oral	Single daily dose	• Severe hepatic impairment: Consider reducing the starting and titration incremental dose by half and monitor for signs and symptoms of toxicity or overdose.
Vivitrol (naltrexone extended-release)	Intramuscular injection	IM	Monthly or every 4 weeks	• Can only be administered by a healthcare provider • Use caution in patients with moderate to severe renal impairment
Combination Products				
Bunavail, Suboxone, Zubsolv (buprenorphine/ naloxone)	Buccal film (Bunavail) Sublingual film (Suboxone) Sublingual tablet (Zubsolv; generics equivalent to Suboxone tablet)	Oral	Bunavail: Single daily dose (except day 1 of induction for patients dependent on heroin or other short-acting opioid products: start with an initial dose of 2.1 mg/0.3 mg and repeat at approximately 2 hours, under supervision, to a total dose of 4.2 mg/0.7 mg based on the control of acute withdrawal symptoms) Suboxone: Single daily dose (except day 1 of induction:	• These products should generally be avoided in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			titrate in buprenorphine 2 mg to 4 mg increments at approximately 2 hour intervals based on the control of acute symptoms) Sublingual tablet generics (Suboxone): Single daily dose Zubsolv: Single daily dose (except day 1 of induction: divided into 1 to 2 tablets of 1.4 mg/0.36 mg at 1.5 to 2 hour intervals)	

See the current prescribing information for full details

Table 6b. Equivalent Doses of Buprenorphine/Naloxone Combination Products[a]

Bunavail buccal film	buprenorphine/naloxone sublingual tablets and/or Suboxone sublingual film	Zubsolv sublingual tablets
-	2 mg/0.5 mg	1.4 mg/0.36 mg
2.1 mg/ 0.3 mg	4 mg/1 mg	2.9 mg/0.71 mg
4.2 mg/ 0.7 mg	8 mg/2 mg	5.7 mg/1.4 mg
6.3 mg/1 mg	12 mg/3 mg	8.6 mg/2.1 mg
	16 mg/4 mg	11.4 mg/2.9 mg

[a] Systemic exposures of buprenorphine and naloxone may differ when patients are switched from tablets to films or vice versa.

Table 7. Dosing and Administration for Products for Emergency Treatment of Opioid Overdose

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Evzio (naloxone HCl)	Auto-injector	IM/SC	• After initial dose, additional doses should be administered, using a new device, if the patient does not respond or responds and then relapses into respiratory depression. • Additional doses may be given every 2 to 3 minutes until emergency medical assistance arrives.	• The requirement for repeat doses depends upon the amount, type, and route of administration of the opioid being antagonized.
Naloxone HCl	Vials, prefilled syringe, solution cartridge	IV	*Adults:* • An initial dose may be administered IV. It may be repeated at 2 to 3 minute intervals if the desired degree of counteraction and improvement in respiratory functions are not obtained.	• IM or SC administration may be necessary if the IV route is not available. • The American Academy of Pediatrics, however, does not endorse SC or IM administration in opiate intoxication since absorption may be erratic or delayed.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Children: • The usual initial dose in children is given IV; a subsequent dose may be administered if the desired degree of clinical improvement is not obtained.	
Narcan (naloxone HCl)	Nasal spray	Intranasal	• A single spray should be administered into 1 nostril. • Additional doses should be administered, using a new nasal spray device in alternating nostrils, if the patient does not respond or responds and then relapses into respiratory depression. Additional doses may be given every 2 to 3 minutes until emergency medical assistance arrives.	

CONCLUSION

Products for Treatment of Opioid Dependence

- Buprenorphine sublingual tablets, buprenorphine/naloxone sublingual tablets, Bunavail (buprenorphine/naloxone) buccal film, Sublocade (buprenorphine) subcutaneous injection, Suboxone (buprenorphine/naloxone) sublingual film, and Zubsolv (buprenorphine/naloxone) sublingual tablets are used for the treatment of opioid dependence. Some products are indicated for maintenance treatment only, while others are indicated for both induction and maintenance.
- Buprenorphine is suggested as a first-line maintenance treatment for opioid use disorder; it may be preferred over methadone because it is safer and does not require clinic-based treatment. Buprenorphine is typically administered in a combination product with naloxone, an opioid antagonist, to discourage abuse. These agents are Schedule III controlled substances (*Strain 2018*).
- Clinical trials have demonstrated that buprenorphine/naloxone is practical and safe for use in diverse community treatment settings including primary care offices (*Amass et al 2004, Fiellin et al 2008*).
- Physicians prescribing buprenorphine for opioid dependency must undergo specialized training due to the potential for abuse and diversion. Because of these risks, buprenorphine monotherapy should be reserved for patients who are pregnant or have a documented allergy to naloxone (*DATA 2000, CSAT 2004*).
- Overall, studies have demonstrated that buprenorphine-based therapy was as effective as methadone in the management of opioid dependence (*Farre et al 2002, Gibson et al 2008, Gowing et al 2017, Johnson et al 1992, Kamien et al 2008, Meader et al 2010, Petitjean et al 2001, Soyka et al 2008, Mattick et al 2014, Strain et al 2011*).
- The most common adverse reactions observed with buprenorphine and buprenorphine/naloxone products include headache, insomnia, nausea, pain, sweating, and withdrawal syndrome. These products also have REMS criteria.
- Lofexidine is an oral central alpha-2 agonist indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation.
- Meta-analyses have found that although lofexidine reduces withdrawal symptoms compared to placebo, it is less effective than buprenorphine for managing opioid withdrawal in terms of withdrawal severity, withdrawal duration, and likelihood of treatment completion *(Gowing et al 2016, Gowing et al 2017)*. It is likely to be less effective than buprenorphine or methadone for opioid detoxification (*Meader 2010*).

- The most common adverse reactions observed with lofexidine include orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth.
- Naltrexone is an opioid antagonist. Oral naltrexone is indicated for the treatment of alcohol dependence and blockade of the effects of exogenously administered opioids. Extended-release intramuscular naltrexone is indicated for the treatment of alcohol dependence and the prevention of relapse to opioid dependence following opioid detoxification. In order to initiate naltrexone treatment, patients must be opioid-free for at least 7 to 10 days to avoid precipitation of withdrawal.
- In a meta-analysis examining the efficacy of oral naltrexone for maintenance treatment of opioid dependence, oral naltrexone was no better than placebo or no pharmacologic treatment in terms of treatment retention or use of the primary substance of abuse. Based on the results of 1 study, it was also not significantly different from buprenorphine for retention, abstinence, and side effects (*Minozzi et al 2011*). Extended-release intramuscular naltrexone has been shown to have similar efficacy to oral buprenorphine/naloxone among patients who are able to successfully initiate treatment (*Lee et al 2018, Tanum et al 2017*).
- The most common adverse reactions observed with oral naltrexone include difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea/vomiting, low energy, joint and muscle pain, and headache. The most common adverse reactions observed with extended-release intramuscular naltrexone include hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache. Extended-release intramuscular naltrexone also has a REMS program.
- The AAP, APA, ASAM, CSAT/SAMHSA, and VHA publish guidelines for the treatment of opioid dependence. These guidelines support access to pharmacological therapy for the management of opioid dependence. Buprenorphine/naloxone combination products may be used for induction and maintenance. In pregnant women for whom buprenorphine therapy is selected, buprenorphine alone (ie, without naloxone) is recommended. Naltrexone may be considered for the prevention of relapse, although outcomes with this medication are often adversely affected by poor adherence. Extended-release injectable naltrexone may reduce, but not eliminate, some of the problems with oral naltrexone adherence. The VHA guideline recommends extended-release injectable naltrexone if opioid agonist treatment is not feasible; it does not recommend for or against oral naltrexone (*CSAT 2004, CSUP 2016, Kampman et al 2015, Kleber et al 2006, Kraus et al 2011, VHA 2015).*
- Clinical practice guidelines from ASAM and VHA recommend against withdrawal management alone due to the high risk of relapse compared with treatment with maintenance therapy. However, opioid withdrawal can be managed with either gradually tapering doses of opioid agonists or use of alpha-2 adrenergic agonists (eg, clonidine) along with other non-narcotic medications. Lofexidine has not been added to practice guidelines but it likely has a similar place in therapy as clonidine *(Kampman 2015, VHA 2015).*

Products for Emergency Treatment of Opioid Overdose

- Naloxone is the standard of care to treat opioid overdose. It has been used by medical personnel for over 40 years and its use outside of the medical setting has gained traction through improvements in legislation and community-based opioid overdose prevention programs.
- Evzio (naloxone HCl) auto-injector, naloxone HCl injection, and Narcan (naloxone HCl) nasal spray are approved for treatment of known or suspected opioid overdose. Prior to the approval of Evzio and Narcan nasal spray, naloxone was only available in glass vials and ampules, which were distributed with syringes and needles for manual injection or with syringes and atomizers for off-label IN administration (*Evzio FDA Summary Review 2014*).
- Naloxone can be administered IV, IM, or SC using naloxone vials/syringes as well as IM or SC using an auto-injector device (Evzio). Although Narcan nasal spray is the first IN formulation to be FDA-approved, naloxone has historically been given IN off-label via kits containing a syringe and an atomization device. Potential advantages of IN administration of naloxone include easier disposal, no needle stick risk, and avoidance of needle anxiety. Both Evzio and Narcan nasal spray are designed for use by laypersons.
- The approval of Evzio and Narcan nasal spray were based on pharmacokinetic bioequivalence studies. No new clinical studies were required by the FDA.
- Various organizations including WHO and ASAM have endorsed the availability of naloxone for patients, bystanders, and first responders for the emergency management of suspected opioid overdose. It is recommended that people who are likely to witness an overdose should have access to and be trained in the use of naloxone (*WHO 2014, Kampman 2015*).

- According to the WHO guidelines for community management of opioid overdose, naloxone is effective when delivered by IV, IM, SC, and IN routes of administration. Persons using naloxone should select a route of administration based on the formulation available, their skills in administration, the setting, and local context.

REFERENCES

- Abrahamsson T, Berge J, Ojehagen A, Hakansson A. Benzodiazepine, z-drug and pregabalin prescriptions and mortality among patients in opioid maintenance treatment-A nation-wide register-based open cohort study. Drug Alcohol Depend. 2017;174:58-64.
- Amass L, Ling W, Freese TE, et al. Bringing buprenorphine-naloxone to community treatment providers: the NIDA clinical trials network field experience. Am J Addict. 2004;13 Suppl 1:S42-66.
- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth Ed. Arlington, VA: American Psychiatric Association; 2013:541-546.
- American Society of Addiction Medicine. Opioid Addiction 2016 Facts & Figures. http://www.asam.org/docs/default-source/advocacy/opioid-addiction-disease-facts-figures.pdf. Accessed August 14, 2018.
- Bickel WK, Amass L, Crean JP, et al. Buprenorphine dosing every one, two or three days in opioid-dependent patients. Psychopharmacology (Berl). 1999;146(2):111-118.
- Bunavail prescribing information. Biodelivery Sciences International, Inc. Raleigh, NC. February 2018.
- Buprenorphine prescribing information. Actavis Pharma, Inc. Parsippany, NJ. March 2018.
- Buprenorphine and naloxone tablet prescribing information. Actavis Pharma, Inc. Parsippany, NJ. February 2018.
- Center for Substance Abuse Treatment; Substance Abuse and Mental Health Services Administration (SAMHSA). Clinical Guidelines for the use of buprenorphine in the treatment of opioid addiction. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 04-3939. Rockville (MD): Substance Abuse and Mental Health Services Administration 2004. Available from: http://www.ncbi.nlm.nih.gov/books/NBK64245/. Accessed August 13, 2018.
- Centers for Disease Control and Prevention (CDC). Community-based opioid overdose prevention programs providing naloxone - United States, 2010. MMWR Morb Mortal Wkly Rep. 2012;61(6):101-105.
- Coffin P. Prevention of lethal opioid overdose in the community. UpToDate Web site. http://www.uptodate.com. Updated June 25, 2018. Accessed August 14, 2018.
- Coffin PO, Behar E, Rowe C, et al. Nonrandomized intervention study of naloxone coprescription for primary care patients receiving long-term opioid therapy for pain. Ann Intern Med. 2016;165(4):245-252.
- Committee on Substance Use and Prevention (CSUP). Medication-Assisted Treatment of Adolescents With Opioid Use Disorders. Pediatrics. 2016 Sep;138(3). http://pediatrics.aappublications.org/content/138/3/e20161893.long. Accessed August 13, 2018.
- Daulouède JP, Caer Y, Galland P, et al. Preference for buprenorphine/naloxone and buprenorphine among patients receiving buprenorphine maintenance therapy in France: a prospective, multicenter study. J Subst Abuse Treat. 2010;38(1):83-89.
- Doe-Simkins M, Quinn E, Xuan Z, et al. Overdose rescues by trained and untrained participants and change in opioid use among substance-using participants in overdose education and naloxone distribution programs: a retrospective cohort study. BMC Public Health. 2014;14:297.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2018. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed August 13, 2018.
- Evzio FDA Summary Review. Drugs@FDA Web site. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205787Orig1s000SumR.pdf. Accessed August 14, 2018.
- Evzio prescribing information. Kaleo, Inc. Richmond, VA. October 2016.
- Fareed A, Vayalapalli S, Casarella J, et al. Effect of buprenorphine dose on treatment outcome. J Addict Dis. 2012;31(1):8-18.
- Farré M, Mas A, Torrens M, et al. Retention rate and illicit opioid use during methadone maintenance interventions: a meta-analysis. Drug Alcohol Depend. 2002;65:283-290.
- FDA Drug Safety Communication: FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks. FDA website. Updated September 26, 2017. https://www.fda.gov/Drugs/DrugSafety/ucm575307.htm. Accessed August 14, 2018.
- FDA: Joint Meeting of Psychopharmacologic Drug Advisory Committee and Drug Safety and Risk Management Advisory Committee. Sublocade FDA Briefing Document. October 31, 2017. https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee. Accessed August 14, 2018.
- Fiellin DA, Schottenfeld RS, Cutter CJ, et al. Primary-care based buprenorphine taper vs maintenance therapy for prescription opioid dependence: a randomized clinical trial. JAMA Intern Med. 2014;174(12):1947-1954.
- Fudala PJ, Bridge TP, Herbert S, et al. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. N Engl J Med. 2003;349(10):949-958.
- Gibson A, Degemhardt L, Mattick RP, et al. Exposure to opioid maintenance treatment reduces long term mortality. Addiction. 2008; 103(3):462-468.
- Giglio RE, Li G, DiMaggio CJ. Effectiveness of bystander naloxone administration and overdose education programs: a meta-analysis. Inj Epidemiol. 2015;2(1):10.
- Gorodetzky CW, Walsh SL, Martin PR, Saxon AJ, Gullo KL, Biswas K. A phase III, randomized, multi-center, double blind, placebo controlled study of safety and efficacy of lofexidine for relief of symptoms in individuals undergoing inpatient opioid withdrawal. Drug Alcohol Depend. 2017;176:79-88. doi: 10.1016/j.drugalcdep.2017.02.020.
- Gowing L, Ali R, White JM, Mbewe D. Buprenorphine for the management of opioid withdrawal. Cochrane Database Syst Rev. 2017;2:CD002025. doi: 10.1002/14651858.CD002025.pub5.
- Gowing L, Farrell M, Ali R, White JM. Alpha$_2$-adrenergic agonists for the management of opioid withdrawal. Cochrane Database Syst Rev. 2016;(5):CD002024. doi: 10.1002/14651858.CD002024.pub5.

- Gunderson EW, Hjelmström P, Sumner M; 006 Study Investigators. Effects of a higher-bioavailability buprenorphine/naloxone sublingual tablet versus buprenorphine/naloxone film for the treatment of opioid dependence during induction and stabilization: a multicenter, randomized trial. Clin Ther. 2015;37(10):2244-2255.
- Johnson RE, Jaffe JH, Fudala PJ. A controlled trial of buprenorphine treatment for opioid dependence. JAMA. 1992;267:2750–2755.
- Kakko J, Svanborg KD, Kreek MJ, et al. One-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomized, placebo-controlled trial. Lancet. 2003;361(9358):662-668.
- Kamien J, Branstetter S, Amass L. Buprenorphine-naloxone vs methadone maintenance therapy: a randomized double-blind trial with opioid-dependent patients. Heroin Addict Relat Clin Probl. 2008;10:5-18.
- Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) national practice guideline for the use of medications in the treatment of addiction involving opioid use. J Addict Med. 2015;9(5):358-367.
- Kelly AM, Derr D, Dietze P, et al. Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. MJA. 2005; 182:24-27.
- Kerr D, Kelly AM, Dietze P, et al. Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. Addiction. 2009;104:2067-2074.
- Kleber HD, Weiss RD, Anton RF, et al. for the American Psychiatric Association Workgroup on Substance Use Disorders, Treatment of patients with substance use disorders, second edition. American Psychiatric Association. Am J Psychiatry. 2006;163(8 Suppl):5-82.
- Kraus ML, Alford DP, Kotz MM, et al. Statement of the American Society of Addiction Medicine Consensus Panel on the use of buprenorphine in office-based treatment of opioid addiction. J Addict Med. 2011;5(4):254-263.
- Law FD, Diaper AM, Melichar JK, Coulton S, Nutt DJ, Myles JS. Buprenorphine/naloxone versus methadone and lofexidine in community stabilisation and detoxification: A randomised controlled trial of low dose short-term opiate-dependent individuals. J Psychopharmacol. 2017;31(8):1046-1055. doi: 10.1177/0269881117711710.
- Lee JD, Nunes EV Jr, Novo P, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. Lancet. 2018;391(10118):309-318. doi: 10.1016/S0140-6736(17)32812-X.
- Lexicomp Online. Lexicomp Web site. 2018. http://online.lexi.com/lco/action/home. Accessed August 14, 2018.
- Ling W, Wesson D, Charuvastra C, et al. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. Arch Gen Psychiatry. 1996;53:401-407.
- Lintzeris N, Leung SY, Dunlop AJ, et al. A randomized controlled trial of sublingual buprenorphine-naloxone film versus tablets in the management of opioid dependence. Drug Alcohol Depend. 2013;131:119-126.
- Lucemyra prescribing information. US WorldMeds, LLC. Louisville, KY. May 2018.
- Mattick RP, Breen C, Kimber J, et al. Buprenorphine maintenance vs placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2014;2:CD002207.
- Meader N. A comparison of methadone, buprenorphine and alpha(2) adrenergic agonists for opioid detoxification: a mixed treatment comparison meta-analysis. Drug Alcohol Depend. 2010;108(1-2):110-114.
- Merlin MA, Saybolt M, Kapitanyan R, et al. Intranasal naloxone delivery is an alternative to intravenous naloxone for opioid overdoses. Am J Emerg Med. 2010;28(3):296-303.
- Micromedex® 2.0 [database on the Internet]. Truven Health Analytics; 2018. Available from: http://www.micromedexsolutions.com/home/dispatch. Accessed August 14, 2018.
- Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. Cochrane Database Syst Rev. 2011;(4):CD001333. doi: 10.1002/14651858.CD001333.pub4.
- Naloxone prescribing information. West-Ward Pharmaceuticals. Eatontown, NJ. March 2015.
- Naltrexone tablet prescribing information. SpecGx LLC. Webster Groves, MO. July 2017.
- Narcan Nasal Spray FDA Summary Review. Drugs@FDA Web site. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208411Orig1s000SumR.pdf. November 18, 2015. Accessed August 14, 2018.
- Narcan nasal spray prescribing information. Adapt Pharma, Inc. Radnor, PA. July 2017.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2018. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed August 13, 2018.
- Perry AE, Neilson M, Martyn-St James M, et al. Pharmacological interventions for drug-using offenders. Cochrane Database Syst Rev. 2013;12:CD010862.
- Petitijean S, Stohler R, Deglon J, et al. Double-blind randomized trial of buprenorphine and methadone in opiate dependence. Drug Alcohol Depend. 2001;62:97-104.
- Petry NM, Bickel WK, Badger GJ. A comparison of four buprenorphine dosing regimens in the treatment of opioid dependence. Clin Pharmacol Ther. 1999;66(3):306-314.
- REMS@FDA [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2018. Available at: http://www.accessdata.fda.gov/scripts/cder/rems/. Accessed August 14, 2018.
- Robertson TM, Hendey GW, Stroh G, et al. Intranasal naloxone is a viable alternative to intravenous naloxone for prehospital narcotic overdose. Prehosp Emerg Care. 2009;13(4):512-515.
- Sabzghabaee AM, Eizadi-Mood N, Yaraghi A, et al. Naloxone therapy in opioid overdose patients: intranasal or intravenous? A randomized clinical trial. Arch Med Sci. 2014;10(2):309-314.
- SAMHSA Opioid Overdose Prevention Toolkit. HHS Publication No. (SMA) 16-4742. Substance Abuse and Mental Health Services Administration Web site. 2016. http://store.samhsa.gov/shin/content//SMA16-4742/SMA16-4742.pdf. Accessed August 14, 2018.
- Schottenfeld R, Pakes J, Oliveto A, et al. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. Arch Gen Psychiatry. 1997;54:713-720.
- Schottenfeld RS, Pakes J, O'Connor P, et al. Thrice-weekly vs daily buprenorphine maintenance. Biol Psychiatry. 2000;47(12):1072-1079.

- Soyka M, Zingg C, Koller G, et al. Retention rate and substance use in methadone and buprenorphine maintenance therapy and predictors of outcome: results from a randomized study. Int J Neuropsychopharmacol. 2008;11:641-653.
- Strain E. Pharmacotherapy for opioid use disorder. UpToDate Web site. https://www.uptodate.com. Updated August 1, 2018. Accessed August 14, 2018.
- Strain EC, Harrison JA, Bigelow GE. Induction of opioid-dependent individuals onto buprenorphine and buprenorphine/naloxone soluble-films. Clin Pharmacol Ther. 2011;89(3):443-449.
- Sublocade prescribing information. Indivior, Inc. North Chesterfield, VA. March 2018.
- Suboxone film prescribing information. Indivior, Inc. North Chesterfield, VA. June 2018.
- Tanum L, Solli KK, Latif ZE, et al. Effectiveness of injectable extended-release naltrexone vs daily buprenorphine-naloxone for opioid dependence: a randomized clinical noninferiority trial. JAMA Psychiatry. 2017;74(12):1197-1205. doi: 10.1001/jamapsychiatry.2017.3206.
- Veterans Health Administration, Department of Defense. VA/DoD clinical practice guideline for the management of substance use disorders (SUD). Washington (DC): Veterans Health Administration, Department of Defense; 2015. Available at: http://www.healthquality.va.gov/Substance_Use_Disorder_SUD.asp . Accessed August 13, 2018.
- Vivitrol prescribing information. Alkermes, Inc. Waltham, MA. December 2015.
- Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a two-phase randomized controlled trial. Arch Gen Psychiatry. 2011;68(12):1238-1246.
- World Health Organization: Community management of opioid overdose. WHO Web site. 2014. http://www.who.int/substance_abuse/publications/management_opioid_overdose/en/. Accessed August 13, 2018.
- Woody GE, Poole SA, Subramaniam G, et al. Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth: a randomized trial. JAMA. 2008;300(17):2003-2011.
- Zubsolv prescribing information. Orexo US, Inc. New York, NY. February 2018.

Publication Date: August 23, 2018

Therapeutic Class Overview
Multiple Sclerosis Agents

INTRODUCTION

- Multiple Sclerosis (MS), a chronic, immune-mediated disease of the central nervous system (CNS), is the leading cause of disability in young and middle-aged people in developed areas of the world *(MS Coalition 2017)*. MS is characterized by repeated episodes of inflammation within the brain and spinal cord, resulting in injury to the myelin sheaths that surround and insulate nerves, and subsequently the nerve cell axons *(Goodin et al 2002)*. There are 4 clinical subtypes of MS:
  - Relapsing-remitting MS (RRMS), which is characterized by acute attacks followed by partial or full recovery. This is the most common form of MS, accounting for 80 to 85% of cases.
  - Secondary progressive MS (SPMS) begins as RRMS; however, the attack rate declines over time. Patients experience a gradual deterioration. Patients with RRMS for more than 10 years may transition to SPMS.
  - Primary progressive MS (PPMS) occurs in approximately 10% of patients with MS. Patients have a continuous and gradual decline in function without evidence of acute attacks.
  - Progressive relapsing MS (PRMS) patients have a continuous decline in function while experiencing occasional attacks. Only 5% of MS patients have PRMS *(Goodin et al 2002, Sanvito et al 2011, National MS Society 2014a)*.
- A more recent revision of the MS clinical course descriptions recommended that the core MS phenotype descriptions of relapsing and progressive disease be retained with some of the following modifications: (1) an important modifier of these core phenotypes is an assessment of disease activity, as defined by clinical assessment of relapse occurrence or lesion activity detected by CNS imaging; (2) the second important modifier of these phenotypes is a determination of whether progression of disability has occurred over a given time period; and (3) the prior category of PRMS can be eliminated since subjects so categorized would now be classified as PPMS patients with disease activity *(Lublin et al 2014)*.
- An estimated 2.3 million people worldwide have been diagnosed with MS. Most patients are diagnosed between the ages of 20 and 50 years, and MS is reported more frequently in women than in men *(National MS Society 2014b)*.
- Diagnosis of MS requires evidence of damage in at least 2 separate areas of the CNS, evidence of damage that occurred at 2 separate time points at least 1 month apart, and that other possible diagnoses have been ruled out. The clinically isolated syndrome (CIS) includes 1 attack and objective evidence of 1 lesion *(Polman et al 2011)*. Following CIS, the course of MS is variable. The inclusion of CIS in the spectrum of MS phenotypes with prospective follow-up of most such patients determining their subsequent disease phenotype was also recommended in the recent revision of the MS clinical course descriptions *(Lublin et al 2014)*.
- Disease-modifying therapies (DMTs) delay the development from CIS to clinically definite MS (CDMS) *(Miller et al 2012, Armoiry et al 2018)*. Evaluation includes an extensive patient history, neurological examination, laboratory tests to rule out other possible causes, magnetic resonance imaging (MRI) to evaluate for new disease and signs of more chronic damage, and lumbar puncture.
- Exacerbations, also known as flares, relapses, or attacks of MS are caused by inflammation in the CNS that leads to damage to the myelin and slows or blocks transmission of nerve impulses. An exacerbation must last at least 24 hours and be separated from a previous exacerbation by at least 30 days. Exacerbations can be mild or severe. Intravenous (IV) corticosteroids may be used to treat severe exacerbations of MS. Corticosteroids decrease acute inflammation in the CNS but do not provide any long-term benefits *(Frohman et al 2007)*.
- The approach to treating MS includes the management of symptoms, treatment of acute relapses and utilization of DMTs to reduce the frequency and severity of relapses and delay disease and disability progression *(Goodin et al 2002)*. The American Academy of Neurology (AAN) and the European Committee for Research and Treatment of Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) recently updated their guidelines on MS. Both guidelines recommend initiation of DMTs treatment early on in the patient's disease course (*Rae Grant et al 2018[b], Montalban et al 2018*). The MS Coalition, the AAN, and the Association of British Neurologists guidelines support access to the available DMTs for patients with MS. While there are no precise algorithms to determine the order

of product selection, therapy should be individualized and patients' clinical response and tolerability to medications should be monitored *(Corboy et al 2015, Goodin et al 2002, MS Coalition 2017, Scolding et al 2015)*.

- All agents in this class review are listed as Multiple Sclerosis Agents in Medispan; the exceptions are mitoxantrone (listed as an antineoplastic antibiotic) and Ampyra (dalfampridine) [listed as a potassium channel blocker].

Table 1. Medications Included Within Class Review‡

Drug	Generic Availability
Ampyra (dalfampridine)	-
Aubagio (teriflunomide)	-
Avonex (interferon β-1a)	-
Betaseron (interferon β-1b)	-
Copaxone, Glatopa† (glatiramer acetate)	✔
Extavia (interferon β-1b)	-
Gilenya (fingolimod)	-
Lemtrada (alemtuzumab)	-
mitoxantrone*	✔
Ocrevus (ocrelizumab)	-
Plegridy (peginterferon β-1a)	-
Rebif (interferon β-1a)	-
Tecfidera (dimethyl fumarate)	-
Tysabri (natalizumab)	-

*Although brand Novantrone has been discontinued, generic mitoxantrone remains available.
†Glatopa by Sandoz is an FDA-approved generic for Copaxone (glatiramer acetate); it is available in 20 mg/mL and 40 mg/mL injections. Mylan launched generic versions of the 20 mg/mL and the 40 mg/mL strengths of Copaxone on October 5, 2017.
‡As of April 30, 2018, Zinbryta (daclizumab) has been voluntarily withdrawn from the market by the manufacturer; cases of encephalitis and meningoencephalitis have been reported in patients treated with Zinbryta. All references to the drug have been removed from this document.

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Drug	Improve walking in MS‡	Relapsing forms of MS	Slow accumulation of physical disability	Decrease frequency of clinical exacerbations	First clinical episode	Progressive forms of MS
Ampyra (dalfampridine)‡	✔	-	-	-	-	-
Aubagio (teriflunomide)	-	✔	-	-	-	-
Avonex (IM interferon β-1a)	-	✔	✔	✔	✔	-
Betaseron/Extavia (interferon β-1b)	-	✔	-	✔	✔	-
Copaxone/Glatopa (glatiramer acetate)	-	✔	-	-	-	-
Gilenya (fingolimod)	-	✔	✔	✔	-	-

Drug	Improve walking in MS‡	Relapsing forms of MS	Slow accumulation of physical disability	Decrease frequency of clinical exacerbations	First clinical episode	Progressive forms of MS
Lemtrada (alemtuzumab)	-	✔ (3rd line)*	-	-	-	-
mitoxantrone	-	✔ (2nd line)	✔ (neurologic disability)	✔	-	✔ §
Ocrevus (ocrelizumab)	-	✔	-	-	-	✔ ¶
Plegridy (peginterferon β-1a)	-	✔	-	-	-	-
Rebif (interferon β-1a)	-	✔	✔	✔	-	-
Tecfidera (dimethyl fumarate)	-	✔	-	-	-	-
Tysabri (natalizumab)	-	✔ †	-	-	-	-

IM=intramuscular; SC=subcutaneous
‡Ampyra is indicated as a treatment to improve walking in patients with MS. This was demonstrated by an increase in walking speed.
*Because of its safety profile, Lemtrada should generally be reserved for patients who have had an inadequate response to 2 or more drugs indicated for the treatment of MS
†Tysabri increases the risk of Progressive Multifocal Leukoencephalopathy (PML) (a rare, but often fatal demyelinating disease of the central nervous system caused by the John Cunningham virus [JCV]). When initiating and continuing treatment with Tysabri in patients with MS, physicians should consider whether the expected benefit of Tysabri is sufficient to offset this risk. Tysabri is also indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease (CD) with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α.
§Mitoxantrone is indicated for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening RRMS (ie, patients whose neurologic status is significantly abnormal between relapses). Mitoxantrone is not indicated for the treatment of patients with PPMS. The product has additionally been approved for several cancer indications.
¶Ocrevus is approved for PPMS.

(Prescribing information: Ampyra 2017, Aubagio 2016, Avonex 2016, Betaseron 2016, Copaxone 2018, Extavia 2016, Gilenya 2017, Glatopa 2018, Lemtrada 2017, mitoxantrone 2016, Novantrone 2012, Ocrevus 2017, Plegridy 2016, Rebif 2015, Tecfidera 2017, Tysabri 2018)

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

CLINICAL EFFICACY SUMMARY

- In the management of MS, numerous clinical trials have established the safety and efficacy of the biologic response modifiers in reducing the frequency of relapses and delaying disease progression and disability.

Interferons and glatiramer acetate

- Pivotal clinical trials demonstrating efficacy in reducing the rate of relapses, burden of disease on MRI, and disability progression for the interferons and glatiramer acetate were published in the 1990's *(Jacobs et al 1996, Johnson et al, 1995, The IFNβ Multiple Sclerosis Study Group 1993, The IFNβ Multiple Sclerosis Study Group 1995)*. Long-term follow-up data for IFN β-1b show that overall survival in MS is improved *(Goodin et al 2012)*.
- Head-to-head trials have found Copaxone (glatiramer acetate), Rebif (IFNβ-1a SC), and Betaseron (IFNβ-1b) to be comparable in terms of relapse rate reduction and disease and disability progression *(PRISMS 1998, Kappos et al 2006, Mikol et al 2008, Flechter et al 2002, Cadavid et al 2009, O'Connor et al 2009)*. The results of several studies suggest that lower dose Avonex (IFNβ-1a 30 mcg IM once weekly) may be less efficacious while being more tolerable compared to higher dose Rebif (IFNβ-1a SC 3 times weekly or every other day) or glatiramer acetate *(Khan et al 2001a, Khan et al 2001b, Barbero et al 2006, Durelli et al 2002, Panitch et al 2002, Panitch et al 2005, Schwid et al 2005, Schwid et al 2007, Traboulsee et al 2008)*.
- In a meta-analysis of 5 randomized studies comparing IFNs with glatiramer acetate, there were no significant differences between IFNs and glatiramer acetate in terms of the number of patients with relapses, confirmed progression, or discontinuation due to adverse events at 24 months *(La Mantia et al 2016)*.

- At 36 months, however, evidence from a single study suggested that relapse rates were higher in the group given IFNs than in the glatiramer acetate group (risk ratio [RR] 1.40, 95% confidence interval [CI]: 1.13 to 1.74; p = 0.002).
- While MRI outcomes analysis showed that effects on newer enlargingT2- or new contrast-enhancing T1 lesions at 24 months were similar, the reduction in T2- and T1-weighted lesion volume was significantly greater in the groups given IFNs than in the glatiramer acetate groups (mean difference [MD] −0.58, 95% CI: −0.99 to −0.18; p = 0.004, and MD −0.20, 95% CI: −0.33 to −0.07; p = 0.003, respectively).

- A meta-analysis of 6 placebo-controlled trials failed to find a significant advantage of Avonex (IFNβ-1a) 30 mcg IM once weekly compared to placebo in the number of relapse-free patients after 1 year of therapy (*Freedman et al 2008*). In contrast, other studies found Avonex (IFNβ-1a) 30 mcg IM once weekly to be comparable to the other IFNβ products in terms of relapse rate reduction, disability progression, and SPMS development *(Carra et al 2008, Limmroth et al 2007, Minagara et al 2008, Rio et al 2005, Trojano et al 2003, Trojano et al 2007)*. Moreover, IFN therapy, especially the higher dose products, is associated with the production of neutralizing antibodies (NAb), which may result in decreased radiographic and clinical effectiveness of treatment *(Goodin et al 2007, Sorensen et al 2005)*. Exploratory post-hoc analyses of the PRISMS trial linked the development of NAb with reduced efficacy *(Alsop et al 2005)*. Development of NAb among patients (N = 368) randomized to receive Rebif (IFNβ-1a) 44 or 22 mcg SC 3 times weekly for 4 years was associated with higher relapse rates (adjusted relapse rate ratio, 1.41; 95% CI: 1.12 to 1.78; P=0.004), a greater number of active lesions, and percentage change in T2 lesion burden from baseline on MRI scan (p < 0.001). In a systematic review of 40 studies of MS agents including IFNβ-1a and IFNβ-1b, the primary outcome measure was the frequency of IFN NAb *(Govindappa et al 2015)*. NAb development was most frequent with IFN β-1b, followed by IFN β-1a SC, and lowest with IFN β-1a IM. Higher doses were associated with a higher rate of NAb development.
- The CombiRx trial evaluated the combination of Copaxone (glatiramer acetate) and Avonex (IFNβ-1a IM) over 3 years. The annualized relapse rate (ARR) for the combination therapy (IFNβ-1a + glatiramer) was not statistically superior to the better of the 2 single treatment arms (glatiramer) (p = 0.27). The ARRs were 0.12 for the combination therapy, 0.16 for IFNβ-1a, and 0.11 for glatiramer acetate. Glatiramer acetate performed significantly better than IFNβ-1a, reducing the risk of exacerbation by 31% (p = 0.027), and IFNβ-1a + glatiramer acetate performed significantly better than IFNβ-1a, reducing the risk of exacerbation by 25% (p = 0.022). The 3 treatment groups did not show a significant difference in disability progression over 6 months. Combination therapy was superior to either monotherapy in reducing new lesion activity and accumulation of total lesion volume *(Lublin et al 2013)*.
- It is estimated that within a few years of initiating treatment, at least 30 and 15% of patients discontinue MS biological response modifiers due to perceived lack of efficacy or side effects, respectively *(Coyle 2008, Portaccio et al 2008)*. According to several observational studies, switching patients who have failed to adequately respond to initial treatment to another first-line therapy is safe and effective *(Caon et al 2006, Zwibel 2006, Carra et al 2008)*. Patients switching to glatiramer acetate after experiencing inadequate response to IFNβ-1a therapy experienced a reduction in relapse rates and disability progression. Likewise, switching to IFNβ-1a therapy after suboptimal efficacy with glatiramer acetate increased the number of relapse-free patients in 1 study *(Carra et al 2008)*. The smallest reduction in the ARR was seen in patients who had switched from one IFNβ-1a preparation to another.
- The GALA study evaluated glatiramer acetate SC 40 mg 3 times weekly compared to placebo in 1404 patients with relapsing MS over 12 months. Results demonstrated that glatiramer acetate 40 mg 3 times weekly, compared to placebo, reduced the ARR and MRI endpoints *(Khan et al 2013)*.
- Glatiramer acetate 20 mg daily and 40 mg 3 times weekly have not been directly compared. A Phase 3 dose comparison study evaluated glatiramer acetate 20 mg and 40 mg each given daily in 1155 patients with MS. The primary endpoint, mean ARR, was similar in both groups: ARR = 0.33 (20 mg group) vs ARR = 0.35 (40 mg group). For patients from both groups who completed the entire 1-year treatment period, the mean ARR = 0.27. *(Comi et al 2011)*.
- The efficacy and safety of Plegridy (peginterferon β-1a) in adult patients with MS (N=1516) were evaluated in ADVANCE, a Phase 3, multi-center, randomized, placebo-controlled trial. Eligible adult patients had RRMS with baseline Expanded Disability Status Scale (EDSS) score ≤ 5 and 2 clinically documented relapses in the previous 3 years with at least 1 relapse in the previous 12 months. Patients were randomized to placebo or SC peginterferon β-1a 125 mcg every 2 weeks or every 4 weeks for 48 weeks. Approximately 81% of patients were treatment naïve.
  - At week 48, ARRs were significantly lower in the peginterferon β-1a every 2 week group (ARR = 0.256; p = 0.0007) and peginterferon β-1a every 4 week group (ARR = 0.288; p = 0.0114) compared to placebo (ARR = 0.397).
  - There were also significant differences between the peginterferon β-1a every 2 weeks and every 4 weeks groups compared to placebo in the proportion of patients with relapse at week 48 (p = 0.0003 and p = 0.02, respectively). The proportions of patients with 12 weeks of sustained disability progression at the end of the 48 week study period

was significantly lower in the peginterferon β-1a groups (both 6.8%; p = 0.0383 for every 2 weeks group; p = 0.038 for every 4 weeks group) compared to placebo (10.5%).
  - The mean number of new or newly enlarging T2 hyperintense lesions on MRI were significantly reduced in the peginterferon β-1a every 2 weeks group compared to placebo (3.6 lesions vs 10.9 lesions, respectively; p < 0.0001). Significant beneficial effects on the mean number of Gadolinium (Gd)-enhancing lesions were also observed with peginterferon β-1a every 2 weeks compared to placebo (p < 0.0001).
  - During the 48 weeks of treatment, the most commonly reported adverse effects included influenza-like illness and injection site erythema. Discontinuations due to adverse effects were higher in the peginterferon β-1a groups compared to placebo *(Calabresi et al 2014b)*.
  - NAb to interferon β-1a were identified in < 1% of all groups after 1 year (peginterferon β-1a every 2 weeks, 4 patients; peginterferon β-1a every 4 weeks, 2 patients; placebo, 2 patients) *(Calabresi et al 2014b)*. Preliminary data on NAb development to peginterferon β-1a over 2 years showed < 1% for all groups *(White et al 2014)*.
- The ADVANCE study continued into a second year. Patients originally randomized to placebo were re-randomized to peginterferon β-1a (the "placebo-switch group"). Peginterferon β-1a patients were continued on their original assigned therapy. A total of 1332 patients entered the second year of the study. After 96 weeks, the ARR was significantly lower in the peginterferon β-1a every 2 weeks group (ARR 0.221; p = 0.0001 vs placebo-switch group; p = 0.0209 vs every 4 week regimen) compared to both the placebo-switch group (ARR 0.351) and the peginterferon β-1a every 4 week group (ARR 0.291). The peginterferon β-1a every 4 week group (ARR 0.291; p = NS vs placebo-switch group) was not significantly different than the placebo-switch group (ARR 0.351) after 96 weeks based on the intent-to-treat (ITT) analysis. Peginterferon β-1a every 2 weeks was also associated with a lower proportion of patients who had relapse and a lower proportion of patients who had disability progression. Mean number of new or newly enlarging T2-weight hyperintense MRI lesions over 2 years was numerically lower with the peginterferon β-1a every 2 weeks group compared to the placebo-switch group *(Calabresi et al 2014b, Kieseier et al 2015)*.

Gilenya (fingolimod)
- Gilenya (fingolimod) has been evaluated in 2 large, randomized controlled trials (RCTs) against placebo and against Avonex (IFNβ-1a IM). In FREEDOMS, a 24-month placebo-controlled trial, fingolimod (0.5 and 1.25 mg once daily) was associated with significant reductions in ARR compared to placebo (54 and 60%, respectively; p < 0.001 for both). Moreover, fingolimod was associated with reductions in disability progression and a prolonged time to first relapse compared to placebo *(Kappos et al 2010)*. In the 12-month TRANSFORMS trial, fingolimod 0.5 and 1.25 mg once daily significantly reduced ARR by 52 and 40%, respectively, compared to IFNβ-1a 30 mcg IM once weekly (p < 0.001 for both) *(Cohen et al 2010)*. In a 12-month extension of TRANSFORMS, patients initially randomized to IM IFNβ-1a were switched to either dose of fingolimod for 12 additional months and experienced significant reductions in ARR compared to initial treatment with IM IFNβ-1a. Patients switched from IFNβ-1a to fingolimod experienced fewer adverse events compared to treatment with IFNβ-1a in the core study (86 vs 91% and 91 vs 94% for the 0.5 and 1.25 mg groups, respectively; p values not reported). Fewer patients continuing fingolimod from the core study reported adverse events in the extension period compared to the core study (72 vs 86% and 71 vs 90% for the 0.5 and 1.25 mg doses, respectively; p values not reported) *(Khatri et al 2011)*. The TRANSFORMS extension study followed patients for up to 4.5 years with results consistent with those observed in the first 12 months of the extension study; however, there was significant attrition bias with very few patients enrolled past 36 months *(Cohen et al 2015)*.
- In the FREEDOMS II study, a 24-month placebo-controlled study, fingolimod (0.5 mg and 1.25 mg) significantly reduced ARR compared to placebo (48 and 50%, respectively; both p < 0.0001) *(Calabresi et al 2014a)*. Mean percentage brain volume change was lower with both fingolimod doses compared to placebo. Fingolimod did not show a significant effect on time to disability progression at 3 months compared to placebo.

Aubagio (teriflunomide)
- Efficacy and safety of Aubagio were evaluated in two Phase 3, randomized, double-blind, placebo-controlled trials – the TEMSO trial (*O'Connor et al, 2011*) and the TOWER trial *(Confavreux et al 2014)*. In the TEMSO trial, 1088 patients with relapsing MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for a total of 108 weeks. Results demonstrated that compared to placebo, teriflunomide at both doses, reduced the ARR.
- The percentage of patients with confirmed disability progression was significantly lower only in the teriflunomide 14 mg group (20.2%) compared to placebo (27.3%; p = 0.03) *(O'Connor et al 2011)*.
- Teriflunomide has demonstrated beneficial effects on MRI scans in a Phase 2, randomized, double-blind, clinical trial. A total of 179 patients with MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for 36 weeks and were

followed every 6 weeks with MRI scans during the treatment period. The teriflunomide groups had significant reductions in the average number of unique active lesions per MRI scan *(O'Connor et al 2006)*.

- In the TOWER trial, 1165 patients with relapsing MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for at least 48 weeks of therapy. The study ended 48 weeks after the last patient was randomized. Results demonstrated that, compared to placebo, teriflunomide 14 mg significantly reduced the ARR and the risk of sustained accumulation of disability *(Confavreux et al 2014)*.
- Teriflunomide and Rebif were compared in the 48-week TENERE study evaluating 324 patients with relapsing MS. The primary outcome, time to failure defined as a confirmed relapse or permanent discontinuation for any cause, was comparable for teriflunomide 7 mg and 14 mg and Rebif *(Vermersch et al 2014)*.

Tecfidera (dimethyl fumarate)

- Tecfidera (dimethyl fumarate) was evaluated in two Phase 3 studies: DEFINE and CONFIRM *(Gold et al 2012, Fox et al 2012, Xu et al 2015)*. DEFINE was a multicenter RCT that compared 2 dosing regimens of dimethyl fumarate (240 mg twice daily and 240 mg 3 times daily) to placebo in patients with RRMS. There were 1237 patients enrolled, and the trial duration was 96 weeks. Results demonstrated that, compared to placebo, treatment with both doses of dimethyl fumarate reduced the proportion of patients with a relapse within 2 years, the ARR, the number of lesions on MRI, and the proportion of patients with disability progression *(Gold et al 2012)*.
- CONFIRM was a multicenter RCT that compared 2 dosing regimens of dimethyl fumarate (240 mg twice daily and 240 mg 3 times daily) to placebo, with an additional, open-label study arm evaluating glatiramer acetate 20 mg SC daily. Glatiramer acetate was included as a reference comparator, but the study was not designed to test the superiority or non-inferiority of dimethyl fumarate vs glatiramer acetate. There were 1430 patients enrolled, and the trial duration was 96 weeks. Results of CONFIRM were similar to DEFINE, with the exception that there was no significant difference between groups in the likelihood of disability progression. The CONFIRM trial demonstrated that, compared to placebo, treatment with both doses of dimethyl fumarate reduced the proportion of patients with a relapse within 2 years, the ARR, and the number of lesions on MRI *(Fox et al 2012)*.

Tysabri (natalizumab)

- Tysabri (natalizumab) reduced the risk of experiencing at least 1 new exacerbation at 2 years and reduced the risk of experiencing progression at 2 years *(Polman et al 2006, Pucci et al 2011, Rudick et al 2006)*. The AFFIRM trial compared natalizumab to placebo in patients with MS with less than 6 months of treatment experience with any DMT. Natalizumab reduced the ARR at 1 and 2 years compared to placebo. The cumulative probability of sustained disability progression and lesion burden on MRI were significantly reduced with natalizumab compared to placebo *(Polman et al 2006)*. In the SENTINEL trial, natalizumab was compared to placebo in patients who were receiving IFNβ-1a IM 30 mcg once weekly for at least 1 year. The combination of natalizumab and IFNβ-1a IM resulted in a significant reduction in ARR at year 1 and 2 and significant reduction in cumulative probability of sustained disability progression at year 2. Lesion burden on MRI was also significantly reduced with the combination therapy. Two cases of PML were reported in the SENTINEL patient population resulting in the early termination of the trial *(Rudick et al 2006)*.

Lemtrada (alemtuzumab)

- The efficacy and safety of alemtuzumab were compared to Rebif (IFNβ-1a SC) in two randomized, Phase 3, open-label trials in patients with relapsing forms of MS – CARE-MS I and CARE-MS II (*Cohen et al 2012, Coles et al 2012)*. In the 2-year studies, patients were randomized to alemtuzumab infused for 5 consecutive days followed by a 3 consecutive day treatment course 12 months later or to Rebif (IFNβ-1a SC) 44 mcg 3 times weekly after an initial dosage titration. All patients received methylprednisolone 1 g IV for 3 consecutive days at the initiation of treatment and at month 12.
  - The CARE-MS I trial enrolled treatment-naïve patients with MS (N = 581) who were high functioning based on the requirement of a score of 3 or lower on the EDSS.
  - Patients (N = 840) enrolled in the CARE-MS II trial had experienced at least 1 relapse while on IFNβ or glatiramer acetate after at least 6 months of treatment. Patients were required to have an EDSS score of ≤ 5.
  - The co-primary endpoints for both trials were the relapse rate and the time to 6-month sustained accumulation of disability.
  - In the CARE-MS I trial, alemtuzumab reduced the risk of relapse by 55% compared to IFNβ-1a SC ($p < 0.0001$). Relapses were reported in 22% of alemtuzumab-treated patients and 40% of IFNβ-1a SC patients over 2 years. The proportion of patients having sustained accumulation of disability over 6 months was not significantly different between alemtuzumab (8%) vs IFNβ-1a SC (11%) ($p = 0.22$).

- In the CARE-MS II trial, alemtuzumab significantly reduced relapse rate and sustained accumulation of disability compared to IFNβ-1a SC. The relapse rate at 2 years was reduced by 49% with alemtuzumab ($p < 0.0001$). The percent of patients with sustained accumulation of disability confirmed over 6 months was 13% with alemtuzumab and 20% with IFNβ-1a SC, representing a 42% risk reduction with alemtuzumab ($p = 0.0084$).
- Both studies evaluated MRI outcomes, specifically the median percent change in T2 hyperintense lesion volume from baseline. Neither study found a significant difference between the 2 drugs for this measure.
- During extension studies of CARE-MS I and CARE-MS II, approximately 80% of patients previously treated with alemtuzumab did not require additional treatment during the first year *(Garnock-Jones 2014)*.

- A Cochrane review by Zhang et al (2017) that compared the efficacy, tolerability, and safety of alemtuzumab vs IFNβ-1a in the treatment of RRMS identified 3 RCTs in 1694 total patients from the CARE-MS I, CARE-MS II, and CAMMS223 studies. In the alemtuzumab 12 mg/day group, the results showed statistically significant differences in reducing relapses (RR = 0.60, 95% CI: 0.52 to 0.70); preventing disease progression (RR = 0.60, 95% CI: 0.45 to 0.79); and developing new T2 lesions on MRI (RR = 0.75, 95% CI: 0.61 to 0.93) after 24 and 36 months' follow-up, but found no statistically significant difference in the changes of EDSS score (MD = -0.35, 95% CI: -0.73 to 0.03). In the alemtuzumab 24 mg/day group, the results showed statistically significant differences in reducing relapses (RR = 0.38, 95% CI: 0.23 to 0.62); preventing disease progression (RR = 0.42, 95% CI: 0.21 to 0.84); and the changes of EDSS score (MD = -0.83, 95% CI: -1.17 to -0.49) after 36 months' follow-up. The most frequently reported adverse effects with alemtuzumab were infusion-associated reactions, infections, and autoimmune events.

Ocrevus (ocrelizumab)

- The Phase 3 clinical development program for ocrelizumab (ORCHESTRA) included 3 studies: OPERA I, OPERA II, and ORATORIO *(Hauser et al 2017[a], Montalban et al 2017)*.
  - OPERA I and OPERA II were 2 identically-designed, 96-week, Phase 3, active-controlled, double-blind, double-dummy, multi-center, parallel-group, RCTs that evaluated the efficacy and safety of ocrelizumab (600 mg administered as an IV infusion given as 2-300 mg infusions separated by 2 weeks for dose 1 and then as a single 600 mg infusion every 6 months for subsequent doses) compared with Rebif (IFNβ-1a; 44 mcg administered by SC injection 3 times per week) in 1656 patients with RMS *(Hauser et al 2017, ClinicalTrials.gov Web site, Ocrevus Formulary Submission Dossier 2017)*.
    - Across both studies, the majority of patients had not been treated with a DMT in the 2 years before screening (range: 71.4% to 75.3%); of those patients that had received a previous DMT as allowed by the protocol, most received IFN (18.0% to 21.0%) or glatiramer acetate (9.0% to 10.6%). Two patients previously treated with natalizumab for < 1 year were included, while 5 patients previously treated with fingolimod and 1 patient previously treated with dimethyl fumarate (both not within 6 months of screening) were also included.
    - Ocrelizumab achieved statistically significant reductions in the ARR vs Rebif across both trials (primary endpoint).
      - OPERA I (0.16 vs 0.29; 46% lower rate with ocrelizumab; $p < 0.001$)
      - OPERA II (0.16 vs 0.29; 47% lower rate; $p < 0.001$)
    - In pre-specified pooled analyses (secondary endpoints), the percentage of patients with disability progression confirmed at 12 weeks was statistically significantly lower with ocrelizumab vs Rebif (9.1% vs 13.6%; hazard ratio [HR] = 0.60, 95% CI: 0.45 to 0.81; $p < 0.001$). The results were similar for disability progression confirmed at 24 weeks: 6.9% vs 10.5%; HR = 0.60, 95% CI: 0.43 to 0.84; $p = 0.003$. The percentages of patients with disability improvement confirmed at 12 weeks were 20.7% in the ocrelizumab group vs 15.6% in the Rebif group (33% higher rate of improvement with ocrelizumab; $p = 0.02$).
    - The mean numbers of Gd-enhancing lesions per T1-weighted MRI scan were statistically significantly reduced with ocrelizumab vs Rebif (secondary endpoint).
      - OPERA I: 0.02 vs 0.29 (rate ratio = 0.06, 95% CI: 0.03 to 0.10; 94% lower number of lesions with ocrelizumab; $p < 0.001$)
      - OPERA II: 0.02 vs 0.42 (rate ratio = 0.05, 95% CI: 0.03 to 0.09; 95% lower number of lesions; $p < 0.001$)
    - The most common adverse events were infusion-related reactions and infections.
  - No opportunistic infections, including PML were reported in any group over the duration of either trial.
    - An imbalance of malignancies was observed with ocrelizumab; across both studies and through 96 weeks, neoplasms occurred in 0.5% (4/825) of ocrelizumab-treated patients vs 0.2% (2/826) of Rebif-treated patients.

- Among the ocrelizumab-treated patients that developed neoplasms, there were 2 cases of invasive ductal breast carcinoma, 1 case of renal-cell carcinoma, and 1 case of malignant melanoma. Rebif-treated patients with neoplasms included 1 case of mantle-cell lymphoma and 1 case of squamous-cell carcinoma in the chest.
  - Between the clinical cutoff dates of the 2 trials (April 2, 2015 [OPERA I] and May 12, 2015 [OPERA II]) and June 30, 2016, 5 additional cases of neoplasm (2 cases of breast cancer, 2 cases of basal-cell skin carcinoma, and 1 case of malignant melanoma) were observed during the OL extension phase in which all continuing patients received ocrelizumab.

- ORATORIO was an event-driven, Phase 3, double-blind, multi-center, placebo-controlled, RCT evaluating the efficacy and safety of ocrelizumab (600 mg administered by IV infusion every 6 months; given as 2-300 mg infusions 2 weeks apart for each dose) compared with placebo in 732 people with PPMS *(Montalban et al 2017, ClinicalTrials.gov Web site, Ocrevus Formulary Submission Dossier 2017)*. DB treatment was administered for a minimum of 5 doses (120 weeks) until the occurrence of ~253 events of disability progression in the trial cohort that was confirmed for at least 12 weeks.
  - The majority of patients (~88%) reported no previous use of DMTs within 2 years of trial entry. The proportion of patients with Gd-enhancing lesions was similar (27.5% in the ocrelizumab group vs 24.7% in the placebo group); however, there was an imbalance in the mean number of Gd-enhancing lesions at baseline (BL), with nearly 50% fewer lesions in the placebo group (1.21 vs 0.6) (*FDA Medical and Summary Reviews 2017*).
  - The percentages of patients with 12-week confirmed disability progression (CDP; primary endpoint) were 32.9% with ocrelizumab vs 39.3% with placebo (HR = 0.76, 95% CI: 0.59 to 0.98; relative risk reduction of 24%; p = 0.03).
  - The percentages of patients with 24-week CDP (secondary endpoint) were 29.6% with ocrelizumab vs 35.7% with placebo (HR=0.75, 95% CI: 0.58 to 0.98; relative risk reduction of 25%; p = 0.04).
  - Additional secondary endpoints included changes in the timed 25-foot walk, the total volume of hyperintense brain lesions on T2-weighted MRI, and brain volume loss.
    - The proportion of patients with 20% worsening of the timed 25-foot walk confirmed at 12 weeks was 49% in ocrelizumab-treated patients compared to 59% in placebo-treated patients (25% risk reduction).
    - From BL to Week 120, the total volume of hyperintense brain lesions on T2-weighted MRI decreased by 3.37% in ocrelizumab-treated patients and increased by 7.43% in placebo-treated patients (p < 0.001).
    - From Weeks 24 to 120, the percentage of brain volume loss was 0.90% with ocrelizumab vs 1.09% with placebo (p = 0.02).
  - Infusion-related reactions, upper respiratory tract infections, and oral herpes infections occurred more frequently with ocrelizumab vs placebo.
  - Neoplasms occurred in 2.3% (11/486) of patients treated with ocrelizumab vs 0.8% (2/239) of patients who received placebo. Among the ocrelizumab-treated patients that developed neoplasms, there were 4 cases of breast cancer, 3 cases of basal-cell carcinoma, and 1 case in each of the following: endometrial adenocarcinoma, anaplastic large-cell lymphoma (mainly T cells), malignant fibrous histiocytoma, and pancreatic carcinoma. In the placebo group, 1 patient developed cervical adenocarcinoma in situ and 1 patient developed basal-cell carcinoma.
    - Between the clinical cutoff date (July 24, 2015) and June 30, 2016, 2 additional cases of neoplasm (1 case of basal-cell skin carcinoma and 1 case of squamous-cell carcinoma) were detected during the open-label extension phase in which all patients received ocrelizumab.

<u>Symptomatic MS</u>

- Despite the demonstrated efficacy of DMTs, for many patients there is little evidence of their effect on quality of life (QOL) in general or symptom management in particular. Impaired mobility contributes to direct and indirect costs *(Miravelle et al 2011)*.
  - Ampyra (dalfampridine) is the only FDA-approved agent for the symptomatic treatment of impaired mobility in patients with MS. Improvement of walking ability with dalfampridine was demonstrated in two 14-week, double-blind, Phase 3, RCTs of 540 patients of all MS types. Compared to placebo, dalfampridine significantly improved the walking speed by about 25% in approximately one-third of MS patients as measured by the timed 25-foot walk (T25FW) *(Goodman et al 2009, Jensen et al 2014, Ruck et al 2014)*.
  - However, questions have been raised regarding the cost-effectiveness of dalfampridine, and whether treatment leads to a long-term clinically meaningful therapeutic benefit. To address the benefit of long-term therapy with dalfampridine, an open-label, observational study of 52 MS patients with impaired mobility was conducted. Results demonstrated that about 60% of patients were still on treatment after 9 to 12 months. Two weeks after treatment

initiation, significant ameliorations could be found for T25FW, maximum walking distance, as well as motoric and cognitive fatigue, which persisted after 9 to 12 months *(Ruck et al 2014)*.

Clinically Isolated Syndrome (CIS)

- Avonex (IFNβ-1a IM) and Betaseron (IFNβ-1b) are FDA-approved for the treatment of the first clinical episode with MRI features consistent with MS. Copaxone (glatiramer acetate) and Aubagio (teriflunomide) have evidence supporting a significant delay in the time to development of a second exacerbation, compared to placebo, in patients with an isolated demyelinating event.
- In the PRECISE trial, glatiramer acetate significantly reduced the risk of converting to a clinically definite MS diagnosis by 45% compared to placebo in patients with CIS (p = 0.005). In addition, the time for 25% of patients to convert to clinically definite MS was significantly prolonged with glatiramer acetate compared to placebo (722 vs 336 days; p = 0.0041) *(Comi et al 2009)*. In the 2 year, open-label extension phase of PRECISE, early initiation of glatiramer acetate demonstrated a 41% reduced risk of clinically definite MS compared to delayed glatiramer acetate (HR: 0.59; 95% CI: 0.44 to 0.8; p = 0.0005). Over the 2 year extension, the baseline-adjusted proportions of patients who developed clinically definite MS were 29.4% and 46.5% for the early and late initiation treatment groups (odds ratio [OR]: 0.48; 95% CI: 0.33 to 0.7; p = 0.0002) *(Comi et al 2012)*.
- A meta-analysis of randomized, double-blind, placebo-controlled trials in patients with CIS found a significantly lower risk of clinically definite MS with IFN therapy compared to placebo (p < 0.0001) *(Clerico et al 2008)*. A 10-year, multicenter, randomized clinical trial with IFNβ-1a IM demonstrated that immediate initiation of therapy in patients with CIS reduced the risk for relapses over 10 years, but it was not associated with improved disability outcomes compared to a control group that also initiated therapy relatively early in the disease *(Kinkel et al 2012)*. Over the 10-year study, the drop-out rate was significant. Similar results were observed with IFNβ-1b (BENEFIT study) over an 8-year observation period. Patients who received treatment early had a lower overall ARR compared to those patients who delayed treatment *(Kappos et al 2007, Edan et al 2014)*. In the first 3 years of BENEFIT, early treatment with IFNβ-1b reduced the risk for progression of disability by 40% compared to delayed treatment (16% vs 25%, respectively; HR = 0.6; 95% CI: 0.39 to 0.92; p = 0.022).
- A 2018 systematic review and network meta-analysis of RCTs was conducted to assess the potential short- and long-term benefits of treatment with IFN-β or glatiramer acetate in patients with CIS (*Armoiry et al 2018)*. The review identified 5 primary RCTs that assessed the time to clinically definite multiple sclerosis (CDMS) in patients with CIS treated with IFN-β or glatiramer acetate vs placebo. They found that all drugs reduced the time to CDMS when compared with placebo, with a pooled HR of 0.51 (95% CI: 0.44 to 0.61) and low heterogeneity, and there was no evidence that indicated that one active treatment was superior to another when compared indirectly. The authors noted that there was insufficient information to rate the risk of selection bias, 4 of the 5 studies were at high risk of performance bias, and 1 study was rated to have a high risk for attrition bias. Four of the trials had open-label extension studies performed over 5 to 10 years, all of which indicated that early DMT therapy (regardless of agent) led to an increase in time to CDMS when compared with placebo (HR = 0.64, 95% CI: 0.55 to 0.74; low heterogeneity). These results should be taken with caution; however, as all of the open-label extension arms were at a high risk for attrition bias and had large losses to follow-up noted.
- The TOPIC study enrolled 618 patients with CIS and found teriflunomide 7 and 14 mg doses reduced the risk of relapse defining clinically definite MS compared to placebo *(Miller et al 2014)*. Teriflunomide 14 mg reduced the risk of conversion to clinically definite MS by 42.6% compared to placebo (HR, 0.574; 95% CI: 0.379 to 0.869; p = 0.0087) whereas teriflunomide 7 mg reduced the conversion to clinically definite MS by 37.2% compared to placebo (HR, 0.628; 95% CI: 0.416 to 0.949; p = 0.0271).

Progressive MS

- The role of the MS biologic response modifiers in the treatment of primary or secondary progressive MS has not been determined; mitoxantrone is FDA-approved for treating some of these forms of MS, while ocrelizumab has been specifically approved for the treatment of PPMS (and relapsing forms of MS).
- Mitoxantrone was shown to reduce the clinical relapse rate and disease progression in aggressive RRMS, SPMS, and progressive-relapsing MS *(Hartung et al 2002, Krapf et al 2005)*. For MRI outcome measures, mitoxantrone was not statistically significantly different than placebo at month 12 or 24 for the total number of MRI scans with positive Gd enhancement or at month 12 for the number of lesions on T2-weighted MRI. However, the baseline MRI lesion number and characteristics were different among the groups *(Krapf et al 2005)*. In 2010, Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology evaluated all published data including cohort data

for mitoxantrone. Evaluation of efficacy found that mitoxantrone is probably effective in modestly reducing clinical attack rate, MRI activity, and disease progression. A confirmatory trial is necessary before widespread adoption of mitoxantrone for DMT for MS can be made in light of the risks of cardiotoxicity and treatment-related leukemia *(Marriott et al 2010)*.

- The results of studies with the other agents for MS have failed to consistently demonstrate a benefit in progressive forms of MS, and due to being off-label, these uses are not included in Table 2. In the PROMISE trial, glatiramer acetate was no more effective than placebo in delaying the time to accumulated disability for patients with PPMS *(Wolinsky et al 2007)*.
- Several IFN trials in this population have yielded conflicting results *(Rizvi et al 2004)*. A systematic analysis evaluated 5 clinical trials (N = 3082) of IFNβ compared to placebo in the treatment of SPMS. In 4 trials with the primary outcome of sustained disability progression at 3 or 6 months, IFNβ demonstrated no benefit. The risk ratio for sustained progression with IFNβ was 0.98 (95% CI: 0.82 to 1.16; p = 0.79); however, between-study heterogeneity was high (I^2 = 57%) *(La Mantia et al 2013)*.

Timing of DMT initiation

- A 2017 systematic review by Merkel et al (2017) evaluated the effect of high-efficacy immunotherapies (ie, fingolimod, natalizumab, alemtuzumab) at different stages of MS. Twelve publications (9 RCTs + 3 observational studies) were identified as reporting information relevant to the outcomes of early vs delayed initiation of high-efficacy DMTs for RRMS. A number of these studies suggested that earlier commencement of high-efficacy DMTs resulted in more effective control of relapse activity than their later initiation. The evidence regarding the effect of the timing of high-efficacy therapies on disability outcomes was conflicting; additional data are required to answer this question.

Decisions to discontinue DMTs in MS

- Patient with RRMS eventually progress to SPMS. Patients experience worsening disability with or without relapses. Current therapies focus on relapsing forms of MS and are not indicated for progressive MS. The decision to discontinue DMTs has not been well studied. The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review evaluating the decision dilemmas surrounding discontinuation of MS therapies in the setting of progressive disease and pregnancy *(Butler et al 2015)*. No studies directly assess continued therapy vs discontinued therapy for MS in comparable populations. Based on low strength of evidence, long-term all-cause survival is higher for treatment-naïve MS patients who did not delay starting IFNβ-1b by 2 years and used DMT for a longer duration than those who delayed therapy. Low strength evidence from 1 study reported that IFN use did not change disability progression in patients with RRMS. Most patients discontinue MS therapy after 2 or 3 years. Several observational studies have been published on the risks of relapse and rebound of disease activity following the interruption or discontinuation of natalizumab. Very little evidence is available about the benefits and risks of discontinuation of therapy for MS in women who desire pregnancy.

Meta-Analyses

- A 2017 systematic review conducted by the Institute for Clinical and Economic Review (ICER) included ocrelizumab in a comparative efficacy analysis with other DMTs used in the treatment of MS.
  - Network meta-analyses demonstrated that for the treatment of RRMS, alemtuzumab, natalizumab, and ocrelizumab (in that order) were the most effective DMTs for reducing ARRs (~70% reduction vs placebo).
  - Ocrelizumab and alemtuzumab had the greatest reductions in disability progression (53% to 58% reduction vs placebo, respectively), closely followed by natalizumab (44%).
- A systematic review that identified 28 RCTs found that the magnitude of ARR reduction varied between15 to 36% for all IFNβ products, glatiramer acetate, and teriflunomide; and from 50 to 69% for alemtuzumab, dimethyl fumarate, fingolimod, and natalizumab. The risk of 3-month disability progression was reduced by 19 to 28% with IFNβ products, glatiramer acetate, fingolimod, and teriflunomide; by 38 to 45% for pegIFNβ, dimethyl fumarate, and natalizumab; and by 68% with alemtuzumab *(Fogarty et al 2016)*.
- RCTs (n = 39) evaluating 1 of 15 treatments for MS were analyzed for benefits and acceptability in 25,113 patients with RRMS *(Tramacere et al 2015)*. Drugs included were IFNβ-1b, IFNβ-1a (IM and SC), glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, pegIFNβ-1a, azathioprine and immunoglobulins. Investigational agents, daclizumab and laquinimod, were also included. The studies had a median duration of 24 months with 60% of studies being placebo-controlled. The network meta-analysis evaluated the recurrence of relapses and disability progression.

- Relapses: Lemtrada, mitoxantrone, Tysabri, and Gilenya were reported to have greater treatment benefit compared to placebo. Over 12 months (29 studies; N = 17,897):
  - Lemtrada: RR = 0.40, 95% CI: 0.31 to 0.51; moderate quality evidence
  - mitoxantrone: RR = 0.40, 95% CI: 0.20 to 0.76; low quality evidence
  - Tysabri: RR = 0.56, 95% CI: 0.43 to 0.73; high quality evidence
  - Gilenya: RR = 0.63, 95% CI: 0.53 to 0.74; low quality evidence
  - Tecfidera: RR = 0.78, 95% CI: 0.65 to 0.93; moderate quality evidence
  - Zinbryta (no longer on the market): RR = 0.79, 95% CI: 0.61 to 1.02; moderate quality evidence
  - Copaxone: RR = 0.80, 95% CI: 0.68 to 0.93; moderate quality evidence
- Relapses over 24 months vs placebo (26 studies; N = 16,800):
  - Lemtrada: RR = 0.46, 95% CI: 0.38 to 0.55; moderate quality evidence
  - mitoxantrone: RR = 0.47, 95% CI: 0.27 to 0.81; very low quality evidence
  - Tysabri: RR = 0.56, 95% CI: 0.47 to 0.66; high quality evidence
  - Gilenya: RR = 0.72, 95% CI: 0.64 to 0.81; moderate quality evidence
- Disability worsening over 24 months vs placebo (26 studies; N = 16,800):
  - mitoxantrone: RR = 0.20, 95% CI: 0.05 to 0.84; low quality evidence
  - Lemtrada: RR = 0.35, 95% CI: 0.26 to 0.48; low quality evidence
  - Tysabri: RR = 0.64, 95% CI: 0.49 to 0.85; moderate quality evidence
- Relapses and disability worsening over 36 months were only tested in 2 studies (CombiRx and CAMMS223). Both studies had a high risk of bias.
- Acceptability: Higher rates of withdrawal due to ADVERSE EVENTs compared to placebo over 12 months were reported for Aubagio (RR = 2.24, 95% CI: 1.5 to 3.34); Plegridy (RR = 2.8, 95% CI: 1.39 to 5.64); Avonex (RR = 4.36, 95% CI: 1.98 to 9.6); Rebif (RR = 4.83, 95% CI: 2.59 to 9); and Gilenya (RR = 8.26, 95% CI: 3.25 to 20.97).
- Over 24 months, only Gilenya had a significantly higher proportion of participants who withdrew due to any ADVERSE EVENT (RR vs placebo = 1.69, 95% CI: 1.32 to 2.17).
  - mitoxantrone: RR = 9.82, 95% CI: 0.54 to 168.84
  - Tysabri: RR = 1.53, 95% CI: 0.93 to 2.53
  - Lemtrada: RR = 0.72, 95% CI: 0.32 to 1.61

- Filippini et al (2013) conducted a Cochrane review of 44 RCTs on the relative effectiveness and acceptability of DMTs and immunosuppressants in patients with either RRMS or progressive MS (N = 17,401).
  - On the basis of high quality evidence, Tysabri and Rebif were superior to all other treatments for preventing clinical relapses in the short-term (24 months) in RRMS compared to placebo (OR = 0.32, 95% CI: 0.24 to 0.43; OR = 0.45, 95% CI: 0.28 to 0.71, respectively); they were also more effective than Avonex (OR = 0.28, 95% CI: 0.22 to 0.36; OR = 0.19, 95% CI: 0.06 to 0.6, respectively).
  - Based on moderate quality evidence, Tysabri and Rebif decreased the odds of patients with RRMS having disability progression in the short-term, with an absolute reduction of 14% and 10%, respectively, vs placebo.
  - Tysabri and Betaseron were significantly more effective (OR = 0.62, 95% CI: 0.49 to 0.78; OR = 0.35, 95% CI: 0.17 to 0.7, respectively) than Avonex in reducing the number of patients with RRMS who had progression at 2 years of follow-up, and confidence in this result was graded as moderate.
  - The lack of convincing efficacy data showed that Avonex, IV immunoglobulins (IVIG), cyclophosphamide, and long-term corticosteroids have an unfavorable benefit-risk balance in RRMS.
- The Canadian Agency for Drugs and Technologies in Health (CADTH) conducted a systematic review of 30 RCTs to assess the comparative clinical- and cost-effectiveness of drug therapies for the treatment of RRMS (N,= 16,998) (*CADTH, 2013).* Results suggested that all active treatments produce statistically significant reductions in ARR compared with no treatment, and that there were clear between-treatment differences.
  - Compared with no treatment, reductions in the ARR were approximately 70% for Tysabri and Lemtrada, 50% for Gilenya or Tecfidera, and 30% for SC IFNs, Copaxone, or Aubagio.
  - Among active comparisons, ARRs were lower for Betaseron (0.69, 95% CI: 0.54 to 0.87); Rebif (0.76, 95% CI: 0.59 to 0.98); and Gilenya (0.49, 95% CI: 0.38 to 0.63) compared with Avonex. In addition, ARRs were statistically lower for Tecfidera (0.76, 95% CI: 0.62 to 0.93) compared with Copaxone.
  - Compared with placebo, all active treatments exhibited a lower risk of sustained disability progression, but results were only statistically significant for Avonex, Rebif, Tysabri, Gilenya, Aubagio, and Tecfidera; RR (95% CI) for these agents ranged from 0.59 (95% CI: 0.46 to 0.75) for Tysabri to 0.74 (95% CI: 0.57 to 0.96) for Aubagio. Between-treatment differences were less apparent.

- Among active comparisons, the risk of sustained disability progression was statistically lower for Lemtrada (0.59, 95% CI: 0.40 to 0.86) compared with Rebif, and for Betaseron (0.44, 95% CI: 0.2 to 0.80) compared with Avonex.
- Among active comparisons, MRI findings were more favorable for Lemtrada compared with Rebif, and more favorable for all 3 of Gilenya, Betaseron, and Rebif compared with Avonex. Compared with Copaxone, Tecfidera resulted in a lower mean number of T2 lesions, but the mean number of Gd-enhancing lesions was not statistically different between these 2 treatments.
- The incidence of serious ADVERSE EVENTs and treatment discontinuations did not differ significantly between treatments in the majority of trials, except for a higher incidence of treatment discontinuation for Rebif compared to placebo and Lemtrada.

- Hamidi et al (2018) conducted a systematic review and network meta-analysis of 37 studies including 26 RCTs from a recent health technology assessment (HTA) report and 11 supplemental RCTs published after the HTA. Eleven agents, including dimethyl fumarate, teriflunomide, interferon beta, peg-interferon, glatiramer acetate, natalizumab, fingolimod, and alemtuzumab were included and were compared to either placebo or any drug treatment in patients of varying treatment experience levels. Key findings from the network meta-analysis include:
  - Alemtuzumab 12 mg had the highest probability of preventing annual relapses (RR = 0.29, 95% CI: 0.23 to 0.35; high quality evidence).
  - Alemtuzumab 24 mg (RR = 0.36, 95% CI: 0.16 to 0.7; low quality evidence) and alemtuzumab 12 mg (RR = 0.40, 95% CI: 0.27 to 0.60; very low quality evidence) were the most effective against progression of disability.
  - Dimethyl fumarate 240 mg and fingolimod 0.5 mg and 1.25 mg were more effective treatments when considering annual relapse and disability progression:
    - Annual relapse:
      - Dimethyl fumarate 240 mg twice daily: RR = 0.5, 95% CI: 0.42 to 0.6; high quality evidence
      - Fingolimod 0.5 mg: RR = 0.46, 95% CI: 0.39 to 0.54; high quality evidence
      - Fingolimod 1.25 mg: RR = 0.45, 95% CI: 0.39 to 0.53; high quality evidence
    - Disability progression:
      - Dimethyl fumarate 240 mg twice daily: RR = 0.65, 95% CI: 0.49 to 0.85; high quality evidence
      - Fingolimod 0.5 mg: RR = 0.71, 95% CI: 0.55 to 0.90; high quality evidence
      - Fingolimod 1.25 mg: RR = 0.71, 95% CI: 0.56 to 0.90; high quality evidence
  - Withdrawal due to adverse events was difficult to assess due to the low quality of available evidence, however, the authors determined that:
    - Fingolimod 1.25 mg (RR = 2.21, 95% CI: 1.42 to 2.5; moderate quality evidence), and interferon beta-1a 44 µg (RR = 2.21, 95% CI: 1.29 to 3.97; low quality evidence) were associated with higher withdrawals due to adverse events when compared with other treatment options.
  - Alemtuzumab 24 mg (mean difference = -0.91; 95% CI: -1.48 to -0.40), and 12 mg (mean difference = -0.6; 95% CI: -1.02 to -0.24) were more effective than other therapies in lowering the EDSS.
  - No treatments were found to significantly increase serious adverse events; peg-interferon beta-1a was associated with more adverse events overall when compared with other medications (RR = 1.66, 95% CI: 1.21 to 2.28).
  - None of the 11 agents studied were associated with a statistically significantly higher risk of mortality when compared to placebo.

CLINICAL GUIDELINES

- The European Committee for Research and Treatment of Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) published updated guidelines in 2018 (*Montalban et al 2018*).
- The main recommendations reported were the following:
  - The entire spectrum of disease-modifying drugs should be prescribed only in centers with adequate infrastructure to provide proper monitoring of patients, comprehensive assessment, detection of side effects, and capacity to address them properly. (Consensus statement)
  - Offer IFN or glatiramer acetate to patients with CIS and abnormal MRI findings with lesions suggesting MS who do not fulfill full criteria for MS. (Strong)
  - Offer early treatment with disease-modifying drugs in patients with active RRMS, as defined by clinical relapses and/or MRI activity (active lesions: contrast-enhancing lesions; new or unequivocally enlarging T2 lesions assessed at least annually). (Strong)

- For active RRMS, choosing among the wide range of available drugs from the modestly effective to the highly effective will depend on patient characteristics and comorbidity, disease severity/activity, drug safety profile, and accessibility of the drug. (Consensus statement)
- Consider treatment with IFN in patients with active SPMS, taking into account, in discussion with the patient, the dubious efficacy, as well as safety and tolerability profile. (Weak)
- Consider treatment with mitoxantrone in patients with active SPMS, taking into account the efficacy and specifically the safety and tolerability profile of this agent. (Weak)
- Consider ocrelizumab for patients with active SPMS. (Weak)
- Consider ocrelizumab for patients with PPMS. (Weak)
- Always consult the summary of product characteristics for dosage, special warnings, and precautions of use, contraindications, and monitoring of side effects and potential harms. (Consensus statement)
- Consider combining MRI with clinical measures when evaluating disease evolution in treated patients. (Weak)
- When monitoring treatment response in patients treated with disease-modifying drugs, perform standardized reference brain MRI within 6 months of treatment onset and compare the results with those of further brain MRI, typically performed 12 months after starting treatment. Adjust the timing of both MRIs, taking into account the drug's mechanism and speed of action and disease activity, including clinical and MRI measures. (Consensus statement)
- When monitoring treatment response in patients treated with disease-modifying drugs, the measurement of new or unequivocally enlarging T2 lesions is the preferred MRI method, supplemented by Gd-enhancing lesions for monitoring treatment response. Evaluation of these parameters requires high-quality standardized MRI scans and interpretation by highly qualified readers with experience in MS. (Consensus statement)
- When monitoring treatment safety in patients treated with disease-modifying drugs, perform standard reference MRI every year in patients at low risk for PML, and more frequently (3 to 6 months) in patients at high risk for PML (JC virus positivity, natalizumab treatment duration over 18 months) and in patients at high risk for PML who switch drugs at the time the current treatment is discontinued and the new treatment is started. (Consensus statement)
- Offer a more efficacious drug to patients treated with IFN or glatiramer acetate who show evidence of disease activity, assessed as recommended above. (Strong)
- When deciding on which drug to switch to, in consultation with the patient, consider patient characteristics and comorbidities, drug safety profile, and disease severity/activity. (Consensus statement)
- When treatment with a highly efficacious drug is stopped, whether due to inefficacy or safety, consider starting another highly efficacious drug. When starting the new drug, take into account disease activity (clinical and MRI; the greater the disease activity, the greater the urgency to start new treatment), the half-life and biological activity of the previous drug, and the potential for resumed disease activity or even rebound (particularly with natalizumab). (Consensus statement)
- In treatment decisions, consider the possibility of resumed disease activity or even rebound when stopping treatment, particularly with natalizumab. (Weak)
- Consider continuing a disease-modifying drug if the patient is stable (clinically and on MRI) and shows no safety or tolerability issues. (Weak)
- Advise all women of childbearing potential that disease-modifying drugs are not licensed during pregnancy, except glatiramer acetate 20 mg/mL. (Consensus statement)
- For women planning a pregnancy, if there is a high risk for disease reactivation, consider using IFN or glatiramer acetate until pregnancy is confirmed. In some very specific (active) cases, continuing this treatment during pregnancy could also be considered. (Weak)
- For women with persistent high disease activity, it would generally be advised to delay pregnancy. For those who still decide to become pregnant or have an unplanned pregnancy, treatment with natalizumab throughout pregnancy may be considered after full discussion of potential implications; or treatment with alemtuzumab could be an alternative for planned pregnancy in very active cases provided that a 4-month interval is strictly observed from the latest infusion until conception. (Weak)

- The American Academy of Neurology (AAN) performed a systematic review that included 20 Cochrane reviews and 73 additional articles in order to assess the available evidence on initiation, switching, and stopping DMTs in patients with MS (*Rae Grant et al 2018[a]*). The results of the systematic review were used to assist in formulating updated AAN treatment guidelines (*Rae Grant et al 2018[b]*). The main recommendations were as follows:
  - Starting DMT
    - Clinicians should discuss the benefits and risks of DMTs for people with a single clinical demyelinating event with 2 or more brain lesions that have imaging characteristics consistent with MS (Level B). After discussing the risks and

benefits, clinicians should prescribe DMTs to people with a single clinical demyelinating event and 2 or more brain lesions characteristic of MS who decide they want this therapy. (Level B)
- Clinicians should offer DMTs to people with relapsing forms of MS with recent clinical relapses or MRI activity. (Level B)
- Clinicians should monitor the reproductive plans of women with MS and counsel regarding reproductive risks and use of birth control during DMT use in women of childbearing potential who have MS. (Level B)
- Clinicians should counsel men with MS on their reproductive plans regarding treatment implications before initiating treatment with teriflunomide. (Level B)
- Because of the high frequency of severe adverse events, clinicians should not prescribe mitoxantrone to people with MS unless the potential therapeutic benefits greatly outweigh the risks. (Level B)
- Clinicians should prescribe alemtuzumab, fingolimod, or natalizumab for people with highly active MS. (Level B)
- Clinicians may initiate natalizumab treatment in people with MS with positive anti-JCV antibody indices above 0.9 only when there is a reasonable chance of benefit compared with the low but serious risk of PML. (Level C)
- Clinicians should offer ocrelizumab to people with PPMS who are likely to benefit from this therapy unless there are risks of treatment that outweigh the benefits. (Level B)

○ Switching DMTs
- Clinicians should discuss switching from one DMT to another in people with MS who have been using a DMT long enough for the treatment to take full effect and are adherent to their therapy when they experience 1 or more relapses, 2 or more unequivocally new MRI-detected lesions, or increased disability on examination, over a 1-year period of using a DMT. (Level B)
- Clinicians should evaluate the degree of disease activity, adherence, adverse event profiles, and mechanism of action of DMTs when switching DMTs in people with MS with breakthrough disease activity during DMT use. (Level B)
- Clinicians should discuss a change to non-injectable or less frequently injected DMTs in people with MS who report intolerable discomfort with the injections or in those who report injection fatigue on injectable DMTs. (Level B)
- Clinicians should inquire about medication adverse events with people with MS who are taking a DMT and attempt to manage these adverse events, as appropriate (Level B). Clinicians should discuss a medication switch with people with MS for whom these adverse events negatively influence adherence. (Level B)
- Clinicians should monitor laboratory abnormalities found on requisite laboratory surveillance (as outlined in the medication's package insert) in people with MS who are using a DMT (Level B). Clinicians should discuss switching DMTs or reducing dosage or frequency (where there are data on different doses [eg, interferons, teriflunomide]) when there are persistent laboratory abnormalities. (Level B)
- Clinicians should counsel people with MS considering natalizumab, fingolimod, ocrelizumab, and dimethyl fumarate about the PML risk associated with these agents (Level B). Clinicians should discuss switching to a DMT with a lower PML risk with people with MS taking natalizumab who are or who become JCV antibody–positive, especially with an index of above 0.9 while on therapy. (Level B)
- Clinicians should counsel that new DMTs without long-term safety data have an undefined risk of malignancy and infection for people with MS starting or using new DMTs (Level B). If a patient with MS develops a malignancy while using a DMT, clinicians should promptly discuss switching to an alternate DMT, especially for people with MS using fingolimod, teriflunomide, alemtuzumab, or dimethyl fumarate (Level B). People with MS with serious infections potentially linked to their DMTs should switch DMTs (does not pertain to PML management in people with MS using DMT). (Level B)
- Clinicians should check for natalizumab antibodies in people with MS who have infusion reactions before subsequent infusions, or in people with MS who experience breakthrough disease activity with natalizumab use (Level B). Clinicians should switch DMTs in people with MS who have persistent natalizumab antibodies. (Level B)
- Physicians must counsel people with MS considering natalizumab discontinuation that there is an increased risk of MS relapse or MRI-detected disease activity within 6 months of discontinuation (Level A). Physicians and people with MS choosing to switch from natalizumab to fingolimod should initiate treatment within 8 to 12 weeks after natalizumab discontinuation (for reasons other than pregnancy or pregnancy planning) to diminish the return of disease activity. (Level B)
- Clinicians should counsel women to stop their DMT before conception for planned pregnancies unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy (Level B). Clinicians should discontinue DMTs during pregnancy if accidental exposure occurs, unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy (Level B). Clinicians

should not initiate DMTs during pregnancy unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy. (Level B)

- Stopping DMTs
  - In people with RRMS who are stable on DMT and want to discontinue therapy, clinicians should counsel people regarding the need for ongoing follow-up and periodic reevaluation of the decision to discontinue DMT (Level B). Clinicians should advocate that people with MS who are stable (that is, those with no relapses, no disability progression, and stable imaging) on DMT should continue their current DMT unless the patient and physician decide a trial off therapy is warranted. (Level B)
  - Clinicians should assess the likelihood of future relapse in individuals with SPMS by assessing patient age, disease duration, relapse history, and MRI-detected activity (eg, frequency, severity, time since most recent relapse or gadolinium-enhanced lesion) (Level B). Clinicians may advise discontinuation of DMT in people with SPMS who do not have ongoing relapses (or gadolinium enhanced lesions on MRI activity) and have not been ambulatory (EDSS 7 or greater) for at least 2 years. (Level C)
  - Clinicians should review the associated risks of continuing DMTs vs those of stopping DMTs in people with CIS using DMTs who have not been diagnosed with MS. (Level B)

- In a 2008 Disease Management Consensus Statement, the National Clinical Advisory Board of the National Multiple Sclerosis Society stated the following: *(Miller et al 2008)*
  - Initiation of treatment with an IFNβ medication or glatiramer acetate should be considered as soon as possible following a definite diagnosis of MS with active, relapsing disease, and may also be considered for selected patients with a first attack who are at high risk of MS.
  - Treatment with mitoxantrone may be considered for selected relapsing patients with worsening disease or patients with SPMS who are worsening, whether or not relapses are occurring.
- According to the 2013 Canadian recommendations for treatment of MS, treatment decisions should be based on the level of concern for the rate and severity of relapses, degree of functional impairment due to relapses and disability progression. First-line treatment recommendations for RRMS include IFNβ products and glatiramer acetate. Second-line therapies for RRMS include fingolimod and natalizumab *(Freedman et al 2013)*.
- With an increasing number of options for the treatment of RRMS, the place in therapy for an individual agent is not straightforward. Treatment decisions will likely be based on a consideration of the risks and benefits of each therapy, physician experience, patient comorbidities, and patient preferences. The 2015 AAN position statement supports access to all DMT for patients with MS. In addition, step therapy should be driven by evidence-based clinical and safety information and not just based on costs. Highly individualized treatment decisions are necessary for patients with MS according to the AAN *(Corboy et al 2015)*.
- The 2015 Association of British Neurologists state that all available DMTs are effective in reducing relapse rate and MRI lesion accumulation *(Scolding et al 2015)*. Evidence is less clear on the impact of DMT on long-term disability. Drugs are separated into 2 categories based on relative efficacy. Category 1 – moderate efficacy includes IFNs (including pegIFN), glatiramer acetate, teriflunomide, dimethyl fumarate, and fingolimod. Category 2 – high efficacy includes alemtuzumab and natalizumab – these drugs should be reserved for patients with very active MS.
- In March 2017, the MS Coalition published an update to its consensus paper on the principles and current evidence concerning the use of DMTs in MS. Major recommendations included the following:
  - Initiation of treatment with an FDA-approved DMT is recommended as soon as possible following a diagnosis of relapsing or primary progressive MS, regardless of the person's age; for individuals with a first clinical event and MRI features consistent with MS in whom other possible causes have been excluded; and for individuals with progressive MS who continue to demonstrate clinical relapses and/or demonstrate inflammatory activity.
  - Treatment with a given DMT should be continued indefinitely unless any of the following occur (in which case an alternative DMT should be considered):
    - Suboptimal treatment response as determined by the individual and his or her treating clinician
    - Intolerable side effects
    - Inadequate adherence to the treatment regimen
    - Availability of a more appropriate treatment option
  - Movement from one DMT to another should occur only for medically appropriate reasons as determined by the treating clinician and patient.
  - When evidence of additional clinical or MRI activity while on treatment suggests a sub-optimal response, an alternative regimen (eg, different mechanism of action) should be considered to optimize therapeutic benefit.

- Due to significant variability in the MS population, people with MS and their treating clinicians require access to the full range of treatment options for several reasons:
  - Different mechanisms of action allow for treatment change in the event of a sub-optimal response.
  - Potential contraindications limit options for some individuals.
  - Risk tolerance varies among people with MS and their treating clinicians.
  - Route of delivery, frequency of dosing, and side effects may affect adherence and quality of life.
  - Individual differences related to tolerability and adherence may necessitate access to different medications within the same class.
- Individuals' access to treatment should not be limited by their frequency of relapses, level of disability, or personal characteristics such as age, sex, or ethnicity.

SAFETY SUMMARY

- Warnings for IFNβ include decreased peripheral blood cell counts including leukopenia, higher rates of depression, suicide and psychotic disorders, injection site reactions, and risk of severe hepatic injury. IFNβ (Avonex, Rebif, Betaseron, Extavia, and Plegridy) is associated with influenza-like symptoms including injection site reactions, musculoskeletal pain, fatigue, and headache. All IFNβ products carry a warning for thrombotic microangiopathy including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Adverse events related to IFNβ therapy appear to be dose-related and transient.
- Glatiramer acetate is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol. Patients treated with glatiramer acetate may experience a transient, self-limited, post-injection reaction of flushing, chest pain, palpitations, tachycardia, anxiety, dyspnea, constriction of the throat, and urticaria immediately following injection. Injection site reactions including lipodystrophy and skin necrosis have been reported. Because glatiramer acetate can modify immune response, it may interfere with immune functions. In controlled studies of glatiramer acetate 20 mg/mL, the most common adverse reactions (≥ 10% and ≥ 1.5 times higher than placebo) were injection site reactions, vasodilatation, rash, dyspnea, and chest pain. In a controlled study of glatiramer acetate 40 mg/mL, the most common adverse reactions (≥ 10% and ≥ 1.5 times higher than placebo) were: injection site reactions.
- Fingolimod was originally approved with a risk evaluation and mitigation strategies program (REMS) to inform healthcare providers about the serious risks including bradyarrhythmia, atrioventricular block, infections, macular edema, respiratory effects, hepatic effects, fetal risk, increased blood pressure, basal cell carcinoma, immune system effects following discontinuation, and hypersensitivity reactions; however, the FDA lifted the REMS requirements in November 2016. Posterior Reversible Encephalopathy Syndrome (PRES) has been reported with fingolimod. Patients with pre-existing cardiac disease may poorly tolerate fingolimod and may require additional monitoring. In clinical trials, the most common adverse reactions (incidence ≥ 10% and > placebo) were headache, liver transaminase elevation, diarrhea, cough, influenza, sinusitis, back pain, abdominal pain, and pain in extremity. If a serious infection develops, consider suspending fingolimod and reassess risks and benefits prior to re-initiation. Elimination may take up to 2 months thus, monitoring for infections should continue during this time. Do not start fingolimod in patients with active acute or chronic infection until the infection is resolved. Life-threatening and fatal infections have been reported in patients taking fingolimod. Establish immunity to varicella zoster virus prior to therapy initiation. Recent safety labeling changes warn of an increased risk of cutaneous malignancies, including melanoma, in patients treated with fingolimod. Cases of PML have occurred in the postmarketing setting in patients who were treated with fingolimod for at least 2 years. A warning for PML has been added to the fingolimod labeling; at the first sign or symptom suggestive of PML, fingolimod should be withheld and an appropriate diagnostic evaluation performed. Monitoring for signs consistent with PML on MRI may be useful to allow for an early diagnosis.
- Teriflunomide is contraindicated in patients with severe hepatic impairment; patients who are pregnant, of childbearing potential, or that are not using reliable contraception; and with concurrent use of leflunomide. Labeling includes boxed warnings regarding hepatotoxicity and teratogenicity/embryolethality that occurred in animal reproduction studies in multiple animal species at plasma teriflunomide exposures similar to or lower than in humans. Other warnings include risk of leukopenia, peripheral neuropathy, severe skin reactions, and elevated blood pressure. Teriflunomide has a half-life of 4 to 5 months; therefore, use of activated charcoal or cholestyramine in an 11-day regimen upon discontinuation of teriflunomide is recommended to reduce serum levels over 2 weeks. The most common adverse reactions (≥ 10% and ≥ 2% greater than placebo) are headache, diarrhea, nausea, alopecia, and an increase in alanine aminotransferase (ALT).

- Dimethyl fumarate has no contraindications, except in patients with hypersensitivity to dimethyl fumarate or any excipients. Warnings include anaphylaxis and angioedema, PML, lymphopenia, and clinically significant cases of liver injury reported in the post-marketing setting. Consider therapy interruption if severe lymphopenia for more than 6 months occurs. Cases of PML have been reported following dimethyl fumarate therapy. Monitoring for signs consistent with PML on MRI may be useful to allow for an early diagnosis. Common adverse events (incidence ≥ 10% and ≥ 2% more than placebo) were flushing, abdominal pain, diarrhea, and nausea. Administration of non-enteric aspirin up to 325 mg given 30 minutes prior to each dose or temporary dose reduction to 120 mg twice daily may reduce flushing.
- Natalizumab has a boxed warning regarding the risk of PML. PML is an opportunistic viral infection of the brain that usually leads to death or severe disability. Due to the risk of PML, natalizumab is only available through the TOUCH® Prescribing Program which is a restricted distribution program. Natalizumab is contraindicated in patients who have or have had PML and in patients who have had a hypersensitivity reaction to natalizumab. Monitoring for signs consistent with PML on MRI may be useful to allow for an early diagnosis. Other warnings with natalizumab include hypersensitivity reactions, increased risk of Herpes encephalitis and meningitis, acute retinal necrosis, increased risk of infections (including opportunistic infections), and hepatotoxicity. The most common adverse reactions (incidence ≥ 10%) were headache, fatigue, arthralgia, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort, diarrhea (not otherwise specified), and rash.
- Mitoxantrone has boxed warnings for the risk of cardiotoxicity, risk of bone marrow suppression, and secondary leukemia. Congestive heart failure (CHF), potentially fatal, may occur either during therapy with mitoxantrone or months to years after termination of therapy. The maximum cumulative lifetime dose of mitoxantrone for MS patients should not exceed 140 mg/kg/m^2. Monitoring of cardiac function is required prior to all mitoxantrone doses.
- Alemtuzumab is contraindicated in patients with human immunodeficiency virus (HIV). The boxed warning for alemtuzumab includes autoimmunity conditions (immune thrombocytopenia and anti-glomerular basement membrane disease), serious and life-threatening infusion reactions, and the possibility of an increased risk of malignancies. Alemtuzumab is only available through a restricted distribution and REMS program which requires the member, provider, pharmacy and infusion facility to be certified by the REMS program. Approximately one-third of patients who receive alemtuzumab develop thyroid disorders. The most commonly reported adverse events reported in at least 10% of alemtuzumab-treated patients and more frequently than with IFNβ-1a were rash, headache, pyrexia, nasopharyngitis, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract infection, herpes viral infection, urticaria, pruritus, thyroid disorders, fungal infection, arthralgia, pain in extremity, back pain, diarrhea, sinusitis, oropharyngeal pain, paresthesia, dizziness, abdominal pain, flushing, and vomiting. Nearly all patients (99.9%) in clinical trials had lymphopenia following a treatment course of alemtuzumab. Alemtuzumab may also increase the risk of acute acalculous cholecystitis; in controlled clinical studies, 0.2% of alemtuzumab-treated MS patients developed acute acalculous cholecystitis, compared to 0% of patients treated with IFNβ-1a. During postmarketing use, additional cases of acute acalculous cholecystitis have been reported in alemtuzumab-treated patients. Recent updates to the safety labeling include a warning that patients taking alemtuzumab are at risk for serious infections caused by *Listeria monocytogenes*. Patients that are prescribed alemtuzumab should be counseled about this risk, and to avoid or appropriately heat any foods that may be a source of *Listeria*, such as deli meats and unpasteurized cheeses.
- The labeling of ocrelizumab does not contain any boxed warnings; however, ocrelizumab is contraindicated in patients with active hepatitis B virus (HBV) infection and in those with a history of life-threatening infusion reactions to ocrelizumab. Additional warnings for ocrelizumab concern infusion reactions, infections, and an increased risk of malignancies.
  - As of June 30, 2016, the overall incidence rate of first neoplasm among ocrelizumab-treated patients across all 3 pivotal studies and a Phase 2, dose-finding study *(Kappos et al [2011])* was 0.40 per 100 patient-years of exposure to ocrelizumab (6467 patient-years of exposure) vs 0.20 per 100 patient-years of exposure in the pooled comparator groups (2053 patient-years of exposure in groups receiving Rebif or placebo) *(Hauser et al 2017, Ocrevus Formulary Submission Dossier 2017)*.
    - Since breast cancer occurred in 6 out of 781 females treated with ocrelizumab (vs in none of 668 females treated with Rebif or placebo), the labeling of ocrelizumab additionally recommends that patients follow standard breast cancer screening guidelines.
    - In related postmarketing requirements, the FDA has asked the manufacturer to conduct a prospective, longitudinal, observational study in adult patients with RMS and PPMS exposed to ocrelizumab to determine the incidence and mortality rates of breast cancer and all malignancies. All patients enrolled in the study need to be followed for a minimum of 5 years or until death following their first exposure to ocrelizumab and the protocol must specify 2

appropriate populations to which the observed incidence and mortality rates will be compared *(FDA approval letter 2017)*.
  - No cases of PML have been reported to date in any studies of ocrelizumab (*Hauser et al 2017, McGinley et al 2017, Montalban et al 2017, Ocrevus Formulary Submission Dossier 2017*).
  - In patients with RMS, the most common adverse reactions with ocrelizumab (incidence ≥ 10% and greater than Rebif) were upper respiratory tract infections and infusion reactions. In patients with PPMS, the most common adverse reactions (incidence ≥ 10% and greater than placebo) were upper respiratory tract infections, infusion reactions, skin infections, and lower respiratory tract infections.
- Dalfampridine is contraindicated in patients with a history of seizure, moderate or severe renal impairment (CrCl ≤ 50 mL/min), and a history of hypersensitivity to dalfampridine or 4-aminopyridine. Dalfampridine can cause anaphylaxis; signs and symptoms of anaphylaxis have included respiratory compromise, urticaria, and angioedema of the throat and or tongue. Urinary tract infections (UTIs) were reported more frequently as adverse reactions in controlled studies in patients receiving dalfampridine 10 mg twice daily (12%) as compared to placebo (8%). The most common adverse events (incidence ≥ 2% and at a rate greater than the placebo rate) for dalfampridine were UTI, insomnia, dizziness, headache, nausea, asthenia, back pain, balance disorder, MS relapse, paresthesia, nasopharyngitis, constipation, dyspepsia, and pharyngolaryngeal pain.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration*

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ampyra (dalfampridine)	Tablets	Oral	Twice daily	May be taken with or without food. Tablets should only be taken whole; do not divide, crush, chew, or dissolve. In patients with mild renal impairment (CrCl 51 to 80 mL/min), dalfampridine may reach plasma levels associated with a greater risk of seizures, and the potential benefits of Ampyra should be carefully considered against the risk of seizures in these patients. Dalfampridine is contraindicated in patients with moderate or severe renal impairment (CrCl ≤ 50 mL/min). Based on animal data, dalfampridine may cause fetal harm.
Aubagio (teriflunomide)	Tablets	Oral	Once daily	May be taken with or without food. No dosage adjustment is necessary for patients with mild and moderate hepatic impairment; contraindicated in patients with severe hepatic impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Teriflunomide is contraindicated for use in pregnant women and in women of reproductive potential who are not using effective contraception because of the potential for fetal harm. Exclude pregnancy before the start of treatment with teriflunomide in females of reproductive potential and advise females of reproductive potential to use effective contraception during teriflunomide treatment and during an accelerated drug elimination procedure after teriflunomide treatment. Teriflunomide should be stopped and an accelerated drug elimination procedure used if the patient becomes pregnant. Teriflunomide is detected in human semen; to minimize any possible risk, men not wishing to father a child and their female partners should use effective contraception. Men wishing to father a child should discontinue use of teriflunomide and either undergo an accelerated elimination procedure or wait until verification that the plasma teriflunomide concentration is less than 0.02 mg/L.
Avonex (interferon β-1a)	Injection	IM	Once weekly Titration: To reduce the incidence and severity of flu-like symptoms that may occur during initiation, Avonex may be started at a dose of 7.5 mcg and the dose may be increased by 7.5 mcg each week for the next 3 weeks until the recommended dose of 30 mcg is achieved.	Following initial administration by a trained healthcare provider, Avonex may be self-administered. Rotate injection sites to minimize the likelihood of injection site reactions. Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with Avonex use.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Use caution in patients with hepatic dysfunction.
Betaseron (interferon β-1b)	Injection	SC	Every other day Titration: Generally, start at 0.0625 mg (0.25 mL) every other day, and increase over a 6-week period to 0.25 mg (1 mL) every other day.	Following initial administration by a trained healthcare provider, IFNβ-1b may be self-administered. Rotate injection sites to minimize the likelihood of injection site reactions. Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with IFNβ-1b use.
Copaxone (glatiramer acetate) [and Glatopa]	Injection	SC	20 mg once daily **OR** 40 mg 3 times per week at least 48 hours apart Note: The 2 strengths are not interchangeable.	Following initial administration by a trained healthcare provider, Glatiramer acetate may be self-administered. Areas for SC self-injection include arms, abdomen, hips, and thighs.
Extavia (interferon β-1b)	Injection	SC	Every other day Titration: Generally, start at 0.0625 mg (0.25 mL) every other day, and increase over a 6-week period to 0.25 mg (1 mL) every other day.	Following initial administration by a trained healthcare provider, IFNβ-1b may be self-administered. Rotate injection sites to minimize the likelihood of injection site reactions. Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with IFNβ-1b use.
Gilenya (fingolimod)	Capsules	Oral	Once daily Note: Patients who initiate fingolimod and those who re-initiate treatment after discontinuation for longer than 14 days require first dose monitoring (see right).	May be taken with or without food. First dose monitoring: Observe all patients for bradycardia for at least 6 hours; monitor pulse and blood pressure hourly. Electrocardiograms (ECGs) prior to dosing and at end of the observation period are required. Monitor until resolution if heart rate < 45 bpm, atrioventricular

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				(AV) block, or if lowest post-dose heart rate is at the end of the observation period. Monitor symptomatic bradycardia with ECG until resolved. Continue overnight if intervention is required; repeat first dose monitoring for second dose. Observe patients overnight if at higher risk of symptomatic bradycardia, heart block, prolonged QTc interval, or if taking drugs with known risk of torsades de pointes. Fingolimod exposure is doubled in patients with severe hepatic impairment; patients with severe hepatic impairment should be closely monitored. No dose adjustment is necessary in mild-to-moderate hepatic impairment. The blood level of some fingolimod metabolites is increased (up to 13-fold) in patients with severe renal impairment; blood levels were not assessed in patients with mild or moderate renal impairment.
Lemtrada (alemtuzumab)†	Injection	IV	**2 treatment courses** First course: 12 mg/day on 5 consecutive days Second course: 12 mg/day on 3 consecutive days 12 months after the first treatment course Important monitoring: Complete blood count with differential (prior to treatment initiation and at monthly intervals thereafter); serum creatinine levels (prior to treatment initiation and at monthly intervals thereafter); urinalysis with urine cell counts (prior to treatment initiation and at monthly intervals thereafter); and a	Infused over 4 hours for both treatment courses; patients should be observed for infusion reactions during and for at least 2 hours after each Lemtrada infusion. Vital signs should be monitored before the infusion and periodically during the infusion. Pre-medicate with corticosteroids prior to Lemtrada infusion for the first 3 days of each treatment course. Administer antiviral agents for herpetic prophylaxis starting on the first day of alemtuzumab dosing and continuing for a minimum of two months after

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			test of thyroid function, such as thyroid stimulating hormone level (prior to treatment initiation and every 3 months thereafter). Conduct baseline and yearly skin exams to monitor for melanoma.	completion of Lemtrada dosing or until CD4+ lymphocyte count is more than 200 cells/microliter, whichever occurs later. Patients should complete any necessary immunizations at least 6 weeks prior to treatment with alemtuzumab.
mitoxantrone	Injection	IV	Every 3 months Note: Left ventricular ejection fraction (LVEF) should be evaluated prior to administration of the initial dose of mitoxantrone injection (concentrate) and all subsequent doses. In addition, LVEF evaluations are recommended if signs or symptoms of congestive heart failure develop at any time during treatment with mitoxantrone. Complete blood counts, including platelets, should be monitored prior to each course of mitoxantrone and in the event that signs or symptoms of infection develop. Liver function tests should be monitored prior to each course of therapy.	For MS-related indications: 12 mg/m^2 given as a short IV infusion over 5 to 15 minutes Mitoxantrone injection (concentrate) should not be administered to MS patients with an LVEF < 50%, with a clinically significant reduction in LVEF, or to those who have received a cumulative lifetime dose of > 140 mg/m^2. Mitoxantrone generally should not be administered to MS patients with neutrophil counts less than 1500 cells/mm^3. Mitoxantrone therapy in MS patients with abnormal liver function tests is not recommended because mitoxantrone clearance is reduced by hepatic impairment and no laboratory measurement can predict drug clearance and dose adjustments. Mitoxantrone may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant.
Ocrevus (ocrelizumab)	Injection	IV	Every 6 months (24 weeks) Titration: Initial dose: 300 mg IV, followed 2 weeks later by a second 300 mg IV infusion.	Observe patients for at least 1 hour after the completion of the infusion. Dose modifications in response to infusion reactions depend on the severity. See package insert for more details.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Subsequent doses: 600 mg IV infusion every 6 months Hepatitis B virus screening is required before the first dose.	Pre-medicate with methylprednisolone (or an equivalent corticosteroid) and an antihistamine (eg, diphenhydramine) prior to each infusion. An antipyretic (eg, acetaminophen) may also be considered. Administer all necessary immunizations according to immunization guidelines at least 6 weeks prior to initiation of ocrelizumab. Women of childbearing potential should use contraception while receiving ocrelizumab and for 6 months after the last infusion of ocrelizumab.
Plegridy (peginterferon β-1a)	Injection	SC	Every 14 days Titration: Start with 63 micrograms on day 1, 94 micrograms on day 15, and 125 micrograms (full dose) on day 29	Following initial administration by a trained healthcare provider, Plegridy may be self-administered. Patients should be advised to rotate injection sites; the usual sites are the abdomen, back of the upper arm, and thigh. Analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms. Monitor for adverse reactions due to increased drug exposure in patients with severe renal impairment.
Rebif (interferon β-1a)	Injection	SC	Three times per week at least 48 hours apart Titration: Generally, the starting dose should be 20% of the prescribed dose 3 times per week, and increased over a 4-week period to the targeted recommended dose of either 22 mcg or 44 mcg injected SC 3 times per week	Following initial administration by a trained healthcare provider, Rebif may be self-administered. Patients should be advised to rotate the site of injection with each dose to minimize the likelihood of severe injection site reactions or necrosis. Decreased peripheral blood counts or elevated liver function tests may necessitate dose

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				reduction or discontinuation of Rebif administration until toxicity is resolved. Concurrent use of analgesics and/or antipyretics may help ameliorate flu-like symptoms associated with Rebif use on treatment days.
Tecfidera (dimethyl fumarate)	Capsules	Oral	Twice daily Titration: 120 mg twice daily for 7 days (initiation), then 240 mg twice daily (maintenance) Temporary dose reductions to 120 mg twice a day may be considered for individuals who do not tolerate the maintenance dose.	May be taken with or without food; must be swallowed whole. Do not crush, chew, or sprinkle capsule contents on food. The incidence of flushing may be reduced by administration of dimethyl fumarate with food. Alternatively, administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to dimethyl fumarate dosing may reduce the incidence or severity of flushing. Obtain a complete blood cell count including lymphocyte count before initiation of therapy. Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to treatment with dimethyl fumarate.
Tysabri (natalizumab)†	Injection	IV	Once a month (every 4 weeks)	Both MS and Crohn's disease indications are dosed the same: 300 mg infused over 1 hour and given every 4 weeks. Tysabri should not be administered as an IV push or bolus injection. Patients should be observed during the infusion and for 1 hour after the infusion is complete.

*See the current prescribing information for full details
†Currently available through a restricted distribution program as part of a REMS requirement.

CONCLUSION

- DMTs for MS have shown benefits in patients with RRMS such as a decreased relapse rate and a slower accumulation of brain lesions on MRI. Therefore, it is recommended that all patients with a diagnosis of definite RRMS begin DMTs *(MS Coalition 2017)*.

- IFNβ products have been shown to decrease MRI lesion activity, prevent relapses, and delay disease progression. In general, patients treated with IFNβ or glatiramer acetate can expect a 30% reduction in ARR during a 2-year period following treatment initiation with IFNβ or Copaxone (glatiramer acetate) *(MS Coalition 2017)*. Head-to-head clinical trials have found IFNβ and glatiramer acetate to be comparable in terms of efficacy. Several studies have demonstrated an improved tolerability at the cost of a decreased therapeutic response with the low dose IM IFNβ-1a compared to the higher dose SC IFNβ-1a *(Panitch et al 2002, Panitch et al 2005, Schwid et al 2005, Schwid et al 2007, Traboulsee et al 2008)*. Influenza-type symptoms, injection site reactions, headache, nausea, and musculoskeletal pain are the most frequently reported adverse events with IFNβ products including Plegridy. With IFNβ, use caution in patients with depression or other mood disorders. Peginterferon β-1a every 2 weeks has demonstrated efficacy in reducing the ARR in relapsing forms of MS compared to placebo. Potential advantages of Plegridy are less frequent administration every 2 weeks and possibly the reduced risk of NAb development. Adverse effect profile is similar among the IFNs.
- The most frequently reported adverse events with glatiramer acetate include a transient, self-limiting, post-injection systemic reaction immediately following drug administration consisting of flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, and urticaria. Glatiramer acetate does not have any known drug interactions and is not associated with an increased risk of hepatotoxicity or depression. Glatiramer acetate is generically available.
- Despite advancements in treatment, many patients fail initial biologic response modifier therapy with glatiramer acetate or IFNβ, primarily due to intolerable adverse effects or perceived inadequate efficacy *(Coyle 2008, Portaccio et al 2008)*. Clinical trials have shown that patients switching from IFNβ to glatiramer acetate therapy and vice versa, due to poor response, may achieve a significant reduction in relapse rates and a delay in disease and disability progression *(Coyle 2008, Caon et al 2006, Zwibel 2006)*. The guidelines suggest that all first-line MS biologic response modifiers should be made accessible, and the choice of initial treatment should be based on patient-specific factors *(Corboy et al 2015, MS Coalition 2017, Scolding et al 2015, Montalban et al 2018)*. Premature discontinuation rate is high among patients with MS; therefore, factors that will maximize adherence should be considered when initiating therapy. Failure with 1 agent does not necessarily predict failure to another. Therefore, patients experiencing an inadequate response or drug-induced adverse event should be switched to a different biologic response modifier *(Coyle 2008, Portaccio et al 2008)*.
- There are now 3 available oral agents: Gilenya (fingolimod), which was approved in 2010, Aubagio (teriflunomide), which was approved 2012, and Tecfidera (dimethyl fumarate), which was approved in 2013. Among other potential benefits, it is expected that the availability of oral agents may increase convenience and improve patient adherence to their drug regimen *(Sanvito et al 2011)*. The available oral drugs each have different mechanisms of action and tolerability profiles. The oral products have not been compared to one another in any head-to-head trials. Cases of PML have been reported in patients taking fingolimod and dimethyl fumarate.
- Gilenya (fingolimod) is a sphingosine 1-phosphate receptor modulator. In a trial comparing fingolimod to placebo, fingolimod-treated patients had a decreased ARR, improved MRI outcomes, and a lower likelihood of disability progression *(Kappos et al 2010)*. In a trial comparing fingolimod to IFNβ-1a IM (Avonex), fingolimod-treated patients had a decreased ARR and improved MRI outcomes, but disability progression was similar in the 2 groups *(Cohen et al, 2010)*. The adverse event profile for fingolimod includes cardiovascular risks including bradycardia. First dose administration of fingolimod requires at least 6 hours of observation with hourly monitoring of heart rate and blood pressure, and patients should have an ECG before dosing and at the end of the observation period.
  - In the postmarketing setting, third degree atrioventricular (AV) block and AV block with junctional escape have been observed. Isolated delayed events, including transient asystole and unexplained death, have occurred within 24 hours of the first dose. The relationship of these events to fingolimod is uncertain.
- Tecfidera (dimethyl fumarate) has efficacy similar to that of fingolimod; its benefit-risk profile makes it a reasonable initial or later stage DMT option for most patients with RRMS *(CADTH 2013, Wingerchuk et al 2014)*. Gastrointestinal intolerance and flushing are common side effects that may wane with time; slow titration to maintenance doses, taking the medication with food, and premedication with aspirin may reduce their severity.
- Aubagio (teriflunomide) inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme involved in de novo pyrimidine synthesis. Although its exact mechanism of action is unknown, it may involve a reduction in the number of activated lymphocytes in the CNS. Patients treated with teriflunomide in a clinical trial experienced a reduction in the ARR and improved MRI outcomes compared to placebo. Patients in the higher dose group (14 mg) also had a lower likelihood of disability progression, but this difference was not statistically significant in the lower dose group (7 mg) *(O'Connor et al, 2011)*. Teriflunomide has boxed warnings for the possibility of severe liver injury and teratogenicity. The most common adverse reactions include increases in ALT, alopecia, diarrhea, influenza, nausea, and paresthesia.
- Tysabri (natalizumab) has demonstrated very high efficacy vs placebo and although PML is a major safety concern, the overall incidence of PML has remained low (0.4%). The FDA's update to the labeled indication of Tysabri, with removal

of the statement that it is recommended for patients who have had an inadequate response to, or are unable to tolerate an alternate MS therapy, suggests that natalizumab can be considered a first-line agent in RMS, as long as the benefit of higher efficacy is sufficient to offset the risk. Natalizumab can only be obtained through a restricted distribution program.

- Lemtrada (alemtuzumab) is a second highly efficacious DMT that has demonstrated superiority in reducing relapses when compared to Rebif in both treatment-naïve and treatment-experienced patients. The convenient dosing schedule of 2 annual treatment courses is counterbalanced by the need for regular monitoring of the increased risk for autoimmunity. Lemtrada is best reserved for patients who have failed at least 2 other DMTs and are not candidates for natalizumab (*Garnock-Jones 2014*).
- Ocrevus (ocrelizumab) is a recombinant monoclonal antibody designed to selectively target CD20-positive B cells. As a humanized form of Rituxan (rituximab), ocrelizumab is expected to be less immunogenic with repeated infusions and may have a more favorable benefit-to-risk profile than Rituxan *(Sorensen et al 2016)*.
  - The approval of Ocrevus provides another DMT option to the growing armamentarium of highly effective agents indicated for the treatment of RMS. Ocrelizumab is also indicated for the treatment of PPMS, making it the first DMT with substantial evidence supporting its use in this form of MS. Although the pivotal studies of ocrelizumab were of sufficient length to assess efficacy, more long-term safety data are needed to evaluate the effects of ocrelizumab on emergent neoplasms and the risk of PML.
- Mitoxantrone is a synthetic intercalating chemotherapeutic agent. While it is approved for the treatment of RRMS, SPMS, and PRMS, cumulative dose-related cardiac toxicity and the risk for secondary leukemia markedly limit its use. Mitoxantrone is, therefore, reserved for use in patients with aggressive disease.
- While DMTs do not sufficiently address QOL in RRMS, symptomatic agents such as Ampyra (dalfampridine) can be used to complement treatment with DMTs. Although a 25% improvement in T25FW may appear marginal, it has been established that improvements in T25FW speed of ≥ 20% are meaningful to people with MS. Dalfampridine can complement DMTs, which do not address the specific symptom of walking speed. Improved walking could potentially contain some of the direct and indirect costs (eg, reduced productivity, disability, unemployment, costs of assistive devices and caregivers) associated with MS.
- With an increasing number of DMTs currently on the market and no specific MS algorithm in place to guide treatment decisions, the selection of an agent is generally based on considerations of the risks and benefits of each therapy, physician experience, patient comorbidities, and patient preferences.

REFERENCES

- Alsop JC for the PRISMS (Prevention of Relapses and Disability by Interferon β-1a Subcutaneously in Multiple Sclerosis) Study Group. Interferon β-1a in MS: results following development of neutralizing antibodies in PRISMS. *Neurology*. 2005;65:48-55.
- Armoiry X, Kan A, Melendez-Torres GJ, et al. Short- and long-term clinical outcomes of use of beta-interferon or glatiramer acetate for people with clinically isolated syndrome: a systematic review of randomised controlled trials and network meta-analysis. *J Neurol*. 2018;265(5):999-1009.
- Ampyra [package insert], Ardsley, NY: Acorda Therapeutics, Inc., September 2017.
- Aubagio [package insert], Cambridge, MA: Genzyme; November 2016.
- Avonex [package insert], Cambridge, MA: Biogen Idec.; March 2016.
- Barbero P, Bergui M, Versino E. Every-other-day interferon beta-1b vs once-weekly interferon ß-1a for multiple sclerosis (INCOMIN Trial) II: analysis of MRI responses to treatment and correlation with Nab. *Mult Scler*. 2006;12:72-6.
- Betaseron [package insert], Whippany, NJ: Bayer Healthcare Pharmaceuticals; September 2016.
- Biogen. Subject: voluntary withdrawal of zinbryta (daclizumab) in United States [letter]. March 12, 2018. https://www.zinbryta.com/content/dam/commercial/multiple-sclerosis/zinbryta/pat/en_us/pdfs/zinbryta-prescriber-letter.pdf. Accessed May 4, 2018.
- Butler M, Forte ML, Schwehr N, et al. Decisional Dilemmas in Discontinuing Prolonged Disease-Modifying Treatment for Multiple Sclerosis. Comparative Effectiveness Review No. 150. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2012-00016-I.) AHRQ Publication No. 15-EHC012-EF. Rockville, MD: Agency for Healthcare Research and Quality; April 2015. www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed May 10, 2018.
- Cadavid D, Wolansky LJ, Skurnick J, et al. Efficacy of treatment of MS with IFNβeta-1b or glatiramer acetate by monthly brain MRI in the BECOME study. *Neurology*. 2009;72(23):1976-83.
- CADTH. Management of relapsing-remitting multiple sclerosis. 2013. http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0060853/?report. Accessed May 10, 2018.
- Calabresi PA, Kieseier BC, Arnold DL, et al. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomized, phase 3, double-blind study. *Lancet Neurol*. 2014b;13:657-65.
- Calabresi PA, Radue EW, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2014a;13(6):545-56.
- Caon C, Din M, Ching W, et al. Clinical course after change of immunomodulating therapy in relapsing-remitting multiple sclerosis. *Eur J Neurol*. 2006;13:471-4.

- Carra A, Onaha P, Luetic G. Therapeutic outcome three years after switching of immunomodulatory therapies in patients with relapsing-remitting multiple sclerosis in Argentina. *Eur J Neurol*. 2008;15:386-93.
- Clerico M, Faggiano F, Palace J, et al. Recombinant interferon beta or glatiramer acetate for delaying conversion of the first demyelinating event to multiple sclerosis. *Cochrane Database Syst Rev*. 2008; (2):CD005278.
- ClinicalTrials.gov Web site. http://clinicaltrials.gov/. May 10, 2018.
- Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med*. 2010;362:402-15.
- Cohen JA, Coles AJ, Arnold DL, et al for the CARE-MS 1 investigators. Alemtuzumab versus interferon beta-1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomized controlled phase 3 trials. *Lancet*. 2012;380:1819-28.
- Cohen JA, Khatri B, Barkhof F, et al for the TRANSFORMS (TRial Assessing injectable interferon vS. FTY720 Oral in RRMS) Study Group. Long-term (up to 4.5 years) treatment with fingolimod in multiple sclerosis: results from the extension of the randomized TRANSFORMS study. *J Neurol Neurosurg Psychiatry*. 2015;0:1–8.
- Coles AJ, Twyman CL, Arnold DL, et al for the CARE-MS II investigators. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomized controlled phase 3 trial. *Lancet*. 2012;380:1829-39.
- Comi G, Cohen JA, Arnold DL, et al for the FORTE Study Group. Phase III dose-comparison study of glatiramer acetate for multiple sclerosis. *Ann Neurol*. 2011;69(1):75-82.
- Comi G, Martinelli V, Rodegher M, et al. Effects of early treatment with glatiramer acetate in patients with clinically isolated syndrome. *Mult Scler*. 2012;19(8):1074-1083.
- Comi G, Martinelli V, Rodegher M, et al. Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): a randomized, double-blind, placebo-controlled trial. *Lancet*. 2009;374(9700):1503-11.
- Confavreux C, O'Connor P, Comi G, et al for the TOWER trial group. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2014;13:247-56.
- Copaxone [package insert], Overland Park, KS: Teva Neuroscience Inc.; January 2018.
- Corboy JR, Halper J, Langer-Gould AM, et al. Position Statement: Availability of Disease Modifying Therapies (DMT) for the Treatment of Relapsing Forms of Multiple Sclerosis. 2015. https://www.aan.com/siteassets/home-page/policy-and-guidelines/policy/position-statements/availability-of-disease-modifying-therapies-dmt/diseasemodtherams_posstatement.pdf. Accessed May 10, 2018.
- Coyle PK. Switching algorithms: from one immunomodulatory agent to another. *J Neurol*. 2008; 255(Suppl 1):44-50.
- Disease-Modifying Therapies for Relapsing-Remitting and Primary-Progressive Multiple Sclerosis: Effectiveness and Value (Final Evidence Report; March 6, 2017). Prepared for the California Technology Assessment Forum by the Institute for Clinical and Economic Review (ICER). ICER Web site. https://icer-review.org/wp-content/uploads/2016/08/CTAF_MS_Final_Report_030617.pdf. Accessed May 10, 2018.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed May 7, 2018.
- Durelli L, Verdun E, Barbero P. Every-other-day interferon beta-1b vs once-weekly interferon ß-1a for multiple sclerosis: results of a 2-year prospective randomized multicentre study (INCOMIN). *Lancet*. 2002;359:1453-60.
- Edan G, Kappos L, Montalban X et al for the BENEFIT Study Group. Long-term impact of interferon beta-1b in patients with CIS: 8-year follow-up of BENEFIT. *J Neurol Neurosurg Psychiatry*. 2014;85:1183-1189.
- Extavia [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corporation.; May 2016.
- FDA Center for Drug Evaluation and Research. Approval letter for BLA 761053. FDA Web site. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/761053Orig1s000ltr.pdf. Accessed May 10, 2018.
- FDA Grants Priority Review for Genentech's OCREVUS™ (Ocrelizumab) Biologics License Application. Genentech Press Release June 27, 2016. https://www.gene.com/media/press-releases/14631/2016-06-27/fda-grants-priority-review-for-genentech. Accessed May 10, 2018.
- Filippini G, Del Giovane C, Vacchi L, et al. Immunomodulators and immunosuppressants for multiple sclerosis: a network meta-analysis. *Cochrane Database Syst Rev*. 2013, Issue 6. Art. No.: CD008933.
- Flechter S, Vardi J, Rabey JM. Comparison of glatiramer acetate (Copaxone®) and interferon β-1b (Betaseron®) in multiple sclerosis patients: an open-label 2-year follow-up. *J Neurol Sci*. 2002;197:51-5.
- Fogarty E, Schmitz S, Tubridy N, Walsh C, Barry M. Comparative efficacy of disease-modifying therapies for patients with relapsing remitting multiple sclerosis: Systematic review and network meta-analysis. *Mult Scler Relat Disord*. 2016;9:23-30.
- Fox RJ, Miller DH, Phillips T, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med*. 2012;367:1087-97.
- Freedman MS, Hughes B, Mikol DD, et al. Efficacy of disease-modifying therapies in relapsing-remitting multiple sclerosis: a systematic comparison. *Eur Neurol*. 2008;60(1):1-11.
- Freedman MS, Selchen D, Arnold DL, et al for the Canadian Multiple Sclerosis Working Group. Treatment Optimization in MS: Canadian MS Working Group Updated Recommendations. *Can J Neurol Sci*. 2013;40:307-323.
- Frohman EM, Shah A, Eggenberger E, et al. Corticosteroids for multiple sclerosis: I. Application for treating exacerbations. *Neurotherapeutics*. 2007;4(4):618–626.
- Garnock-Jones KP. Alemtuzumab: a review of its use in patients with relapsing MS. *Drugs.* 2014;74:489-504.
- Gilenya [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corporation; December 2017.
- Glatopa [package insert], Princeton, NJ: Sandoz Inc.; January 2018.
- Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med*. 2012;367:1098-107.
- Goodin DS, Frohman EM, Garmany GP. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology*. 2002;58(2):169-78.
- Goodin DS, Frohman EM, Hurwitz B. Neutralizing antibodies to interferon beta: assessment of their clinical and radiographic impact: an evidence report: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2007;68(13):977-84.
- Goodin DS, Reder AT, Ebers GC, et al. Survival in MS: A randomized cohort study 21 years after the start of the pivotal IFN β-1b trial. *Neurology*. 2012;78:1315-1322.

- Goodman AD, Brown TR, Krupp LB et al. Sustained-release oral fampridine in multiple sclerosis: a randomized, double-blind, controlled trial. *Lancet.* 2009;373:732-38.
- Govindappa K, Sathish J, Park K, et al. Development of interferon beta-neutralizing antibodies in multiple sclerosis – a systematic review and meta-analysis. *Eur J Clin Pharmacol*. 2015;71:1287-1298.
- Hamidi V, Couto E, Ringerike T, Klemp M. A multiple treatment comparison of eleven disease-modifying drugs used for multiple sclerosis. *J Clin Med Res*. 2018;10(2):88-105.
- Hartung HP, Gonsette R, Konig N, et al for the Mitoxantrone in Multiple Sclerosis Study Group (MIMS). Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomized, multicenter trial. *Lancet*. 2002;360(9350):2018-25.
- Hauser SL, Bar-Or A, Comi G, et al; OPERA I and OPERA II Clinical Investigators. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med*. 2017;376(3):221-234.
- Jacobs LD, Cookfair DL, Rudick RA, et al for The Multiple Sclerosis Collaborative Research Group (MSCRG). Intramuscular interferon ß-1a for disease progression in relapsing multiple sclerosis. *Ann Neurol*. 1996;39:285-294.
- Jensen HB, Ravnborg M, Dalgas U, et al. 4-Aminopyridine for symptomatic treatment of multiple sclerosis: a systematic review. *Ther Adv Neurol Disord.* 2014;7(2):97-113.
- Johnson KP, Brooks BR, Cohen JA, et al for the Copolymer 1 Multiple Sclerosis Study Group. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: Results of a phase III multicenter, double-blind, placebo-controlled trial. *Neurology*. 1995;45:1268-1276.
- Kappos L, Freedman MS, Polman CH, et al for the BENEFIT Study Group. Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT Study. *Lancet*. 2007;370:389-97.
- Kappos L, Li D, Calabresi PA, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. *Lancet*. 2011;378(9805):1779-87.
- Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med*. 2010;362(5):387-401.
- Kappos L, Traboulsee A, Constantinescu C. Long-term subcutaneous interferon ß-1a therapy in patients with relapsing-remitting MS. *Neurology*. 2006;67:944-53.
- Khan O, Rieckmann P, Boyko A, et al for the GALA Study Group. Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis. *Ann Neurol*. 2013;73:705-713.
- Khan OA, Tselis AC, Kamholz JA, et al. A prospective, open-label treatment trial to compare the effects of IFNβ-1a (Avonex), IFNβ-1b (Betaseron), and glatiramer acetate (Copaxone) on the relapse rate in relapsing-remitting multiple sclerosis: results after 18 months of therapy. *Mult Scler*. 2001b;7:349-53.
- Khan OA, Tselis AC, Kamholz JA. A prospective, open-label treatment trial to compare the effect of IFN β-1b (Betaseron), and glatiramer acetate (Copaxone) on the relapse rate in relapsing-remitting multiple sclerosis. *Eur J Neurol*. 2001a;8:141-8.
- Khatri B, Barkhof F, Comi G, et al. Comparison of fingolimod with interferon ß-1a in relapsing-remitting multiple sclerosis: a randomized extension of the TRANSFORMS study. *Lancet Neurol*. 2011;10(6):520-9.
- Kieseier BC, Arnold DL, Balcer LJ et al. Peginterferon beta-1a in multiple sclerosis: 2-year results from ADVANCE. *Mult Scler*. 2015;21(8):1025-35.
- Kinkel RP, Dontchev M, Kollman C, et al for the Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurological Surveillance Investigators. Association between immediate initiation of intramuscular interferon ß-1a at the time of a clinically isolated syndrome and long-term outcomes: a 10-year follow-up of the Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurological Surveillance. *Arch Neurol*. 2012;69(2):183-90.
- Krapf H, Morrissey SP, Zenker O, et al for the MIMS Study Group. Effect of mitoxantrone on MRI in progressive MS: results of the MIMS trials. *Neurology*. 2005;65(5):690-5.
- La Mantia L, Di Pietrantonj C, Rovaris M, et al. Interferons-beta versus glatiramer acetate for relapsing-remitting multiple sclerosis. *Cochrane Database Syst Rev*. 2016;11:CD009333.
- La Mantia L, Vacchi L, Rovaris M, et al. Interferon β for Secondary Progressive Multiple Sclerosis: A Systematic Review. *J Neurol Neurosurg Psychiatry*. 2013; 84(4):420-426.
- Lemtrada [package insert], Cambridge, MA: Genzyme Corporation; December 2017.
- Limmroth V, Malessa R, Zettl UK. Quality assessments in multiple sclerosis therapy (QUASIMS). *J Neurol*. 2007;254:67-77.
- Lublin FD, Cofield SS, Cutter GR, et al. Randomized study combining interferon and glatiramer acetate in multiple sclerosis. *Ann Neurol*. 2013;73:327-340.
- Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83(3):278-86.
- Marriott JJ, Miyasaki JM, Gronseth G, et al for Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Evidence report: the efficacy and safety of mitoxantrone (Novantrone) in the treatment of multiple sclerosis: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2010;74(18):1463-70.
- McGinley MP, Moss BP, Cohen JA. Safety of monoclonal antibodies for the treatment of multiple sclerosis. *Expert Opin Drug Saf*. 2017;16(1):89-100.
- Merkel B, Butzkueven H, Traboulsee AL, Havrdova E, Kalincik T. Timing of high-efficacy therapy in relapsing-remitting multiple sclerosis: A systematic review. *Autoimmun Rev*. 2017;16(6):658-665.
- Mikol DD, Barkhof F, Chang P, et al. Comparison of subcutaneous acetate in patients with relapsing multiple sclerosis (the Rebif vs Glatiramer acetate in Relapsing MS Disease [REGARD] study): a multicenter, randomized, parallel, open-label trial. *Lancet Neurol*. 2008;7:903-14.
- Miller A, Cohen B, Cohen J, et al. National Clinical Advisory Board of the National Multiple Sclerosis Society. MS Disease Management Consensus Statement. 2008. http://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/Clinical_Bulletin_Disease-Management-Consensus-Statement-(under-revision).pdf. Accessed May 10, 2018.
- Miller AE, Wolinsky JS, Kappos L, et al for the TOPIC Study Group. Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2014;13:977-86.
- Miller DH, Chard DT, Ciccarelli O. Clinically Isolated Syndromes. *Lancet Neurol*. 2012;11(2):157-69.

- Minagara A, Murray TJ. Efficacy and tolerability of intramuscular interferon ß-1a compared to subcutaneous interferon ß-1a in relapsing MS: results from PROOF. *Curr Med Res Opin*. 2008; 24(4):1049-55.
- Miravelle AA. Guidelines and best practices for appropriate use of dalfampridine in managed care populations. *Am J Manag Care.* 2011;17:S154-S160.
- Mitoxantrone [package insert], Lake Zurich, IL: Fresenius Kabi USA, LLC; October 2016.
- Montalban X, Gold R, Thompson AJ, et al. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. *Mult Scler*. 2018;24(2):96-120.
- Montalban X, Hauser SL, Kappos L, et al; ORATORIO Clinical Investigators. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med*. 2017;376(3):209-220.
- MS Coalition. The use of disease-modifying therapies in multiple sclerosis: principles and current evidence. Updated March 2017. http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed May 10, 2018.
- National Multiple Sclerosis Society, 2014a. Overview of Relapsing-remitting MS (RRMS). https://www.nationalmssociety.org/What-is-MS/Types-of-MS/Relapsing-remitting-MS. Accessed May 10, 2018.
- National Multiple Sclerosis Society, 2014b. Who Gets MS? http://www.nationalmssociety.org/What-is-MS/Who-Gets-MS. Accessed May 10, 2018.
- Novantrone [package insert], Rockland, MA: EMD Serono; March 2012.
- O'Connor P, Filippi M, Arnason B, et al. 250 mcg or 500 mcg interferon beta-1b vs 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomized, multicentre study. *Lancet Neurol*. 2009;8(10):889-97.
- O'Connor PW, Li D, Freedman MS, et al. A Phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses. *Neurology*. 2006;66:894-900.
- O'Connor P, Wolinsky JS, Confavreux C, et al for the TEMSO Trial Group. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med*. 2011;365:1293-303
- Ocrevus [dossier], South San Francisco, CA: Genentech, Inc.; 2017.
- Ocrevus [package insert], South San Francisco, CA: Genentech, Inc.; November 2017.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed May 7, 2018.
- Panitch H, Goodin D, Francis G. Benefits of high-dose, high-frequency interferon ß-1a in relapsing-remitting multiple sclerosis are sustained to 16 months: final comparative results of the EVIDENCE trial. *J Neurol Sci*. 2005;239:67-74.
- Panitch H, Goodin D, Francis G. Randomized, comparative study of interferon ß-1a treatment regimens in MS: the EVIDENCE trial. *Neurology*. 2002;59:1496-506.
- Plegridy [package insert], Cambridge, MA: Biogen Inc.; July 2016.
- Polman CH, O'Connor PW, Havrdova, et al for the AFFIRM Study Investigators. Randomized, Placebo-Controlled Trial of Natalizumab for Relapsing Multiple Sclerosis. *N Engl J Med*. 2006; 354:899-910.
- Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol*. 2011;69(2):292–302.
- Portaccio E, Zipoli V, Siracusa G, et al. Long-term adherence to interferon β therapy in relapsing-remitting multiple sclerosis. *Eur Neurol*. 2008;59:131-5.
- PRISMS Study Group. Randomized double-blind placebo-controlled study of interferon β-1a in relapsing/remitting multiple sclerosis. *Lancet*. 1998;352:1498-504.
- Pucci E, Giuliani G, Solari A, et al. Natalizumab for relapsing remitting multiple sclerosis (Review). *Cochrane Database Syst Rev*. 2011;(10):CD007621.
- Rae-Grant A, Day GS, Marrie RA, et al. Comprehensive systematic review summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018[a];90(17):789-800.
- Rae-Grant A, Day GS, Marrie RA et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis: report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. *Neurology*. 2018[b];90(17):777-88.
- Rebif [package insert], Rockland, MA: EMD Serono; November 2015.
- Rio J, Tintore M, Nos C, et al. Interferon beta in relapsing-remitting multiple sclerosis: an eight years' experience in a specialist multiple sclerosis centre. *J Neurol*. 2005;252:795-800.
- Rizvi SA, Agius MA. Current approved options for treating patients with multiple sclerosis. *Neurology*. 2004;63(12 Suppl 6):S8-14.
- Ruck T, Bittner S, Simon OJ et al. Long-term effects of dalfampridine in patients with multiple sclerosis. *J Neurol Sci.* 2014;337(1-2):18-24.
- Rudick RA, Stuart WH, Calabresi PA, et al. Natalizumab plus Interferon ß-1a for Relapsing Multiple Sclerosis. *N Engl J Med*. 2006;354:911-23.
- Sanvito L, Constantinescu CS, Gran B. Novel therapeutic approaches to autoimmune demyelinating disorders. *Curr Pharm Des*. 2011;17(29):3191-201.
- Schwid SR, Panitch HS. Full results of the evidence of interferon dose-response European North American comparative efficacy (EVIDENCE) study: a multicenter, randomized, assessor-blinded comparison of low-dose weekly vs high dose, high-frequency interferon β-1a for relapsing multiple sclerosis. *Clin Ther*. 2007;29(9):2031-48.
- Schwid SR, Thorpe J, Sharief M. Enhanced benefit of increasing interferon ß-1a dose and frequency in relapsing multiple sclerosis. The EVIDENCE study. *Arch Neurol*. 2005;62:785-92.
- Scolding N, Barnes D, Cader S, et al. Association of British Neurologists: Revised (2015) Guidelines for Prescribing Disease-Modifying Treatments in Multiple Sclerosis. http://pn.bmj.com/content/early/2015/06/20/practneurol-2015-001139. Accessed May 10, 2018.
- Sorensen PS, Blinkenberg M. The potential role for ocrelizumab in the treatment of multiple sclerosis: current evidence and future prospects. *Ther Adv Neurol Disord*. 2016;9(1):44-52.

- Sorensen PS, Deisenhammer F, Duda P, et al for the EFNS Task Force on Anti-IFN-beta Antibodies in Multiple Sclerosis. Guidelines on use of anti-IFN-beta antibody measurements in multiple sclerosis: report of an EFNS Task Force on IFN-beta antibodies in multiple sclerosis. *Eur J Neurol*. 2005;12(11):817-27.
- Tecfidera [package insert], Cambridge, MA: Biogen Idec Inc.; December 2017.
- The IFNB Multiple Sclerosis Study Group. Interferon beta-Ib is effective in relapsing-remitting - multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology*. 1993;43:655-661.
- The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. Interferon beta-Ib in the treatment of multiple sclerosis: Final outcome of the randomized controlled trial. *Neurology*. 1995;45:1277-1285.
- Traboulsee A, Sabbagh AL, Bennett R, et al. Reduction in magnetic resonance imaging T2 burden of disease in patients with relapsing-remitting sclerosis: analysis of 48-week data from the EVIDENCE (evidence of interferon dose-response: European North American comparative efficacy) study. *BMC Neurol*. 2008;8:11.
- Tramacere I, DelGiovane C, Salanti G, et al. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. *Cochrane Database Syst Rev*. 2015, Issue 9. Art. No.: CD011381.
- Trojano M, Liguori M, Paolicelli D. Interferon beta in relapsing-remitting multiple sclerosis: an independent post marketing study in southern Italy. *Mult Scler*. 2003;9:451-7.
- Trojano M, Pellegrini F, Fuiani A. New natural history of interferon-beta-treated relapsing multiple sclerosis. *Ann Neurol*. 2007;61:300-6.
- Tysabri [package insert], Cambridge, MA: Biogen Inc.; April 2018.
- Vermersch P, Czlonkowska A, Grimaldi LME, et al for the TENERE Trial Group. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomized, controlled phase 3 trial. *Mult Sclerosis Journal*. 2014;20(6):705-716.
- White JT, Kieseier BC, Newsome SD, et al. Immunogenicity with peginterferon beta-1a in patients with relapsing-remitting multiple sclerosis: 2-year data from the randomized phase 3, multicenter ADVANCE study in relapsing-remitting multiple sclerosis (EP4152). *Eur J Neurol*. 2014;21(Suppl 1):104-387 [abstract].
- Wingerchuk DM, and Carter JL. Multiple sclerosis: current and emerging disease-modifying therapies and treatment strategies. *Mayo Clin Proc*. 2014;89(2):225-240.
- Wolinsky JS, Narayana PA, O'Connor P. Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial. *Ann Neurol*. 2007;61:14-24.
- Xu Z, Zhang F, Sun F, et al. Dimethyl fumarate for multiple sclerosis. *Cochrane Database Syst Rev*. 2015, Issue 4. Art. No.: CD011076.
- Zhang J, Shi S, Zhang Y, Luo J, Xiao Y, Meng L, Yang X. Alemtuzumab versus interferon beta 1a for relapsing-remitting multiple sclerosis. *Cochrane Database Syst Rev*. 2017;11:CD010968.
- Zwibel HL. Glatiramer acetate in treatment-naïve and prior interferon b-1b-treated multiple sclerosis patients. *Acta Neurol Scand*. 2006;113:378-86.

Publication Date: July 2, 2018

Therapeutic Class Overview
Attention-Deficit/Hyperactivity Disorder (ADHD) Agents

INTRODUCTION

- Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder among children, with an estimated prevalence of up to 10% of school-age children in the United States (U.S.). It is more common in boys than girls and frequently persists into adulthood (*Feldman et al 2014*). Epidemiologic studies of adult ADHD have estimated the current prevalence to be 4.4% in the U.S. (*Bukstein 2017*).
  - In children, this chronic disorder is characterized by symptoms of hyperactivity, impulsivity, and/or inattention. These symptoms affect cognitive, academic, behavioral, emotional, and social functioning (*Krull 2017a*). Common comorbid psychiatric disorders include oppositional defiant disorder, conduct disorder, depression, anxiety disorder, and learning disabilities (*Krull 2017b*). Approximately 20% of children with ADHD develop chronic tic disorders and approximately 50% of children with chronic tics or Tourette syndrome have comorbid ADHD (*Krull 2017c*).
  - ADHD in adults is characterized by symptoms of inattention, impulsivity, and restlessness. Impairment in executive function and emotional dysregulation frequently occur. Common comorbid psychiatric disorders include mood and anxiety disorders, substance use disorder, and intermittent explosive disorder (*Bukstein 2017*).
- For children < 17 years of age, the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) diagnosis of ADHD requires ≥ 6 symptoms of hyperactivity and impulsivity or ≥ 6 symptoms of inattention. For adolescents ≥ 17 years of age and adults, ≥ 5 symptoms of hyperactivity and impulsivity or ≥ 5 symptoms of inattention are required.
  - The symptoms of hyperactivity/impulsivity or inattention must occur often; be present in more than 1 setting; persist for at least 6 months; be present before the age of 12 years; impair function in academic, social, or occupational activities; and be excessive for the developmental level of the child.
  - Other physical, situational, or mental health conditions that could account for the symptoms must be excluded.
- Treatment of ADHD may involve behavioral/psychologic interventions, medication, and/or educational interventions, alone or in combination (*Krull 2017d*).
  - For preschool children (age 4 through 5 years), behavioral therapy is considered the first-line treatment; when medication is necessary, methylphenidate is generally recommended.
  - For children and adolescents with moderate to severe ADHD, medication and behavioral therapy are recommended. In general, stimulants are the first-line agents; however, non-stimulant medications may be more appropriate for certain children.
    - About 30% of patients do not respond to or may not tolerate the initial stimulant treatment. At least one-half of children who do not respond to one type of stimulant will respond to the other. If there is still no improvement, consideration should be given to switching to or adding a non-stimulant ADHD medication (*Pharmacist's Letter 2015, Krull 2017e*).
- Multiple agents are currently approved by the Food and Drug Administration (FDA) for the treatment of ADHD. They include central nervous system (CNS) stimulants (amphetamine- and methylphenidate-based formulations), as well as non-stimulants: a selective norepinephrine reuptake inhibitor (SNRI), atomoxetine, and 2 alpha$_2$-adrenergic agonists, clonidine extended-release (ER) and guanfacine ER.
  - Due to the potential for abuse, the stimulant agents are classified as Schedule II controlled substances.
  - Several stimulants are also approved for the treatment of narcolepsy and exogenous obesity; the use of stimulants for the treatment of obesity will not be covered in this review. Lisdexamfetamine dimesylate is the only FDA-approved drug for the treatment of binge eating disorder (BED).
- Medispan Classes: ADHD Agents – Amphetamines, Dexmethylphenidate, Methylphenidate, Selective Alpha Adrenergic Agonists, Selective Norepinephrine Reuptake Inhibitor

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Stimulants	

Drug	Generic Availability
Evekeo (amphetamine sulfate)	-
Adderall (mixed amphetamine salts)	✔
Focalin (dexmethylphenidate hydrochloride [HCl])	✔
ProCentra (dextroamphetamine sulfate)	✔
Zenzedi (dextroamphetamine sulfate)	✔
Desoxyn (methamphetamine HCl)	✔
methylphenidate HCl chewable tablets	✔
Methylin Oral Solution (methylphenidate HCl)	✔
Ritalin (methylphenidate HCl)	✔
Dexedrine Spansule (dextroamphetamine sulfate sustained-release)	✔
Metadate ER (methylphenidate HCl ER)	✔
Adzenys ER (amphetamine ER)	-
Adzenys XR-ODT (amphetamine ER)	-
Dyanavel XR (amphetamine ER)	✔
Adderall XR (mixed amphetamine salts ER)	✔
Mydayis (mixed amphetamine salts ER)	-
Focalin XR (dexmethylphenidate HCl ER)	✔
Vyvanse (lisdexamfetamine dimesylate)	-
Aptensio XR (methylphenidate HCl ER)	-
Concerta (methylphenidate HCl ER)	✔
Cotempla XR-ODT (methylphenidate ER)	-
methylphenidate HCl ER (CD)	✔ *
methylphenidate HCl ER	✔
QuilliChew ER (methylphenidate HCl ER)	-
Quillivant XR (methylphenidate HCl ER)	-
Ritalin LA (methylphenidate HCl ER)	✔
Daytrana (methylphenidate transdermal system)	-
Non-stimulants	
Strattera (atomoxetine HCl)	✔
Kapvay (clonidine HCl ER)	✔
Intuniv (guanfacine HCl ER)	✔

*Note: Brand Metadate CD has been discontinued, but generics are available.

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

vs

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Evekeo (amphetamine sulfate)	Adzenys ER, Adzenys XR-ODT, Dyanavel XR (amphetamine ER)	Adderall (mixed amphetamine salts)	Adderall XR, Mydayis (mixed amphetamine salts ER)	Strattera (atomoxetine HCl)	Kapvay (clonidine HCl ER)	Focalin (dexmethylphenidate IR); Focalin XR (dexmethylphenidate ER)	ProCentra, Zenzedi (dextroamphetamine sulfate IR); Dexedrine Spansule (dextroamphetamine sulfate SR)	Intuniv (guanfacine HCl ER)	Vyvanse (lisdexamfetamine dimesylate)	Desoxyn (methamphetamine HCl)	Methylin Oral Solution, Ritalin (methylphenidate HCl IR); methylphenidate HCl [illegible] ER)	Aptensio XR, Concerta , Cotempla XR-ODT, Daytrana, methylphenidate ER (CD), QuilliChew ER, Quillivant [illegible]
ADHD*		✓	✓	✓	✓		✓			✓			✓
ADHD, as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, and social) for a stabilizing effect in pediatric patients with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal electroencephalogram (EEG) may or may not be present, and a diagnosis of CNS	✓							✓			✓	✓	

Indication	Evekeo (amphetamine sulfate)	Adzenys ER, Adzenys XR-ODT, Dyanavel XR (amphetamine ER)	Adderall (mixed amphetamine salts)	Adderall XR, Mydayis (mixed amphetamine salts ER)	Strattera (atomoxetine HCl)	Kapvay (clonidine HCl ER)	Focalin (dexmethylphenidate IR); Focalin XR (dexmethylphenidate ER)	ProCentra, Zenzedi (dextroamphetamine sulfate IR); Dexedrine Spansule (dextroamphetamine sulfate SR)	Intuniv (guanfacine HCl ER)	Vyvanse (lisdexamfetamine dimesylate)	Desoxyn (methamphetamine HCl)	Methylin Oral Solution, Ritalin (methylphenidate HCl IR); methylphenidate HCl [illegible] ER)	Aptensio XR, Concerta , Cotempla XR-ODT, Daytrana, methylphenidate ER (CD), QuilliChew ER, Quillivant [illegible]
dysfunction may or may not be warranted.*													
Treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications						✓			✓				
Narcolepsy**	✓		✓					✓				✓	
Exogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction for patients refractory to alternative therapy (eg, repeated diets, group programs, and other drugs).†	✓										✓		
Moderate to severe BED in adults										✓			

(*Prescribing Information*: *Adderall 2016*, *Adderall XR 2017*, *Adzenys ER 2017*, *Adzenys XR-ODT 2017*, *Aptensio XR 2017*, *Concerta 2017*, *Cotempla 2017*, *Daytrana 2017, Desoxyn 2017, Dexedrine Spansule 2017*, *Dyanavel XR 2017*, *Evekeo 2016*, *Focalin 2017*, *Focalin XR 2017*, *Intuniv 2016, Kapvay 2016, Mydayis 2017, Methylin Oral Solution 2016, methylphenidate chewable tablets 2015, methylphenidate ER 2015, methylphenidate ER (CD) 2017, ProCentra 2017*, *QuilliChew ER 2017*, *Quillivant XR 2017*, *Ritalin 2017*, *Ritalin LA 2017*, *Strattera 2017*, *Vyvanse 2017, Zenzedi 2017*)

* Adderall, Evekeo, ProCentra, and Zenzedi are approved for use in children 3 years of age and older. Daytrana, Desoxyn, Dexedrine Spansule, Dyanavel XR, Intuniv, and Kapvay are approved for use in children 6 years of age and older. Adderall XR, Adzenys ER, Adzenys XR-ODT, Aptensio XR, Focalin, Focalin XR, methylphenidate ER (CD), Metadate ER, Methylin Oral Solution, methylphenidate chewable tablets, QuilliChew ER, Quillivant XR, Ritalin, Ritalin LA, Strattera, and Vyvanse are approved for use in patients 6 years of age and older. Cotempla XR-ODT is approved for use in pediatric patients 6 to 17 years of age. Concerta is approved for use in children 6 years of age and older, adolescents, and adults up to 65 years of age. Mydayis is approved for use in patients 13 years of age and older.
**These drugs are approved for use in patients 6 years of age and older.
†These drugs are not recommended for use in children under 12 years of age for treatment of exogenous obesity. The limited usefulness of these products should be weighed against possible risks inherent in use of the drugs.

- Limitation of use:

- Lisdexamfetamine: Lisdexamfetamine is not indicated or recommended for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular (CV) adverse events (AEs). The safety and effectiveness of this drug for the treatment of obesity have not been established.
- Mydayis: Pediatric patients 12 years and younger experienced higher plasma exposure than patients 13 years and older at the same dose and experienced higher rates of AEs, mainly insomnia and decreased appetite.

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

CLINICAL EFFICACY SUMMARY

- Randomized trials, systematic reviews, and meta-analyses have found stimulants, atomoxetine, and alpha$_2$-adrenergic agonists to be more efficacious than placebo in reducing the core symptoms of ADHD in children and adolescents.
  - Adzenys ER, a new amphetamine ER oral suspension, was approved under the 505(b)(2) regulatory pathway and was found to be bioequivalent to Adderall XR. No clinical efficacy studies were conducted.
  - Cotempla XR-ODT, a new methylphenidate ER orally disintegrating tablet formulation, was approved based on a randomized, double-blind (DB), multi-center (MC), placebo-controlled (PC) laboratory classroom study (*Childress et al 2017*) (N = 87) which found that the average Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP)-Combined score was significantly better for Cotempla XR-ODT than for placebo (least squares [LS] mean 14.3 [95% CI, 12.2 to 16.4] vs 25.3 [9% CI, 23.0 to 27.6], respectively, p < 0.0001).
  - Mydayis, a new mixed amphetamine salts product, was approved for the treatment of ADHD based on the results of 5 MC, DB, PC, randomized controlled trials (RCTs): 3 in adults and 2 in pediatric patients 13 to 17 years of age. The studies found that Mydayis demonstrated a statistically significant treatment effect compared with placebo on various ADHD outcomes measures (eg, ADHD-Rating Scale [ADHD-RS] score, Permanent Product Measure of Performance [PERMP] score) (*Mydayis Prescribing Information 2017, Weisler et al 2017*) (see results below in Table 3 below).

Table 3. Summary of Primary Efficacy Results for Mydayis

Study Number (Age range)	Primary Endpoint	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline	Placebo-subtracted Difference (95% CI)
Adult Studies					
Study 1 (18 to 55 years)	ADHD-RS	Mydayis 12.5 mg/day§ Mydayis 37.5 mg/day§ Placebo	39.8 (6.38) 39.9 (7.07) 40.5 (6.52)	-18.5 -23.8 -10.4	-8.1 (-11.7 to -4.4) -13.4 (-17.1 to -9.7)
Study 2 (18 to 55 years)	Average PERMP	Mydayis 50 mg/day§ Placebo	239.2 (75.6)† 249.6 (76.7)†	293.23* 274.85*	18.38 (11.28 to 25.47)
Study 3 (18 to 55 years)	Average PERMP	Mydayis 25 mg/day§ Placebo	217.5 (59.6)† 226.9 (61.7)†	267.96* 248.67*	19.29 (10.95 to 27.63)
Pediatric Studies					
Study 4 (13 to 17 years)‡	ADHD-RS-IV	Mydayis 12.5 to 25 mg/day§ Placebo	36.7 (6.15) 38.3 (6.67)	-20.3 -11.6	-8.7 (-12.6 to -4.8)
Study 5 (13 to 17 years)	Average PERMP	Mydayis 25 mg/day§ Placebo	214.5 (87.8)† 228.7 (101)†	272.67* 231.41*	41.26 (32.24 to 50.29)

SD= standard deviation; LS = least squares; CI = confidence interval
†Pre-dose PERMP total score
*LS mean for PERMP is post-dose average score over all sessions of the treatment day, rather than change from baseline
‡Results are for a subgroup of study 4 and not the total population
§Doses statistically significant for placebo

- A systematic (Cochrane) review of 185 RCTs (*Storebø et al 2015*) (N = 12,245) in children and adolescents with ADHD found that methylphenidate may improve teacher-rated ADHD symptoms, teacher-reported general behavior, and parent-reported quality of life (QOL) vs placebo. However, the evidence was of low quality.
- An RCT called the Preschool ADHD Treatment Study (PATS) (*Greenhill et al 2006*) evaluated the efficacy of methylphenidate immediate-release (IR) in 303 preschool children with ADHD and found that it demonstrated significant reductions on ADHD symptom scales; however, the effect sizes (0.4 to 0.8) were smaller than those generally reported for school-age children.
- A systematic (Cochrane) review of 23 PC, RCTs (*Punja et al 2016*) (N = 2675) found that amphetamines were effective at improving the core symptoms of ADHD, but they were also associated with a higher risk of AEs compared to placebo. There was no evidence that one kind of amphetamine was better than another and there was no difference between short-acting and long-acting formulations.
- A meta-analysis of 25 DB, PC, RCTs (*Schwartz et al 2014*) (N = 3928) in children and adolescents with ADHD found atomoxetine to be superior to placebo for overall ADHD symptoms, with a medium effect size (-0.64).
- A meta-analysis of 12 RCTs (*Hirota et al 2014*) (N = 2276) in pediatric patients with ADHD found that alpha$_2$-adrenergic agonists were significantly superior to placebo for overall ADHD symptoms both as monotherapy and, to a lesser extent, as augmentation therapy to stimulants.
  - Meta-analytic results failed to demonstrate a significant difference in efficacy between alpha$_2$-adrenergic agonists. In sub-analyses of individual formulations, the ER formulations separated robustly from placebo whereas the IR formulations did not separate from placebo.
- A systematic review of 16 RCTs and 1 meta-analysis (*Chan et al 2016*) (N = 2668) found evidence supporting the use of methylphenidate ER and amphetamine ER formulations, atomoxetine, and guanfacine ER for the treatment of ADHD in adolescents. For the primary outcome measure of mean change in ADHD-RS total symptom score, both stimulant and non-stimulant medications led to clinically significant reductions of 14.93 to 24.60 points.

- For the treatment of ADHD in children and adolescents, stimulants typically have a slightly larger treatment effect size (standardized mean difference [SMD]) than non-stimulants (approximately 1.0 vs approximately 0.7 for both atomoxetine and alpha$_2$-adrenergic agonists). However, there is insufficient evidence to definitively conclude that one stimulant is more efficacious than another (*Krull 2017e*, *AAP 2011).*
  - An Agency for Healthcare Research and Quality (AHRQ) review of 78 studies (*Jadad et al 1999*) evaluating the efficacy of various interventions for the treatment of ADHD in children and adults found few, if any, differences between methylphenidate and dextroamphetamine.
  - A meta-analysis of 23 DB, PC trials (*Faraone 2010a*) comparing the efficacy of methylphenidate and amphetamine formulations found that amphetamine products may be moderately more efficacious than methylphenidate products.
  - A DB, PC, RCT (*Newcorn et al 2008*) (N = 516) comparing the efficacy of atomoxetine vs methylphenidate ER (osmotic-release formulation) in patients 6 to 16 years of age with ADHD found that both drugs were superior to placebo in terms of response rate, and that methylphenidate ER was superior to atomoxetine.
  - A meta-analysis of 29 DB, PC trials (*Faraone et al 2006*) evaluated the efficacy of various medications (methylphenidate and amphetamine compounds, atomoxetine, pemoline [no longer available in the U.S.], bupropion, and modafinil) for the treatment of ADHD. The effect sizes for non-stimulant medications were significantly less than those for IR stimulants or long-acting stimulants. The 2 classes of stimulant medications did not differ significantly from one another.
  - A meta-analysis of 28 DB, PC, RCTs (*Stuhec et al 2015*) (N = 4699) compared the efficacy of various medications for the treatment of ADHD in children and adolescents. Efficacy in reducing ADHD symptoms compared to placebo was small for bupropion (SMD = -0.32; 95% confidence interval [CI], -0.69 to 0.05), modest for atomoxetine (SMD = -0.68; 95% CI, -0.76 to -0.59) and methylphenidate (SMD = -0.75; 95% CI, -0.98 to -0.52), and highest for lisdexamfetamine (SMD = -1.28; 95% CI, -1.84 to -0.71).
  - A network meta-analysis and mixed treatment comparison of 36 RCTs (*Joseph et al 2017*) evaluating the comparative efficacy and safety of ADHD pharmacotherapies in children and adolescents found that lisdexamfetamine had greater efficacy than guanfacine ER, atomoxetine, and methylphenidate ER. Guanfacine ER had a high posterior probability of being more efficacious than atomoxetine, but their credible intervals overlapped.
- Alpha$_2$-adrenergic agonists have been associated with improvements in ADHD symptoms and comorbid tics.
  - A meta-analysis of 9 DB, PC, RCTs (*Bloch et al 2009*) (N = 477) was conducted to determine the relative efficacy of different medications in treating ADHD and tic symptoms in children with both Tourette syndrome and ADHD.
  - Methylphenidate seemed to offer the greatest improvement of ADHD symptoms and did not seem to worsen tic symptoms.

- Alpha$_2$-adrenergic agonists offered the best combined improvement in both tic and ADHD symptoms.
- Atomoxetine significantly improved both tic and ADHD severity compared to placebo.
- One small study found that tic severity was significantly increased with higher doses of dextroamphetamine treatment.

- There are limited efficacy data regarding the treatment of ADHD in the adult population. Comparison of effect sizes in clinical trials suggests that stimulant medications are more efficacious in adult ADHD than non-stimulants.
  - In a meta-analysis of 12 clinical trials (*Cunill et al 2009*) (N = 3375) comparing atomoxetine with placebo in adult ADHD, atomoxetine led to a modestly greater reduction in ADHD symptom severity, but was associated with higher all-cause discontinuation.
  - A meta-analysis (*Faraone 2010b*) of 19 randomized trials of 13 medications for adult ADHD found a greater average effect size for reduction in ADHD symptoms in patients receiving short- and long-acting stimulant medications (vs placebo; 0.86 and 0.73, respectively) compared with patients receiving non-stimulant medication (vs placebo; 0.39). No difference in effect size was found between short- and long-acting stimulants.
- Lisdexamfetamine dimesylate has demonstrated efficacy in the treatment of BED. Direct comparison trials between lisdexamfetamine and other drugs used off-label to treat BED are lacking.
  - In 2 Phase 3, 12-week, randomized, DB, PC trials (*McElroy et al 2016*) (N = 773) in patients with moderate to severe BED, lisdexamfetamine-treated patients had a statistically significantly greater reduction from baseline in mean number of binge days per week at week 12 vs placebo (treatment difference in study 1: -1.35 [-1.70 to -1.01]; study 2: -1.66 [-2.04 to -1.28]; both $p < 0.001$).
    - A 12-month, open-label (OL) extension study (*Gasior et al 2017*) (N = 599) in adults with BED found that the long-term safety and tolerability of lisdexamfetamine were generally consistent with the safety profile observed in 3 previous short-term trials in BED as well as its established profile for ADHD. Common treatment-emergent AEs included dry mouth, headache, insomnia, and upper respiratory tract infection. Weight loss and increases in blood pressure and pulse rate were also observed.
  - In a phase 3, DB, randomized, PC, withdrawal study (*Hudson et al 2017*) (N = 418) in adults with moderate to severe BED, responders to lisdexamfetamine during a 12-week OL phase were randomized to placebo or continued lisdexamfetamine during a 26-week, DB phase. The percentage of patients meeting relapse criteria was 3.7% with lisdexamfetamine vs 32.1% with placebo; time to relapse statistically favored lisdexamfetamine ($p < 0.001$). The hazard ratio (HR) was 0.09 (95% CI, 0.04 to 0.23).
  - A systematic review and meta-analysis of 9 waitlist-controlled psychological trials and 25 PC trials evaluating pharmacologic (n = 19) or combination (n = 6) treatment for BED (*Brownley et al 2016*) found that therapist-led cognitive behavioral therapy (CBT), lisdexamfetamine, and second-generation antidepressants (SGAs) increased binge-eating abstinence (relative risk [RR], 4.95 [95% CI, 3.06 to 8.00], 2.61 [CI, 2.04 to 3.33], and 1.67 [CI, 1.24 to 2.26], respectively), while lisdexamfetamine and SGAs decreased binge-eating frequency (mean difference in days/week, -1.35 [CI, -1.77 to -0.93] and -0.67 [CI, -1.26 to -0.09], respectively). Topiramate and other forms of CBT also increased abstinence and reduced binge-eating frequency.

CLINICAL GUIDELINES

ADHD

- Several clinical guidelines have provided recommendations on the treatment of ADHD in children and adolescents.
  - According to the American Academy of Pediatrics (AAP) guidelines (2011), the evidence is particularly strong for stimulant medications, and sufficient but less strong for atomoxetine, guanfacine ER, and clonidine ER (in that order). Guanfacine ER and clonidine ER have evidence to support their use as adjunctive therapy with stimulant medications. Methylphenidate is recommended for preschool-aged children who have had an inadequate response to behavioral interventions.
  - The American Academy of Child and Adolescent Psychiatry (AACAP) guidelines (*Pliszka et al 2007*) state that both methylphenidate and amphetamines are equally efficacious in the treatment of ADHD. The long-acting formulations are equally efficacious as the IR formulations and may be used as initial therapy. Short-acting stimulants are often used as initial treatment in small children (< 16 kg in weight), for whom there are no long-acting preparations in a sufficiently low dose. Some patients may respond similarly to different stimulant classes, whereas other patients may respond preferentially to only 1 of the classes of stimulants. Although stimulants have demonstrated greater efficacy compared to atomoxetine in published studies, atomoxetine may be used first-line in patients with an active substance abuse problem, comorbid anxiety or tics, and in those who experience severe AEs with stimulants.
  - The Medical Letter (2015) recommends that treatment of ADHD in school-age children or adults should begin with an oral stimulant, either a methylphenidate- or amphetamine-based formulation. Mixing short- and long-acting stimulants

can be helpful to achieve an immediate effect for early-morning school classes or for reducing rebound irritability or overactivity, especially in the evening. An ER alpha$_2$-adrenergic agonist may be helpful as adjunctive therapy with a stimulant in patients who cannot tolerate usual doses of the stimulant, particularly those with tics. Atomoxetine is an alternative for patients who cannot tolerate stimulants or for whom treatment with a controlled substance is undesirable.

- The AACAP practice parameter for the treatment of children and adolescents with tic disorders (2013) states that alpha$_2$-adrenergic agonists have demonstrated an effect size of 0.5 for the amelioration of tics and may be preferred by some prescribers over antipsychotics due to their relatively favorable AE profile.

Narcolepsy

- The American Academy of Sleep Medicine (AASM) practice parameters (*Morgenthaler et al 2007*) recommend various drugs for the treatment of daytime sleepiness due to narcolepsy including modafinil (high degree of clinical certainty); amphetamine, methamphetamine, dextroamphetamine, and methylphenidate (moderate degree of clinical certainty); sodium oxybate (high degree of clinical certainty); and selegiline (uncertain clinical certainty).

BED

- According the American Psychiatric Association (APA) practice guidelines on eating disorders (*Yager et al 2006*, *Yager et al 2012* [guideline watch update]), treatment of BED may include the following:
  - Nutritional rehabilitation and counseling
  - Psychosocial treatment
    - CBT, behavior therapy, dialectical behavior therapy (DBT), and interpersonal therapy (IPT) have all been associated with binge frequency reduction rates of 67% or more and significant abstinence rates during active treatment.
    - Self-help programs using self-guided, professionally designed manuals have been effective in reducing the symptoms of BED in the short-run for some patients and may have long-term benefit.
  - Medications
    - Antidepressant treatment is associated with short-term reductions in binge-eating but generally does not result in substantial weight loss. Selective serotonin reuptake inhibitors (SSRIs) have the fewest difficulties with AEs and the most evidence for efficacy when used at the high end of the recommended dose range.
    - Topiramate can reduce bingeing and decrease weight, but its use may be limited by AEs.
  - Combination psychotherapy and pharmacotherapy
    - For most patients, adding antidepressant therapy to a behavioral weight control and/or CBT regimen does not have a significant effect on binge suppression.
    - Although limited evidence is available, combined treatment is frequently used in clinical practice.
- The Task Force on Eating Disorders of the World Federation of Societies of Biological Psychiatry (*Aigner et al 2011*) concluded that for the treatment of BED, grade A evidence supports the use of imipramine (moderate risk-benefit ratio), sertraline (good risk-benefit ratio), citalopram/escitalopram (good risk-benefit ratio), orlistat (low to moderate risk-benefit ratio), and topiramate (moderate risk-benefit ratio). Atomoxetine has grade B evidence supporting its use.

SAFETY SUMMARY

- Due to the potential for abuse, the stimulants are classified as Schedule II controlled substances. Atomoxetine, clonidine ER, and guanfacine ER are not classified as controlled substances.
- Various stimulants are contraindicated for use in patients with advanced arteriosclerosis, symptomatic CV disease, moderate to severe hypertension, hyperthyroidism, hypersensitivity to sympathomimetic amines, glaucoma, agitated states, history of drug abuse, tics, and in those using monoamine oxidase inhibitors (MAOIs). The stimulants carry a boxed warning for potential drug abuse and dependence. They also have warnings for increased risks of serious CV reactions, psychiatric AEs, suppression of growth, peripheral vasculopathy, and priapism. Amphetamines have a warning for risk of serotonin syndrome when used in combination with other drugs affecting the serotonergic neurotransmitter systems.
  - Common AEs of stimulants include anorexia, decreased weight, tachycardia, anxiety, irritability, and insomnia.
  - Refer to the prescribing information for details on warnings, precautions, and AEs for individual products. For example:
    - QuilliChew ER can be harmful to patients with phenylketonuria (PKU) since it contains phenylalanine.
    - Because the Concerta tablet is nondeformable and does not appreciably change in shape in the gastrointestinal tract, it should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing.

- The use of Daytrana may result in chemical leukoderma and contact sensitization; in addition, exposure of the application site to external heat sources should be avoided due to increased absorption of the drug.

- Atomoxetine is contraindicated for use in patients with glaucoma, pheochromocytoma, severe CV disorders, hypersensitivity to any component of the product, and in those taking MAOIs. It carries a boxed warning for rare increased risk of suicidal ideation in children and adolescents. It also has warnings for serious CV events, effects on blood pressure and heart rate, effects on growth, psychiatric AEs, rare cases of severe liver injury, and priapism.
  - Common AEs associated with atomoxetine include somnolence, nausea, and vomiting.
- The alpha$_2$-adrenergic agonists are contraindicated in patients known to be hypersensitive to any constituent of the product. They carry warnings for increased risk of hypotension, bradycardia, and syncope; sedation and somnolence; rebound hypertension; and cardiac conduction abnormalities.
  - Common AEs associated with clonidine ER include somnolence, fatigue, and irritability while common AEs with guanfacine ER include somnolence, fatigue, and hypotension.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Stimulants					
Evekeo (amphetamine)	4 to 6 h	Tablets	Oral	*ADHD, narcolepsy*: Daily up to divided doses daily *Exogenous obesity*: Divided doses daily	*ADHD and narcolepsy* The first dose should be given upon awakening; additional doses at intervals of 4 to 6 hours.
Adzenys ER (amphetamine ER)	10 to 12 h	Suspension	Oral	Daily in the morning	
Adzenys XR-ODT (amphetamine ER)	10 to 12 h	Orally disintegrating tablets	Oral	Daily in the morning	As soon as the blister pack is opened, the tablet should be placed on the patient's tongue and allowed to disintegrate without chewing or crushing. The tablet will disintegrate in saliva so that it can be swallowed.
Dyanavel XR (amphetamine ER)	Up to 13 h	Suspension	Oral	Daily in the morning	The bottle should be shaken before administration.
Adderall (mixed amphetamine salts)	4 to 6 h	Tablets	Oral	*ADHD, narcolepsy*: Daily up to divided doses daily	The first dose should be given on awakening, then additional doses at intervals of 4 to 6 hours.

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Adderall XR (mixed amphetamine salts ER)	10 to 12 h	Capsules	Oral	Daily in the morning	Capsules may be taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce and consumed immediately. The dose of a single capsule should not be divided.
Mydayis (mixed amphetamine salts ER)	16 h	Capsules	Oral	Daily in the morning	Dosage adjustment is needed for severe renal impairment. Use in end stage renal disease (ESRD) is not recommended. Capsules may be taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce and consumed immediately in its entirety without chewing. The dose of a single capsule should not be divided.
Focalin (dexmethylphenidate)	5 to 6 h	Tablets	Oral	Twice daily	
Focalin XR (dexmethylphenidate ER)	10 to 12 h	Capsules	Oral	Daily in the morning	ER capsules may be taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce.
ProCentra, Zenzedi (dextroamphetamine)	4 to 6 h	Solution (ProCentra) Tablets (Zenzedi)	Oral	*ADHD, narcolepsy*: Daily up to divided doses daily	The first dose should be given upon awakening; additional doses at intervals of 4 to 6 hours

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Dexedrine Spansule (dextroamphetamine SR)	6 to 8 h	Capsules	Oral	*ADHD* Daily or twice daily Narcolepsy Daily	
Vyvanse (lisdexamfetamine)	10 to 12 h	Capsules, chewable tablets	Oral	*ADHD, BED*: Daily in the morning	Dosage adjustment is needed for renal impairment/ESRD. The capsules may be swallowed whole or can be opened, emptied, and mixed with yogurt, water, or orange juice and consumed immediately. A single capsule should not be divided. The chewable tablets must be chewed thoroughly before swallowing. A single dose should not be divided.
Desoxyn (methamphetamine)	3 to 5 h	Tablets	Oral	*ADHD*: Daily to twice daily *Obesity*: 30 min before each meal	
Methylin, Ritalin (methylphenidate)	3 to 5 h	Chewable tablets, tablets (Ritalin), solution (Methylin)	Oral	Twice daily to 3 times daily	The chewable tablets should be taken with at least 8 ounces (a full glass) of water or other fluid. The ER tablets may be used in place of

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Methylphenidate ER	3 to 8 h	Tablets			the IR tablets when the 8-hour dosage of the ER product corresponds to the titrated 8-hour dosage of the IR products. The ER tablets must be swallowed whole and never crushed or chewed.
Aptensio XR (methylphenidate ER)	12 h	Capsules	Oral	Daily in the morning	The capsules may be taken whole or they can be opened and sprinkled onto applesauce; the applesauce should be consumed immediately and it should not be chewed. The dose of a single capsule should not be divided.
Concerta (methylphenidate ER)	10 to 12 h	Tablets	Oral	Daily in the morning	The tablets should not be chewed or crushed. Note: An FDA analysis of methylphenidate ER products manufactured by UCB/Kremers (formerly Kudco) and Mallinckrodt indicated that in some individuals, they may deliver the drug in the body at a

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Methylphenidate ER					slower rate during the 7- to 12-hour range. As a result, the FDA changed the therapeutic equivalence of these products from AB to BX. Because these manufacturers have subsequently failed to demonstrate that their products are bioequivalent to the brand-name reference drug, the FDA proposes to withdraw their approval (*FDA 2016*).
Cotempla XR-ODT (methylphenidate ER)	12 h	Orally disintegrating tablets	Oral	Daily in the morning	As soon as the blister pack is opened, the tablet should be placed on the patient's tongue and allowed to disintegrate without chewing or crushing. The tablet will disintegrate in saliva so that it can be swallowed.
Methylphenidate ER (CD)	8 to 12 h	Capsules	Oral	Daily in the morning	The capsule may be swallowed whole or it may be opened and the contents sprinkled onto a small amount (tablespoon) of applesauce and given immediately. The capsule contents must not be crushed or chewed.
QuilliChew ER (methylphenidate ER)	12 h	Chewable tablets	Oral	Daily in the morning	
Quillivant XR (methylphenidate ER)	12 h	Suspension	Oral	Daily in the morning	The bottle of Quillivant XR should be shaken

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
					vigorously for 10 seconds prior to administration.
Ritalin LA (methylphenidate ER)	8 to 12 h	Capsules	Oral	Daily in the morning	The capsule may be swallowed whole or may be administered by sprinkling the capsule contents on a small amount of applesauce; the contents should not be crushed, chewed, or divided. The mixture should be consumed immediately.
Daytrana (methylphenidate transdermal system)	10 to 12 h	Transdermal system	Transdermal	The patch should be applied 2 hours before an effect is needed and removed within 9 hours. It may be removed earlier than 9 hours if a shorter duration of effect is desired or late day side effects appear.	
Non-stimulants					
Strattera (atomoxetine)	24 h	Capsules	Oral	Daily in the morning or divided dose in the morning and late/afternoon early evening	Dosage adjustment is recommended for patients with moderate or severe hepatic insufficiency. The capsules are not intended to be opened and should be taken whole.
Kapvay (clonidine ER)	12 h	Tablets	Oral	Daily at bedtime or twice daily divided doses.	With twice daily dosing, either an equal or higher split dosage should be given at bedtime. The tablets should not be crushed,

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
					chewed, or broken prior to swallowing. The initial dosage should be based on the degree of renal impairment.
Intuniv (guanfacine ER)	8 to 24 h	Tablets	Oral	Daily in the morning or evening	The tablets should not be crushed, chewed, or broken prior to swallowing. It may be necessary to reduce the dosage in patients with significant renal and hepatic impairment.

See the current prescribing information for full details
*References: Prescribing information for individual products, *Medical Letter 2015, Pharmacist's Letter 2016, Krull 2017e*

CONCLUSION

- Both CNS stimulants and non-stimulants may be used for the treatment of ADHD. In general, stimulants are first-line treatment due to their superior efficacy. Clinical evidence suggests that methylphenidate and amphetamines are equally efficacious, but some patients may respond to one stimulant and not the other. Various short-, intermediate- and long-acting formulations (eg, tablets/capsules, chewable/orally disintegrating tablets, solution/suspension, transdermal patch) are available to provide a range of dosing options. Although non-stimulants such as atomoxetine and alpha$_2$-adrenergic agonists have smaller effect sizes, they may be used in patients who have failed or are intolerant to stimulants or when there is concern about possible abuse or diversion. The alpha$_2$-adrenergic agonists are approved both as monotherapy and as adjunctive therapy to stimulants, and they have been shown to improve both tic and ADHD symptoms in patients with comorbid tic disorder.
  - Current consensus clinical guidelines for the treatment of children and adolescents with ADHD recommend that stimulants are highly effective for reducing core symptoms of ADHD in children (*AACAP 2007*; *AAP 2011*).
- Ultimately, the choice of the initial agent for treatment of ADHD depends upon various factors such as: duration of desired coverage; ability of the child to swallow pills; coexisting tic disorder (use of alpha$_2$-adrenergic agonists may be warranted); potential AEs, history of substance abuse in the patient or household member (eg, avoid stimulants or use stimulants with less potential for abuse [eg, lisdexamfetamine, osmotic-release preparation, methylphenidate patch]); and preference of the patient and parent/guardian (*Krull 2017e*).
- Various stimulants are indicated for treatment of narcolepsy and are generally considered to be second-line agents after modafinil/armodafinil due to their sympathomimetic AEs (*Scammell 2017*).
- Lisdexamfetamine is the only FDA-approved drug indicated for the treatment of moderate to severe BED, with demonstrated efficacy in reduction of mean binge days per week vs placebo. Direct comparison trials between lisdexamfetamine and other drugs used off-label to treat BED are lacking.

REFERENCES

- Adderall [package insert], Horsham, PA: Teva Select Brands; December 2016.
- Adderall XR [package insert], Lexington, MA: Shire US Inc.; January 2017.
- Adzenys ER [package insert], Grand Prairie, TX: Neos Therapeutics, Inc.; September 2017.
- Adzenys XR-ODT [package insert], Grand Prairie, TX: Neos Therapeutics, Inc.; January 2017.
- Aigner M, Treasure J, Kaye W, Kasper S; WFSBP Task Force On Eating Disorders. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of eating disorders. *World J Biol Psychiatry*. 2011;12(6):400-443.
- Aptensio XR [package insert], Coventry, RI: Rhodes Pharmaceuticals, L.P.; January 2017.

- Brownley KA, Berkman ND, Peat CM, et al. Binge-eating disorder in adults: A systematic review and meta-analysis. *Ann Intern Med*. 2016;165(6):409-420.
- Bukstein O. Attention deficit hyperactivity disorder in adults: Epidemiology, pathogenesis, clinical features, course and diagnosis. UpToDate Web site. 2017. http://www.uptodate.com. Updated November 3, 2016. Accessed September 20, 2017.
- Chan E, Fogler JM, Hammerness PG. Treatment of attention-deficit/hyperactivity disorder in adolescents: a systematic review. *JAMA*. 2016;315(18):1997-2008.
- Childress AC, Kollins SH, Cutler AJ, Marraffino A, Sikes CR. Efficacy, safety, and tolerability of an extended-release orally disintegrating methylphenidate tablet in children 6-12 years of age with attention-deficit/hyperactivity disorder in the laboratory classroom setting. *J Child Adolesc Psychopharmacol*. 2017;27(1):66-74.
- Concerta [package insert], Titusville, NJ: Janssen Pharmaceuticals, Inc.; January 2017.
- Cotempla XR-ODT [package insert], Grand Prairie, TX: Neos Therapeutics Brands, LCC; June 2017.
- Cooper WO, Habel LA, Sox CM, et al. ADHD drugs and serious cardiovascular events in children and young adults. *N Engl J Med*. 2011;365(20):1896-1904.
- Cunill R, Castells X, Tobias A, Capellà D. Atomoxetine for attention deficit hyperactivity disorder in the adulthood: a meta-analysis and meta-regression. *Pharmacoepidemiol Drug Saf*. 2013;22(9):961-969.
- Daytrana [package insert], Miami, FL: Noven Therapeutics, LLC; January 2017.
- Desoxyn [package insert], Lebanon, NJ: Recordati Rare Diseases Inc.; May 2017.
- Dexedrine Spansule [package insert], Horsham, PA: Amedra Pharmaceuticals LLC; May 2017.
- Drug scheduling. Drug Enforcement Administration Web site. http://www.dea.gov/druginfo/ds.shtml. Accessed September 20, 2017.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available from: http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. Accessed September 20, 2017.
- Drugs for ADHD. *Med Lett Drugs Ther*. 2015;57(1464):37-40.
- Dyanavel XR [package insert], Monmouth Junction: Tris Pharma, Inc.; May 2017.
- Evekeo [package insert], Atlanta, GA: Arbor Pharmaceuticals, LLC; September 2016.
- Facts & Comparisons Website. https://fco.factsandcomparisons.com. Accessed September 20, 2017.
- Faraone SV, Biederman J, Spencer TJ, Aleardi M. Comparing the efficacy of medications for ADHD using meta-analysis. *MedGenMed*. 2006;8(4):4.
- Faraone SV, Buitelaar J. Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis. *Eur Child Adolesc Psychiatry*. 2010a;19(4):353-364.
- Faraone SV, Glatt SJ. A comparison of the efficacy of medications for adult attention-deficit/hyperactivity disorder using meta-analysis of effect sizes. *J Clin Psychiatry*. 2010b;71(6):754-763.
- Feldman HM, Reiff MI. Clinical practice. Attention deficit-hyperactivity disorder in children and adolescents. *N Engl J Med*. 2014;370(9):838-846.
- Focalin [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corporation.; January 2017.
- Focalin XR [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corporation.; January 2017.
- Gasior M, Hudson J, Quintero J, Ferreira-Cornwell MC, Radewonuk J, McElroy SL. A phase 3, multicenter, open-label, 12-month extension safety and tolerability trial of lisdexamfetamine dimesylate in adults with binge eating disorder. *J Clin Psychopharmacol*. 2017;37(3):315-322.
- Greenhill L, Kollins S, Abikoff H, et al. Efficacy and safety of immediate-release methylphenidate treatment for preschoolers with ADHD. *J Am Acad Child Adolesc Psychiatry*. 2006;45(11):1284-1293.
- Habel LA, Cooper WO, Sox CM, et al. ADHD medications and risk of serious cardiovascular events in young and middle-aged adults. *JAMA.* 2011;306(24):2673-2683.
- Hirota T, Schwartz S, Correll CU. Alpha-2 agonists for attention-deficit/hyperactivity disorder in youth: a systematic review and meta-analysis of monotherapy and add-on trials to stimulant therapy. *J Am Acad Child Adolesc Psychiatry*. 2014;53(2):153-173.
- Intuniv [package insert], Lexington, MA: Shire US Inc.; July 2016.
- Hudson JI, McElroy SL, Ferreira-Cornwell MC, Radewonuk J, Gasior M. Efficacy of lisdexamfetamine in adults with moderate to severe binge-eating disorder: A randomized clinical trial. *JAMA Psychiatry*. 2017;74(9):903-910.
- Jadad AR, Boyle M, Cunningham C, Kim M, Schachar R. Treatment of attention-deficit/hyperactivity disorder. *Evid Rep Technol Assess (Summ).* 1999;(11):i-viii, 1-341.
- Joseph A, Ayyagari R, Xie M, et al. Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison. *Eur Child Adolesc Psychiatry*. 2017;26(8):875-897.
- Kapvay [package insert], St. Michel, Barbados: Concordia, Pharmaceuticals, Inc.; August 2016.
- Krull KR. Attention deficit hyperactivity disorder in children and adolescents: Clinical features and diagnosis. UpToDate Web site. 2017a. http://www.uptodate.com. Updated January 4, 2017. Accessed September 20, 2017.
- Krull KR. Attention deficit hyperactivity disorder in children and adolescents: Epidemiology and pathogenesis. UpToDate Web site. 2017b. http://www.uptodate.com. Updated September 12, 2017. Accessed September 20, 2017.
- Krull KR. Attention deficit hyperactivity disorder in children and adolescents: Overview of treatment and prognosis. UpToDate Web site. 2017d. http://www.uptodate.com. Updated June 14, 2017. Accessed September 20, 2017.
- Krull KR. Attention deficit hyperactivity disorder in children and adolescents: Treatment with medications. UpToDate Web site. 2017e. http://www.uptodate.com. Updated September 13, 2017. Accessed September 20, 2017.
- Krull KR. Pharmacology of drugs used to treat attention deficit hyperactivity disorder in children and adolescents. UpToDate Web site. 2017c. http://www.uptodate.com. Updated August 14, 2017. Accessed September 20, 2017.
- McElroy SL, Hudson J, Ferreira-Cornwell MC, Radewonuk J, Whitaker T, Gasior M. Lisdexamfetamine dimesylate for adults with moderate to severe binge eating disorder: Results of two pivotal phase 3 randomized controlled trials. *Neuropsychopharmacology*. 2016;41(5):1251-1260.
- Methylin oral solution [package insert], Florham Park, NJ: Shionogi Inc.; September 2016.
- Methylphenidate chewable tablets [package insert]: Somerset, NJ: GAVIS Pharmaceuticals, LLC; December 2015.
- Methylphenidate ER [package insert], Newtown, PA: KVK-Tech, Inc.; July 2015.
- Methylphenidate ER (CD) [package insert], North Wales, PA: Teva Pharmaceuticals; February 2017.

- Methylphenidate hydrochloride extended-release tablets (generic Concerta) made by Mallinckrodt and Kudco. FDA Web site. November 4, 2016. http://www.fda.gov/Drugs/DrugSafety/ucm422568.htm. Accessed September 20, 2017.
- Morgenthaler TI, Kapur VK, Brown T, et al; Standards of Practice Committee of the American Academy of Sleep Medicine. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. *Sleep*. 2007;30(12):1705-1711.
- Mydayis [package insert], Lexington, MA: Shire US Inc.; June 2017.
- Newcorn JH, Kratochvil CJ, Allen AJ, et al; Atomoxetine/Methylphenidate Comparative Study Group. Atomoxetine and osmotically released methylphenidate for the treatment of attention deficit hyperactivity disorder: acute comparison and differential response. *Am J Psychiatry*. 2008;165(6):721-730.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Food and Drug Administration Web site. http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed June 23, 2017.
- PL Detail-Document, Comparison of ADHD medications. *Pharmacist's Letter/Prescriber's Letter*. March 2016.
- PL Detail-Document, Management of ADHD: When a stimulant is not enough. *Pharmacist's Letter/Prescriber's Letter*. April 2015.
- Pliszka S; AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;46(7):894-921.
- Practice parameter for the assessment and treatment of children and adolescents with tic disorders. *J Am Acad Child Adolesc Psychiatry*. 2013;52(12):1341-1359.
- ProCentra [package insert], Newport, KY: Independence Pharmaceuticals, LLC; February 2017.
- Punja S, Shamseer L, Hartling L, et al. Amphetamines for attention deficit hyperactivity disorder (ADHD) in children and adolescents. *Cochrane Database Syst Rev*. 2016;2:CD009996.
- QuilliChew ER [package insert], New York, NY: Pfizer, Inc.; March 2017.
- Quillivant XR [package insert], New York, NY: Pfizer, Inc.; June 2017.
- Ritalin [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corporation; January 2017.
- Ritalin LA [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corporation.; January 2017.
- Scammell TE. Treatment of narcolepsy in adults. UpToDate Web site. 2017. http://www.uptodate.com. Updated June 21, 2017. Accessed September 20, 2017.
- Schwartz S, Correll CU. Efficacy and safety of atomoxetine in children and adolescents with attention-deficit/hyperactivity disorder: results from a comprehensive meta-analysis and metaregression. *J Am Acad Child Adolesc Psychiatry*. 2014;53(2):174-187.
- Storebø OJ, Ramstad E, Krogh HB, et al. Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD). *Cochrane Database Syst Rev*. 2015;11:CD009885.
- Strattera [package insert], Indianapolis, IN: Lilly USA, Inc.; May 2017.
- Stuhec M, Munda B, Svab V, Locatelli I. Comparative efficacy and acceptability of atomoxetine, lisdexamfetamine, bupropion and methylphenidate in treatment of attention deficit hyperactivity disorder in children and adolescents: a meta-analysis with focus on bupropion. *J Affect Disord*. 2015;178:149-159.
- Subcommittee on Attention-Deficit/Hyperactivity Disorder; Steering Committee on Quality Improvement and Management, Wolraich M, Brown L, Brown RT, et al. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*. 2011;128(5):1007-1122.
- Vyvanse [package insert], Lexington, MA: Shire US Inc.; July 2017.
- Weisler RH, Greenbaum M, Arnold V, et al. Efficacy and safety of SHP465 mixed amphetamine salts in the treatment of attention-deficit/hyperactivity disorder in adults: results of a randomized, double-blind, placebo-controlled, forced-dose clinical study. *CNS Drugs*. 2017;31(8):685-697.
- Yager J, Devlin MF, Halmi KA, et al. Guideline watch (August 2012): Practice guideline for the treatment of patients with eating disorders, 3rd edition. Psychiatry Online Web site. http://psychiatryonline.org/guidelines. Accessed September 20, 2017.
- Yager J, Devlin MF, Halmi KA, et al. Practice guideline for the treatment of patients with eating disorders, 3rd edition (2006). Psychiatry Online Web site. http://psychiatryonline.org/guidelines. Accessed September 20, 2017.
- Zenzedi [package insert], Atlanta, GA: Arbor Pharmaceuticals, LLC; February 2017.

Publication Date: October 9, 2017