BRIAN SANDOVAL
Governor

STATE OF NEVADA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
DIVISION OF HEALTH CARE FINANCING AND POLICY
1100 E. William Street, Suite 101
Carson City, Nevada 89701
http://dhcfp.nv.gov

RICHARD WHITLEY
Director

LAURIE SQUARTSOFF
Administrator

NOTICE OF OPEN PUBLIC MEETING

The Division of Health Care Financing and Policy (DHCFP) Pharmacy and Therapeutics Committee will conduct a public meeting on **September 24, 2015**, beginning at **1:00 p.m.** at the following location:

JW Marriott – Las Vegas
Marbella Room
221 N Rampart Blvd
Las Vegas, NV 89145
702-869-7777

This meeting will be held only in Las Vegas, NV, there will be no teleconference to Carson City, NV.

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

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

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

AGENDA

I. CALL TO ORDER AND ROLL CALL

II. PUBLIC COMMENT

No action may be taken on a matter raised under this item of the agenda until the matter itself has been specifically included on the agenda as an item upon which action can be taken.

III. **FOR POSSIBLE ACTION**: Review and Approval of the March 26, 2015 Meeting Minutes

IV. STATUS UPDATE BY DHCFP

A. Public Comment

B. Program Updates

1. Agents used to treat opioid overdose

V. ANNUAL REVIEW - NEW DRUG CLASSES

A. ANTI-EMETIC – MISCELLANEOUS

1. Public Comment
2. Drug Class Review Presentation – Catamaran
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 Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

B. PSYCHOSTIMULANTS - NARCOLEPSY AGENTS

1. Public Comment
2. Drug Class Review Presentation – Catamaran
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 Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

C. LONG-ACTING ABUSE DETERRENT OPIOIDS

1. Public Comment
2. Drug Class Review Presentation – Catamaran
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 Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

D. ANTILIPEMICS – OMEGA-3 FATTY ACIDS

1. Public Comment
2. Drug Class Review Presentation – Catamaran
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 Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

E. RESPIRATORY LONG-ACTING BETA AGONISTS/LONG-ACTING ANTIMUSCARINIC COMBINATIONS

1. Public Comment
2. Drug Class Review Presentation – Catamaran
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 Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

VI. ANNUAL REVIEW - ESTABLISHED DRUG CLASSES

A. NEUROPATHIC PAIN AGENTS

1. Public Comment
2. Drug Class Review Presentation – Catamaran
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 Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

B. FIBROMYALGIA AGENTS

1. Public Comment
2. Drug Class Review Presentation – Catamaran
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 Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

C. OPIATE AGONISTS
1. Public Comment
2. Drug Class Review Presentation – Catamaran
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 Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

D. MULTIPLE SCLEROSIS AGENTS - INJECTABLE
1. Public Comment
2. Drug Class Review Presentation – Catamaran
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 Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

E. MULTIPLE SCLEROSIS AGENTS - ORAL
1. Public Comment
2. Drug Class Review Presentation – Catamaran
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 Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

F. VASODILATORS – ORAL
1. Public Comment
2. Drug Class Review Presentation – Catamaran
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 Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

G. PHOSPHATE BINDING AGENTS

1. Public Comment
2. Drug Class Review Presentation – Catamaran
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 Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

H. INCRETIN MIMETICS

1. Public Comment
2. Drug Class Review Presentation – Catamaran
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 Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

I. SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS

1. Public Comment
2. Drug Class Review Presentation – Catamaran
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 Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

J. ANTI-MIGRAINE AGENTS - SEROTONIN-RECEPTOR AGONISTS

1. Public Comment

2. Drug Class Review Presentation – Catamaran
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 Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

K. ADHD AGENTS

1. Public Comment
2. Drug Class Review Presentation – Catamaran
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 Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

L. RESPIRATORY CORTICOSTEROIDS

1. Public Comment
2. Drug Class Review Presentation – Catamaran
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 Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

M. SUBSTANCE ABUSE AGENTS - MIXED OPIATE AGONISTS/ANTAGONISTS

1. Public Comment
2. Drug Class Review Presentation – Catamaran
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 Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

VII. ANNUAL REVIEW - ESTABLISHED DRUG CLASSES BEING REVIEWED DUE TO THE RELEASE OF NEW DRUGS.

A. ANTICOAGULANTS - ORAL
   1. Public Comment
   2. Drug Class Review Presentation – Catamaran
   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 Catamaran and the Division of Health Care Financing and Policy
   5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

B. INSULINS (VIALS AND PENS)
   1. Public Comment
   2. Drug Class Review Presentation – Catamaran
   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 Catamaran and the Division of Health Care Financing and Policy
   5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

C. ANXIOLYTICS, SEDATIVES, AND HYPNOTICS
   1. Public Comment
   2. Drug Class Review Presentation – Catamaran
   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 Catamaran and the Division of Health Care Financing and Policy
   5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

D. BETA-BLOCKERS
   1. Public Comment
   2. Drug Class Review Presentation – Catamaran
   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 Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

E. TOPICAL ANTIFUNGALS (ONYCHOMYCOSIS)

1. Public Comment
2. Drug Class Review Presentation – Catamaran
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 Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

F. ANTICONVULSANTS

1. Public Comment
2. Drug Class Review Presentation – Catamaran
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 Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

G. ANDROGENS

1. Public Comment
2. Drug Class Review Presentation – Catamaran
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 Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

H. DISEASE-MODIFYING ANTIRHEUMATIC AGENTS

1. Public Comment

2. Drug Class Review Presentation – Catamaran
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 Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

VIII. ANNUAL REVIEW – DRUG CLASSES WITHOUT PROPOSED CHANGES

A. TRAMADOL AND RELATED DRUGS
B. NON-SEDATING H1 BLOCKERS
C. INHALED AMINOGLYCOSIDES
D. ANTIVIRALS - ALPHA INTERFERONS
E. ANTI-HEPATITIS AGENTS – POLYMERASE INHIBITORS/COMBINATION PRODUCTS
F. ANTI-HEPATITIS AGENTS – PROTEASE INHIBITORS
G. ANTI-HEPATITIS AGENTS – RIBAVRINS
H. ANTI-HERPETIC AGENTS
I. INFLUENZA AGENTS
J. SECOND-GENERATION CEPHALOSPORINS
K. THIRD-GENERATION CEPHALOSPORINS
L. MACROLIDES
M. QUINOLONES - 2ND GENERATION
N. QUINOLONES - 3RD GENERATION
O. SELF-INJECTABLE EPINEPHRINE
P. MULTIPLE SCLEROSIS AGENTS - SPECIFIC SYMPTOMATIC TREATMENT
Q. ANGIOTENSIN II RECEPTOR ANTAGONISTS
R. ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACE INHIBITORS)
S. CALCIUM-CHANNEL BLOCKERS
T. DIRECT RENIN INHIBITORS
U. VASODILATORS – INHALED
V. BILE ACID SEQUESTRANTS
W. CHOLESTEROL ABSORPTION INHIBITORS
X. FIBRIC ACID DERIVATIVES
Y. HMG-COA REDUCTASE INHIBITORS (STATINS)
Z. NIACIN AGENTS
AA. ANTIPSORIATIC AGENTS - TOPICAL VITAMIN D ANALOGS
BB. TOPICAL ANALGESICS
CC. ACNE AGENTS: TOPICAL, BENZOYL PEROXIDE, ANTIBIOTICS AND COMBINATION PRODUCTS
DD. IMPETIGO AGENTS: TOPICAL
EE. TOPICAL ANTIVIRALS

FF. TOPICAL SCABICIDES
GG. IMMUNOMODULATORS: TOPICAL
HH. TOPICAL RETINOIDS
II. SEROTONIN-RECEPTOR ANTAGONISTS/COMBO
JJ. H2 BLOCKERS
KK. PROTON PUMP INHIBITORS (PPIS)
LL. GASTROINTESTINAL ANTIINFLAMMATORY AGENTS
MM. GASTROINTESTINAL ENZYMES
NN. 5-ALPHA REDUCTASE INHIBITORS
OO. ALPHA-BLOCKERS
PP. BLADDER ANTISPASMODICS
QQ. ANTICOAGULANTS – INJECTABLE
RR. COLONY STIMULATING FACTORS
SS. PLATELET INHIBITORS
TT. ALPHA-GLUCOSIDASE INHIBITORS/AMYLIN ANALOGS/MISC.
UU. BIGUANIDES
VV. DIPEPTIDYL PEPTIDASE-4 INHIBITORS
WW. MEGLITINIDES
XX. SULFONYLUREAS
YY. THIAZOLIDINEDIONES
ZZ. GROWTH HORMONE MODIFIERS
AAA. PROGESTINS FOR CACHEXIA
BBB. ANTIGOUT AGENTS
CCC. BISPHOSPHONATES
DDD. NASAL CALCITONINS
EEE. RESTLESS LEG SYNDROME AGENTS
FFF. SKELETAL MUSCLE RELAXANTS
GGG. ALZHEIMERS AGENTS
HHH. BARBITURATES
III. BENZODIAZEPINES
JJJ. HYDANTOINS
KKK. NON-ERGOT DOPAMINE AGONISTS
LLL. CARBONIC ANHYDRASE INHIBITORS/BETA-BLOCKERS
MMM. OPHTHALMIC PROSTAGLANDINS
NNN. OPHTHALMIC ANTIHISTAMINES
OOO. OPHTHALMIC MACROLIDES
PPP. OPHTHALMIC QUINOLONES
QQQ. OPHTHALMIC CORTICOSTEROIDS
RRR. OPHTHALMIC NONSTEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDS)
SSS. OTIC QUINOLONES
TTT. ANTIDEPRESSANTS – OTHER
UUU. SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)

VVV. ATYPICAL ANTIPSYCHOTICS
WWW. NASAL ANTIHISTAMINES
XXX. LEUKOTRIENE RECEPTOR ANTAGONISTS
YYY. NASAL CORTICOSTEROIDS
ZZZ. PHOSPHODIESTERASE TYPE 4 INHIBITORS
AAAA. RESPIRATORY ANTIMUSCARINICS
BBBB. LONG-ACTING RESPIRATORY BETA-AGONIST
CCCC. SHORT-ACTING RESPIRATORY BETA-AGONIST
DDDD. RESPIRATORY CORTICOSTERIOD/LONG-ACTING BETA-AGONIST COMBINATIONS
EEEE. ANTIDOTES - OPIATE ANTAGONISTS

VIII. REPORT BY CATAMARAN ON NEW DRUGS TO MARKET, NEW GENERIC DRUGS TO MARKET, AND NEW LINE EXTENSIONS

IX. REVIEW OF NEXT MEETING LOCATION, DATE, AND TIME
A. December 3, 2015

X. PUBLIC COMMENT

XI. ADJOURNMENT

This notice and agenda has been posted on or before 9:00 a.m. on the third working day before the meeting at the following locations:

Notice of this meeting will be available on or after the posting date of this Agenda at the DHCFP Web site (http://dhcfp.nv.gov/)

Posting of the Agenda will be at the Nevada Medicaid Central offices in Carson City and Las Vegas; Nevada State Library; Carson City Library; Churchill County Library; Las Vegas Library; Douglas County Library; Elko County Library; Lincoln County Library; Lyon County Library; Mineral County Library; Tonopah Public Library; Pershing County Library; Goldfield Public Library; Eureka Branch Library; 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 action items will be mailed to you or they may be reviewed Monday through Friday from 9:00 a.m. until 5:00 p.m., or at the meeting. Please call at least one day ahead for an appointment for document review. Written comments on the proposed changes may be sent to the DHCFP, 1100 E. William Street, Suite 102, Carson City, NV 89701.

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

Anyone presenting documents for consideration during the public comment portion of the meeting must provide sufficient copies for each member of the committee and the official record. Copies are to be distributed at the time of the meeting and should be provided at both meeting locations; DHCFP or its contractor will not distribute public comment information or materials prior to the public meeting.

Tab: PDL

Division of Health Care Financing and Policy

Nevada Medicaid Preferred Drug List

Effective Sept. 1, 2015

			Preferred Products	PA Criteria	Non-Preferred Products
Analgesics					
	Analgesic/Miscellaneous				
		Neuropathic Pain Agents			
			CYMBALTA® GABAPENTIN LYRICA®	* PA Required	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	**PA Required for Fentanyl Patch** **General PA Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-59.pdf	AVINZA® QL BUTRANS® DOLOPHINE® DURAGESIC® PATCHES QL EMBEDA® EXALGO® HYSINGLA ER® KADIAN® QL METHADONE METHADOSE® MS CONTIN® QL NUCYNTA® ER OPANA ER® OXYCODONE SR QL OXYCONTIN® QL OXYMORPHONE SR XARTEMIS XR® QL ZOHYDRO ER® QL
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®

Nevada Medicaid Preferred Drug List

Effective Sept. 1, 2015

	Preferred Products	PA Criteria	Non-Preferred Products
Antiinfective Agents			
Aminoglycosides			
Inhaled Aminoglycosides			
	BETHKIS® KITABIS® PAK TOBI PODHALER® TOBRAMYCIN NEBULIZER		
Antivirals			
Alpha Interferons			
	PEGASYS® PEGASYS® CONVENIENT PACK PEG-INTRON® and REDIPEN		
Anti-hepatitis Agents			
Polymerase Inhibitors/Combination Products			
	HARVONI® SOVALDI® VIEKIRA PAK®	**PA Required** 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	
Protease Inhibitors			
	INCIVEK® VICTRELIS® OLYSIO®	**PA Required** https://www.medicaid.nv.gov/Downloads/provider/FA-75.pdf	
Ribavrins			
	RIBAVIRIN		RIBASPHERE RIBAPAK® MODERIBA® REBETOL®
Anti-Herpetic Agents			
	ACYCLOVIR FAMVIR® VALCYCLOVIR		
Influenza Agents			
	AMANTADINE TAMIFLU® RIMANTADINE RELENZA®		

	Preferred Products	PA Criteria	Non-Preferred Products
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 and SUSP CEFPODOXIME TABS and SUSP		CEDAX® CAPS and SUSP CEFDITOREN OMNICEF® SPECTRACEF® SUPRAX® VANTIN®
Macrolides			
	AZITHROMYCIN TABS/SUSP CLARITHROMYCIN TABS/SUSP ERYTHROMYCIN BASE ERYTHROMYCIN ESTOLATE ERYTHROMYCIN ETHYLSUCCINATE ERYTHROMYCIN STEARATE		BIAXIN® DIFICID® ZITHROMAX® ZMAX®
Quinolones			
Quinolones - 2nd Generation			
	CIPROFLOXACIN TABS CIPRO® SUSP		FLOXIN® OFLOXACIN
Quinolones - 3rd Generation			
	AVELOX® AVELOX ABC PACK® LEVOFLOXACIN		LEVAQUIN®
Autonomic Agents			
Sympathomimetics			
Self-Injectable Epinephrine			
	AUVI-Q® * EPINEPHRINE® EPIPEN® EPIPEN JR.®	* PA Required	ADRENACLICK® QL
Biologic Response Modifiers			
Immunomodulators			
Disease-Modifying Antirheumatic Agents			
	ENBREL® HUMIRA®	Prior authorization is required for all drugs in this	ACTEMRA® CIMZIA®

			Preferred Products	PA Criteria	Non-Preferred Products
				class https://www.medicaid.nv.gov/Downloads/provider/FA-61.pdf	KINERET® REMICADE® SIMPONI® ORENCIA® STELARA®
	Multiple Sclerosis Agents				
		Injectable			
			AVONEX® AVONEX® ADMIN PACK BETASERON® COPAXONE® QL EXTAVIA® REBIF® QL TYSABRI®	*Trial of only one agent is required before moving to a non-preferred agent*	
		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® EDARBI® EDARBYCLOR® EPROSARTAN IRBESARTAN MICARDIS® TELMISARTAN TEVETEN®
		Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors)			
			BENAZEPRIL BENAZEPRIL HCTZ CAPTOPRIL CAPTOPRIL HCTZ ENALAPRIL ENALAPRIL HCTZ EPANED® £ LISINOPRIL LISINOPRIL HCTZ RAMIPRIL	£ PREFERRED FOR AGES 10 AND UNDER ‡ NONPREFERRED FOR OVER 10 YEARS OLD	ACCURETIC® EPANED® ‡ FOSINOPRIL MAVIK® MOEXIPRIL QUINAPRIL QUINARETIC® TRANDOLAPRIL UNIVASC®

			Preferred Products	PA Criteria	Non-Preferred Products
		Beta-Blockers			
			ACEBUTOLOL ATENOLOL ATENOLOL/CHLORTH BETAXOLOL BISOPROLOL BISOPROLOL/HCTZ BYSTOLIC®* CARVEDILOL LABETALOL METOPROLOL (Regular Release) NADOLOL PINDOLOL PROPRANOLOL PROPRANOLOL/HCTZ SOTALOL TIMOLOL	*Restricted to ICD-9 codes 490-496	
		Calcium-Channel Blockers			
			AFEDITAB CR® AMLODIPINE CARTIA XT® DILTIA XT® DILTIAZEM ER DILTIAZEM HCL DYNACIRC CR® EXFORGE® EXFORGE HCT® FELODIPINE ER ISRADIPINE LOTREL® NICARDIPINE NIFEDIAC CC NIFEDICAL XL NIFEDIPINE ER NISOLDIPINE ER TAZTIA XT® VERAPAMIL VERAPAMIL ER		
		Direct Renin Inhibitors			
			TEKAMLO® TEKTURNA® TEKTURNA HCT® VALTURNA®		AMTURNIDE®

			Preferred Products	PA Criteria	Non-Preferred Products
		Vasodilators			
		Inhaled			
			VENTAVIS® TYVASO®		
		Oral			
			ADCIRCA® LETAIRIS® SILDENAFIL TRACLEER®		ADEMPAS® OPSUMIT® ORENITRAM® REVATIO ®
	Antilipemics				
		Bile Acid Sequestrants			
			COLESTIPOL CHOLESTYRAMINE WELCHOL®		QUESTRAN®
		Cholesterol Absorption Inhibitors			
			ZETIA®		
		Fibric Acid Derivatives			
			FENOFIBRATE FENOFIBRIC GEMFIBROZIL LIPOFEN®		ANTARA® FENOGLIDE® FIBRICOR® LOFIBRA® TRICOR® TRIGLIDE® TRILIPIX®
		HMG-CoA Reductase Inhibitors (Statins)			
			ATORVASTATIN CRESTOR® QL FLUVASTATIN LOVASTATIN PRAVASTATIN SIMVASTATIN		ADVICOR® ALTOPREV® AMLODIPINE/ATORVASTATIN CADUET® LESCOL® LESCOL XL® LIPITOR® LIPTRUZET® LIVALO® MEVACOR® PRAVACHOL® SIMCOR® VYTORIN® ZOCOR®
		Niacin Agents			
			NIASPAN® (Brand only) NIACIN ER (ALL GENERICS)		NIACOR®

	Preferred Products	PA Criteria	Non-Preferred Products
Dermatological Agents			
Antipsoriatic Agents			
Topical Vitamin D Analogs			
	CALCIPOTRIENE		CALCITENE® DOVONEX® CREAM SORILUX® TACLONEX® VECTICAL®
Topical Analgesics			
	LIDOCAINE LIDOCAINE HC LIDOCAINE VISCOUS VOLTAREN® GEL		EMLA® FLECTOR® LIDODERM® QL LIDAMANTLE® PENNSAID®
Topical Antiinfectives			
Acne Agents: Topical, Benzoyl Peroxide, Antibiotics and Combination Products			
	AZELEX® 20% cream BENZACLIN® BENZOYL PEROXIDE (2.5, 5 and 10% only) CLINDAMYCIN ERYTHROMYCIN/BENZOYL PEROXIDE SODIUM SULFACETAMIDE	PA required if over 21 years old	ACANYA DUAC CS® ERYTHROMYCIN CLINDAMYCIN/BENZOYL PEROXIDE GEL SODIUM SULFACETAMIDE/SULFUR
Impetigo Agents: Topical			
	MUPIROCIN OINT		ALTABAX® CENTANY® MUPIROCIN CREAM
Topical Antifungals (onychomycosis)			
	CICLOPIROX SOLN TERBINAFINE TABS	**PA Required**	
Topical Antivirals			
	ABREVA® DENAVIR® ZOVIRAX®, OINTMENT		
Topical Scabicides			
	NATROBA® * NIX® PERMETHRIN RID® SKLICE®	* PA Required	EURAX® LINDANE MALATHION OVIDE® ULESFIA®
Topical Antiinflammatory Agents			
Immunomodulators: Topical			
	ELIDEL® QL	Prior authorization is	

			Preferred Products	PA Criteria	Non-Preferred Products
			PROTOPIC® QL	required for all drugs in this class	
	Topical Antineoplastics				
		Topical Retinoids			
			RETIN-A MICRO®(Pump and Tube) TAZORAC® ZIANA®	Payable only for recipients up to age 21.	ADAPALENE GEL AND CREAM ATRALIN® AVITA® DIFFERIN® EPIDUO® TRETINOIN TRETIN-X® VELTIN®
Electrolytic and Renal Agents					
	Phosphate Binding Agents				
			CALCIUM ACETATE ELIPHOS® FOSRENOL® RENAGEL® RENVELA®		PHOSLO® PHOSLYRA® SEVELAMER CARBONATE VELPHORO®
Gastrointestinal Agents					
	Antiemetics				
		Serotonin-receptor antagonists/Combo			
			GRANISETRON QL ONDANSETRON QL	PA Required for all	AKYNZEO® ANZEMET® QL KYTRIL® QL SANCUSO® ZOFRAN® QL ZUPLENZ® QL
	Antiulcer Agents				
		H2 blockers			
			FAMOTIDINE RANITIDINE RANITIDINE SYRUP*	*PA not required for < 12 years	
		Proton Pump Inhibitors (PPIs)			
			NEXIUM® CAPSULES NEXIUM® POWDER FOR SUSP* PANTOPRAZOLE	PA required if exceeding 1 per day *for children ≤ 12 yrs.	ACIPHEX® DEXILANT® LANSOPRAZOLE OMEPRAZOLE OTC TABS PREVACID® PRILOSEC® PRILOSEC® OTC TABS PROTONIX®

			Preferred Products	PA Criteria	Non-Preferred Products
Gastrointestinal Antiinflammatory Agents					
			ASACOL®SUPP BALSALAZIDE® CANASA® DELZICOL® MESALAMINE ENEMA SUSP PENTASA® SULFASALAZINE DR SULFASALAZINE IR		APRISO® ASACOL HD® COLAZAL® GIAZO® LIALDA ®
Gastrointestinal Enzymes					
			CREON® ZENPEP®		PANCREAZE® PANCRELIPASE PERTZYE® ULTRESA® VIOKACE®
Genitourinary Agents					
Benign Prostatic Hyperplasia (BPH) Agents					
	5-Alpha Reductase Inhibitors				
			AVODART® FINASTERIDE		JALYN® PROSCAR®
	Alpha-Blockers				
			DOXAZOSIN TAMSULOSIN TERAZOSIN		ALFUZOSIN CARDURA® FLOMAX® MINIPRESS® PRAZOSIN RAPAFLO® UROXATRAL®
Bladder Antispasmodics					
			OXYBUTYNIN TABS/SYRUP/ER SANCTURA XR® TOVIAZ® VESICARE®		DETROL® DETROL LA® DITROPAN XL® ENABLEX® FLAVOXATE GELNIQUE® OXYTROL® SANCTURA® TOLTERODINE TROSPIUM
Hematological Agents					
Anticoagulants					
	Oral				
			COUMADIN® ELIQUIS® *	* No PA required if approved Dx code transmitted on claim	

			Preferred Products	PA Criteria	Non-Preferred Products
			JANTOVEN® PRADAXA® * QL WARFARIN XARELTO ® *		
		Injectable			
			ARIXTRA® ENOXAPARIN FRAGMIN®		FONDAPARINUX INNOHEP® LOVENOX®
	Colony Stimulating Factors				
			ARANESP® QL PROCRIT® QL	PA Required Quantity Limit	EPOGEN® QL OMONTYS® QL
	Platelet Inhibitors				
			AGGRENOX® ANAGRELIDE ASPIRIN BRILINTA® * QL CILOSTAZOL® CLOPIDOGREL DIPYRIDAMOLE TICLOPIDINE	* PA Required	EFFIENT® * QL PLAVIX® ZONTIVITY®
Hormones and Hormone Modifiers					
	Androgens				
			ANDROGEL® ANDRODERM®	**PA Required** **PA Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-72.pdf	AXIRON® FORTESTA® 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®		

			Preferred Products	PA Criteria	Non-Preferred Products
		Dipeptidyl Peptidase-4 Inhibitors			
			JANUMET® JANUMET XR® JANUVIA® JENTADUETO® JUVISYNC® KOMBIGLYZE XR® ONGLYZA® TRADJENTA®		KAZANO® NESINA® OSENI®
		Incretin Mimetics			
			BYDUREON® * BYETTA® * VICTOZA® *	* PA Required	TANZEUM® TRULICITY®
		Insulins (Vials and Pens)			
			APIDRA® HUMALOG® HUMULIN® LANTUS® LEVEMIR ® NOVOLIN® NOVOLOG®		
		Meglitinides			
			NATEGLINIDE (Starlix®) PRANDIMET® PRANDIN® STARLIX®		
		Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors			
			FARXIGA® INVOKANA®		INVOKAMET® JARDIANCE® XIGDUO XR®
		Sulfonylureas			
			AMARYL® CHLORPROPAMIDE DIABETA® GLIMEPIRIDE (Amaryl®) GLIPIZIDE (Glucotrol®) GLUCOTROL® GLUCOVANCE® GLIPIZIDE EXT-REL (Glucotrol XL®) GLIPIZIDE/METFORMIN (Metaglip®) GLYBURIDE MICRONIZED (Glynase®)		

			Preferred Products	PA Criteria	Non-Preferred Products
			GLYBURIDE/METFORMIN (Glucovance®) GLUCOTROL XL® GLYBURIDE (Diabeta®) GLYNASE® METAGLIP® TOLAZAMIDE TOLBUTAMIDE		
		Thiazolidinediones			
			ACTOPLUS MET XR® ACTOS® ACTOPLUS MET® AVANDAMET® AVANDARYL® AVANDIA® DUETACT®		
	Pituitary Hormones				
		Growth hormone modifiers			
			GENOTROPIN® NORDITROPIN®	**PA Required for entire class** https://www.medicaid.nv.gov/Downloads/provider/FA-67.pdf	HUMATROPE® NUTROPIN AQ® OMNITROPE® NUTROPIN® SAIZEN® SEROSTIM® SOMAVERT® TEV-TROPIN® ZORBTIVE®
	Progestins for Cachexia				
			MEGESTROL ACETATE, SUSP		MEGACE ES®
Musculoskeletal Agents					
	Antigout Agents				
			ALLOPURINOL		
	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®		
	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 NAMENDA® TABS NAMENDA® XR TABS RIVASTIGMINE CAPS		ARICEPT® 23mg ARICEPT® GALANTAMINE GALANTAMINE ER RAZADYNE® RAZADYNE® ER
	Anticonvulsants				
			BANZEL® CARBAMAZEPINE CARBAMAZEPINE XR CARBATROL ER® CELONTIN® DEPAKENE® DEPAKOTE ER® DEPAKOTE® DIVALPROEX SODIUM DIVALPROEX SODIUM ER EPITOL® ETHOSUXIMIDE FELBATOL® GABAPENTIN GABITRIL® KEPPRA® KEPPRA XR®	PA Required for members under 18 years old	APTIOM® FYCOMPA® OXTELLAR XR® POTIGA® QUDEXY XR® TROKENDI XR®

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

			Preferred Products	PA Criteria	Non-Preferred Products
			PHENYTEK® PHENYTOIN PRODUCTS		
	Anti-Migraine Agents				
		Serotonin-Receptor Agonists			
			RELPAX® SUMATRIPTAN NASAL SPRAY SUMATRIPTAN INJECTION SUMATRIPTAN TABLET ZOMIG® ZMT	PA Required for exceeding Quantity Limit	AMERGE® AXERT® FROVA® IMITREX® MAXALT® TABS MAXALT® MLT NARATRIPTAN SUMAVEL® TREXIMET® ZOMIG®
	Antiparkinsonian Agents				
		Non-ergot Dopamine Agonists			
			PRAMIPEXOLE ROPINIROLE ROPINIROLE ER		MIRAPEX® MIRAPEX® ER NEUPRO® REQUIP® REQUIP XL®
	Fibromyalgia agents				
			CYMBALTA® LYRICA® SAVELLA®	*No PA required for drugs in this class if ICD-9 code=729.1.*	
Ophthalmic Agents					
	Antiglaucoma Agents				
		Carbonic Anhydrase Inhibitors/Beta-Blockers			
			ALPHAGAN P® AZOPT® BETAXOLOL BETOPTIC S® BRIMONIDINE CARTEOLOL COMBIGAN® DORZOLAM DORZOLAM / TIMOLOL LEVOBUNOLOL METIPRANOLOL SIMBRINZA® TIMOLOL DROPS/ GEL SOLN		ALPHAGAN® BETAGAN® BETOPTIC ® COSOPT® COSOPT PF® OCUPRESS® OPTIPRANOLOL® TIMOPTIC® TIMOPTIC XE® TRUSOPT®
		Ophthalmic Prostaglandins			
			LATANOPROST TRAVATAN®		LUMIGAN® XALATAN®

			Preferred Products	PA Criteria	Non-Preferred Products
			TRAVATAN Z® ZIOPTAN®		
	Ophthalmic Antihistamines				
			ALAWAY® BEPREVE® PATADAY® ZADITOR OTC®		ELESTAT® EMADINE® LASTACRAFT® OPTIVAR® PATANOL®
	Ophthalmic Antiinfectives				
		Ophthalmic Macrolides			
			ERYTHROMYCIN OINTMENT		
		Ophthalmic Quinolones			
			BESIVANCE® CIPROFLOXACIN MOXEZA® OFLOXACIN® VIGAMOX®		CILOXAN® ZYMAXID®
	Ophthalmic Antiinflammatory Agents				
		Ophthalmic Corticosteroids			
			ALREX® DEXAMETHASONE DUREZOL® FLUOROMETHOLONE LOTEMAX® PREDNISOLONE		FLAREX® FML® FML FORTE® MAXIDEX® OMNIPRED® PRED FORTE® PRED MILD® VEXOL®
		Ophthalmic Nonsteroidal Antiinflammatory Drugs (NSAIDs)			
			ACULAR® ACULAR LS® ACULAR PF® DICLOFENAC FLURBIPROFEN NEVANAC®		ACUVAIL® BROMDAY® BROMFENAC® ILEVRO® PROLENSA®
Otic Agents					
	Otic Antiinfectives				
		Otic Quinolones			
			CIPRODEX® OFLOXACIN		
Psychotropic Agents					
	ADHD Agents				
			AMPHETAMINE SALT COMBO XR	**PA Required for entire class**	ADDERALL® ADDERALL XR®

			Preferred Products	PA Criteria	Non-Preferred Products
			AMPHETAMINE SALT COMBO DEXMETHYLPHENIDATE DEXTROAMPHETAMINE SA DEXTROAMPHETAMINE TAB DEXTROSTAT® FOCALIN XR® INTUNIV® METADATE CD® METHYLIN® METHYLIN ER® METHYLPHENIDATE METHYLPHENIDATE ER (All forms generic extended release) METHYLPHENIDATE SOL QUILLIVANT® XR SUSP RITALIN LA® STRATTERA® VYVANSE®	**Adult Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-68.pdf **Children's Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-69.pdf * (No PA required for ICD-9 codes 347.00, 347.01, 347.10, 347.11, 780.53 and 780.57)	CONCERTA® DAYTRANA® DESOXYN® DEXEDRINE® FOCALIN® KAPVAY® MODAFINIL NUVIGIL® METADATE ER® PROVIGIL®* PROCENTRA® RITALIN®
Antidepressants					
	Other				
			BUPROPION BUPROPION SR BUPROPION XL CYMBALTA®(PA not required for ICD-9 code 729.1 or MIRTAZAPINE MIRTAZAPINE RAPID TABS PRISTIQ® TRAZODONE VENLAFAXINE (ALL FORMS)	PA Required for members under 18 years old	APLENZIN® BRINTELLIX® DULOXETINE 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					

			Preferred Products	PA Criteria	Non-Preferred Products
		Atypical Antipsychotics			
			ABILIFY® CLOZAPINE FANAPT® LATUDA® OLANZAPINE QUETIAPINE RISPERIDONE SAPHRIS® SEROQUEL XR® ZIPRASIDONE	**PA Required for Ages under 18 years old** **PA Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-70.pdf	CLOZARIL® FAZACLO® GEODON® INVEGA® RISPERDAL® SEROQUEL® ZYPREXA®
	Anxiolytics, Sedatives, and Hypnotics				
			ESTAZOLAM FLURAZEPAM ROZEREM® * TEMAZEPAM TRIAZOLAM ZOLPIDEM	*(PA not required for ICD-9 code 307.42) PA Required for members under 18 years old	AMBIEN® AMBIEN CR® DORAL® EDLUAR® INTERMEZZO® LUNESTA® SILENOR® SOMNOTE® SONATA® ZALEPLON ZOLPIDEM CR ZOLPIMIST®
Respiratory Agents					
	Nasal Antihistamines				
			ASTEPRO® DYMISTA® PATANASE®		AZELASTINE
	Respiratory Antiinflammatory Agents				
		Leukotriene Receptor Antagonists			
			MONTELUKAST ZAFIRLUKAST		ACCOLATE® SINGULAIR®
		Respiratory Corticosteroids			
			ASMANEX® BUDESONIDE NEBS* FLOVENT DISKUS® QL FLOVENT HFA® QL PULMICORT FLEXHALER® PULMICORT RESPULES®* QVAR®	*No PA required if < 4 years old	AEROSPAN HFA® ALVESCO® ARNUITY ELLIPTA®
		Nasal Corticosteroids			
			FLUTICASONE NASONEX®		BECONASE AQ® FLONASE®

			Preferred Products	PA Criteria	Non-Preferred Products
					FLUNISOLIDE NASACORT AQ® OMNARIS® QNASL® RHINOCORT AQUA® TRIAMCINOLONE ACETONIDE VERAMYST® ZETONNA®
		Phosphodiesterase Type 4 Inhibitors			
			DALIRESP® QL	PA Required	
	Respiratory Antimuscarinics				
			ANORO ELLIPTA® COMBIVENT RESPIMAT® IPRATROPIUM/ALBUTEROL NEBS QL IPRATROPIUM NEBS SPIRIVA®	Only one agent per 30 days is allowed	INCRUSE ELLIPTA® SPIRIVA RESPIMAT® TUDORZA®
	Respiratory Beta-Agonists				
		Long-Acting Respiratory Beta-Agonist			
			ARCAPTA NEOHALER® FORADIL® SEREVENT DISKUS® QL		BROVANA® PERFOROMIST® SOLUTION FOR INHALATION STRIVERDI RESPIMAT®
		Short-Acting Respiratory Beta-Agonist			
			ALBUTEROL NEB/SOLN PROVENTIL® HFA PROAIR® HFA XOPENEX® HFA* QL XOPENEX® Solution* QL	* PA required	MAXAIR AUTOHALER® VENTOLIN HFA® LEVALBUTEROL
	Respiratory Corticosteroid/Long-Acting Beta-Agonist Combinations				
			ADVAIR DISKUS® ADVAIR HFA® DULERA® SYMBICORT®		BREO ELLIPTA®
Toxicology Agents					
	Antidotes NEW				
		Opiate Antagonists NEW			
			EVZIO ® NEW NALOXONE NEW	* Injectable can be used intranasally with nasal atomizer	
	Substance Abuse Agents				
		Mixed Opiate Agonists/Antagonists			
			BUNAVAIL® SUBOXONE®	PA Required for class	BUPRENORPHINE/NALOXONE ZUBSOLV®

Tab: References

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

STATE OF NEVADA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
DIVISION OF HEALTH CARE FINANCING AND POLICY
1100 E. William Street, Suite 101
Carson City, Nevada 89701
www.dhcfp.nv.gov

RICHARD WHITLEY
Interim Director

LAURIE SQUARTSOFF
Administrator

Nevada Medicaid
P&T Committee.
Draft Meeting Minutes

The Division of Health Care Financing and Policy (DHCFP) P&T Committee. conducted a public meeting on March 26, 2015 beginning at 1:00 pm at the following location:

South Point Casino/Hotel
9777 Las Vegas Blvd. S.
Las Vegas, NV 89183

Committee. Members Present:
Mark Decerbo, Pharm.D.; David Fluitt, RPh; Shamim Nagy, MD; Weldon Havins, MD; Joseph Adashek, MD; Bill Evans, MD; Mike Hautekeet, RPh; Adam Zold, Pharm.D.

Committee. Members Absent:
Amir Qureshi, MD; Evelyn Chu, Pharm.D.

Others Present:
DHCFP:
Coleen Lawrence, Chief, Program Services; Mary Griffith, RN, Pharmacy Services Specialist; Shannon Richards, Deputy Attorney General;

HPES:
Beth Slamowitz, Pharm.D.

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

Others:
Pamela Vincent, Indivio; Barbara Glover, CF Center of Southern NV; Julia Harder, AZ; Caroline Nguyen, AZ; Pat Wiseman, AZ; Anne Marie Licos, AZ; Theresa Beukert, Eisai; Charlie Collins, Gilead; Lovell Robinson, Abbvie; Vicky Voss, Salix; Tom O'Connor, Novartis; Becky Gonzales, Viiv Healthcare; Brad Willie, Novartis; Deron Grothe, Teva; Gregg Gittus, Alkerines; Marykay Queener, J&J; Charissa Anne, J&J; Sergio Gonzalez, Takeda; Marcus Laughlin, BI; Kirk B Lane, UT; Cynthia Patterson, BDSI; Bob

Gustafson, Lundbeck; David Melikian, Mallinckrodt; Wendy Joles, Mallinckrodt; Lee Marks, Orexo; Rupa Shah, Purdue, Samantha Min, Otsuka; Shelby Foral, Mylan; Lee Stont, Chesi; Chris Holtzer, Abbvie; Rob Bigham, Shire; George Yasutake, Actelion; Scott Larson, BMS; Melissa Walsh, Novartis; Akshaya Patel, Mylan; Betty Chan, Gilead; Phil Walsh, Sunovion; Berlain Aloune, Marck; Sandy Sierawski, Pfizer

I. CALL TO ORDER AND ROLL CALL

Meeting called to order at 1:13PM

Roll Call
Joseph Adashek
Mike Hautekeet
David Fluit
Shannon Richards
Shamim Nagy
Weldon Havins
Bill Evans
Adam Zold
Mark Decerbo
Coleen Lawrence - DHCFP
Mary Griffith - DHCFP
Beth Slamowitz - HP
Kevin Whittington - Catamaran
Carl Jeffery - Catamaran

II. PUBLIC COMMENT
No Public Comment.

III. **FOR POSSIBLE ACTION**: Review and approval of the November 13, 2014 meeting minutes.
Voted – Ayes across the Committee.
Motion approved.

IV. STATUS UPDATE BY DHCFP – Coleen Lawrence

Update for Preferred Drug List – Yesterday (03/25/15) SV 422, NV Medicaid's budget bill regarding the preferred drug list, was released. The goal was to eliminate the "sunset expiration" on the current NRS 422.4025. That is where the preferred drug list regulation lays for the Division of Healthcare Finance and Policy. The Sunset Bill allows us to manage atypical and typical classes of drugs. If the bill does not go forward, effective 07/01/15, the Division will no longer be able to manage atypical and typical psychotropic medications. The bill that was submitted requests that the sunset be eliminated to allow

the Division to continue to manage this drug list. The Division, along with stakeholders, and the P&T Committee, feels that they have been very transparent since the inception of the PDL in 2003 and implementation in 2004. They have been able to successfully manage the preferred drug list without hampering or impeding access to care for any Medicaid recipients.

There has been discussion that instead of eliminating the sunset timeframe, that it may extended, which happened in the last legislative session. The sunset language was postponed from 2013 to 2015. Due to negotiations, it may be extended again rather than eliminated. With an extension, we would be able to continue to manage the atypical and typical antipsychotic medications on the preferred drug list and the regulation would continue to read as it does today.

The sunset language has nothing to do with the Committee itself, it just allows us to manage the atypical and typical medications on the preferred drug list. If the language remains with no extension, or elimination, it would become a prohibited class that the Division would not be allowed to manage on the preferred drug list. They would still be accessible, but not managed on the preferred drug list. The possible extension length is unknown at this time. Coleen will keep the Committee. members up-to-date as this develops.

PDL Formulary – Overarching goal through the Division to streamline processes and different aspects of the benefit plans between Fee-For-Service and Managed Care. The PDL has received the most feedback from physicians and providers. We cannot have the exact same formulary for both FFS and MC, but we can have the same look and feel between the two. This will result in less effort to look at and review the two because the reviewers will be used to the same look and their eyes will be trained. HP and Catamaran have reworked and created new Fee-For-Service formulary to match the existing Managed Care formulary. Draft formulary was provided to the Committee. Carl Jeffery of Catamaran suggested that the Committee. provide feedback on the formulary and is open to suggestions for any needed changes and recommendations. Beth Slamowitz noted the addition of indicators for quantity limits, age limits, diagnosis codes, PA codes etc. This was a result of changing the formulary to read in a very similar way to the existing Managed Care formularies.

Committee members reappointment – Several members are up for reappointment. Coleen advised that reappointments do not go through her office, but rather the Governor's office. Reappointments will need to be completed before the next Committee. meeting in June 2015.

Discussion / Comment: None

V. **FOR POSSIBLE ACTION**: Discussion of Medicaid Services Manual Chapter 1200 regarding preferred antidepressants

Carl Jeffery – Catamaran – Medicaid Services Manual Chapter 1200 dictates what people need to move to a non-preferred agent. The PDL Exception Criteria was presented and Carl noted that in the list of criteria, #7 is not a good indicator of Continuity of Care due to the possibility that a patient could be taken off their medication after 90 days or be forced to switch to something else.

Carl asked the Committee for their opinions on changing the wording for Criteria #7. Possibly removing the 90 day requirement and saying if the patient comes out of an acute care hospital stabilized on meds, they can continue on those meds indefinitely. These same criteria are true for atypical antipsychotics, anticonvulsants, and antidiabetic medications. The wording is odd that they called out only antidepressants with these criteria.

Coleen added that maybe there should be an institutional clause added to the criteria. Institutional Continuity of Care. She asked the Committee if they want the patients after 90 days to have to change to a PDL drug or do they want them to continue with the regimen they have. For example, one suggestion, for continuity of care from discharge from an institution, the recipient may be grandfathered on that medication. The suggestion is to change the class and the timeframe.
In the very beginning, antidepressants were the original to be reviewed. Atypical and typical were not being reviewed. The antidepressant review was deferred over to the DUR Board. The DUR Board made the first review on this. The goal is Continuity of Care from discharge from an institution. Coleen suggested that the wording be changed to eliminate the distinguishing factor of being a specific class of psychotropic medication and the timeframe. Our Senior Deputy Attorney General wants the change to come through the P&T Committee..

MH: A continuity of care clause for psychotropic medications for discharge from an institution, grandfather those patients who have been discharged from an institution by allowing them to remain on their discharge regimen medication even after the initial 90 days.
Motion seconded., JA.
Committee voted: Ayes across the Committee.
Motion approved.

VI. NEW DRUG CLASSES

A. AGENTS USED TO TREAT OPIOID ADDICTION

1. **Public Comment: Dr. Pam Vincent** – Indivior – presented some important changes in the prescribing information that occurred last spring for Suboxone sublingual
No questions from the Committee.

Public Comment - Lee Marx: State Government Executive with Orexo – Manufacturer of Zubsolv – a drug under a new drug class being considered today. Mr. Marx is asking to include Zubsolv as a preferred drug on the State's PDL. He presented a hand-out to the Committee.

Question from Committee: When Zubsolv is prescribed, does the physician have to have an X number?
Marx: Yes, when it is being used in the treatment of opioid dependency.
Committee. member: This can be circumvented when a prescriber adds the amount and "As needed for pain".

Marx: Yes, a physician can write whatever prescription they want, so they can write for pain.
Question from Committee: As a pharmacist, we are only allowed to dispense the products if the physician has an X number, or if the directions state specifically "As needed for pain." So any physician can write the prescription, and there is no control. We don't know who it is for. We don't know if it's for a dependency, or is it just for pain?
Marx: We would support the motion for any Zubsolv product, for this class of drug, in this category, to be only used for opioid dependency.
Question from Committee.: Could we attach a certain ICD-9 code to allow this drug to be used for dependency rather than for pain?
Marx: I would ask the State of Nevada to add that specification.

Coleen covered the meeting ground rules.

2. **Public Comment - Cynthia Patterson – Medical Science Liaison with BioDelivery Sciences International:** Speaking to the rationale regarding access of Bunavail to the appropriate Nevada Medicaid patients.

No questions from the Committee.

3. **Drug Class Review Presentation** – Catamaran – Carl Jeffery - 4 agents used to treat opioid addiction – Suboxone, Bunavail, Subsolv, and Buprenorphine/Naloxone. Catamaran recommends that these drugs be considered clinically and therapeutically equivalent.

DF, Motion: Approval of all agents in this class being considered clinically and therapeutically equivalent.
Motion seconded.
Committee Voted: Ayes across the Committee.
Motion approved.

Catamaran recommends that the Suboxone and the Bunavail be made preferred and then the Buprenorphine/Naloxone and Zubsolv be made non-preferred on the PDL. The reason for this is that the Suboxone has the gross market share at this point. To shift that would be overtly difficult and the Bunavail because it has the abuse deterrent technology in it.

Question from the Committee: Do all of them still require Prior Authorization?
Carl: Yes, they all still require Prior Authorization.
Question for the Committee: We've seen with some of these drugs that they maybe more tolerant by patients. Is this reflected in the success rate of treatment plans?

Carl: There haven't been any reports of patients dropping out of treatment due to how the medication is administered (holding pill under tongue vs. film).
Question from the Committee: You have to get a Prior Authorization for either preferred or non-preferred, so what is the difference?
Carl: For the non-preferred, you'd have to meet both criteria. You'd have to meet the clinical criteria and the non-preferred criteria. In essence, to get Zubsolv, if this motion were to go through, which is what we recommend, they would have to meet their criteria which is in the chapter 1200 designed by the DUR Board. In addition, they would have to try or have some contraindication as to why they can't take the two preferred agents.

Motion: Approve the drug preferred/non-preferred as presented.
Motion seconded.
Committee Voted: Ayes Across the Committee.
Motion approved.

B. INHALED AMINOGLYCOSIDES FOR THE TREATMENT OF CYSTIC FIBROSIS

1. **Public Comment:** None.

Drug Class Review Presentation – Catamaran – Tobramycin is the only drug currently being reviewed today. There are a couple different dosage forms and that is where they differ. Three agents are nebulized products and then there is the addition of the Tobi Podhaler. Catamaran recommends to consider these all clinically and therapeutically equivalent. No head-to-head trials have seen one agent over the other.

Questions: None.
Motion: Consider all drugs in the class clinically and therapeutically equivalent.
Motion seconded.
Committee. Voted: Ayes Across the Committee.
Motion approved.

Catamaran's recommendation is to accept all drugs in this class as preferred. This is simply to provide access to this vulnerable population.

Questions: None.
Motion: Approve all drugs in this class as preferred.
Motion seconded.
Committee Voted: 7 Aye.
1 Nay.
Motion approved.

VII. ESTABLISHED DRUG CLASSES

A. GASTROINTESTINAL AGENTS: PANCREATIC ENZYMES

1. **Public Comment – Barbara Glover – Cystic fibrosis Coordinator for the CF Center Southern Nevada:** Committee. was given handout. Presentation about pancreatic enzymes. Asks that ALL enzymes be added to the PDL.

Question from Committee: Have you had trouble getting the non-preferred enzymes?
Glover: No trouble, asking as preemptive. Are there any on the non-preferred side that you see being used so much that it would be difficult to get the PA?
Glover: The ones that are non-preferred that are written more are Pancreaze and Ultresa.

2. **Drug Class Review Presentation** – Catamaran – The reason we brought this class up is because it was recommended in the last meeting. There are no recommendations from Catamaran to change the preferred list. We recommend that all drugs be considered clinically and therapeutically equivalent.

Questions: None.
Motion: Consider all drugs in the class clinically and therapeutically equivalent.
Motion seconded.
Committee. Voted: Ayes Across the Committee.
Motion approved.

VIII. ESTABLISHED DRUG CLASSES BEING REVIEWED DUE TO THE RELEASE OF NEW DRUGS.

A. ANALGESICS: LONG ACTING NARCOTICS

1. Public Comment – Sandy Sierawski – Pharmacist in State of Nevada: – Pfizer in Medical Division – She presented on prescription misuse and abuse of opioids in this drug class. She provided a handout to the Committee. with warnings and indications for Embeda.

Public Comment – Rupa Shaw: Medical Science Liaison Purdue Pharma – presentation on Hysingla ER. She went over warnings and indications, and provided the Committee with a handout.

Public Comment – David Malickian: Director of Global Medical Affairs – Mallinckrodt Pharmaceuticals presented on Xartemis XR . This drug was placed in the category of long acting opioids , but the FDA does not consider it a long acting opioid.

Question from the Committee: Are you suggesting that we remove it from long-acting opioids?
Malickian: Yes.

2. Drug Class Review Presentation – Catamaran – presented drugs, makeup, warnings, indications, and tiers.

Questions: None.
Motion: Consider all drugs in the class clinically and therapeutically equivalent.
Motion seconded.
Committee Voted: Ayes Across the Committee.
Motion approved.

Catamaran's recommendation is to make the two new drugs on the market, Embeda and Hysingla ER non-preferred at this time to see what happens with the market.

Questions: None.
Motion: Motion to approve drugs that Catamaran recommended as preferred, but bring back the AD drugs for discussion and consideration next time.
Motion seconded.
Committee Voted: Ayes across the Committee.
Motion approved.

B. DIABETIC AGENTS: SGLT-2 INHIBITORS

1. **Public Comment – Bill O'Neill:** Jardiance – He discussed warnings, indications, and study results. He requested that Jardiance be moved to preferred.

Question from the Committee: Do you see an A1C difference between Jardiance and other drugs in the category?
O'Neill: Similar to Invokana.

Public Comment - Caroline Winn: Pharmacist AstraZenica – Medical Science Liaison. She presented on Xigduo XR. She discussed makeup, warnings, indications, and study results. She requested that Xigduo XR be added to the preferred drug list.

Public Comment – Mary Kay Queener: Medical Science Liaison with Jannssen, Invokana and Invokamet. She gave an update regarding warnings and indications. She encouraged the Committee to add Invokamet to the PDL.

2. **Drug Class Review Presentation** – Catamaran – Reviewing Xigduo XR – Dr. Jeffery discussed studies. Catamaran recommended to the Committee to consider all drugs in the class clinically and therapeutically equivalent.

Questions: None.
Motion: Consider all drugs in the class clinically and therapeutically equivalent.
Motion seconded.
Committee Voted: Ayes Across the Committee.
Motion approved.

Catamaran recommended to make the new Xigduo XR non-preferred and keep the rest the same because each product in the combination is available independently.

Questions: None.
Motion: Approve Catamaran's recommendation.
Motion seconded.
Committee Voted: Ayes across the Committee.
Motion approved.

C. DIABETIC AGENTS: INCRETIN MIMETICS

1. **Public Comment:** None.

2. **Drug Class Review Presentation** – Catamaran –The new drug in the class is Trulicity. Dr. Jeffery went over dosage, administration, and clinical information.

Questions: None.
Motion: Consider all drugs in the class clinically and therapeutically equivalent.
Motion seconded.
Committee Voted: Ayes Across the Committee.
Motion approved.

Catamaran's recommendation is that the new agent Trulicity be considered non-preferred and keep the rest of the medications the same.

Questions: None.
Motion: Approve all drugs in this class as preferred.
Motion seconded.
Committee Voted: Ayes across the Committee.
Motion approved.

D. DIABETIC AGENTS: OTHER AGENTS

1. **Public Comment - Dr. Alex Morray PhD,** for Cycloset. He discussed makeup, warnings, indications, and the study results.

Drug Class Review Presentation – Catamaran – Dr. Jeffery discussed Cycloset, and the study results. Catamaran recommended that these drugs in the class be considered clinically and therapeutically equivalent.

Questions: None.
Motion: Consider all drugs in the class clinically and therapeutically equivalent.
Motion seconded.
Committee Voted: Ayes Across the Committee.
Motion approved.

Catamaran's recommendation is to make Cycloset non-preferred.

Questions: None.
Motion: Make Cycloset non-preferred.
Motion seconded.
Committee Voted: **6 Ayes.**
2 Nays.

Motion approved.

E. RESPIRATORY: INHALED ANTICHOLINERGIC AGENTS

1. **Public Comment – Bill O'Neill:** Spiriva Respimat. He discussed the Respimat device, requesting the Committee consider putting the Respimat device on the PDL.

Question from the Committee: Do you have the studies that show less hospitalizations with the Spiriva medication?
O'Neill: Yes.

Public Comment - Julia Harder, Pharmacist, AstraZeneca. She discussed Tudorza., giving an overview including clinical data. She provided indications, warnings, and studies, and requested Tudorza be included on the PDL.

2. **Drug Class Review Presentation** – Catamaran – Dr. Jeffery discussed the two new agents, Incruse Ellipta and Spiriva Respimat. He gave an overview of studies, indications, and warnings. Catamaran recommends that the agents in this class be considered clinically and therapeutically equivalent.

Questions: None.
Motion: Consider all drugs in the class clinically and therapeutically equivalent.
Motion seconded.
Committee. Voted: Ayes Across the Committee.
Motion approved.

Catamaran's recommendation is the Spiriva Respimat and the Incruse Ellipta be considered non-preferred and the rest stay the same.

Questions: None.
Motion: Accept Catamaran's recommendations for the PDL as indicated.
Motion seconded.
Committee Voted: Ayes across the Committee.
Motion approved.

F. RESPIRATORY: LONG ACTING BETA ADRENERGICS

1. **Public Comment – Bill O'Neill** discussed Striverdi Respimat.

Public Comment – Pharmacist Akshaya Patel for Mylan discussed Performist. It is not listed on the PDL on either the preferred or the non-preferred side. An overview was presented including an overview of the drug, warnings, indications, and study results.

2. Drug Class Review Presentation – Catamaran – Dr. Jeffery discussed drugs in this class. He gave study results, warnings, and indications. Catamaran would like to recommend that all drugs in this class be considered clinically and therapeutically equivalent with the addition of the Performist.

Questions: None.
Motion: Consider all drugs in the class clinically and therapeutically equivalent with the addition of Performist.
Motion seconded.
Committee Voted: Ayes Across the Committee.
Motion approved.

Catamaran's recommendation is to include the Striverdi and Performist as non-preferred and keep the rest of the class the same.

Questions: None.
Motion: Accept Catamaran's recommendations for Striverdi and Perfomist as non-preferred and keep the rest of the class the same.
Motion seconded.
Committee Voted: Ayes across the Committee.
Motion approved.

G. RESPIRATORY: INHALED CORTICOSTEROIDS/NEBS

1. **Public Comment - None**

2. Drug Class Review Presentation – Catamaran – Dr. Jeffery discussed the old and new products on the market. He presented indications, warnings, and study results. Catamaran recommends that all agents in this class of drugs be considered clinically and therapeutically equivalent.

Questions: None.
Motion: Consider all drugs in the class clinically and therapeutically equivalent.
Motion seconded.
Committee Voted: Ayes Across the Committee.
Motion approved.

Catamaran's recommendation is to make Arunuty Ellipta and Aerospan HFA non-preferred and leave all other drugs the same.

Questions: None.
Motion: Accept Catamaran recommendations.
Motion seconded.
Committee voted: **Ayes across the Committee.**
Motion approved.

H. PULMONARY ARTERIAL HYPERTENSION: ORAL AGENTS

1. **Public Comment – Kirk B. Lane,** UT, discussed Orenitram. He provided studies, warnings, indications, and dose information. He requested Orenitram be placed on the PDL.

Public Comment – Dr. George Yasutake, Actelion discussed Opsumit , including studies and outcomes.

2. Drug Class Review Presentation – Catamaran – Dr. Jeffery discussed drugs in this drug class including drug trials. Catamaran recommended that the drugs in this class be considered clinically and therapeutically equivalent.

Questions: None.
Motion: Consider all drugs in the class clinically and therapeutically equivalent.
Motion seconded.
Committee Voted: Ayes Across the Committee.
Motion approved.

Catamaran's recommendation is to consider the new product Orenitram as non-preferred and keep the rest of the drugs on the list as is.

Questions: None.
Motion: Approve Catamaran's recommendation.
Motion seconded.
Committee voted: Ayes Across the Committee.
Motion approved.

I. ANTIEMETICS: ORAL, 5-HT3S

1. **Public Comment – Theresa Beukert**, Eisai Pharmaceuticals, discussed the makeup, dosage, warning, studies, and indications for Akynzeo .

2. Drug Class Review Presentation – Catamaran – Dr Jeffery discussed Akynzeo. Catamaran made the recommendation that the drugs in this class be considered clinically and therapeutically equivalent.
Questions: None.
Motion: Consider all drugs in the class clinically and therapeutically equivalent.
Motion seconded.
Committee Voted: Ayes Across the Committee.
Motion approved.

Catamaran's recommendation is to make Akynzeo non-preferred and leave the other drugs as they are.

Questions: None.
Motion: Approve Catamaran's recommendations.
Motion seconded.
Committee Voted: Ayes Across the Committee.
Motion approved.

J. GASTROINTESTINAL AGENTS: ULCERATIVE COLITIS

1. **Public Comment – Ed Himenson,** discussed Apriso, including indications, dosage, makeup, studies, and warnings.

2. Drug Class Review Presentation – Catamaran – Dr. Jeffery discussed Colazal and Giazo, as well as Balsalazide. He discussed studies, the differences between the drugs, and the dosages. Catamaran made the recommendation that the drugs in this class be considered clinically and therapeutically equivalent.

Questions: None.
Motion: Consider all drugs in the class clinically and therapeutically equivalent.
Motion seconded.
Committee Voted: Ayes Across the Committee.
Motion approved.

Catamaran's recommendation is to consider the generic Balsalazide as preferred and keep Colazal and Giazo as non-preferred.

Questions: None.
Motion: Approve Catamaran's recommendation.
Motions seconded.
Committee Voted: Ayes Across the Committee.
Motion approved.

K. ANDROGENIC AGENTS

2. **Public Comment** – None.

Drug Class Review Presentation – Catamaran –Dr. Jeffery discussed Striant, the application, dosage, and efficacy. Catamaran makes the recommendation that the drugs in this class be considered clinically and therapeutically equivalent.

Questions: None.
Motion: Consider all drugs in the class clinically and therapeutically equivalent.
Motion seconded.
Committee Voted: Ayes Across the Committee.
Motion approved.

Catamaran's recommendation is to make Striant non-preferred and keep the rest of the list as is.

Questions: None.
Motion: Approve Catamaran's recommendation.
Motion seconded.
Committee Voted: Ayes across the Committee.
Motion approved.

L. HEPATITIS C AGENTS - ANTIVIRALS: HEPATITIS C POLYMERASE INHIBITORS/COMBINATIONS

1. **Public Comment –** None.

2. Drug Class Review Presentation – Catamaran – Dr. Jeffery discussed Harvoni and Viekira Pak. He provided an overview of Hep-C. And he discussed indications, dosage, and guidelines of Harvoni and Viekira Pak. Catamaran makes the recommendation that the drugs in this class be considered clinically and therapeutically equivalent.

Questions: None.
Motion: Consider all drugs in the class clinically and therapeutically equivalent.
Motion seconded.
Committee Voted: Ayes Across the Committee.
Motion approved.

Catamaran's recommendation is to make all the drugs in this class preferred.

Questions: None.
Motion: Approve Catamaran's recommendation.

Motion seconded.
Committee Voted: Ayes across the Committee.
Motion approved.

VIII. REPORT BY CATAMARAN ON THE NEW DRUGS TO MARKET, NEW GENERIC DRUGS TO MARKET, AND NEW LINE EXTENSIONS – Outlook is in the meeting binder.

IX. REVIEW OF NEXT MEETING LOCATION, DATE, AND TIME
A. June 25, 2015

X. PUBLIC COMMENT – None.

XI. ADJOURNMENT

Tab: March Meeting Minutes

Tab: New Drug Classes

New Drug Overview
Diclegis® (doxylamine succinate/pyridoxine hydrochloride)

- **Overview/Summary:** Diclegis® (doxylamine succinate/pyridoxine hydrochloride) is a fixed dose combination drug product of doxylamine succinate, an antihistamine, and pyridoxine hydrochloride, a vitamin B6 analog. The agent is Food and Drug Administration (FDA)-approved for the treatment of nausea and vomiting of pregnancy (NVP) in women who do not respond to conservative management. It should be noted that the agent has not been studied in hyperemesis gravidarum.[1] The combination of doxylamine and pyridoxine was previously available in the United States under the brand name Bendectin®. However this product was removed from the market in 1983 due to law suits alleging teratogenicity, although scientific evidence supports the safety and efficacy of the medication. A meta-analysis of controlled studies on outcome of pregnancies exposed to Bendectin® reported no increase in the incidence of birth defects.[2]

  Doxylamine competes with histamine for H1-receptor sites and blocks the chemoreceptor trigger zone thereby decreasing nausea and vomiting. Antihistamine agents also work indirectly on the vestibular system by decreasing stimulation of the vomiting center. Hypotheses to explain the antiemetic effects of pyridoxine include prevention/treatment of vitamin B6 deficiency, intrinsic antinausea properties, and/or synergy with the antinausea properties of antihistamine.[1-3]

  Nausea with or without vomiting is common in early pregnancy and affects 70 to 85% of pregnant women.[2,4] Severe vomiting resulting in dehydration and weight loss is termed hyperemesis gravidarum and occurs infrequently. The treatment goals in patient with NVP are to reduce symptoms through changes in diet/environment and by medication, to correct consequences or complications of nausea and vomiting such as dehydration and to minimize the fetal effects of NVP treatment.[2]

Table 1. Dosing and Administration[1]

Generic Name	Adult Dose	Pediatric Dose	Availability
doxylamine succinate/ pyridoxine hydrochloride	Nausea and Vomiting of Pregnancy: Delayed-release tablet: Initial, two tablets QHS on day one; if symptoms persist into day two increase dose to one tablet QAM and two tablets QHS on day three; if symptoms continue increase to a maximum of four tablets per day with one in the morning, one in the mid-afternoon and two QHS	Safety and efficacy in children have not been established.	Delayed-release tablet: 10 mg/10 mg

NSAID=nonsteroidal anti-inflammatory drug

Evidence-based Medicine

- FDA-approval of Diclegis® (doxylamine succinate/pyridoxine hydrochloride) was based on one double-blind, randomized, multi-center, placebo-controlled study that evaluated the safety and efficacy of the agent in pregnant adult women in the gestational age range of 7 to 14 weeks with nausea and vomiting. Patients (N=298) were randomized to 14 days of placebo or two tablets daily at bedtime and up to a maximum dose of four tablets of doxylamine succinate/pyridoxine hydrochloride.[5] Doxylamine succinate/pyridoxine hydrochloride treatment resulted in a statistically significant improvement in both the symptom and quality of life domains of the Pregnancy Unique-Quantification of Emesis (PUQE) score. There was a 4.8 point mean decrease from baseline in the symptom domain PUQE score at day 15 in the doxylamine succinate/pyridoxine hydrochloride group compared to 3.9 point decrease in the placebo group. For quality of life, there was also a 2.8 point mean increase from baseline in the score at day 15 in the Diclegis® (doxylamine succinate/pyridoxine hydrochloride) group compared to a 1.8 point decrease in the placebo group.[5]

- A second study compared a five-day course of low-dose ondansetron to low-dose doxylamine succinate/pyridoxine hydrochloride. The study concluded that ondansetron provided a statistically significant reduction in the nausea and vomiting (P=0.019 and P=0.049, respectively). There were no difference between groups for the side effects of sedation or constipation (P=0.707 and P=0.412, respectively).[6]

Key Points within the Medication Class

- According to Obstetrician-Gynecologists Clinical Management Guideline for Nausea and Vomiting of Pregnancy[4]
  - Mild cases of nausea and vomiting may be resolved with lifestyle and dietary changes such as eating frequent small meals or avoiding spicy or fatty foods.
  - First-line pharmacotherapy with pyridoxine or in combination with doxylamine.
  - If initial therapy with pyridoxine monotherapy fails and if this is inadequate for symptom control then the addition of doxylamine is recommended.
  - For patients who fail this combination, promethazine or dimenhydrinate can be substituted for doxylamine. After this point, if the patient is still experiencing nausea and vomiting, options include metoclopramide, trimethobenzamide, methylprednisolone or ondansetron.

- Other Key Facts:
  - Only FDA-approved agent for the treatment of nausea and vomiting of pregnancy.
  - Initial dosing allows for once daily dosing.

References

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Therapeutic Class Overview
Narcolepsy Agents (non-stimulant)

Overview/Summary:
This review will focus on agents used for the symptomatic treatment of narcolepsy. This includes the wakefulness promoting agents armodafinil (Nuvigil®) and modafinil (Modafinil®), along with the central nervous system agent, sodium oxybate (Xyrem®).[1-3] Although several stimulant products are indicated for the treatment of narcolepsy, they will not be covered in this review. Narcolepsy is clinical syndrome that affects the control of sleep and wakefulness. Etiologies of narcolepsy may include loss of orexin signaling, genetic factors and rarely, brain lesions. People with narcolepsy often experience excessive daytime sleepiness (EDS) and intermittent, uncontrollable episodes of falling asleep during the daytime.[4] It is important to note that EDS is distinct from fatigue. Generally, fatigue is a subjective feeling of lack of energy that interferes with normal daily activities while EDS is an inability to stay awake or alert during the time of wakefulness in the sleep-wake cycle.[5] Specifically, modafinil and its R-enantiomer, armodafinil, are Food and Drug Administration (FDA)-approved for EDS associated with narcolepsy as well as EDS that results from obstructive sleep apnea (OSA) and shift work disorder (SWD).[1-2] In addition to EDS in narcolepsy, sodium oxybate is also FDA-approved for the treatment of cataplexy associated with narcolepsy.[3] Cataplexy is a term used to describe a sudden loss of muscle tone or weakness that ultimately leads to loss of voluntary muscle control. Additional symptoms caused by cataplexy can range from slurred speech to total body collapse, depending on the muscles involved. Cataplexy is often triggered by intense emotions such as surprise, laughter, or anger.[5] The exact mechanisms by which these agents exert their therapeutic effects are not completely understood.[1-3]

Efficacy of these agents has been well documented in placebo-controlled trials.[6-34] Head-to-head studies are limited, but it appears as though modafinil and armodafinil are equal in therapeutic effect.[34] Current clinical guidelines have not been updated to include armodafinil's place in therapy. Generally modafinil is recommended as a first line agent for the treatment of EDS. Central Nervous System (CNS) stimulants such as methylphenidate and amphetamine/dextroamphetamine as well sodium oxybate are recommended as alternatives. Recommendations regarding the use of certain types of antidepressants vary by guidelines, with some offering a recommendation for use and others not.[35-38] For cataplexy in narcolepsy, sodium oxybate is considered the first-line agent, but its use may be limited due to side effects.[36]

Table 1. Current Medications Available in Therapeutic Class[1-47]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Armodafinil (Nuvigil®)	EDS associated with narcolepsy, OSA and SWD	Tablet: 50 mg 150 mg 200 mg 250 mg	-
Modafinil (Provigil®*)	EDS associated with narcolepsy, OSA and SWD	Tablet: 100 mg 200 mg	a
Sodium oxybate (Xyrem®)	Cataplexy in narcolepsy; EDS associated with narcolepsy	Oral solution: 500 mg/mL	-

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

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- EDS in narcolepsy:
  - The ability for patients to remain awake, based on the Maintenance of Wakefulness Test (MWT), was significantly enhanced with each dose of armodafinil studied compared with placebo at the final visit (P<0.01).[6]
  - Modafinil demonstrated a significant improvement in objective and subjective measures of EDS for the modafinil groups compared to placebo (P<0.001 for both). There was also a statistically significant improvement in MWT and overall condition (Clinical Global Impression of Change [CGI-C]) with each dose compared to placebo.[7,8]
  - Sodium oxybate, provided statistically significant improvements in the Epworth Sleepiness Scale (ESS) and CGI-C compared to placebo at end of therapy (P≤0.001 for both).[15]
  - Sodium oxybate plus modafinil significantly improved MWT scores at week eight compared to the placebo group (P<0.001).[16]
- EDS in OSA:
  - Armodafinil and modafinil significantly improved MWT compared to placebo at the conclusion of their respective studies (armodafinil, P<0.001 and P=0.0003; modafinil, P<0.001 for both).[22,23]
- EDS in SWD:
  - Both armodafinil and modafinil were evaluated in one clinical trial each. Patients treated with armodafinil or modafinil showed a statistically significant prolongation in the time to sleep onset compared to placebo-treated patients, as measured by the nighttime Multiple Sleep Latency Test (MSLT) at the final visit compared with placebo (P<0.001 and P=0.002, respectively).[29,30]
- Cataplexy in narcolepsy:
  - Sodium oxybate resulted in statistically significant reductions in the frequency of cataplexy attacks (P<0.05).[13]
  - In a second trial, patients were randomized to blinded placebo after discontinuing long-term open-label sodium oxybate therapy or blinded sodium oxybate. These patients that discontinued sodium oxybate experienced a significant increase in cataplexy attacks (P<0.001).[14]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - EDS
    - Generally modafinil is recommended as a first line agent.
    - Guidelines have not been updated to include armodafinil's place in therapy.
    - CNS stimulants such as methylphenidate and amphetamine/dextroamphetamine as well sodium oxybate are recommended as alternatives.
    - Recommendations regarding the use of certain types of antidepressants vary by guidelines, with some offering a recommendation for use and others not.[35-38]
  - For cataplexy in narcolepsy, sodium oxybate is considered the first-line agent, but its use may be limited due to side effects.36.[18-23]

- Other Key Facts:
  - Modafinil and armodafinil have produced psychoactive and euphoric effects along with other feelings typical of CNS stimulants and have been classified as Schedule IV drugs by the FDA.[1,2]
  - Sodium oxybate includes a black box warning in its FDA approved labeling regarding abuse potential and its depressive CNS effects that has led to serious adverse events and even death. It has been classified as a Schedule III controlled-substance by the FDA.[3]
  - Modafinil and armodafinil are administered once daily. Sodium oxybate has to be taken twice daily, once before bed and then once again approximately 2.5 to 4 hours later.[1-3]
  - Only modafinil is available generically.

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Therapeutic Class Overview
Long-acting Opioids

Therapeutic Class

- **Overview/Summary:** As a class, opioid analgesics encompass a group of naturally occurring, semisynthetic, and synthetic drugs that stimulate opiate receptors and effectively relieve pain without producing loss of consciousness. The long-acting opioids and their Food and Drug Administration (FDA)-approved indications are outlined in Table 2.[1-18] Previously, they were prescribed for the management of moderate to severe chronic pain; however, starting in March 2014, the FDA's required label changes were made for most of the agents, updating their indication.[19] Currently, long-acting opioids are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. This change was made for all long-acting opioids in an effort to help prescribers and patients make better decisions about who benefits from opioids and also to help prevent problems associated with their use.[19] In addition to indication changes, the long-acting opioid label must include statements that the long-acting opioid is not for "as needed" use, that it has an innate risk of addiction, abuse and misuse even at recommended doses, and finally it must include an update to the black box warning for increased risk of neonatal opioid withdrawal syndrome (NOWS).[19] Long-acting opioids are available in a variety of different dosage forms, and currently several agents are available generically.

  Pain is one of the most common and debilitating patient complaints, with persistent pain having the potentially to lead to functional impairment and disability, psychological distress, and sleep deprivation. Two broad categories of pain include adaptive and maladaptive. Adaptive pain contributes to survival by protecting individuals from injury and/or promoting healing when injury has occurred. Maladaptive, or chronic pain, is pain as a disease and represents pathologic functioning of the nervous system. Various definitions of chronic pain currently exist and may be based on a specified duration of pain; however, in general, the condition can be defined as pain which lasts beyond the ordinary duration of time that an insult or injury to the body needs to heal. Pain can also be categorized as being either nociceptive or neuropathic, and treatments for each are specific. Nociceptive pain is caused by damage to tissue and can further be divided into somatic (pain arising from injury to body tissues) and visceral pain (pain arising from the internal organs). Visceral pain is often described as poorly localized, deep, dull, and cramping. In contrast, neuropathic pain arises from abnormal neural activity secondary to disease, injury, or dysfunction of the nervous system.[20]

  Several mechanisms are thought to be involved in the promotion and/or facilitation of chronic pain, and include peripheral and central sensitization, ectopic excitability, structural reorganization/phenotypic switch of neurons, primary sensory degeneration, and disinhibition. Patients not responding to traditional pain treatments may require individualized and supplemental conventional treatment approaches that target different mechanisms.[20] Several pharmacologic and nonpharmacologic options are currently available for the management of chronic pain. Available treatment options make up six major categories: pharmacologic, physical medicine, behavioral medicine, neuromodulation, interventional, and surgical approaches. As stated previously, some patients may require multiple treatment approaches in order to achieve adequate control of their chronic pain. Pharmacologic therapy should not be the sole focus of pain treatment; however, it is the most widely utilized option to manage chronic pain. Major pharmacologic categories used in the management of pain include nonopioid analgesics, tramadol, opioid analgesics, α-2 adrenergic agonists, antidepressants, anticonvulsants, muscle relaxants, N-methyl-d-aspartate receptor antagonists, and topical analgesics. Combining pharmacologic therapies may result in improved analgesia, and because lower doses of each agent can be used, patients may experience fewer treatment-emergent adverse events. Response to pharmacologic therapies will vary between individual patients, and currently no one approach has been demonstrated to be appropriate for all patients. Treatment decisions are largely based on the type of pain (e.g., neuropathic, nociceptive), comorbidities, concurrent medications, pharmacokinetic/pharmacodynamic properties of the agent, and anticipated adverse events.[21]

For the treatment of neuropathic pain, generally accepted first line therapies include calcium channel α 2-detla ligand anticonvulsants (e.g., gabapentin, pregabalin) and tricyclic antidepressants. Serotonin norepinephrine reuptake inhibitors should be utilized second line, and opioids should be considered as a second or third line option for most patients. Ideally, nociceptive pain is primarily managed with the use of non-opioid analgesics, with acetaminophen and nonsteroidal anti-inflammatory drugs utilized first line in the management of mild to moderate pain. Opioids are associated with a risk of abuse and overdose, and the evidence for the effectiveness of long term opioid therapy in providing pain relief and improving functional outcomes is limited. Use of opioids in the management of chronic noncancer pain remains controversial, and consideration for their use in this clinical setting should be weighed carefully. Opioids should be reserved for the treatment of pain of any severity not adequately controlled with non-opioid analgesics or antidepressants, more severe forms of acute pain, and cancer pain. If being considered for the treatment of chronic noncancer pain, opioids should be further reserved for patients with moderate to severe chronic pain that is adversely affecting patient function and/or quality of life.[21]

The long-acting opioid agents primarily produce intense analgesia via their agonist actions at mu receptors, which are found in large numbers within the central nervous system. The binding of these agents to mu receptors produces a variety of other effects including bradycardia, sedation, euphoria, physical dependence, and respiratory depression. Key safety concerns associated with the opioid analgesics include respiratory depression, and to a lesser degree, circulatory depression.[21,22]

All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of buprenorphine transdermal systems which are a Schedule III controlled substance. Buprenorphine is a partial opiate agonist, and the transdermal system is the first and only seven day transdermal opioid approved by the FDA.[1] On July 9, 2012, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for all long-acting opioids. The program requires companies who manufacture long-acting opioids to make training regarding proper prescribing practices available for health care professionals who prescribe these agents, as well as distribute educational materials to both prescribers and patients on the safe use of these agents. The new REMS program is part of the national prescription drug abuse plan announced by the Obama Administration in 2011 to combat prescription drug misuse and abuse.[23]

On March 11, 2014, the FDA approved a new combination product Xartemis XR® (oxycodone/acetaminophen), which contains oxycodone and acetaminophen. It has a bilayer formulation which has an immediate- and extended-release portion allowing for rapid analgesia with prolonged effects. This product, although new, is not formulated as an abuse-deterrent product. It has the unique indication of management of acute, severe pain, which is not shared with any of the other long-acting opioids. Due to the acetaminophen component use of this medication is limited, as a maximum of 4,000 mg/day is recommended by the manufacturer.[18]

There are currently four abuse deterrent formulations of extended-release (ER), long acting opioids approved by the FDA. The abuse deterrent products are Oxycodone ER (OxyContin®), morphine sulfate/naltrexone (Embeda) and two hydrocodone ER products (Zohydro ER® and Hysingla ER®).

Even though OxyContin® (oxycodone extended-release [ER]) has received increased attention regarding overuse, abuse, and diversion, oxycodone itself does not appear to have a greater dependence or abuse liability compared to the other available opioids.[24] In April of 2010, the FDA approved a new formulation of OxyContin® that was designed to help discourage misuse and abuse of the medication. Specifically, the reformulated OxyContin® is intended to prevent the opioid medication from being cut, broken, chewed, crushed, or dissolved to release more medication. The FDA states that the new formulation may be an improvement that may result in less risk of overdosage due to tampering, and will likely result in less abuse by snorting or injection, but the agent can still be abused or misused by simply ingesting larger doses than are recommended. The manufacturers of the medication will be required by the FDA to conduct a postmarket study to evaluate the extent to which this new formulation reduces abuse and misuse of the medication.[25]

Similarly, a new, crush-resistant formulation of Opana ER® (oxymorphone) was approved in December 2011; however, the manufacturer notes that it has not been established that the new formulation is less subject to misuse, abuse, diversion, overdose, or addiction.[26]

In October 2013, the FDA approved the first sole entity hydrocodone product in an ER formulation known as Zohydro ER® (hydrocodone) for the treatment of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate.[3] The approval of Zohydro ER® (hydrocodone) was somewhat controversial for a number of reasons. The advisory panel to the FDA voted 11 to 2 against the approval of Zohydro ER® (hydrocodone), due in large part to growing concerns regarding opioid abuse and the product's lack of an abuse deterrent mechanism. Despite the advisory committee vote, Zohydro ER® (hydrocodone ER) was approved based on an FDA Division Director's rationale that the benefit-risk balance for Zohydro ER® (hydrocodone ER) and other non-abuse deterrent opioid analgesics is still favorable for patients requiring chronic opioid therapy. In addition, the case was made for having another alternative long-acting opioid for patients that cannot tolerate other options or who are on an opioid rotation.[11] As of February 2015, two abuse-deterrent formulations of hydrocodone ER have been FDA-approved. Hysingla ER® (hydrocodone ER) was approved on November 20, 2014 and the reformulated Zohydro ER® was FDA approved January 30, 2015.[3,4,27] It is important to note that the FDA does not require updates to drug labels that have already been approved for manufacturing changes. Thus, the FDA-approved label for Zohydro ER® did not require any changes and does not specifically mention a change in formulation.[3,27]

Embeda® (morphine sulfate/naltrexone) was the first long-acting opioid to become available. This particular agent combines an opioid agonist with an opioid antagonist to deter abuse. The combination product contains ER morphine sulfate with sequestered naltrexone; therefore, if crushed the naltrexone is released and the euphoric effects of morphine are reduced.[17,28] On March 16, 2011 it was announced that King Pharmaceuticals Inc., a wholly owned subsidiary of Pfizer, has voluntarily recalled from United States wholesalers and retailers all dosage forms of Embeda® due to a pre-specified stability requirement that was not met during routine testing. According to a press release, on October 17, 2014, the FDA-approved label for Embeda® has been updated to include abuse-deterrent studies and is once again available.[29] Overall, while these new long-acting opioid formulations intended to deter abuse may be promising, there is no evidence demonstrating that they truly prevent abuse.[30]

Table 1. Current Medications Available in the Therapeutic Class[1-18]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Buprenorphine (Butrans®)	The management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	Transdermal patch: 5 µg/hour 7.5 µg/hour 10 µg/hour 15 µg/hour 20 µg/hour	-
Fentanyl (Duragesic®*)	The management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.†	Transdermal system‡: 12 µg/hour§ 25 µg/hour 50 µg/hour 75 µg/hour 100 µg/hour	a
Hydrocodone (Hysingla ER®, Zohydro ER®)	The management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative	Capsule, extended release (Zohydro ER®):	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	treatment options are inadequate.	10 mg 15 mg 20 mg 30 mg 40 mg 50 mg‡ Tablet, extended release (Hysingla ER®): 20 mg 30 mg 40 mg 60 mg 80 mg‡ 100 mg‡ 120 mg‡	
Hydromorphone (Exalgo®*)	The management of pain in opioid-tolerant patients severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.†	Tablet, extended release: 8 mg‡ 12 mg‡ 16 mg‡ 32 mg‡	a
Methadone (Dolophine®*, Methadose®*)	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (solution, tablet). For detoxification treatment of opioid addiction (heroin or other morphine-like drugs) (concentrate solution, dispersible tablet, solution, tablet). For maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services (concentrate solution, dispersible tablet, solution, tablet).	Concentrate solution, oral (sugar-free available): 10 mg/mL Solution, oral: 5 mg/5 mL 10 mg/5 mL Tablet, extended release: 5 mg 10 mg Tablet for oral suspension: 40 mg	a
Morphine sulfate (Avinza®*, Kadian®*, MS Contin®*)	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate (biphasic capsule, capsule, tablet).	Capsule, biphasic extended release: 30 mg 45 mg 60 mg 75 mg 90 mg‡ 120 mg‡ Capsule, extended release: 10 mg	a

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		20 mg 30 mg 40 mg 50 mg 80 mg 100 mg‡ 200 mg‡ Tablet, extended release: 15 mg 30 mg 60 mg 100 mg‡ 200 mg‡	
Oxycodone (OxyContin®*)	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.¶	Tablet, extended release: 10 mg 15 mg 20 mg 30 mg 40 mg 60 mg‡ 80 mg‡	a #
Oxymorphone (Opana® ER*)	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	Tablet extended release: 5 mg 7.5 mg 10 mg 15 mg 20 mg 30 mg 40 mg	a
Tapentadol (Nucynta ER®)	Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	Tablet, extended release: 50 mg 100 mg 150 mg 200 mg 250 mg	-
Combination Products			
Morphine sulfate/ naltrexone (Embeda®)	Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.‡	Capsule, extended release: 20 mg/0.8 mg 30 mg/1.2 mg 50 mg/2 mg 60 mg/2.4 mg 80 mg/3.2 mg 100 mg/4 mg‡	-
Oxycodone/	For the management of acute pain severe	Biphasic tablet,	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Acetaminophen (Xartemis XR®)	enough to require opioid treatment and for which alternative treatment options are inadequate	extended release: 7.5 mg/325 mg	

*Generic is available in at least one dosage form or strength.
†Opioid-tolerant are those who are taking, for one week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, 25 mcg fentanyl/hr, or an equianalgesic dose of another opioid.
‡Specific dosage form or strength should only be used in patients with opioid tolerance.
§Actual fentanyl dose is 12.5 µg/hour, but it is listed as 12 µg/hr to avoid confusion with a 125 µg dose.
#Generic availability is sporadic and does not include all strengths.
¶ A single dose of OxyContin® >40 mg or a total daily dose of 80 mg are only for use in patients who are tolerant to opioids.

Evidence-based Medicine

- Food and Drug Administration (FDA) approval of hydrocodone ER tablets (Hysingla ER®) was evaluated in an unpublished randomized double-blind, placebo controlled, multi-center, 12-week clinical trial in both opioid-experienced and opioid-naïve patients with moderate to severe chronic low back pain. Patients received either hydrocodone ER 20 to 120 mg tablets or matching placebo in a 1:1 ratio. There was a statistically significant difference in the weekly average pain scores at week 12 between the hydrocodone ER and placebo groups with a least square mean (standard deviation [SD]) difference of -0.53 (0.180) (95% confidence interval [CI], -0.882 to -0.178; P=0.0016). There were also significant improvements in proportion of responders, and Patient's Global Impression of Change scores.[4,31]
- The effectiveness of fentanyl in relieving pain appears to be similar to that of morphine sulfate sustained-release for the treatment of cancer and noncancer pain, and chronic lower back pain. Compared to morphine sulfate sustained-release, fentanyl transdermal systems appear to be associated with less constipation.[32-34]
- A trial comparing hydrocodone ER capsules to placebo in patients with moderate to severe chronic low back pain demonstrated hydrocodone ER had a lower mean change from baseline in pain intensity scores compared to placebo at 12 weeks (P=0.008). In addition, there was a significantly higher amount of treatment responders in the hydrocodone ER group compared to the placebo group (P<0.001) at the end of treatment, and subject global assessment of medication scores increased from baseline significantly in the hydrocodone ER group compared to placebo (P<0.0001).[35]
- In one trial, hydromorphone ER demonstrated greater efficacy in the treatment of lower back pain with regard to reducing pain intensity (P<0.001) and pain scores (P<0.01) compared to placebo.[36] In a noninferiority analysis of a hydromorphone ER compared to oxycodone ER, two agents provided similar pain relief in the management of osteoarthritic pain.[37]
- Methadone has demonstrated a greater efficacy over placebo for the treatment of nonmalignant neuropathic pain and similar efficacy compared to slow-release morphine sulfate for the treatment of cancer pain.[38,39]
- A trial comparing different long-acting formulations of morphine sulfate for the treatment of osteoarthritis pain demonstrated that both Avinza® (morphine sulfate ER) and MS Contin® (morphine sulfate ER) significantly reduced pain from baseline (P≤0.05 for both). Both treatments also reduced overall arthritis pain intensity, and achieved comparable improvements in physical functioning and stiffness. Each treatment significantly improved certain sleep parameters compared to placebo.[39] In a crossover trial, morphine sulfate (MS Contin®) was compared to fentanyl transdermal systems, and more patients preferred fentanyl transdermal systems (P<0.001), and reported on average, lower pain intensity scores than morphine sulfate phase (P<0.001).[41]
- Clinical trial data evaluating the combination long acting opioid agent morphine/naltrexone is limited. As mentioned previously, this product was recalled by the manufacturer due to not meeting a pre-specified stability requirement during routine testing in March 2011.[29]
- Morphine/naltrexone has demonstrated significantly better pain control compared to placebo in patients with osteoarthritis pain.[42]
- Oxycodone ER has demonstrated significantly greater efficacy compared to placebo for the treatment of neuropathic pain and chronic refractory neck pain.[43-45] For the treatment of cancer pain, no significant differences were observed between oxycodone ER and morphine sulfate ER in reducing

pain intensity. The average number of rescue doses used within a 24 hour period was significantly less with morphine sulfate ER (P=0.01), and the incidence of nausea and sedation were similar between treatments.[46]

- Oxymorphone ER has produced similar mean daily pain intensity scores compared to both morphine sulfate and oxycodone ER for the treatment of chronic cancer pain.[47,48] The average scheduled daily dose of study drug and average total daily dose decreased after patients crossed over to oxymorphone ER from morphine sulfate or oxycodone ER. No significant changes were observed in visual analog pain scores, quality of life domains, or quality of sleep in any of the treatment groups.[47] In another trial, oxymorphone ER demonstrated greater efficacy for the relief of osteoarthritis pain compared to placebo.[49]
- In a 12-week active comparator and placebo-controlled trial, significant pain relief was achieved with tapentadol ER compared to placebo (least squares mean difference, - 0.7; 95% CI, -1.04 to -0.33) at week 12. The average pain intensity rating at endpoint with oxycodone ER was reduced significantly compared to placebo for the overall maintenance period (least squares mean difference vs placebo, -0.3), but was not significantly lower at week 12 (least squares mean, -0.3; P values not reported).[50] In a, placebo-controlled and active comparator trial in adults with moderate to severe low back pain, improvements in average pain intensity scores occurred with tapentadol ER and oxycodone ER relative to placebo (P<0.001).[51] Schwartz et al evaluated tapentadol ER among adults with painful diabetic peripheral neuropathy. The least squares mean change in average pain intensity at week 12 was 1.4 in the placebo group, indicating a worsening in pain intensity, and 0.0 in the tapentadol ER group, indicating no change in pain intensity, (least squares mean difference, -1.3; 95% CI, -1.70 to -0.92; P<0.001).[52]
- The combination product oxycodone/acetaminophen's efficacy was established in a clinical trial evaluating its effectiveness at treating pain over the 48 hours after surgery. Singla et al concluded that pain, evaluated by the summed pain intensity difference (SPID) score, was significantly higher in the oxycodone/acetaminophen group (P<0.001) through that time period. Mean total pain relief values for oxycodone/APAP XR and placebo from 0 to 48 hours were 91.3 and 70.9, respectively, resulting in a treatment difference of 20.5 (95% CI, 11.0 to 30.0; *P*<0.001). The median time to perceptible pain relief for oxycodone/APAP XR was 33.56 minutes vs 43.63 minutes for placebo (*P*=0.002). The median times to confirmed pain relief and meaningful pain relief for the oxycodone/APAP XR group were 47.95 minutes and 92.25 minutes; however, neither of these metrics could be determined for the placebo group (*P*<0.001). The percentage of patients reporting at least a 30% reduction in PI after 2 hours was 63.1% for oxycodone/APAP XR versus 27.2% for placebo (*P*<0.0001).[53]
- Methadone is the only long-acting narcotic that is Food and Drug Administration-approved for the management of opioid addiction; however, in one study slow-release morphine sulfate demonstrated noninferiority to methadone in terms of completion rate for the treatment of opioid addiction (51 vs 49%).[54]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Patients with pain should be started on acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). If sufficient pain relief is not achieved, patients should be escalated to a "weak opioid" and then to a "strong opioid", such as morphine.[55,56]
  - Opioid selection, initial dosing, and titration should be individualized according to the patient's health status, previous exposure to opioids, attainment of therapeutic goals, and predicted or observed harms. There is insufficient evidence to recommend short-acting vs long-acting opioids, or as needed vs around-the-clock dosing of opioids.[56]
  - Patients with chronic persistent pain controlled by stable doses of short-acting opioids should be provided with round-the-clock ER or long-acting formulation opioids with provision of a 'rescue dose' to manage break-through or transient exacerbations of pain.[55]
  - Opioids with rapid onset and short duration are preferred as rescue doses. The repeated need for rescue doses per day may indicate the necessity to adjust the baseline treatment.[55,56]

- In a patient who has not been exposed to opioids in the past, morphine is generally considered the standard starting drug of choice.[55]
- Pure agonists (such as codeine, fentanyl, oxycodone, and oxymorphone) are the most commonly used medications in the management of cancer pain. Opioid agonists with a short half-life are preferred and include fentanyl, hydromorphone, morphine, and oxycodone.[55]
- Meperidine, mixed agonist-antagonists, and placebos are not recommended for cancer patients. Meperidine is contraindicated for chronic pain especially in patients with impaired renal function or dehydration.[55]
- In patients who require relatively high doses of chronic opioid therapy, clinicians should evaluate for unique opioid-related adverse events, changes in health status, and adherence to the chronic opioid therapy treatment plan on an ongoing basis, and consider more frequent follow-up visits.[55,56]

· Other Key Facts:
- There are currently four abuse deterrent formulations of extended-release, long acting opioids approved by the FDA. These include oxycodone ER (OxyContin®), morphine sulfate/naltrexone (Embeda) and two hydrocodone ER products (Zohydro ER® and Hysingla ER®).
- All long-acting opioids are pregnancy category C, with the exception of oxycodone.
- Only fentanyl transdermal system is approved in children (age 2 to 17 years).
- Tapentadol is contraindicated with monoamine oxidase inhibitors; although, caution should be used when used in combination with any long-acting opioid.
- Only oxymorphone is contraindicated in severe hepatic disease.
- Methadone and buprenorphine have been implicated in QT prolongation and serious arrhythmias, use caution in patients at increased risk of QT prolongation.
- Besides the two transdermal agents, almost all long-acting opioids are dosed twice daily. Buprenorphine patches are applied once every seven days, while fentanyl transdermal systems are applied every 72 hours.[1,2] Exalgo® ER (hydromorphone) and Hysingla ER (hydrocodone) tablets and Avinza® (morphine) capsules are dosed once daily.[4,5,10] Kadian® (morphine) capsules and Embeda® (morphine/naltrexone) capsules can to be administered once or twice daily.[12,17] MS Contin® (morphine) tablets or all methadone formulations are dosed twice or three times daily.[6-10,13] The remaining long-acting agents are dosed twice daily only (oxycodone, oxymorphone, tapentadol, oxycodone/acetaminophen).[3,15,16,18] Avinza® (morphine) and Xartemis XR® (oxycodone/acetaminophen) are the only long-acting opioids with a maximum daily dose. Avinza® (morphine) has a max dose of 1,600 mg/day due to the capsules being formulated with fumaric acid, which at that dose has not been shown to be safe and effective and may cause renal toxicity[11]. Xartemis XR (oxycodone/acetaminophen) is limited to four tablets per day, and/or if taking other acetaminophen products, a maximum of 4,000 mg/day.[18]
- Buprenorphine patch and fentanyl transdermal systems are intended for transdermal use only and should be applied to intact, nonirritated, nonirradiated skin on a flat surface. The application site should be hairless, or nearly hairless, and if required hair should be clipped not shaven. Fentanyl may be applied to the chest, back, flank or upper arm while buprenorphine should be applied to the right or left outer arm, upper chest, upper back or side of chest.[1,2]
- Most solid, long-acting opioid formulations (e.g., tablets, capsules) should be swallowed whole and should not be broken, chewed, cut, crushed, or dissolved before swallowing.[1-18] The only exceptions are the morphine-containing capsules (Avinza®, Kadian®, and Embeda®); all can be opened and the pellets sprinkled on applesauce and then swallowed whole.[11,12,17] Kadian® pellets can also be placed in 10 mL of water and used through a 16 French gastrostomy tube.[12] Neither Avinza®, Kadian®, nor Embeda® pellets may be used thorough a nasogastric tube.[11,12,17] It is recommended to only swallow one Zohydro ER® (hydrocodone) capsule, or one OxyContin® (oxycodone), Opana® ER (oxymorphone), and Nucynta® ER (tapentadol) tablet at a time.[3,14-16]
- Differences in pharmacokinetics result in differences in how often the dose of an opioid may be titrated upward. Each long-acting opioid has a certain time period before which a dose

titration can occur. The amount of time required before dose titration can occur can range from one to seven days. The specific times required for titration are listed in Table 10.[1-18] When switching between agents, an appropriate dose conversion table must be used. When discontinuing any long-acting opioid without starting another, always use a slow taper to prevent severe withdrawal symptoms.

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Therapeutic Class Overview
Omega-3 Fatty Acids

Therapeutic Class

- **Overview/Summary:** This overview will focus on the omega-3 fatty acids products, which include icosapent ethyl (Vascepa®) and omega-3-acid ethyl esters (Lovaza®, Omtryg®). The agents are Food and Drug (FDA)-approved as an adjunct to diet to reduce triglyceride levels in adult patients with severe hypertriglyceridemia, defined as 500 mg/dL or more.[1-3] Icosapent ethyl is an ethyl ester of eicosapentaenoic acid (EPA), while omega-3-acid ethyl esters is a mixture of ethyl esters or free fatty acids primarily composed of EPA and docosahexaenoic acid (DHA). Each omega-3 acid ethyl esters capsule contains at least 900 mg of ethyl esters of omega-3 fatty acids sourced from fish oil, which are predominantly EPA (approximately 465 mg) and DHA (approximately 375 mg). Icosapent ethyl is a newer omega-3 fatty acid formulation that also contains EPA obtained from fish oil; however, it contains at least 96% EPA and does not contain DHA. Studies suggest that this formulation does not cause significant increases in low density lipoprotein cholesterol (LDL-C) which has been associated with large doses of omega-3-acid ethyl esters.[1-4] The exact mechanism by which the agents reduce triglyceride levels is not completely understood. Inhibition of acyl-coenzyme A:1,2-diacylglycerol acyltransferase, increased mitochondrial and hepatic peroxisomal beta-oxidation, decreased hepatic lipogenesis, and increased plasma lipoprotein lipase activity are potential mechanisms of action that have been proposed.[1-4]

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

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
icosapent ethyl (Vascepa®)	Adjunct to diet to reduce triglyceride levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia	Capsule: 1 gram	-
omega-3-acid ethyl esters (Lovaza®*, Omtryg®)	Adjunct to diet to reduce triglyceride levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia	Capsule: 1 gram (Lovaza®) 1.2 gram (Omtryg®)	a

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

Evidence-based Medicine

- Safety and efficacy of omega-3 fatty acids have been evaluated in several clinical trials.[5-27]
  - Most studies have demonstrated that icosapent ethyl and prescription omega-3 acid ethyl esters can effectively lower triglycerides, as well as positively impact other lipid/lipoprotein parameters when used as monotherapy or in combination with fenofibrate or statins.[5-23]
  - Other studies have suggested no difference between omega-3 fatty acids and placebo or dietary therapy for the reducing the rate of graft occlusion, restenosis and cardiac events or revascularizations.[24-26]
  - In another study, omega-3 acid ethyl esters significantly reduced the risk of death, nonfatal myocardial infarction, and nonfatal stroke compared to vitamin E in patients who have experienced a recent myocardial infarction.[27]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[28-34]
  - Recommendations in clinical guidelines regarding the use of omega-3 fatty acids are varied.
  - In general, therapeutic lifestyle changes, including diet, exercise, and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia.

- When LDL lowering is required, initial treatment with a statin is recommended and considered first line therapy for patients with established coronary heart disease (CHD) or CHD equivalents.
- Older guidelines suggest omega-3 fatty acids may reduce the risk of cardiovascular disease and may be reasonable for cardiovascular disease risk reduction while newer guidelines do not address the use or recommend against the use of omega-3 fatty acids for reducing the risk of cardiovascular disease due to limited data.

· Other Key Facts:[1-3]
- Dosing recommendations are similar for both icosapent ethyl and omega-3-acid ethyl esters, with 2 grams twice daily being recommended (2.4 grams twice daily for Omtryg®).
  - Omega-3-acid ethyl esters may be given once daily at a dose of 4 or 4.8 grams, respectively.
- All omega-3 fatty acid products should be taken with food.
- These agents are considered safe, with very minimal side effects.
- Omega-3-acid ethyl esters and icosapent ethyl have not been studied in renal or hepatic impairment.
- Currently, only Lovaza® (omega-3-acid ethyl esters) is available generically.

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Therapeutic Class Overview
Inhaled Anticholinergics

Therapeutic Class

- **Overview/Summary:** The inhaled anticholinergics (anticholinergics) are a class of bronchodilators primarily used in the management of chronic obstructive pulmonary disease (COPD), a condition characterized by progressive airflow restrictions that are not fully reversible.[1-3] Symptoms associated with COPD typically include dyspnea, cough, sputum production, wheezing and chest tightness. Specifically, inhaled anticholinergics work via the inhibition of acetylcholine at parasympathetic sites in bronchial smooth muscle causing bronchodilation. Meaningful increases in lung function can be achieved with the use of inhaled anticholinergics in patients with COPD.[1-3] The available single-entity inhaled anticholinergics include aclidinium (Tudorza® Pressair), ipratropium (Atrovent®, Atrovent® HFA), tiotropium (Spiriva® HandiHaler, Spiriva Respimat®) and umeclidinium (Incruse Ellipta®).[4-13] Ipratropium, a short-acting bronchodilator, has a duration of action of six to eight hours and requires administration four times daily. Aclidinium and tiotropium are both considered long-acting bronchodilators. Aclidinium is dosed twice daily, while tiotropium and umeclidinium are administered once daily. Ipratropium is available as a metered dose aerosol inhaler for oral inhalation as well as a solution for nebulization. Both aclidinium and tiotropium are available as dry powder inhalers for oral inhalation. Additionally, tiotropium is formulated as a soft mist inhaler.[4-9] The combination products include ipratropium/albuterol, which is available as an inhaler (Combivent Respimat®) and solution for nebulization (DuoNeb®), and umeclidinium/vilanterol (Anoro Ellipta®), which is available as a powder inhaler for oral inhalation.[10-12] Aclidinium, ipratropium, tiotropium, umeclidinium and umeclidinium/vilanterol are Food and Drug Administration (FDA)-approved for the maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. Tiotropium is the only inhaled anticholinergic that is FDA-approved for reducing exacerbations associated with COPD. Ipratropium/albuterol is indicated for the treatment of bronchospasms associated with COPD in patients who require more than one bronchodilator. Ipratropium and ipratropium/albuterol solutions for nebulization are the only inhaled anticholinergic products that are currently available generically.[11-12] According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, inhaled bronchodilators are preferred for the management of COPD. Regular use of long-acting β_2-agonists or short- or long-acting anticholinergics improves health status and long-acting anticholinergics reduce the rate of COPD exacerbations and improve the effectiveness of pulmonary rehabilitation. The choice of agent should be based on availability and individual response in terms of symptom relief and side effects. The GOLD guidelines emphasize that the use of long-acting bronchodilators is more effective and convenient than the use of short-acting bronchodilators.[1]

Table 1. Current Medications Available in Therapeutic Class[4-12]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agents			
Aclidinium (Tudorza®)	Bronchospasm associated with COPD, maintenance treatment	Powder for oral inhalation: 400 µg	-
Ipratropium* (Atrovent HFA®)	Bronchospasm associated with COPD, maintenance treatment	Aerosol for oral inhalation (Atrovent HFA®): 17 µg Solution for nebulization: 500 µg	a
Tiotropium (Spiriva®	Bronchospasm associated with COPD, maintenance treatment; reduce	Aerosol for inhalation (Spiriva Respimat®):	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
HandiHaler, Spiriva Respimat®)	exacerbations in patients with COPD	2.5 µg/actuation Powder for oral inhalation (Spiriva® HandiHaler): 18 µg	
Umeclidinium (Incruse Ellipta®)	Bronchospasm associated with COPD, maintenance treatment	Powder for oral inhalation: 62.5 µg	-
Combination Products			
Ipratropium/ albuterol (Combivent®, DuoNeb®*)	Patients with chronic obstructive pulmonary disease on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator†; treatment of bronchospasm associated with chronic obstructive pulmonary disease in patients requiring more than one bronchodilator‡	Inhalation spray (inhaler) (Combivent Respimat®): 20/100 µg§ Solution for nebulization (DuoNeb®*): 0.5/3.0 mg (3 mL vials)	a
Umeclidinium/ vilanterol (Anoro Ellipta®)	Long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and/or emphysema	Powder for oral inhalation: 62.5/25 µg	-

COPD=chronic obstructive pulmonary disease
* Generic available in at least one dosage form or strength.
† Combivent Respimat®.
‡ DuoNeb®.
§ Delivering 18 µg of ipratropium and 103 µg of albuterol (90 µg albuterol base).

Evidence-based Medicine

- The inhaled anticholinergics have demonstrated to improve lung function and/or exercise tolerance in patients with chronic obstructive pulmonary disease (COPD).[14-72]
- FDA approval of tiotropium soft mist inhaler (Spiriva Respimat®) was based on five double-blind, placebo/active controlled, randomized clinical trials. Patients were ≥40 years of age with a diagnosis of COPD, FEV_1 ≤60% of predicted, FEV_1/FVC ≤0.7 and a smoking history ≥10 pack-years.[8,15-17]
  - Significant improvement in trough FEV_1 compared to placebo in all five confirmatory trials. Mean change from baseline in trough FEV_1 at end of treatment for trials one and two (12 weeks) were 0.11 L (95% CI, 0.04 to 0.18) and 0.13 L (95% CI, 0.07 to 0.18). Mean change in trough FEV_1 at end of treatment for trails three, four and five (48 weeks) was 0.14 (95% CI, 0.10 to 0.18), 0.11 (95% CI, 0.08 to 0.15), and 0.10 (95% CI, 0.09 to 0.12; P values not reported).[8,15-17]
  - In the pooled analysis of trials three and four, tiotropium soft mist inhaler 5 µg significantly reduced the number of COPD exacerbations compared to placebo with 0.78 exacerbations per patient year compared to 1.0 exacerbations per patient year, respectively, with a rate ratio of 0.78 (95% CI, 0.67 to 0.92). Time to first exacerbation was also delayed in tiotropium soft mist inhaler patients.[8,16]
  - The TIOSPIR (Tiotropium Respimat Inhaler and the Risk of Death in COPD) study evaluated mortality. All-cause mortality at the end of the study was similar between the two tiotropium groups (soft mist compared to dry powder), with an estimated hazard ratio of 0.96 (95% CI, 0.84 to 1.09).[8,18]
- In general, the inhaled anticholinergics have been demonstrated to improve lung function and exercise tolerance in patients with COPD. Few head-to-head trials have noted significant differences in improvements in lung function favoring tiotropium over ipratropium.[15,37-38]

- In a large study of current or former smokers with COPD (N=828), patients were randomized to receive aclidinium 200 or 400 µg twice daily or placebo over 24 weeks. The mean change from baseline in trough forced expiratory volume in one second (FEV_1), the primary endpoint, was significantly higher in patients treated with aclidinium 200 or 400 µg compared to patients randomized to receive placebo (99±22 and 128±22 mL, respectively; P<0.0001).[21]
- In a 12-week study by Kerwin et al, patients randomized to receive aclidinium 200 or 400 µg twice daily experienced a statistically significant increase from baseline in trough FEV_1 compared to patients in the placebo group (86 and 124 mL, respectively; P<0.0001 for both).[22] Significant improvements persisted through 52 weeks in an extension study.[23]
- Singh and colleagues conducted a small, five-way crossover study evaluating 100, 200 and 400 µg of aclidinium, formoterol 12 µg or placebo. Following seven days of treatment, the change from baseline in FEV_1 area under the curve over 12 hours (FEV_1 area under the curve $[AUC]_{0–12}$) was 154 mL in the aclidinium 100 µg group, 176 mL in the aclidinium 200 µg group, 208 mL in the aclidinium 400 µg group and 210 mL for the formoterol 12 µg group compared to placebo (P<0.0001 for all compared to placebo). The difference in FEV_1 $AUC_{0–12}$ between the aclidinium 400 µg and formoterol 12 µg treatment groups was not statistically significant (P value not reported).[48]
- **T**here is inconsistent data regarding a clinical advantage of tiotropium over other long-acting bronchodilators, although in one trial, tiotropium significantly increased the time to first exacerbation by 42 days compared to salmeterol (187 vs 145 days; P<0.001).[57]
- When tiotropium is used in combination with a bronchodilator from a different pharmacologic class, a significant clinical advantage is demonstrated.[61,62]
- In comparison to other short-acting bronchodilators, ipratropium does not appear to offer any significant advantages. In a systematic review, there was no statistically significant difference in short-term FEV_1 changes (up to 90 minutes post dose) between individuals receiving ipratropium compared to a β_2-adrenergic agonist (P value not reported).[48]
- As with tiotropium, improved outcomes are achieved when ipratropium is used in combination with other bronchodilators.[50,51] Furthermore, ipratropium/albuterol has consistently demonstrated statistically significant improvements in FEV_1 and forced vital capacity in clinical studies when compared to either agent alone.[41-45]
- The ipratropium/albuterol (Combivent Respimat®) inhaler has demonstrated improvements in FEV_1 that are equivalent to the aerosol metered dose inhaler.[46]
- Umeclidinium/vilanterol 62.5/25 µg once daily was compared to placebo and the single agents, umeclidinium 62.5 µg once daily and vilanterol 25 µg once daily. The primary endpoint of trough FEV_1 on treatment day 169 was significantly improved in all treatment groups compared to placebo (P<0.001 for all). In addition, umeclidinium/vilanterol treated patients also had significant improvements compared to monotherapy with umeclidinium and vilanterol (0.052 L; P=0.004 and 0.095 L; P<0.001 respectively).[71]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - The Global Initiative for Chronic Obstructive Lung Disease guidelines state that inhaled bronchodilators are preferred for the management of chronic obstructive pulmonary disease (COPD). Regular use of long-acting β_2-agonists or short- or long-acting anticholinergics improves health status and long-acting anticholinergics reduce the rate of COPD exacerbations and improve the effectiveness of pulmonary rehabilitation. The choice of agent should be based on availability and individual response in terms of symptom relief and side effects. The use of long-acting bronchodilators is more effective and convenient than short-acting bronchodilators.[1]
  - The National Institute for Clinical Excellence states that short-acting bronchodilators should be the initial empiric treatment for the relief of breathlessness and exercise limitation while long-acting bronchodilators should be used in patients who remain symptomatic with use of short-acting agents. Once-daily long-acting anticholinergic agents are preferred compared to four-times-daily short-acting anticholinergic agents in patients with stable COPD who remain

symptomatic despite use of short-acting agents and in whom the decision has been made to begin regular maintenance therapy with an anticholinergic.[2]

- Other Key Facts:
  - Tiotropium (Spiriva® HandiHaler, Spiriva Respimat®) is the only agent within the class that is Food and Drug Adminisatrion-approved to reduce the risk of COPD exacerbations.[7,8]
  - Umeclidinium/vilanterol is the first combination product containing a long-acting anticholinergic and long-acting β_2-agonist.[12]

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Tab: Established Drug Classes

Therapeutic Class Overview
Neuropathic Pain Agents

Therapeutic Class

- **Overview/Summary:** The agents approved by the Food and Drug Administration (FDA) for the treatment of neuropathic pain include duloxetine (Cymbalta®), gabapentin (Neurontin®), gabapentin extended-release (Gralise®), gabapentin enacarbil (Horizant®), lidocaine patches (Lidoderm®) and pregabalin (Lyrica®).[1-6] These agents and their respective FDA-approved indications are listed in Table 1. The exact mechanisms by which these agents exert their analgesic effects are unknown. Neuropathic pain arises as a consequence of a lesion or disease that affects the nervous system. Symptoms often include a burning, tingling, sharp or stabling pain and may occur at any time of day. Despite the available medications for symptomatic relief and analgesia, their effectiveness is unpredictable, dosing can be complicated, onset of action is delayed and adverse events are common.[7]

  The analgesic properties of duloxetine are believed to result from potent inhibition of neuronal serotonin and norepinephrine reuptake and a less potent inhibition of dopamine reuptake. Duloxetine is typically dosed once daily for the treatment of diabetic neuropathy.[1] Gabapentin is structurally related to the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) but has no effect on GABA binding, uptake or degradation.[2] Gabapentin is administered three times daily, while the extended-release formulation is administered once daily. Gabapentin enacarbil, a prodrug of gabapentin, is rapidly hydrolyzed to gabapentin in the gastrointestinal tract and is dosed twice daily for the management of postherpetic neuralgia. Gabapentin enacarbil does not demonstrate saturable absorption, resulting in a higher bioavailability and less variability in serum levels compared to gabapentin. Due to pharmacokinetic differences, the three gabapentin products are not interchangeable with one another.[2-4] Lidocaine is an amide-type local anesthetic that stabilizes neuronal membranes by inhibiting the ionic fluxes required for conduction of impulses. Topical application of the lidocaine patch is sufficient to produce analgesia, but results in minimal absorption.[5] The lidocaine topical patch should be applied to the painful area for 12 hours and then removed for the following 12 hours.[5] Pregabalin may produce anti-nociceptive effects through its high affinity binding to the α2Δ subunit of voltage-gated sodium channels. As with gabapentin, pregabalin is structurally similar to GABA but does not directly bind to or augment the response of GABA.[6] Only gabapentin immediate-release is currently available generically.

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

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Duloxetine (Cymbalta®)	Management of chronic musculoskeletal pain. Management of fibromyalgia. Management of neuropathic pain associated with diabetic peripheral neuropathy. Treatment of generalized anxiety disorder. Treatment of major depressive disorder.	Delayed-release capsule: 20 mg 30 mg 60 mg	a
Gabapentin (Neurontin®*)	Adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients >12 years of age with epilepsy.	Capsule: 100 mg 300 mg 400 mg	a

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	Adjunctive therapy in the treatment of partial seizures in patients 3 to 12 years of age. Management of postherpetic neuralgia.	Solution: 250 mg/5 mL Tablet: 600 mg 800 mg	
Gabapentin extended-release (Gralise®)	Management of postherpetic neuralgia.	Extended-release tablet: 300 mg 600 mg	-
Gabapentin enacarbil (Horizant®)	Management of postherpetic neuralgia. Moderate-to-severe primary restless legs syndrome.	Extended-release tablet: 300 mg 600 mg	-
Lidocaine patch (Lidoderm®)	Management of postherpetic neuralgia.	Topical patch: 5%	a
Pregabalin (Lyrica®)	Adjunctive therapy for adult patients with partial onset seizures. Management of fibromyalgia. Management of neuropathic pain associated with diabetic peripheral neuropathy. Management of neuropathic pain associated with spinal cord injury. Management of postherpetic neuralgia.	Capsule: 25 mg 50 mg 75 mg 100 mg 150 mg 200 mg 225 mg 300 mg Oral solution: 20 mg/mL	-

*Generic available in one dosage form or strength.

Evidence-based Medicine

- All of the agents Food and Drug Administration (FDA)-approve for the treatment of neuropathic pain have demonstrated safety and efficacy in clinical studies when compared to placebo.[8-31]
- Patients with postherpetic neuralgia who were transitioned from gabapentin to pregabalin demonstrated no significant difference in pain scores, based on a visual analog scale, with pregabalin compared to gabapentin. In a subset of patients who required an increase in the dosage of pregabalin to improve the analgesic effect after the transition, significant improvement in pain scores was observed.[32]
- In a 52-week, open-label study comparing duloxetine to routine care (gabapentin, amitriptyline or venlafaxine) for the treatment of diabetic peripheral neuropathic pain, there were no significant treatment-group differences observed in Euro Quality of Life assessment questionnaire scores; however, results differed with regard to short form (SF)-36 subscale scores. In one study, there were no significant treatment-group differences in SF-36 subscale scores, but other subscale scores for physical functioning, bodily pain, mental health and vitality favored duloxetine.[33,34]
- A second head-to-head study demonstrated duloxetine to be non-inferior to pregabalin for the treatment of pain in patients with diabetic peripheral neuropathy who had experienced an inadequate pain response to gabapentin.[35]

- Several large meta-analyses and systematic reviews have been conducted that further support the safety and efficacy of these agents in their FDA-approved indications.[36-43]
- In a meta-analysis by Quilici et al, limited available clinical study data suitable for indirect comparison, demonstrated that duloxetine provides comparable efficacy and tolerability to that of gabapentin and pregabalin for the treatment of diabetic peripheral neuropathic pain.[43]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - First-line treatments for postherpetic neuralgia include a tricyclic antidepressant, gabapentin, pregabalin or topical lidocaine patches.[44,45]
  - Topical lidocaine may be considered first-line in the elderly, especially if there are concerns of adverse events with oral medications.[45]
  - For the treatment of diabetic neuropathy, the American Association of Clinical Endocrinology and American Academy of Neurology (AAN) recommend tricyclic antidepressants, anticonvulsants and topical capsaicin to provide symptomatic relief. Moreover, the AAN states that the use of duloxetine or venlafaxine should be considered. There is insufficient evidence to recommend one agent over another. [46,47]

- Other Key Facts:
  - Immediate-release gabapentin (Neurontin®), duloxetine, and topical lidocaine patches are the agents within the class that are available generically.
  - Pregabalin (Lyrica®) is the only neuropathic pain agent that is classified as a controlled substance (Schedule V).

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Therapeutic Class Overview
Long-acting Opioids

Therapeutic Class

- **Overview/Summary:** As a class, opioid analgesics encompass a group of naturally occurring, semisynthetic, and synthetic drugs that stimulate opiate receptors and effectively relieve pain without producing loss of consciousness. The long-acting opioids and their Food and Drug Administration (FDA)-approved indications are outlined in Table 2.[1-18] Previously, they were prescribed for the management of moderate to severe chronic pain; however, starting in March 2014, the FDA's required label changes were made for most of the agents, updating their indication.[19] Currently, long-acting opioids are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. This change was made for all long-acting opioids in an effort to help prescribers and patients make better decisions about who benefits from opioids and also to help prevent problems associated with their use.[19] In addition to indication changes, the long-acting opioid label must include statements that the long-acting opioid is not for "as needed" use, that it has an innate risk of addiction, abuse and misuse even at recommended doses, and finally it must include an update to the black box warning for increased risk of neonatal opioid withdrawal syndrome (NOWS).[19] Long-acting opioids are available in a variety of different dosage forms, and currently several agents are available generically.

  Pain is one of the most common and debilitating patient complaints, with persistent pain having the potentially to lead to functional impairment and disability, psychological distress, and sleep deprivation. Two broad categories of pain include adaptive and maladaptive. Adaptive pain contributes to survival by protecting individuals from injury and/or promoting healing when injury has occurred. Maladaptive, or chronic pain, is pain as a disease and represents pathologic functioning of the nervous system. Various definitions of chronic pain currently exist and may be based on a specified duration of pain; however, in general, the condition can be defined as pain which lasts beyond the ordinary duration of time that an insult or injury to the body needs to heal. Pain can also be categorized as being either nociceptive or neuropathic, and treatments for each are specific. Nociceptive pain is caused by damage to tissue and can further be divided into somatic (pain arising from injury to body tissues) and visceral pain (pain arising from the internal organs). Visceral pain is often described as poorly localized, deep, dull, and cramping. In contrast, neuropathic pain arises from abnormal neural activity secondary to disease, injury, or dysfunction of the nervous system.[20]

  Several mechanisms are thought to be involved in the promotion and/or facilitation of chronic pain, and include peripheral and central sensitization, ectopic excitability, structural reorganization/phenotypic switch of neurons, primary sensory degeneration, and disinhibition. Patients not responding to traditional pain treatments may require individualized and supplemental conventional treatment approaches that target different mechanisms.[20] Several pharmacologic and nonpharmacologic options are currently available for the management of chronic pain. Available treatment options make up six major categories: pharmacologic, physical medicine, behavioral medicine, neuromodulation, interventional, and surgical approaches. As stated previously, some patients may require multiple treatment approaches in order to achieve adequate control of their chronic pain. Pharmacologic therapy should not be the sole focus of pain treatment; however, it is the most widely utilized option to manage chronic pain. Major pharmacologic categories used in the management of pain include nonopioid analgesics, tramadol, opioid analgesics, α-2 adrenergic agonists, antidepressants, anticonvulsants, muscle relaxants, N-methyl-d-aspartate receptor antagonists, and topical analgesics. Combining pharmacologic therapies may result in improved analgesia, and because lower doses of each agent can be used, patients may experience fewer treatment-emergent adverse events. Response to pharmacologic therapies will vary between individual patients, and currently no one approach has been demonstrated to be appropriate for all patients. Treatment decisions are largely based on the type of pain (e.g., neuropathic, nociceptive), comorbidities, concurrent medications, pharmacokinetic/pharmacodynamic properties of the agent, and anticipated adverse events.[21]

For the treatment of neuropathic pain, generally accepted first line therapies include calcium channel α 2-detla ligand anticonvulsants (e.g., gabapentin, pregabalin) and tricyclic antidepressants. Serotonin norepinephrine reuptake inhibitors should be utilized second line, and opioids should be considered as a second or third line option for most patients. Ideally, nociceptive pain is primarily managed with the use of non-opioid analgesics, with acetaminophen and nonsteroidal anti-inflammatory drugs utilized first line in the management of mild to moderate pain. Opioids are associated with a risk of abuse and overdose, and the evidence for the effectiveness of long term opioid therapy in providing pain relief and improving functional outcomes is limited. Use of opioids in the management of chronic noncancer pain remains controversial, and consideration for their use in this clinical setting should be weighed carefully. Opioids should be reserved for the treatment of pain of any severity not adequately controlled with non-opioid analgesics or antidepressants, more severe forms of acute pain, and cancer pain. If being considered for the treatment of chronic noncancer pain, opioids should be further reserved for patients with moderate to severe chronic pain that is adversely affecting patient function and/or quality of life.[21]

The long-acting opioid agents primarily produce intense analgesia via their agonist actions at mu receptors, which are found in large numbers within the central nervous system. The binding of these agents to mu receptors produces a variety of other effects including bradycardia, sedation, euphoria, physical dependence, and respiratory depression. Key safety concerns associated with the opioid analgesics include respiratory depression, and to a lesser degree, circulatory depression.[21,22]

All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of buprenorphine transdermal systems which are a Schedule III controlled substance. Buprenorphine is a partial opiate agonist, and the transdermal system is the first and only seven day transdermal opioid approved by the FDA.[1] On July 9, 2012, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for all long-acting opioids. The program requires companies who manufacture long-acting opioids to make training regarding proper prescribing practices available for health care professionals who prescribe these agents, as well as distribute educational materials to both prescribers and patients on the safe use of these agents. The new REMS program is part of the national prescription drug abuse plan announced by the Obama Administration in 2011 to combat prescription drug misuse and abuse.[23]

On March 11, 2014, the FDA approved a new combination product Xartemis XR® (oxycodone/acetaminophen), which contains oxycodone and acetaminophen. It has a bilayer formulation which has an immediate- and extended-release portion allowing for rapid analgesia with prolonged effects. This product, although new, is not formulated as an abuse-deterrent product. It has the unique indication of management of acute, severe pain, which is not shared with any of the other long-acting opioids. Due to the acetaminophen component use of this medication is limited, as a maximum of 4,000 mg/day is recommended by the manufacturer.[18]

There are currently four abuse deterrent formulations of extended-release (ER), long acting opioids approved by the FDA. The abuse deterrent products are Oxycodone ER (OxyContin®), morphine sulfate/naltrexone (Embeda) and two hydrocodone ER products (Zohydro ER® and Hysingla ER®).

Even though OxyContin® (oxycodone extended-release [ER]) has received increased attention regarding overuse, abuse, and diversion, oxycodone itself does not appear to have a greater dependence or abuse liability compared to the other available opioids.[24] In April of 2010, the FDA approved a new formulation of OxyContin® that was designed to help discourage misuse and abuse of the medication. Specifically, the reformulated OxyContin® is intended to prevent the opioid medication from being cut, broken, chewed, crushed, or dissolved to release more medication. The FDA states that the new formulation may be an improvement that may result in less risk of overdosage due to tampering, and will likely result in less abuse by snorting or injection, but the agent can still be abused or misused by simply ingesting larger doses than are recommended. The manufacturers of the medication will be required by the FDA to conduct a postmarket study to evaluate the extent to which this new formulation reduces abuse and misuse of the medication.[25]

Similarly, a new, crush-resistant formulation of Opana ER® (oxymorphone) was approved in December 2011; however, the manufacturer notes that it has not been established that the new formulation is less subject to misuse, abuse, diversion, overdose, or addiction.[26]

In October 2013, the FDA approved the first sole entity hydrocodone product in an ER formulation known as Zohydro ER® (hydrocodone) for the treatment of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate.[3] The approval of Zohydro ER® (hydrocodone) was somewhat controversial for a number of reasons. The advisory panel to the FDA voted 11 to 2 against the approval of Zohydro ER® (hydrocodone), due in large part to growing concerns regarding opioid abuse and the product's lack of an abuse deterrent mechanism. Despite the advisory committee vote, Zohydro ER® (hydrocodone ER) was approved based on an FDA Division Director's rationale that the benefit-risk balance for Zohydro ER® (hydrocodone ER) and other non-abuse deterrent opioid analgesics is still favorable for patients requiring chronic opioid therapy. In addition, the case was made for having another alternative long-acting opioid for patients that cannot tolerate other options or who are on an opioid rotation.[11] As of February 2015, two abuse-deterrent formulations of hydrocodone ER have been FDA-approved. Hysingla ER® (hydrocodone ER) was approved on November 20, 2014 and the reformulated Zohydro ER® was FDA approved January 30, 2015.[3,4,27] It is important to note that the FDA does not require updates to drug labels that have already been approved for manufacturing changes. Thus, the FDA-approved label for Zohydro ER® did not require any changes and does not specifically mention a change in formulation.[3,27]

Embeda® (morphine sulfate/naltrexone) was the first long-acting opioid to become available. This particular agent combines an opioid agonist with an opioid antagonist to deter abuse. The combination product contains ER morphine sulfate with sequestered naltrexone; therefore, if crushed the naltrexone is released and the euphoric effects of morphine are reduced.[17,28] On March 16, 2011 it was announced that King Pharmaceuticals Inc., a wholly owned subsidiary of Pfizer, has voluntarily recalled from United States wholesalers and retailers all dosage forms of Embeda® due to a pre-specified stability requirement that was not met during routine testing. According to a press release, on October 17, 2014, the FDA-approved label for Embeda® has been updated to include abuse-deterrent studies and is once again available.[29] Overall, while these new long-acting opioid formulations intended to deter abuse may be promising, there is no evidence demonstrating that they truly prevent abuse.[30]

Table 1. Current Medications Available in the Therapeutic Class[1-18]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Buprenorphine (Butrans®)	The management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	Transdermal patch: 5 µg/hour 7.5 µg/hour 10 µg/hour 15 µg/hour 20 µg/hour	-
Fentanyl (Duragesic®*)	The management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.†	Transdermal system‡: 12 µg/hour§ 25 µg/hour 50 µg/hour 75 µg/hour 100 µg/hour	a
Hydrocodone (Hysingla ER®, Zohydro ER®)	The management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative	Capsule, extended release (Zohydro ER®):	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	treatment options are inadequate.	10 mg 15 mg 20 mg 30 mg 40 mg 50 mg‡ Tablet, extended release (Hysingla ER®): 20 mg 30 mg 40 mg 60 mg 80 mg‡ 100 mg‡ 120 mg‡	
Hydromorphone (Exalgo®*)	The management of pain in opioid-tolerant patients severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.†	Tablet, extended release: 8 mg‡ 12 mg‡ 16 mg‡ 32 mg‡	a
Methadone (Dolophine®*, Methadose®*)	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (solution, tablet). For detoxification treatment of opioid addiction (heroin or other morphine-like drugs) (concentrate solution, dispersible tablet, solution, tablet). For maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services (concentrate solution, dispersible tablet, solution, tablet).	Concentrate solution, oral (sugar-free available): 10 mg/mL Solution, oral: 5 mg/5 mL 10 mg/5 mL Tablet, extended release: 5 mg 10 mg Tablet for oral suspension: 40 mg	a
Morphine sulfate (Avinza®*, Kadian®*, MS Contin®*)	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate (biphasic capsule, capsule, tablet).	Capsule, biphasic extended release: 30 mg 45 mg 60 mg 75 mg 90 mg‡ 120 mg‡ Capsule, extended release: 10 mg	a

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		20 mg 30 mg 40 mg 50 mg 80 mg 100 mg‡ 200 mg‡ Tablet, extended release: 15 mg 30 mg 60 mg 100 mg‡ 200 mg‡	
Oxycodone (OxyContin®*)	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.¶	Tablet, extended release: 10 mg 15 mg 20 mg 30 mg 40 mg 60 mg‡ 80 mg‡	a #
Oxymorphone (Opana® ER*)	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	Tablet extended release: 5 mg 7.5 mg 10 mg 15 mg 20 mg 30 mg 40 mg	a
Tapentadol (Nucynta ER®)	Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	Tablet, extended release: 50 mg 100 mg 150 mg 200 mg 250 mg	-
Combination Products			
Morphine sulfate/ naltrexone (Embeda®)	Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.‡	Capsule, extended release: 20 mg/0.8 mg 30 mg/1.2 mg 50 mg/2 mg 60 mg/2.4 mg 80 mg/3.2 mg 100 mg/4 mg‡	-
Oxycodone/	For the management of acute pain severe	Biphasic tablet,	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Acetaminophen (Xartemis XR®)	enough to require opioid treatment and for which alternative treatment options are inadequate	extended release: 7.5 mg/325 mg	

*Generic is available in at least one dosage form or strength.
†Opioid-tolerant are those who are taking, for one week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, 25 mcg fentanyl/hr, or an equianalgesic dose of another opioid.
‡Specific dosage form or strength should only be used in patients with opioid tolerance.
§Actual fentanyl dose is 12.5 µg/hour, but it is listed as 12 µg/hr to avoid confusion with a 125 µg dose.
#Generic availability is sporadic and does not include all strengths.
¶ A single dose of OxyContin® >40 mg or a total daily dose of 80 mg are only for use in patients who are tolerant to opioids.

Evidence-based Medicine

- Food and Drug Administration (FDA) approval of hydrocodone ER tablets (Hysingla ER®) was evaluated in an unpublished randomized double-blind, placebo controlled, multi-center, 12-week clinical trial in both opioid-experienced and opioid-naïve patients with moderate to severe chronic low back pain. Patients received either hydrocodone ER 20 to 120 mg tablets or matching placebo in a 1:1 ratio. There was a statistically significant difference in the weekly average pain scores at week 12 between the hydrocodone ER and placebo groups with a least square mean (standard deviation [SD]) difference of -0.53 (0.180) (95% confidence interval [CI], -0.882 to -0.178; P=0.0016). There were also significant improvements in proportion of responders, and Patient's Global Impression of Change scores.[4,31]
- The effectiveness of fentanyl in relieving pain appears to be similar to that of morphine sulfate sustained-release for the treatment of cancer and noncancer pain, and chronic lower back pain. Compared to morphine sulfate sustained-release, fentanyl transdermal systems appear to be associated with less constipation.[32-34]
- A trial comparing hydrocodone ER capsules to placebo in patients with moderate to severe chronic low back pain demonstrated hydrocodone ER had a lower mean change from baseline in pain intensity scores compared to placebo at 12 weeks (P=0.008). In addition, there was a significantly higher amount of treatment responders in the hydrocodone ER group compared to the placebo group (P<0.001) at the end of treatment, and subject global assessment of medication scores increased from baseline significantly in the hydrocodone ER group compared to placebo (P<0.0001).[35]
- In one trial, hydromorphone ER demonstrated greater efficacy in the treatment of lower back pain with regard to reducing pain intensity (P<0.001) and pain scores (P<0.01) compared to placebo.[36] In a noninferiority analysis of a hydromorphone ER compared to oxycodone ER, two agents provided similar pain relief in the management of osteoarthritic pain.[37]
- Methadone has demonstrated a greater efficacy over placebo for the treatment of nonmalignant neuropathic pain and similar efficacy compared to slow-release morphine sulfate for the treatment of cancer pain.[38,39]
- A trial comparing different long-acting formulations of morphine sulfate for the treatment of osteoarthritis pain demonstrated that both Avinza® (morphine sulfate ER) and MS Contin® (morphine sulfate ER) significantly reduced pain from baseline (P≤0.05 for both). Both treatments also reduced overall arthritis pain intensity, and achieved comparable improvements in physical functioning and stiffness. Each treatment significantly improved certain sleep parameters compared to placebo.[39] In a crossover trial, morphine sulfate (MS Contin®) was compared to fentanyl transdermal systems, and more patients preferred fentanyl transdermal systems (P<0.001), and reported on average, lower pain intensity scores than morphine sulfate phase (P<0.001).[41]
- Clinical trial data evaluating the combination long acting opioid agent morphine/naltrexone is limited. As mentioned previously, this product was recalled by the manufacturer due to not meeting a pre-specified stability requirement during routine testing in March 2011.[29]
- Morphine/naltrexone has demonstrated significantly better pain control compared to placebo in patients with osteoarthritis pain.[42]
- Oxycodone ER has demonstrated significantly greater efficacy compared to placebo for the treatment of neuropathic pain and chronic refractory neck pain.[43-45] For the treatment of cancer pain, no significant differences were observed between oxycodone ER and morphine sulfate ER in reducing

pain intensity. The average number of rescue doses used within a 24 hour period was significantly less with morphine sulfate ER (P=0.01), and the incidence of nausea and sedation were similar between treatments.[46]

- Oxymorphone ER has produced similar mean daily pain intensity scores compared to both morphine sulfate and oxycodone ER for the treatment of chronic cancer pain.[47,48] The average scheduled daily dose of study drug and average total daily dose decreased after patients crossed over to oxymorphone ER from morphine sulfate or oxycodone ER. No significant changes were observed in visual analog pain scores, quality of life domains, or quality of sleep in any of the treatment groups.[47] In another trial, oxymorphone ER demonstrated greater efficacy for the relief of osteoarthritis pain compared to placebo.[49]
- In a 12-week active comparator and placebo-controlled trial, significant pain relief was achieved with tapentadol ER compared to placebo (least squares mean difference, - 0.7; 95% CI, -1.04 to -0.33) at week 12. The average pain intensity rating at endpoint with oxycodone ER was reduced significantly compared to placebo for the overall maintenance period (least squares mean difference vs placebo, -0.3), but was not significantly lower at week 12 (least squares mean, -0.3; P values not reported).[50] In a, placebo-controlled and active comparator trial in adults with moderate to severe low back pain, improvements in average pain intensity scores occurred with tapentadol ER and oxycodone ER relative to placebo (P<0.001).[51] Schwartz et al evaluated tapentadol ER among adults with painful diabetic peripheral neuropathy. The least squares mean change in average pain intensity at week 12 was 1.4 in the placebo group, indicating a worsening in pain intensity, and 0.0 in the tapentadol ER group, indicating no change in pain intensity, (least squares mean difference, -1.3; 95% CI, -1.70 to -0.92; P<0.001).[52]
- The combination product oxycodone/acetaminophen's efficacy was established in a clinical trial evaluating its effectiveness at treating pain over the 48 hours after surgery. Singla et al concluded that pain, evaluated by the summed pain intensity difference (SPID) score, was significantly higher in the oxycodone/acetaminophen group (P<0.001) through that time period. Mean total pain relief values for oxycodone/APAP XR and placebo from 0 to 48 hours were 91.3 and 70.9, respectively, resulting in a treatment difference of 20.5 (95% CI, 11.0 to 30.0; *P*<0.001). The median time to perceptible pain relief for oxycodone/APAP XR was 33.56 minutes vs 43.63 minutes for placebo (*P*=0.002). The median times to confirmed pain relief and meaningful pain relief for the oxycodone/APAP XR group were 47.95 minutes and 92.25 minutes; however, neither of these metrics could be determined for the placebo group (*P*<0.001). The percentage of patients reporting at least a 30% reduction in PI after 2 hours was 63.1% for oxycodone/APAP XR versus 27.2% for placebo (*P*<0.0001).[53]
- Methadone is the only long-acting narcotic that is Food and Drug Administration-approved for the management of opioid addiction; however, in one study slow-release morphine sulfate demonstrated noninferiority to methadone in terms of completion rate for the treatment of opioid addiction (51 vs 49%).[54]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Patients with pain should be started on acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). If sufficient pain relief is not achieved, patients should be escalated to a "weak opioid" and then to a "strong opioid", such as morphine.[55,56]
  - Opioid selection, initial dosing, and titration should be individualized according to the patient's health status, previous exposure to opioids, attainment of therapeutic goals, and predicted or observed harms. There is insufficient evidence to recommend short-acting vs long-acting opioids, or as needed vs around-the-clock dosing of opioids.[56]
  - Patients with chronic persistent pain controlled by stable doses of short-acting opioids should be provided with round-the-clock ER or long-acting formulation opioids with provision of a 'rescue dose' to manage break-through or transient exacerbations of pain.[55]
  - Opioids with rapid onset and short duration are preferred as rescue doses. The repeated need for rescue doses per day may indicate the necessity to adjust the baseline treatment.[55,56]

- In a patient who has not been exposed to opioids in the past, morphine is generally considered the standard starting drug of choice.[55]
- Pure agonists (such as codeine, fentanyl, oxycodone, and oxymorphone) are the most commonly used medications in the management of cancer pain. Opioid agonists with a short half-life are preferred and include fentanyl, hydromorphone, morphine, and oxycodone.[55]
- Meperidine, mixed agonist-antagonists, and placebos are not recommended for cancer patients. Meperidine is contraindicated for chronic pain especially in patients with impaired renal function or dehydration.[55]
- In patients who require relatively high doses of chronic opioid therapy, clinicians should evaluate for unique opioid-related adverse events, changes in health status, and adherence to the chronic opioid therapy treatment plan on an ongoing basis, and consider more frequent follow-up visits.[55,56]

· Other Key Facts:
- There are currently four abuse deterrent formulations of extended-release, long acting opioids approved by the FDA. These include oxycodone ER (OxyContin®), morphine sulfate/naltrexone (Embeda) and two hydrocodone ER products (Zohydro ER® and Hysingla ER®).
- All long-acting opioids are pregnancy category C, with the exception of oxycodone.
- Only fentanyl transdermal system is approved in children (age 2 to 17 years).
- Tapentadol is contraindicated with monoamine oxidase inhibitors; although, caution should be used when used in combination with any long-acting opioid.
- Only oxymorphone is contraindicated in severe hepatic disease.
- Methadone and buprenorphine have been implicated in QT prolongation and serious arrhythmias, use caution in patients at increased risk of QT prolongation.
- Besides the two transdermal agents, almost all long-acting opioids are dosed twice daily. Buprenorphine patches are applied once every seven days, while fentanyl transdermal systems are applied every 72 hours.[1,2] Exalgo® ER (hydromorphone) and Hysingla ER (hydrocodone) tablets and Avinza® (morphine) capsules are dosed once daily.[4,5,10] Kadian® (morphine) capsules and Embeda® (morphine/naltrexone) capsules can to be administered once or twice daily.[12,17] MS Contin® (morphine) tablets or all methadone formulations are dosed twice or three times daily.[6-10,13] The remaining long-acting agents are dosed twice daily only (oxycodone, oxymorphone, tapentadol, oxycodone/acetaminophen).[3,15,16,18] Avinza® (morphine) and Xartemis XR® (oxycodone/acetaminophen) are the only long-acting opioids with a maximum daily dose. Avinza® (morphine) has a max dose of 1,600 mg/day due to the capsules being formulated with fumaric acid, which at that dose has not been shown to be safe and effective and may cause renal toxicity[11]. Xartemis XR (oxycodone/acetaminophen) is limited to four tablets per day, and/or if taking other acetaminophen products, a maximum of 4,000 mg/day.[18]
- Buprenorphine patch and fentanyl transdermal systems are intended for transdermal use only and should be applied to intact, nonirritated, nonirradiated skin on a flat surface. The application site should be hairless, or nearly hairless, and if required hair should be clipped not shaven. Fentanyl may be applied to the chest, back, flank or upper arm while buprenorphine should be applied to the right or left outer arm, upper chest, upper back or side of chest.[1,2]
- Most solid, long-acting opioid formulations (e.g., tablets, capsules) should be swallowed whole and should not be broken, chewed, cut, crushed, or dissolved before swallowing.[1-18] The only exceptions are the morphine-containing capsules (Avinza®, Kadian®, and Embeda®); all can be opened and the pellets sprinkled on applesauce and then swallowed whole.[11,12,17] Kadian® pellets can also be placed in 10 mL of water and used through a 16 French gastrostomy tube.[12] Neither Avinza®, Kadian®, nor Embeda® pellets may be used thorough a nasogastric tube.[11,12,17] It is recommended to only swallow one Zohydro ER® (hydrocodone) capsule, or one OxyContin® (oxycodone), Opana® ER (oxymorphone), and Nucynta® ER (tapentadol) tablet at a time.[3,14-16]
- Differences in pharmacokinetics result in differences in how often the dose of an opioid may be titrated upward. Each long-acting opioid has a certain time period before which a dose

titration can occur. The amount of time required before dose titration can occur can range from one to seven days. The specific times required for titration are listed in Table 10.[1-18] When switching between agents, an appropriate dose conversion table must be used. When discontinuing any long-acting opioid without starting another, always use a slow taper to prevent severe withdrawal symptoms.

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Therapeutic Class Overview
Multiple Sclerosis Agents

Therapeutic Class

- **Overview/Summary:** Several biologic response modifiers are Food and Drug Administration (FDA)-approved for the treatment of relapsing-remitting multiple sclerosis (RRMS) including alemtuzumab (Lemtrada®), dimethyl fumarate (Tecfidera®), fingolimod (Gilenya®), glatiramer acetate (Copaxone®), interferon β (IFNβ)-1b (Betaseron®, Extavia®), intramuscular (IM) IFNβ-1a (Avonex®), subcutaneous (SC) IFNβ-1a (Rebif®), SC peginterferon β-1a (Plegridy®) and teriflunomide (Aubagio®).[1-11] In addition, glatiramer acetate, IFNβ-1b and IM IFNβ-1a are FDA-approved for the treatment of patients experiencing a first clinical episode with magnetic resonance imaging evidence of multiple sclerosis (MS), referred to as a clinically isolated syndrome.[4-7,9,10] The exact mechanisms of dimethyl fumarate, glatiramer acetate, the IFNβs and teriflunomide have not been fully established; however, they are likely due to their antiproliferative and immunomodulatory effects.[2,4-10] Glatiramer acetate is a polymer containing four amino acids that are found in the myelin basic protein.[4] The IFNβ products are produced by recombinant deoxyribonucleic acid technology in different cell systems, resulting in differences in amino acid sequence, molecular weight and degree of glycosylation.[12] Three orally administered agents are currently available including fingolimod, a first-in-class sphingosine 1-phosphate receptor modulator, dimethyl fumarate and teriflunomide. Fingolimod and teriflunomide are administered once daily, while dimethyl fumarate should be administered twice daily.[2,3,10] Each IFNβ has a different FDA-approved dosing and administration schedule. Avonex® is administered IM once weekly, while Rebif® is administered SC three times weekly and Betaseron® and Extavia® are administered SC every other day.[5-7,9] Alemtuzumab must be administered in a health care setting via intravenous infusion over four hours. Patients receive two courses of alemtuzumab with the second course given 12 months after the first.[8]

- MS is a chronic and potentially disabling neurological disease characterized by repeated episodes of inflammation within the nervous tissue of the brain and spinal cord, resulting in injury to the myelin sheaths and subsequently the nerve cell axons.[12] Of the four clinical subtypes of MS (primary progressive, progressive relapsing, RRMS and secondary progressive), RRMS is the most common and is characterized by acute relapses followed by partial or full recovery.[12-14] The most common adverse events associated with IFNβ therapy are influenza-type symptoms, injection site reactions, headache, nausea and musculoskeletal pain. Hepatotoxicity has rarely been reported in patients treated with IFNβ therapy.[5-7,9] Therapy with IFNβ should be used cautiously in patients with depression or other mood disorders. Patients receiving glatiramer acetate therapy may experience a transient, self-limiting, post-injection systemic reaction immediately following drug administration consisting of flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction and urticaria.[3] Substantial cardiac monitoring is required when initiating treatment with fingolimod as post-marketing cases of cardiac-related death have been reported. In addition, fingolimod is contraindicated in patients with certain pre-existing cardiovascular conditions.[3] The labeling of teriflunomide contains two black box warnings regarding the risk of hepatotoxicity and teratogenicity.[10] Dimethyl fumarate, although it has limited post-marketing data, appears to have the most mild adverse event profile with flushing and gastrointestinal effects reported most frequently.[2]

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

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Alemtuzumab (Lemtrada)	Relapsing-remitting multiple sclerosis*		
Dimethyl fumarate (Tecfidera®)	Relapsing-remitting multiple sclerosis*	Delayed-release capsule: 120 mg 240 mg	-
Fingolimod (Gilenya®)	Relapsing-remitting multiple sclerosis†	Capsule:	-

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
		0.5 mg	
Glatiramer acetate (Copaxone®)	Relapsing-remitting multiple sclerosis‡, treatment of first clinical episode with magnetic resonance imaging features consistent with multiple sclerosis	Prefilled syringe: 20 mg	-
Interferon β-1b (Betaseron®, Extavia®)	Relapsing-remitting multiple sclerosis§, treatment of first clinical episode with magnetic resonance imaging features consistent with multiple sclerosis	Single use vial: 0.3 mg lyophilized powder	-
Interferon β-1a (Rebif®)	Relapsing-remitting multiple sclerosis‖	Prefilled syringe: 8.8 µg 22 µg 44 µg	-
Interferon β-1a (Avonex®, Avonex Administration Pack®)	Relapsing-remitting multiple sclerosis¶, treatment of first clinical episode with magnetic resonance imaging features consistent with multiple sclerosis	Prefilled syringe: 30 µg Single use vial: 30 µg lyophilized powder	-
Peginterferon β-1a (Plegridy®)	Relapsing-remitting multiple sclerosis*		
Teriflunomide (Aubagio®)	Relapsing-remitting multiple sclerosis*	Tablet: 7 mg 14 mg	-

*Treatment of patients with relapsing forms of multiple sclerosis.
†Treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.
‡Reduction of the frequency of relapses in patients with relapsing-remitting multiple sclerosis.
§Treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations.
‖Treatment of patients with relapsing forms of multiple sclerosis to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability.
¶ Treatment of patients with relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations.

Evidence-based Medicine

- The safety and efficacy of glatiramer acetate and interferon (IFNβ) products are well established. Recent clinical trials have not produced clinically different results compared to trials published previously.
- In two large, randomized trials with dimethyl fumarate 240 mg twice-daily or three times daily compared to placebo, there were statistically significant reductions in the annualized relapse rate (ARR) with both dimethyl fumarate regimens compared to placebo (P≤0.001 for both).[15,16] Fox et al also included an open-label glatiramer acetate comparator group. In a post-hoc analysis, there were significant improvements favoring dimethyl fumarate over glatiramer acetate with regard to ARR (three times daily group only), new or enlarging T2 hyperintense lesions and new T1 hypointense lesions (three times daily group only).[16]
- In the 24-month, placebo-controlled FREEDOMS trial, treatment with fingolimod 0.5 or 1.25 mg once daily significantly reduced ARR compared to placebo (54 and 60%, respectively; P<0.001 for both).[15]
- The FREEDOMS II trial had similar results, with fingolimod providing a lower ARR over 24 months compared to placebo.[18]
- In the 12-month TRANSFORMS trial, fingolimod 0.5 or 1.25 mg once-daily significantly reduced ARR by 52 and 40%, respectively, compared to IFNβ-1a 30 µg intramuscularly (IM) once-weekly (P<0.001 for both).[19] 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.[20]

- In the TEMSO trial, treatment with teriflunomide 7 or 14 mg was associated with significantly greater relative reductions in ARR compared to placebo (31.2 and 31.5%. respectively; *P*<0.001).[21] In an unpublished extension study, ARR remained low after five years and the adverse event rates were similar to those reported in previous trials.[22,23]
- The TOWER study showed that over one year teriflunomide had a lower ARR than placebo.[24]
- The ComiRX trial, evaluated the combination of IFNβ-1a and glatiramer acetate versus IFNβ-1a alone versus glatiramer acetate alone. After three years, the ARR of the combination was not statistically significantly improved to the better of the two single-agent arms when adjusting for baseline age. Glatiramer acetate provided statistically significant greater reduction in risk of exacerbation compared to interferon by 31%, and the combination group provided statistically significant greater reduction in risk of exacerbation compared to interferon by 25% (P=0.027, P=0.022 respectively).[25]
- Two phase III clinical trials evaluated treatment outcomes with IFNβ-1a 44 µg SC three times weekly and alemtuzumab 12 mg. One trial evaluated a study population of treatment-experienced MS patients and the second study evaluated treatment outcomes in treatment-naive patients. In both trials, treatment with alemtuzumab resulted in a statistically significant reduction in the annualized relapse rate compared to treatment with IFNβ-1a. Time to onset of six-month disability progression was only significantly delayed in treatment-experience patients.[26,27]
- The safety and efficacy of peginterferon β-1a, was established in a single, randomized, double-blind, placebo controlled study. Annualized relapse rate was 0.26 in the peginterferon β-1a group compared to 0.40 with placebo (P=0.007). This represented a hazard ratio of 0.61 (95% CI, 0.47 to 0.80; P=0.0003). The proportion of patients with a relapse was also significantly lower with the peginterferon β-1a group compared to placebo (0.19 vs 0.29; P=0.003). [28]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - The American Academy of Neurology and the National Multiple Sclerosis (MS) Society guidelines recommend the use of interferon β (IFNβ) products or glatiramer acetate as first-line therapy in all patients with clinically definite relapsing-remitting MS (RRMS) and in select patients with clinically isolated syndrome.[29]
  - The most appropriate agent may be selected on an individual basis and monitored for clinical response and tolerability.[29]
  - Consensus guidelines have not been updated to address the role of alemtuzumab, dimethyl fumarate, peginterferon β-1a or teriflunomide in the treatment of MS.[29]
  - The National Institute for Clinical Excellence has recommended that due to its adverse event profile, fingolimod be reserved as an option for highly active RRMS in adults, only if patients have an unchanged or increased relapse rate or ongoing severe relapses compared to the previous year despite treatment with IFNβ.[30]
- Other Key Facts:
  - No generic products are currently available.
  - The safety and efficacy of retreatment with alemtuzumab after the initial standard treatment cycles remains uncertain. There is no information regarding retreatment in alemtuzumab's FDA-approved label.[1]
  - There are no head-to-head trials comparing IFNβ-1b products (Betaseron® and Extavia®) and the drugs are not interchangeable despite Extavia® being approved with the same active ingredient and registration trials as Betaseron®.[4,5]
  - Extavia® comes with a 27-gauge needle, packaged with 15 vials for a 30 day supply, while the Betaseron® has 30-gauge needles, packaged with 14 vials for a 28 day supply.[4,5]

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Therapeutic Class Overview
Pulmonary Arterial Hypertension Agents

Therapeutic Class

Overview/Summary: The oral pulmonary hypertension agents are Food and Drug Administration (FDA)-approved for the treatment of patients with World Health Organization (WHO) Group I pulmonary arterial hypertension (PAH); however, there are differences in the study populations for which their FDA-approvals were based.[1-9] Typically, PAH is characterized by an elevated pulmonary arterial pressure and an increased pulmonary vascular resistance leading to right-sided heart failure. The prevalence of PAH is estimated to be 15 cases/million adults. The disease has a poor prognosis and an approximate mortality rate of 15% within one year on therapy.[10] The WHO classifies pulmonary hypertension into five groups. WHO Group I encompasses PAH, including idiopathic PAH, familial PAH, and PAH associated with connective tissue disorders, portal hypertension, human immunodeficiency virus infection, drugs and toxins and other disorders that affect the small pulmonary muscular arterioles. Patients with PAH are assessed based on the WHO and New York Heart Association (NYHA) functional classes that describe the disease severity from little (class I) to significant (class IV) impact on patient physical activity.[11] Four classes of medications are currently FDA-approved for the treatment of WHO Group I PAH: prostanoids, endothelin receptor antagonists (ERAs), phosphodiesterase (PDE)-5 inhibitors and soluble guanylate cyclase stimulators.[12] In PAH, prostacyclin synthase is reduced resulting in inadequate production of prostacyclin I_2, a potent vasodilator with antiproliferative effects and an inhibitor of platelet aggregation.[10] The prostanoids act as vasodilators and platelet aggregation inhibitors. Currently, iloprost (Ventavis®) and treprostinil (Tyvaso®) inhaled formulations and treprostinil (Orenitram®) extended-release tablets are the only prostanoids available orally; however, other products are available for intravenous or subcutaneous administration.[1,4,9] Endothelial dysfunction in PAH causes increased production of endothelin-1 resulting in vasoconstriction, which is mediated by the endothelin receptors, ET_A and ET_B.[2,3,7,10] Stimulation of ET_A causes vasoconstriction and cell proliferation, while stimulation of ET_B results in vasodilatation, antiproliferation and endothelin-1 clearance.[2,3] The ERAs, ambrisentan (Letairis®), bosentan (Tracleer®) and macitentan (Opsumit®) competitively bind to both receptors with different affinities. Ambrisentan is highly selective for the ET_A receptor, while bosentan is slightly more selective for the ET_A receptor than the ET_B receptor. Macitentan is associated with a high affinity and sustained occupancy of both ET receptors. However, the clinical significance of receptor affinities of the ERAs has not been established.[2,3] In patients with PAH there is also an impaired release of nitric oxide by the vascular endothelium thereby reducing cyclic guanosine monophosphate (cGMP) concentrations. The PDE-5 enzyme is the predominant phosphodiesterase in the pulmonary vasculature and is responsible for the degradation of cGMP.[10] The PDE-5 inhibitors, sildenafil (Revatio®) and tadalafil (Adcirca®), increase the concentrations of cGMP resulting in relaxation of pulmonary vascular bed.[5,6] Currently, sildenafil tablets are the only oral PAH agent available generically.[9] Soluble guanylate cyclase (sGC) is an enzyme present in the cardiopulmonary system and is the receptor for nitric oxide. When bound to nitric oxide, sGC catalyzes synthesis of cGMP, which plays a role in the regulating processes that influence vascular tone, proliferation, fibrosis and inflammation. Riociguat (Adempas®) stimulation of this nitric oxide-sGC-cGMP pathway leads to increased generation of cGMP and thus, vasodilation.[8]

Table 1. Current Medications Available in Therapeutic Class[1-9,12]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Ambrisentan (Letairis®)	Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening.*	Tablet: 5 mg 10 mg	-
Bosentan (Tracleer®)	Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening.†	Tablet: 62.5 mg 125 mg	-
Iloprost	Treatment of PAH (WHO Group I) to improve a	Ampule for	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
(Ventavis®)	composite endpoint consisting of exercise tolerance symptoms (NYHA class) and lack of deterioration.‡	inhalation: 10 µg/mL 20 µg/mL	
Macitentan (Opsumit®)	Treatment of PAH (WHO Group I) to delay disease progression.‖#	Tablet: 10 mg	-
Riociguat (Adempas®)	Treatment of PAH (WHO Group I) to improve exercise ability, improve WHO functional class and delay clinical worsening and treatment of persistent/recurrent CTEPH after surgical treatment or inoperable CTEPH to improve exercise capacity.‖	Tablet: 0.5 mg 1 mg 1.5 mg 2 mg 2.5 mg	-
Sildenafil (Revatio®)	Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening.§‖	Tablet: 20 mg Vial for injection: 0.8 mg/mL Powder for oral suspension: 10 mg/mL	a
Tadalafil (Adcirca®)	Treatment of PAH (WHO Group I) to improve exercise ability.¶	Tablet: 20 mg	-
Treprostinil (Tyvaso®)	Treatment of PAH (WHO Group I) to improve exercise ability. **	Ampule for inhalation: 0.6 mg/mL	-
Treprostinil (Orenitram®)	Treatment of PAH (WHO Group I) to improve exercise ability.††	Extended-release tablet: 0.125 mg 0.25 mg 1 mg 2.5 mg	-

CTEPH=Chronic Thromboembolic Pulmonary Hypertension, NYHA=New York Heart Association, PAH=pulmonary arterial hypertension, WHO=World Health Organization

*Studies establishing effectiveness included predominantly patients with World Health Organization (WHO) Functional Class II to III symptoms and etiologies of idiopathic or heritable pulmonary arterial hypertension (PAH) (64%) or PAH associated with connective tissue diseases (32%).

†Studies establishing effectiveness included predominately patients with New York Heart Association (NYHA) Functional Class II to IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%).

‡Studies establishing effectiveness included predominately patients with NYHA Functional Class III to IV symptoms and etiologies of idiopathic or heritable PAH (65%), PAH associated with connective tissue diseases (23%).

§Studies included predominately patients with NYHA class II or III symptoms and etiologies of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%).

‖ Approved for use in adults only.

¶Studies included predominately patients with NYHA class II or III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

#Disease progression included death, initiation of intravenous or subcutaneous prostanoids or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment).

** Studies included predominantly patients with NYHA class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

††Studies included predominately patients with NYHA class II or III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue diseases (19%).

Evidence-based Medicine

- Randomized controlled trials have demonstrated the efficacy of the oral pulmonary arterial hypertension agents in increasing exercise capacity and improving World Health Organization and New York Heart Association functional class; however, no head to head trials have been conducted.[15-45]
- Only small studies evaluating the effect of combination therapy have been conducted, and statistically significant improvements have not consistently been demonstrated.[10,22,33,34,39, 41,43]
- Common adverse events in the prostanoids class are jaw pain, diarrhea, headache and flushing.[12] Endothelin receptor antagonists are associated with peripheral edema and elevated liver function tests. [12] The phosphodiesterase-5 inhibitors are generally well tolerated and common adverse effects include headache, flushing, and dyspepsia.[12] The most common adverse events associated with the soluble guanylate cyclase stimulators can be ascribed to the vasodilatory mechanism of action, including headache, dizziness, nausea and hypotension.[8]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Oral calcium-channel blockers (CCB) are recommended only for patients with positive acute vasodilator response to testing.[10,13,14]
  - Oral therapy with either a phosphodiesterase-5 inhibitor or an endothelin receptor antagonist or riociguat is recommended as first-line treatment in patients who are considered lower risk and are not candidates for CCBs.[10,13,14]
  - Use of inhaled or parenteral prostanoids should not be chosen as initial therapy for treatment naïve PAH patients with WHO functional class II symptoms or as second line agents for PAH patients with WHO functional class II symptoms who have not met their treatment goals.[13]
  - For WHO class III patients, addition of a parenteral or inhaled prostanoid to mono- or dual-oral therapy is recommended if rapid progression occurs, or there is poor clinical prognosis.[10,13]
  - Intravenous prostanoids are the preferred treatment in patients at higher risk and poor prognostic indexes.[10,13]
  - If a patient cannot or does not wish to use intravenous medications, they may use inhaled prostanoids and an endothelin receptor antagonist for higher risk or poorer prognostic indexes.[13]

- Other Key Facts:
  - Ambrisentan, bosentan, macitentan and riociguat are distributed through a restricted distribution program.[2,3,7,8]
  - Sildenafil tablets are the only oral pulmonary arterial hypertension agent that are available generically.
  - In August 2012, the prescribing information for sildenafil was updated to include a warning against the use of sildenafil in pediatric patients. This was due to increased mortality seen in long-term clinical trials that included pediatric patients.[5]

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Therapeutic Class Overview
Phosphorus Depleters

Therapeutic Class

- **Overview/Summary:** Hyperphosphatemia, an important and inevitable clinical consequence of advanced stages of chronic kidney disease (CKD), requires appropriate management due to the risk for secondary hyperparathyroidism and cardiovascular disease. Persistent or chronic hyperphosphatemia, along with an elevated calcium times phosphorus (CaxP) product, is associated with an increased risk of vascular, valvular and other soft-tissue calcification in patients with CKD. The two principal modalities used to control serum phosphorus levels in patients with CKD include restricting dietary phosphorus intake and the administration of phosphorus binders (or phosphorus depleters). When dietary phosphorus restriction is inadequate in controlling serum phosphorus levels, the administration of phosphorus binders is recommended. There are several different phosphorus binders that are currently available; however, the class can be divided into two subcategories: calcium- and non-calcium-containing products.[1-4] In general, calcium-containing phosphorus binders (Eliphos®, PhosLo®, Phoslyra®) are associated with higher serum calcium and lower serum parathyroid hormone levels compared to the non-calcium-containing products.[5-7] Increased serum calcium levels leads to hypercalcemia and also increases the risk of vascular calcification and arterial disease in CKD patients.[4] As a result, these products are typically avoided in CKD patients with hypercalcemia or severe vascular calcification.[2-4] The available non-calcium-containing phosphorus binders include sevelamer, available in two salt forms (hydrochloride [Renagel®] and carbonate [Renvela®]), lanthanum carbonate (Fosrenol®), ferric citrate (Auryxia®) and sucroferric oxyhydroxide (Velphoro®).[8-10] These products are typically reserved for use in CKD patients with hypercalcemia, or as adjunct to a regimen supplying the maximum allotted dose of elemental calcium from calcium-containing phosphorus binders.[1-4] The sevelamer hydrochloride salt was the initial sevelamer formulation developed; however, because of the incidence of metabolic acidosis associated with its use, a new, buffered formulation was created. The newer, sevelamer carbonate formulation will most likely be thought of as the preferred formulation of sevelamer because it does not lower a patient's bicarbonate level and does not result in the development of metabolic acidosis. An advantage to the use of lanthanum carbonate is a decrease in the pill burden compared to other products.[4]

Table 1. Current Medications Available in the Class[5-12]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Calcium acetate (Eliphos®*, PhosLo®*, Phoslyra®)	Control hyperphosphatemia in end stage renal failure. Reduce Phosphate with End Stage renal disease (Phoslyra®).	Capsule: 667 mg Oral solution: 667 mg/5 mL Tablet: 667 mg	a
Ferric citrate (Auryxia®)	Control serum phosphorus in patients with chronic kidney disease on dialysis.	Tablet: 1 gram	
Lanthanum carbonate (Fosrenol®)	Reduce phosphate with end stage renal disease.	Tablet, chewable: 250 mg 500 mg 750 mg 1,000 mg	-
Sevelamer carbonate (Renvela®*)	Control serum phosphorus in patients with chronic kidney disease on dialysis.	Powder for oral suspension: 0.8 g 2.4 g	a

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		Tablet: 800 mg	
Sevelamer hydrochloride (Renagel®)	Control serum phosphorus in patients with chronic kidney disease on dialysis.†	Tablet: 400 mg 800 mg	-
Sucroferric oxyhydroxide (Velphoro®)	Control serum phosphorus in patients with chronic kidney disease on dialysis.	Tablet, chewable: 500 mg	

*Generic available in at least one dosage form or strength.
† The safety and efficacy of sevelamer hydrochloride in chronic kidney disease patients who are not on dialysis have not been studied.

Evidence-based Medicine

- The available evidence supports the hypothesis that all of the phosphorus binders (or phosphorus depleters) are efficacious in controlling serum phosphorus levels.[13-54] In general, the true benefits of phosphorus lowering with respect to hard clinical outcomes have not been established, and most clinical trials evaluate surrogate endpoints. In addition, due to ethical concerns regarding a prolonged lack of appropriate treatment, most trials evaluating the newer phosphorus binders against placebo have been short term, with longer trials using calcium-containing binders as the comparator.[1]
- No prospective trials have specifically examined the benefits of targeting different phosphorus levels to determine the effect on patient-level endpoints. Epidemiological data suggests that phosphorus levels above the normal range are associated with increased morbidity and mortality.[1]
- The results of a recent Cochrane Systematic Review by Navaneethan and colleagues demonstrated that there was no statistically significant reduction in all-cause mortality when patients received sevelamer hydrochloride compared to those receiving calcium-based phosphate binders (relative risk, 0.73; 95% confidence interval, 0.46 to 1.16). No comparison of lanthanum carbonate to calcium-containing salts was made.[47]
- Two meta-analysis have been published reviewing the clinical trials of the phosphate binders.[48,49] Tonelli et al compared sevelamer products to any other therapy or placebo in patients with ESRD, on dialysis or who had had a kidney transplant. The pooled analysis showed that phosphate levels with sevelamer was similar or slightly higher than with calcium-based phosphate binders by 0.12 mmol/L (95% CI, 0.05 to 0.19). However, the overall weighted mean difference in serum calcium was significantly lower with sevelamer therapy (0.10 mmol/L; 95% CI, −0.12 to −0.07).[48] Jamal et al evaluated all-cause mortality and compared calcium-based phosphate binders to non-calcium phosphate binders in patients with chronic kidney disease. The results of this meta-analysis showed that patients randomly assigned to non-calcium-based phosphate binders had a statistically significant 22% reduction in all-cause mortality compared with those randomly assigned to calcium-based phosphate binders (RR,0.78; 95% CI, 0.61 to 0.98). When non-randomized trials were added to the pooled analysis, the reduction in all-cause mortality was 13% (RR,0.87; 0.77 to 0.97) in favor of non-calcium-based phosphate binders.[49]
- The safety and efficacy of ferric citrate was established in two clinical trials.[50,51]
    - The demonstrated reductions from baseline to week four in mean serum phosphorus were significantly greater with 6 and 8 grams/day than with 1 gram/day dose (-1.3 mg/dL and -1.5 mg/dL placebo-corrected differences, respectively; P<0.0001).[50]
    - Patients were eligible to enter a four-week, placebo-controlled withdrawal phase if they had been receiving ferric citrate during the 52-week study. During the placebo-controlled period, the serum phosphorus concentration rose by 2.2 mg/dL in patients receiving placebo compared to patients who remained on ferric citrate (-0.24 mg/dL vs 1.79 mg/dL; P<0.001).[51]

- The safety and efficacy of sucroferric oxyhydroxide was demonstrated in two randomized clinical trials, one six-week, open label, active controlled dose-finding study and one 55-week, active controlled, parallel group, dose-titration and extension study.[12,52-54]
    - In the phase II, dose-finding study, at six weeks, sucroferric oxyhydroxide decreased serum phosphorus compared to baseline in the 5.0, 7.5, 10.0 and 12.5 grams/day arms but not the 1.25 grams/day arm (P≤0.016). A similar decrease to sevelamer hydrochloride was seen in the 5.0 and 7.5 grams/day arms.[1,52]
    - In the after the dose-titration study, serum phosphorus control was maintained with both sucroferric oxyhydroxide and sevelamer throughout the extension study and the difference between groups was not statistically significant (P=0.14).[53,54]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Currently available evidence supports the hypothesis that all of the phosphorus binders are efficacious in controlling serum phosphorus levels. Furthermore, it is generally accepted that no one product is effective and acceptable to every patient.[2,3]
    - Although treatment guidelines recommend serum phosphorus levels to be maintained within or slightly above the normal range (depending on chronic kidney disease [CKD] Stage), there is currently no evidence to demonstrate that lowering phosphorus to a specific target range results in improved clinical outcomes in patients with CKD.
    - It is still reasonable to use phosphorus binders to lower phosphorus levels in CKD patients with hyperphosphatemia to prevent the development of secondary hyperparathyroidism and cardiovascular disease.[1]
    - Combination therapy, with multiple binders, may also be an option in order to control serum phosphorus levels while minimizing the side effects associated with any specific binder.[2,3]
    - Phosphorus binders should be utilized in patients with CKD Stages 3 to 5D who cannot adequately maintain serum phosphorus levels within the normal range with dietary phosphorus restriction.[1-3]
    - Choice of product should take into account the Stage of CKD, the presence of other components of CKD-Mineral and Bone Disorder, concomitant therapies and adverse event profiles.[1]
- Other Key Facts:
    - Currently, the calcium-containing products (Eliphos®, PhosLo®) are available generically in tablet and capsule formulations along with sevelamer carbonate tablets.
    - Calcium acetate (Phoslyra®) is available as an oral solution, and sevelamer carbonate (Renvela®) is available as oral powder for suspension.[7,10]
    - Lanthanum, and sevelamer carbonate/hydrochloride are contraindicated in patients with bowel obstruction, while calcium acetate is contraindicated in hypercalcemia[9-11]
    - Ferric citrate is contraindicated in iron overload syndromes.[8]

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Therapeutic Class Overview
Incretin Mimetics

Therapeutic Class

- **Overview/Summary:** The glucagon-like peptide-1 (GLP-1) receptor agonists, or incretin mimetics, are one of two incretin-based therapies currently available for the management of type 2 diabetes. Specifically, albiglutide (Tanzeum®), dulaglutide (Trulicity®), exenatide (Bydureon®, Byetta®), and liraglutide (Victoza®) are Food and Drug Administration-approved as an adjunct therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes.[1-5] This medication class was developed to mimic the effects of endogenous GLP-1, a hormone that maintains glucose homeostasis through several different mechanisms. The incretin mimetics work by stimulating insulin secretion, inhibiting glucagon secretion, improving β cell responsiveness to glucose, delaying gastric emptying, and enhancing satiety. In addition, these agents increase insulin secretion from pancreatic β cells in the presence of elevated glucose concentrations. Therefore, due to the glucose-dependent manner in which the incretin mimetics work, the medication class is associated with a low risk of hypoglycemia compared to other antidiabetic agents.[6] The incretin mimetics are most commonly associated with gastrointestinal-related adverse events and all agents are associated with the risk of developing pancreatitis. Only albiglutide, dulaglutide, exenatide extended-release, and liraglutide have boxed warnings regarding the risk of thyroid C-cell tumors. The incretin mimetics are available as subcutaneous injections. Albiglutide, dulaglutide and exenatide ER is administered once-weekly (independent of meals), exenatide IR is administered twice-daily (60 minutes before meals) and liraglutide is administered once-daily (independent of meals).[1-5] There are currently no generic incretin mimetics available.

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

Generic (Trade Name)	Food and Drug Administration Approved Indications*	Dosage Form/Strength	Generic Availability
Albiglutide (Tanzeum®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Pre-filled pen powder (solution) for Injection: 30 mg 50 mg	-
Dulaglutide (Trulicity®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Solution for injection (pen or syringe): 0.75 mg/0.5 mL 1.5 mg/0.5 mL	-
Exenatide (Bydureon®, Byetta®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Extended-release powder (suspension) for injection (Bydureon®; pen or dual chamber pen): 2 mg Solution for injection (Byetta®; pen): 250 µg/mL	-
Liraglutide (Victoza®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Solution for Injection (pen): 6 mg/mL	-

* Consider reducing the dosage of concomitantly administered insulin secretagogues (e.g., sulfonylureas) and/or insulin to reduce the risk of hypoglycemia.

Evidence-based Medicine

- In general, the incretin mimetics have been evaluated in clinical trials as add-on therapy to treatment regimens of established antidiabetic agents. Data consistently demonstrate that incretin mimetics are associated with positive effects on glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose (FPG), post-prandial glucose (PPG), and body weight. In addition, glycemic goals were consistently achieved when an incretin mimetic was added to existing treatment regimens.[7-59]
- When compared to other antidiabetic agents (metformin, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, insulin therapy), efficacy data are not consistent, with the incretin mimetics achieving superiority or comparable benefits in glycemic outcomes. However, in general, all incretin-based therapies, including the incretin mimetics, consistently demonstrate a beneficial effect on body weight compared to other antidiabetic agents.[7-59]
- Safety and efficacy of dulaglutide has been evaluated in an extensive clinical trials program including monotherapy trials, add-on therapy to metformin, metformin and sulfonylurea, pioglitazone and insulin (with or without metformin).[7-10]
    - The 52-week double-blind AWARD-3 study of patients inadequately treated with diet and exercise, or with diet and exercise and one anti-diabetic agent used at submaximal dose (N=807). At week 26, noninferiority in reduction of hemoglobin A1c (HbA_{1c}) was demonstrated between dulaglutide and metformin for both the 0.75 mg weekly and 1.5 mg weekly doses (-0.7% and -0.8% vs. -0.6%, respectively).[7]
    - AWARD-1 was a 52-week placebo-controlled study that evaluated dulaglutide safety and efficacy as an add-on to maximally tolerated doses of metformin (≥1500 mg per day) and pioglitazone (up to 45 mg per day) (N=976). At 26 weeks, treatment with dulaglutide 0.75 mg and 1.5 mg once weekly resulted in a statistically significant reduction in HbA_{1c} compared to placebo (-0.8% and -1.1 placebo corrected difference, respectively; P<0.001 for both comparisons) and compared to exenatide (-0.3% and -0.5 exenatide-corrected difference, respectively; P<0.001 for both comparisons).[10]
- Albiglutide was compared in a non-inferiority trial with liraglutide. Albiglutide effectively reduced HbA_{1c}; however, based upon the prespecified non-inferiority parameters, the criteria for non-inferiority of albiglutide were not met. The HbA_{1c} treatment goal of <7.0% was achieved by 42% of albiglutide-treated patients and 52% of liraglutide-treated patients (P=0.0023), while the goal of HbA_{1c} lower than 6.5% was achieved by 20% of albiglutide-treated patients and 28% of liraglutide-treated patients (P=0.0009).[11]
- Few head-to-head clinical trials within the class have been conducted. Compared to exenatide, exenatide extended-release significantly decreased HbA_{1c}, and achieved similar decreases in body weight.[26, 32] In a single trial, liraglutide significantly decreased HbA_{1c} compared to exenatide. Furthermore, liraglutide significantly decreased FPG while exenatide significantly decreased PPG.[40]
- In a 26-week open-label trial, there was a significantly greater reduction from baseline in HbA_{1c} at 26 weeks for patients treated with liraglutide compared to exenatide extended-release (-0.21%; 95% confidence interval [CI], -0.08 to -0.33). In addition, significantly more patients receiving liraglutide achieved an HbA_{1c} <7.0% compared to patients treated with exenatide extended-release (60 vs 53%; P=0.0011). Reductions in bodyweight also favored treatment with liraglutide (-0.90 kg; 95% CI, -0.39 to -1.40).[33]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Type 2 diabetes:[52-57]
        - Metformin remains the cornerstone to most antidiabetic treatment regimens.
        - Patients with high glycosylated hemoglobin will most likely require combination or triple therapy in order to achieve glycemic goals.
        - The incretin mimetics are recommended as a potential second-line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals.

- A lower rate of hypoglycemia, established efficacy and safety profile when used in combination with metformin, demonstrated effectiveness in reducing post-prandial glucose, and the potential for weight loss are noted as advantages associated with the incretin mimetics compared to other classes of antidiabetic agents. [52-57]
- No one incretin mimetic is recommended or preferred over another. [52-57]

- Other Key Facts:
  - Albiglutide, dulaglutide and exenatide ER is administered once-weekly (independent of meals).[1-3]
  - Exenatide IR is administered twice-daily (60 minutes before meals).[4]
  - Liraglutide is administered once-daily (independent of meals).[5]
  - No generic incretin mimetics are available.

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

Therapeutic Class

- **Overview/Summary:** Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a class of oral antidiabetic agents approved by the Food and Drug Association (FDA) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.[1-7] The kidneys play a pivotal role in controlling plasma glucose concentration; reabsorbing nearly all plasma glucose in the proximal tubules and preventing glucose excretion in patients with normal glucose-tolerance. Approximately 90% of the filtered renal glucose is done in the early convoluted segment of the proximal tubule and is facilitated by the SGLT2 transporter. The remaining 10% of filtered glucose is reabsorbed in the distal straight segment of the proximal tube by the SGLT1 transporter. In diabetic patients, the SGLT transporter system is often overwhelmed and unable to reabsorb all filtered plasma glucose due to hyperglycemic conditions. Once this threshold capacity is reached and surpassed, excess glucose that is not reabsorbed is excreted into the urine. In addition, a chronic elevated plasma glucose concentration provides the stimulus that ultimately leads to increased SGLT2 expression by the renal proximal tubular cells, resulting in an undesirable increase in renal capacity and threshold to reabsorb filtered glucose in both type 1 and type 2 diabetic patients.[1,2] SGLT2 inhibitors improve glycemic control by producing glucosuria. This is accomplished by inhibiting SGLT2 and increasing urinary glucose excretion. The net effect is an increase excretion of glucose from the body and normalizing plasma glucose levels. At this time, it is unknown if this mechanism of action serves to reduce the kidney's threshold capacity to reabsorb glucose, thus causing glucose excretion at lower plasma concentrations, or if the mechanism of action serves to prevent reabsorption of glucose load at all plasma glucose concentrations. SGLT2 inhibitors also have beneficial nonglycemic effects, such as weight loss observed during clinical trials and small decreases in systolic and diastolic blood pressure.[1,2]

Table 1. Current Medications Available in Therapeutic Class[3-8]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single Agent Products			
Canagliflozin (Invokana®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 100 mg 300 mg	-
Dapagliflozin (Farxiga®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 5 mg 10 mg	-
Empagliflozin (Jardiance®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 10 mg 25 mg	-
Combination Products			
Canagliflozin/ metformin (Invokamet®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes*	Tablet: 50/500 mg 50/1,000 mg 150/500 mg 150/1,000 mg	-
Dapagliflozin/ metformin ER (Xigduo XR®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes†	Tablet: 5/500 mg 5/1000 mg 10/500 mg 10/1000 mg	-
Empagliflozin/ linagliptin (Glyxambi®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes‡		

ER=extended-release

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

Evidence-based Medicine

- Each agent has been studied as monotherapy and dual and triple therapy compared to placebo and active controls and combinations of placebo and active controls.
- As monotherapy, patients randomized to canagliflozin 100 or 300 mg daily compared to patients randomized to placebo had a statistically significant improvement in HbA_{1c}. Both doses also resulted in a greater proportion of patients achieving an HbA_{1c} <7.0%, significant reductions in FPG and post prandial glucose (PPG), and in percent body weight reduction compared to placebo. There were also small decreases from baseline in systolic blood pressure relative to placebo (P values not reported).[9]
- As monotherapy in treatment-naïve patients, dapagliflozin was evaluated in two placebo-controlled trials. The first trial included 274 patients randomized to treatment with 2.5, 5 and 10 mg or placebo. At week 24, treatment with dapagliflozin 5 and 10 mg resulted in significant improvements in HbA_{1c} compared to placebo (-0.6, -0.8, -0.9 vs -0.2%, respectively; P<0.05 for 5 and 10 mg comparisons). Change in FPG (-24.1 and -28.8 vs -4.1 mg/dL, respectively) from baseline was also significantly greater in the 5 and 10 mg groups compared to placebo (P<0.05 for both comparisons).[11]
- There have been no clinical efficacy studies conducted with Xigduo XR® (dapagliflozin/metformin) combination tablets. FDA-approval of dapagliflozin/metformin ER was based on previous studies conducted with the bioequivalent single-entity agents.[7] Combination therapy with metformin extended-release in patients who were treatment-naïve led to significantly greater reductions in HbA_{1c} compared to either monotherapy (dapagliflozin or metformin) in the first study (-2.0 vs -1.2 and -1.4%, respectively; P<0.0001) and second study (-2.0 vs -1.5 and -1.4%, respectively; P<0.0001). In the second study, treatment with 10 mg strength (as monotherapy) was also non-inferior to metformin (as monotherapy) for reduction of HbA_{1c}.[13]
- The safety and efficacy of empagliflozin monotherapy was evaluated in a double-blind, placebo-controlled study of patients with type 2 DM (N=986). At week 24, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA_{1c} (-0.7% and -0.8% vs. 0.1%, respectively; P<0.0001 for both comparisons), FPG (-19 mg/dL and -25 mg/dL vs. 12 mg/dL, respectively; P values not reported) and body weight (-2.8 kg and -3.2 kg vs. -0.4 kg, respectively; P values not reported) compared with placebo.[14]
- Similar results were observed when comparing sodium glucose co-transport 2 agents in combination for the treatment of diabetes mellitus.[16-30]
- The safety and efficacy of empagliflozin added to linagliptin was evaluated in a 52 week double-blind, active-control, randomized trial. Change from baseline in HbA_{1c} at week 24 was significantly improved in the combination groups compared with the individual component groups (P<0.001).[31] When started as initial therapy, empagliflozin/linagliptin reduced HbA_{1c} from baseline significantly greater when compared with individual linagliptin and empagliflozin 10 mg. Empagliflozin 25 mg/linagliptin 5 mg, however, did not show a statistically significant difference compared with empagliflozin alone (P=0.179).[32]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[33-38]
  - Metformin remains the cornerstone of most antidiabetic treatment regimens.
  - Patients with high glycosylated hemoglobin (HbA_{1c}) will likely require combination or triple therapy in order to achieve glycemic goals.
    - Uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered.
    - The role of sodium-glucose co-transporter 2 (SGLT2) inhibitors are addressed in only one treatment guideline and are recommended as a potential second-line treatment option to be added in combination with metformin in patients not achieving glycemic goals.[37]

- Other Key Facts:
  - Canagliflozin is formulated with metformin in a single tablet (Invokamet®). Empagliflozin is formulated with linagliptin in a single tablet (Glyxambi®). Dapagliflozin is formulated with metformin as a single extended-release tablet (Xigduo XR®).[6-8]
  - All products are dosed once daily, with the exception of canagliflozin/metformin, which is dosed twice dialy.[3-8]
  - Other effects observed in trials include weight loss and small decreases in systolic and diastolic blood pressure.
  - Common adverse side effects associated with SGLT2 inhibitor use included increased incidence of female genital mycotic infections, urinary tract infection, and increased urination.

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Therapeutic Class Overview
5-HT1 Receptor Agonists

Therapeutic Class

- **Overview/Summary:** Migraine is a common disabling primary headache disorder that can present with or without aura. The International Headache Society describes migraine without aura as a clinical syndrome characterized by headache with specific features and associated symptoms. Migraine with aura is primarily characterized by the focal neurological symptoms that usually precede or accompany the headache.[1] Migraine without aura is further described as a recurrent headache disorder manifesting in attacks that can last four to 72 hours. Typical characteristics of these headaches are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia. Migraine with aura is also a recurrent headache disorder; however, it manifests in attacks of reversible focal neurological symptoms that usually develop gradually over five to 20 minutes and last for less than 60 minutes.[1] The serotonin (5-HT) 1 receptor agonists, commonly referred to as triptans, work in the management of migraine via the release of vasoactive peptides, promotion of vasoconstriction and blockade of pain pathways in the brainstem.[2] Triptans are Food and Drug Administration (FDA)-approved for the acute treatment of migraine with or without aura.[3-13] There is a lack of consistent head-to-head data demonstrating "superiority" of any triptan, making it difficult to recommend the use of one over another.[2] Currently there are seven single-entity triptans available (Axert® [almotriptan], Relpax® [eletriptan], Frova® [frovatriptan], Amerge® [naratriptan], Maxalt® and Maxalt-MLT® [rizatriptan], Imitrex® [sumatriptan] and Zomig® and Zomig ZMT® [zolmitriptan]) and one combination product (Treximet® [sumatriptan/naproxen]). Sumatriptan/naproxen is a fixed-dose combination product containing a triptan and a nonsteroidal anti-inflammatory drug. The combination targets the multiple mechanisms of migraine pathology. Almotriptan is approved for use in children 12 years of age and older while rizatriptan is approved for use in children as young as six years of age.[3,7] The triptans are available in several different dosage formulations, including orally disintegrating tablets, nasal sprays, subcutaneous injections and tablets. All triptans are currently available as an oral tablet. Naratriptan, rizatriptan and sumatriptan are currently available generically in various formulations.[14]

Table 1. Current Medications Available in the Class[3-12]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Almotriptan (Axert®)	Acute treatment of migraine attacks in adults with a history of migraine with or without aura and acute treatment of migraine headache pain in children 12 to 17 years of age with a history of migraine attacks with or without aura, and who have migraine attacks usually lasting four hours or more	Tablet: 6.25 mg 12.5 mg	-
Eletriptan (Relpax®)	Acute treatment of migraine attacks with or without aura in adults	Tablet: 20 mg 40 mg	-
Frovatriptan (Frova®)	Acute treatment of migraine attacks with or without aura in adults	Tablet: 2.5 mg	-
Naratriptan (Amerge®*)	Acute treatment of migraine attacks with or without aura in adults	Tablet: 1 mg 2.5 mg	a
Rizatriptan (Maxalt®*, Maxalt-MLT®*)	Acute treatment of migraine with or without aura in adults and in	Orally disintegrating	a

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
	pediatric patients six to 17 years of age	tablet: 5 mg 10 mg Tablet: 5 mg 10 mg	
Sumatriptan (Alsuma®, Imitrex®*, Sumavel DosePro®)	Acute treatment of cluster headache episodes†, acute treatment of migraine attacks with or without aura in adults	Nasal spray: 5 mg 20 mg Subcutaneous injection: 4 mg/0.5 mL 6 mg/0.5 mL Tablet: 25 mg 50 mg 100 mg	a
Zolmitriptan (Zomig®, Zomig-ZMT®)	Acute treatment of migraine attacks with or without aura in adults	Nasal spray: 2.5 mg 5 mg Orally disintegrating tablet: 2.5 mg 5 mg Tablet: 2.5 mg 5 mg	-
Combination Products			
Sumatriptan/naproxen (Treximet®)	Acute treatment of migraine attacks with or without aura in adults	Tablet: 85/500 mg	-

*Generic available in at least one dosage form or strength.
† Subcutaneous injection only.

Evidence-based Medicine

- In general, clinical trial data consistently demonstrates the "superiority" of the triptans over placebo in achieving headache pain relief, freedom from pain at two hours, sustained pain-free response, reducing rescue medication use and improving migraine-associated symptoms such as nausea, photophobia and phonophobia.[15-53]
- Clinical trial data also suggest the available triptans, when administered orally, range in comparative efficacy. Specifically, in a large meta-analysis, consisting of 53 controlled trials and over 24,000 patients, results demonstrated that while all triptans were effective and well tolerated, eletriptan (80 mg) and rizatriptan (10 mg) were "superior" to sumatriptan (100 mg) in terms of achievement of headache response at two hours, pain-free response at two hours and sustained pain-free response. Almotriptan (12.5 mg) demonstrated "superiority" over sumatriptan for pain-free response at two hours and sustained pain-free response. Of note, lower doses of eletriptan and rizatriptan in this analysis did not achieve the same results.[15]

- While there appears to be differences in the relative efficacies among the triptans, direct head-to-head trials do not consistently support the use of one over another, suggesting that individual variations in the response to different triptans exist.[54-66]
- Trials comparing different formulations of triptans measured patient preference as the primary endpoint.[60,65-67]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - The triptans are recommended for initial treatment of an acute migraine attack of moderate to severe severity, especially when "nonspecific" therapies have failed.[68-71]
  - "Nonspecific" therapies, such as nonsteroidal anti-inflammatory drugs are recommended for initial treatment of acute migraine attacks of mild to moderate severity.[68-71]
  - A non-oral route of administration is recommended for patients whose migraines present early with nausea or vomiting. Nausea should be treated with an antiemetic.[68-71]
  - The subcutaneous sumatriptan injection and zolmitriptan nasal spray are recognized as potential treatment options for the acute management of cluster headaches.[68-71]
- Other Key Facts:
  - Almotriptan is approved for use in children 12 years of age and older while rizatriptan is approved for use in children as young as six years of age.[3,7]
  - The subcutaneous sumatriptan injection is also Food and Drug Administration-approved for the acute treatment of cluster headache episodes.[8]
  - The subcutaneous sumatriptan injection has the fastest onset of action, but there is no evidence to suggest that different oral triptan formulations have a faster onset of action than the others.[71]
  - Naratriptan, rizatriptan and sumatriptan are currently available generically in various formulations.[14]

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

Therapeutic Class

- **Overview/Summary:** Attention deficit/hyperactivity disorder (ADHD) is a common psychiatric disorder that is often diagnosed during childhood; however, children with ADHD may continue to manifest symptoms into adulthood.[1] The core symptoms of ADHD utilized in the diagnosis of the disorder include hyperactivity, impulsivity, and inattention. Untreated, or undertreated ADHD is associated with adverse sequelae, including delinquent behavior, antisocial personality traits, substance abuse and other comorbidities.[2] Several central nervous system agents are Food and Drug Administration (FDA)-approved for the treatment of ADHD, including the cerebral stimulants (amphetamines and methylphenidate derivatives), atomoxetine (Strattera®), clonidine extended-release (Kapvay®) and guanfacine extended-release (Intuniv®).[3-23] The cerebral stimulant agents are classified as Schedule II controlled substances due to their potential for abuse.[3-11,14-21,23] Atomoxetine, clonidine extended-release and guanfacine extended-release are not classified as controlled substances.[12,13,22] Clonidine and guanfacine, extended-release formulations, are approved as adjunctive therapy with stimulant medications as well as monotherapy.[12,13,24] Some cerebral stimulant agents are indicated for the treatment of a variety of sleep disorders. Narcolepsy is a sleep disorder characterized by excessive daytime sleepiness and intermittent manifestations of rapid eye movement sleep during wakefulness. Obstructive sleep apnea (OSA) is a common chronic disorder that often requires lifelong care. Cardinal features of OSA include obstructive apneas, hypopneas, or respiratory effort related arousals; daytime symptoms attributable to disrupted sleep (e.g., sleepiness, fatigue, poor concentration); and signs of disturbed sleep (e.g., snoring, restlessness, or resuscitative snorts).[25,26] Circadian rhythm sleep disorder consists of a persistent/recurrent pattern of sleep interruption. The shift work type occurs in individuals who work non-standard hours (e.g., night work, early morning work and rotating schedules) and is characterized by excessive sleepiness and/or insomnia.[25] Modafinil (Provigil®) and armodafinil (Nuvigil®) are both FDA-approved to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, OSA and shift work sleep disorder. These agents are classified as Schedule IV controlled substances because they have been shown to have been shown to produce psychoactive and euphoric effects similar to stimulants.[27,28] Sodium oxybate (Xyrem®) is γ-hydroxybutyric acid, a known drug of abuse. It is approved for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. It is classified as a Schedule III controlled substance. However, non-medical uses of sodium oxybate are classified under Schedule I.[28] Most ADHD agents and stimulants are currently available generically. Specifically, at least one short-, intermediate-, and long-acting agent is available as a generic.[29]

Table 1. Current Medications Available in the Therapeutic Class[3-22, 26-28]

Generic (Trade Name)	Food and Drug Administration- Approved Indications	Dosage Form/Strength	Generic Availability
Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines			
Amphetamine/ dextroamphetamine salts (Adderall®*, Adderall XR®*)	Treatment of ADHD	Capsule: 5 mg 10 mg 15 mg 20 mg 25 mg 30 mg Tablet: 5 mg	a

Generic (Trade Name)	Food and Drug Administration- Approved Indications	Dosage Form/Strength	Generic Availability
		7.5 mg 10 mg 12.5 mg 15 mg 20 mg 30 mg	
Dextroamphetamine (ProCentra®, Dexedrine Spansule®*, Dexedrine®, Zenzedi®*)	Treatment of ADHD, narcolepsy	Solution: 5 mg/5 mL Sustained-release capsule: 5 mg 10 mg 15 mg Tablet: 2.5 mg 5 mg 7.5 mg 10 mg	a
Lisdexamfetamine (Vyvanse®)	Treatment of ADHD	Capsule: 20 mg 30 mg 40 mg 50 mg 60 mg 70 mg	-
Methamphetamine (Desoxyn®*)	Exogenous obesity, treatment of ADHD	Tablet: 5 mg	a
Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous			
Armodafinil (Nuvigil®)	Improve wakefulness in patients with excessive sleepiness associated with OSA and narcolepsy, improve wakefulness in patients with excessive sleepiness associated with shift work disorder	Tablet: 50 mg 150 mg 250 mg	-
Dexmethylphenidate (Focalin®*, Focalin XR®*)	Treatment of ADHD	Extended-release capsule: 5 mg 10 mg 15 mg 20 mg 25 mg 30 mg 35 mg 40 mg Tablet: 2.5 mg 5 mg 10 mg	a

Generic (Trade Name)	Food and Drug Administration- Approved Indications	Dosage Form/Strength	Generic Availability
Methylphenidate (Concerta®*, Daytrana®, Metadate CD®*, Metadate ER®*, Methylin® chew tabs, Methylin® solution*, Quillivant XR®, Ritalin®*, Ritalin LA®*, Ritalin SR®*)	Treatment of ADHD, narcolepsy	Chewable tablet: 2.5 mg 5 mg 10 mg Extended-release capsule (Metadate CD®, generic): 10 mg 20 mg 30 mg 40 mg 50 mg 60 mg Extended-release capsule (Ritalin LA®): 10 mg 20 mg 30 mg 40 mg Extended-release suspension: 25 mg/ 5 mL Extended-release tablet (Concerta®, generic): 18 mg 27 mg 36 mg 54 mg Extended-release tablet (Metadate ER®, generic): 20 mg Solution: 5 mg/5 mL 10 mg/5 mL Sustained-release tablet (Ritalin-SR®, generic): 20 mg Tablet: 5 mg 10 mg 20 mg Transdermal patch: 10 mg/9 hours (1.1 mg/hour)	a

Generic (Trade Name)	Food and Drug Administration- Approved Indications	Dosage Form/Strength	Generic Availability
		15 mg/9 hours (1.6 mg/hour) 20 mg/9 hours (2.2 mg/hour) 30 mg/9 hours (3.3 mg/hour)	
Modafinil (Provigil®*)	Improve wakefulness in patients with excessive sleepiness associated with OSA and narcolepsy, improve wakefulness in patients with excessive sleepiness associated with shift work disorder	Tablet: 100 mg 200 mg	a
Central α-Agonists			
Clonidine extended-release (Kapvay®)	Treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications	Extended-release tablet: 0.1 mg 0.2 mg	a
Guanfacine extended-release (Intuniv®*)	Treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications	Extended-release tablet: 1 mg 2 mg 3 mg 4 mg	-
Central Nervous System Agents-Miscellaneous			
Atomoxetine (Strattera®)	Treatment of ADHD	Capsule: 10 mg 18 mg 25 mg 40 mg 60 mg 80 mg 100 mg	-
Sodium oxybate (Xyrem®)	Treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy	Solution: 500 mg/mL (180 mL)	-

ADHD=attention deficit/hyperactivity disorder, OSA=obstructive sleep apnea
* Generic available in at least one dosage form or strength.

Evidence-based Medicine

- Data from several clinical trials demonstrate that the attention deficit/hyperactivity disorder (ADHD) agents and stimulants are effective in the treatment of ADHD, as measured by significant decreases in ADHD rating scale scores compared to placebo. Although comparative trials have been conducted, it is difficult to interpret the results of these trials due to design flaws (e.g., small population, short treatment duration, variable outcomes). Overall, there is insufficient evidence to suggest that one ADHD agent and stimulant is more efficacious than another for the treatment of ADHD.[38-125]
- The majority of efficacy data supporting the use of the ADHD agents and stimulants is derived from placebo-controlled trials. In addition, the majority of trials were conducted in the pediatric population. Limited data exists to demonstrate the efficacy of a variety of cerebral stimulants (amphetamine/ dextroamphetamine, dexmethylphenidate, and lisdexamfetamine) and atomoxetine in the adult population.[43,51,68,93,94,109]

- Clonidine extended-release and guanfacine extended-release have been shown to improve ADHD symptoms scores both as monotherapy and as adjunctive therapy to psychostimulants. These agents are Food and Drug Administration (FDA)-approved for use in ADHD as monotherapy and as adjunctive treatment to stimulants.[64,65,74-82]
- Armodafinil, modafinil and sodium oxybate have all been shown to be more effective compared to placebo in patients with narcolepsy, obstructive sleep apnea (OSA) and shift work disorder, as measured by significant improvements in sleepiness scale scores. In addition, sodium oxybate has been shown to significantly reduce the rate of inadvertent naps and cataplexy attacks compared to placebo. Similar to ADHD, there is insufficient evidence to suggest that one ADHD agent and stimulant is more efficacious than another for the treatment of sleep disorders.[126-155]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Guidelines recommend the use of Food and Drug Administration (FDA)-approved agents for initial pharmacologic treatment of attention deficit/hyperactivity disorder (ADHD), and preference of one agent over another is not stated.
  - Stimulant medications remain the most effective treatment option for most children with ADHD, and response to one stimulant dose not predict response to another. Other factors associated with treatment decisions include presence of comorbid conditions, patient/family preference, storage/administration issues at school, history and/or presence of substance abuse, pharmacokinetics, and anticipated adverse events.[2,24,31-33]
  - With regard to the use of non stimulant medications in the treatment of ADHD, atomoxetine is recognized as a good option for patients with comorbid anxiety, sleep initiation disorder, substance abuse, or tics, or if initially preferred by parents and/or the physician.
  - Overall, atomoxetine, clonidine extended-release and guanfacine extended-release are effective in reducing ADHD core symptoms; however, these agents have a smaller evidence base compared to the cerebral stimulants.[24]
  - Methylphenidate is recommended as first-line treatment of ADHD in adults, with atomoxetine and dexamphetamine recommended second line.[31-33]
  - For the treatment of narcolepsy, obstructive sleep apnea (OSA), and shift work disorder, guidelines recommend the use of FDA-approved agents for the treatment of such sleep disorders, with modafinil recommended first-line for the treatment of narcolepsy.[25,139-141]
  - Even though guidelines were published prior to FDA-approval of sodium oxybate, the agent is the only one to be recognized as being an effective option for the treatment of cataplexy due to narcolepsy. Armodafinil, was FDA-approved in 2007; however, its role is not defined within current clinical guidelines.[25,34-36]
- Other Key Facts:
  - Armodafinil (Nuvigil®) is the longer half-life enantiomer of modafinil (Provigil®).
  - At least one short-, intermediate-, and long-acting stimulant is available generically.[30]
  - Due to safety concerns and abuse potential, sodium oxybate (Xyrem®) is available only through restricted distribution, the Xyrem Success Program.

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Therapeutic Class Overview
Inhaled Corticosteroids

Therapeutic Class

- **Overview/Summary:** The inhaled corticosteroids (ICSs) are Food and Drug Administration (FDA)-approved for the maintenance treatment of asthma as prophylactic therapy with beclomethasone (QVAR®), flunisolide (Aerospan®) and fluticasone propionate (Flovent Diskus®, Flovent HFA®) also being indicated for use in asthma patients who require systemic corticosteroid therapy. [1-11] These agents are effective in the treatment of asthma due to their wide range of inhibitory activities against multiple cell types (e.g., mast cells and eosinophils) and mediators (e.g., histamine and cytokines) involved in the asthmatic response. The ICSs exert their anti-inflammatory effects by binding to glucocorticoid receptors with a subsequent activation of genes involved in the anti-inflammatory processes as well as an inhibition of pro-inflammatory genes involved in the asthmatic response. Inflammation is also a component of chronic obstructive pulmonary disease (COPD) pathogenesis; however, no single-entity ICS has been FDA-approved for use in COPD. [1-10] Although ICSs exert their therapeutic effects through identical mechanisms of action, they differ in their potency, dosing schedules, and dosage form availability. Clinical trials comparing ICSs of varying potencies have shown that those of higher potencies do not demonstrate greater clinical efficacy than those of lower potencies when administered at equipotent doses and have not demonstrated any major differences in clinical efficacy between the available ICSs. [12-67] Currently, only budesonide nebulizer suspension is available generically.

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

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Beclomethasone (QVAR®)	Maintenance Treatment of Asthma as Prophylactic Therapy¶; Treatment of Asthma Patients Requiring Systemic Corticosteroid Therapy¶	Inhalation aerosol (HFA inhaler, metered dose): 40 µg 80 µg	-
Budesonide (Pulmicort Flexhaler®, Pulmicort Respules®*)	Maintenance Treatment of Asthma as Prophylactic Therapy†,‡	Dry powder for inhalation (inhaler, breath activated, metered dose): 90 µg 180 µg Suspension for inhalation (nebulizer): 0.25 mg/2 mL 0.5 mg/2 mL 1 mg/2 mL	a
Ciclesonide (Alvesco®)	Maintenance Treatment of Asthma as Prophylactic Therapy§	Inhalation aerosol (HFA inhaler, metered dose): 80 µg 160 µg	-
Flunisolide (Aerospan®)	Maintenance Treatment of Asthma as Prophylactic Therapy#; Treatment of Asthma Patients Requiring Systemic Corticosteroid Therapy#	Inhalation aerosol (HFA inhaler, metered dose): 80 µg	-
Fluticasone furoate	Maintenance Treatment of	Aerosol powder (breath	-

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
(Arnuity Ellipta®)	Asthma as Prophylactic Therapy§	activated inhaler): 100 µg 200 µg	
Fluticasone propionate (Flovent Diskus®, Flovent HFA®)	Maintenance Treatment of Asthma as Prophylactic Therapy‖; Treatment of Asthma Patients Requiring Systemic Corticosteroid Therapy‖	Dry powder for inhalation (inhaler with blister pack; Flovent Diskus®): 50 µg 100 µg 250 µg Inhalation aerosol (HFA inhaler, metered dose; Flovent HFA®): 44 µg 110 µg 220 µg	-
Mometasone furoate (Asmanex HFA®, Asmanex Twisthaler®)	Maintenance Treatment of Asthma as Prophylactic Therapy‖	Dry powder for inhalation (inhaler, metered dose; Asmanex Twisthaler®): 110 µg 220 µg Inhalation powder (HFA inhaler, metered dose, breath activated; Asmanex HFA®):	-

* Generic available in at least one dosage form or strength.
¶ In patients five years of age and older.
† Pulmicort Flexhaler®: In patients six years of age and older.
‡ Pulmicort Respules®: In patients 12 months to eight years of age.
§ In patients 12 years of age and older.
‖ In patients four years of age and older.
In patients six years of age and older.

Evidence-based Medicine

- Numerous placebo controlled trials have demonstrated the efficacy of inhaled corticosteroid agents in the treatment of asthma, and these agents are considered the most effective agents in the long-term management of the disease. The results of head-to-head trials directly comparing the inhaled corticosteroids products have not demonstrated one agent to be significantly more effective than another, regardless of the potency or dosage form of the inhaled corticosteroid agent used.[12-67]
- FDA-approval for fluticasone furoate was based on the results of three dose-ranging trials and four confirmatory trials which included a total of 3,611 patients aged ≥12 years with various asthma severities, FEV_1 of 40 to 90% predicted and varied (or no) previous ICS use.[13-15,19-22] Pre-dose, pre-bronchodilator FEV_1 (primary endpoint) was significantly improved upon treatment with the FDA-approved doses of fluticasone furoate when compared to placebo in each of the seven clinical trials.
    - Fluticasone furoate also significantly improved percentage of rescue-free 24-hour periods and although statistical significance could not be determined in some cases, fluticasone furoate also improved symptom-free 24-hour periods over the course of the studies.[13-15,19-22]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - ICSs are the most potent and consistently effective long-term controller medications for asthma patients of all ages. These agents are recommended as first-line therapy for long-term control of persistent asthma symptoms in all age groups. Although ICSs reduce both

impairment and risk of asthma exacerbations, they do not appear to alter the progression or underlying severity of the disease. No ICS is recommended over another.[68,71]
    - § The adverse effect on growth rate associated with these agents does appear to be dose dependant; however, it is not considered predictable. The effect on growth velocity appears to occur mainly in the first several months of treatment and is generally small and not progressive.[68]
  - o For COPD: In patients with an FEV_1 <60% of the predicted value, regular treatment with ICS improves symptoms, lung function and quality of life as well as reduces exacerbations. However, long term therapy ICS as monotherapy is not recommended.[72]
  - o ICSs should be used as adjunctive agents to long-acting bronchodilators to decrease exacerbation frequency in patients with an FEV_1 ≤50% predicted and repeated exacerbations.[73]
- Other Key Facts:
  - o None of the inhaled corticosteroid products are indicated for the relief of acute bronchospasm[1-10]
  - o Currently, budesonide suspension for nebulization is the only generic product available within the therapeutic class.

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Therapeutic Class Overview
Opioid Dependence Agents

Overview/Summary:
Partial opioid agonists and opioid antagonists are used alone or in combination in the treatment of opioid use disorder.[1-7] Buprenorphine (Subutex®) buprenorphine/naloxone (Bunavail®, Suboxone®, Zubsolv®) and naltrexone (ReVia®, Vivitrol®) are Food and Drug Administration (FDA)-approved for the treatment of opioid dependence.[1-7] Naltrexone is also FDA-approved for use in alcohol dependence.[2,3] Buprenorphine is available as a sublingual tablet, buprenorphine/naloxone is available as sublingual tablet sublingual film and buccal film, and naltrexone is available as a tablet and extended-release suspension for injection.[1-7] Products which contain buprenorphine are classified as Schedule III controlled substances. The transdermal and injectable formulations of buprenorphine, Butrans® and Buprenex®, respectively, are FDA-approved for use in the management of pain and will not be discussed within this review.[8,9] Buprenorphine and buprenorphine/naloxone sublingual tablets and naltrexone tablets are currently available generically.

Buprenorphine is a partial opioid agonist at the μ-opioid receptor (associated with analgesia and dependence) and an antagonist at the κ-opioid receptor (related to dysphoria). Partial opioid agonists reach a ceiling effect at higher doses and will displace full opioid agonists from the μ-opioid receptor. Buprenorphine is associated with a lower abuse potential, a lower level of physical dependence and is safer in overdose when compared to full opioid agonists [1,4-7] Naloxone and naltrexone are antagonists at the μ-opioid receptor.[2-7] Naloxone has measurable blood levels following sublingual buprenorphine/naloxone administration. However, due to naloxone's low oral bioavailability, there are no significant physiological or subjective differences when compared to the administration of buprenorphine alone. Following intramuscular or intravenous administration, buprenorphine/naloxone is associated with symptoms of opioid withdrawal and dysphoria which is caused by a stronger affinity of naloxone for the opioid receptor compared to buprenorphine.[4-7] Therefore, the addition of naloxone to buprenorphine results in a decreased risk of diversion compared to buprenorphine monotherapy.[10]

The United States Substance Abuse and Mental Service Clinical Guideline for the Use of Buprenorphine in the Treatment of Opioid Addiction recommends the use of buprenorphine/naloxone for the induction, stabilization and maintenance phases of opioid addiction treatment for most patients. This guideline also notes that buprenorphine alone should be used for pregnant patients and for the induction therapy of patients who are transitioning from methadone treatment.[11]

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

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agents			
Buprenorphine	Opioid dependence, treatment induction*,†; opioid dependence, treatment maintenance*,†	Sublingual tablet: 2 mg 8 mg	a
Naltrexone (ReVia®, Vivitrol®)	Alcohol dependence; opioid dependence‡ (ReVia®); opioid dependence, prevention of relapse following opioid detoxification (Vivitrol®)	Suspension for injection, extended-release (Vivitrol®): 380 mg Tablet (ReVia®): 50 mg	-
Combination Product			
Buprenorphine/naloxone	Opioid dependence, treatment induction† (Suboxone®); opioid	Buccal film (Bunavail®): 2.1/0.3 mg 4.2/0.7 mg	-

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	dependence, treatment maintenance†	6.3/1 mg Sublingual film (Suboxone®): 2/0.5 mg 4/1 mg 8/2 mg 12/3 mg Sublingual tablet: 2/0.5 mg 8/2 mg Sublingual tablet (Zubsolv®): 1.4/0.36 mg 5.7/1.4 mg	

* According to the manufacturer, buprenorphine sublingual tablets are preferred for use only during induction of treatment for opioid dependance, but can be used for maintenance treatment in patients who cannot tolerate the presence of naloxone.
† As part of a complete treatment plan to include counseling and psychosocial support.
‡As part of a comprehensive plan of management that includes some measure to ensure the patient takes the medication.

Evidence-based Medicine

- Buprenorphine and buprenorphine/naloxone significantly improve many different outcomes for patients with opioid dependence compared to placebo and no treatment, but are generally found to not be significantly different from one another.[16-26, 37-44]
- FDA-approval of buprenorphine buccal film (Bunavail®) and buprenorphine/naloxone tablet (Zubsolv®) was via the 505(b)(2) pathway. Clinical and safety data for these medications is based on previously approved buprenorphine or buprenorphine/naloxone formulations.[5,7]
- 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.[18, 27-34]
- A meta-analysis of 1,158 participants in 13 randomized trials compared oral naltrexone maintenance treatment to either placebo or non-medication. No difference was seen between the active and control groups in sustained abstinence or most other primary outcomes.
    - Considering only studies in which patient's adherence were strictly enforced, there was a statistically significant difference in retention and abstinence with naltrexone over non therapy (relative risk [RR], 2.93; 95% CI, 1.66 to 5.18).[54]
- The efficacy and safety of Vivitrol® (naltrexone extended-release) for opioid dependence was evaluated in a 24-week, placebo-controlled randomized control trial. The percentage of subjects achieving each observed percentage of opioid-free weeks was greater in the naltrexone extended release group compared to the placebo group. Complete abstinence (opioid-free at all weekly visits) was sustained by 23% of subjects in the placebo group compared with 36% of subjects in the naltrexone extended release group from Week 5 to Week 24.[55]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - The United States Substance Abuse and Mental Service Clinical Guideline for the Use of Buprenorphine in the Treatment of Opioid Addiction recommends the use of buprenorphine/naloxone for the induction, stabilization and maintenance phases of opioid addiction treatment for most patients.[11]
    - This guideline also notes that buprenorphine alone should be used for pregnant patients and for the induction therapy of patients who are transitioning from methadone treatment.[11]
    - Naltrexone is generally reserved as an alternative regimen after buprenorphine-containing products and methadone.[13]

- Other Key Facts:
  - According to the Drug Addiction Treatment Act of 2000, the ability to prescribe buprenorphine or buprenorphine/naloxone for the maintenance or detoxification of opioid dependence is limited to physicians who have obtained a waiver and a unique Drug Enforcement Agency number beginning with an X.[14]
  - Naltrexone extended-release suspension for injection is injected intramuscularly in the gluteal muscle every 4 weeks by a healthcare provider.[3]

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Tab: Established/New Drugs

Therapeutic Class Overview
Oral Anticoagulants

Therapeutic Class

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

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

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Apixaban (Eliquis®)	DVT/PE prophylaxis* and treatment, DVT prophylaxis following hip or knee replacement surgery, to reduce the risk of stroke and systemic embolism in nonvalvular atrial fibrillation	Tablet: 2.5 mg 5 mg	-
Dabigatran etexilate mesylate (Pradaxa®)	DVT/PE prophylaxis‡ and treatment†, to reduce the risk of stroke and systemic embolism in nonvalvular atrial fibrillation	Capsule: 75 mg 150 mg	-
Enoxaban tosylate (Savaysa®)	DVT/PE treatment†, to reduce the risk of stroke and systemic embolism in nonvalvular atrial fibrillation	Tablet: 15 mg 30 mg 60 mg	-
Rivaroxaban (Xarelto®)	DVT/PE prophylaxis* and treatment, DVT prophylaxis following hip or knee	Tablet: 10 mg	-

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

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

Evidence-based Medicine

- As it has been the principle oral anticoagulant for more than 60 years, the clinical evidence derived from meta-analyses and Cochrane Reviews demonstrating the safety and efficacy of warfarin in Food and Drug Administration-approved indications is well established.[10,12-18]
- The safety and efficacy of the oral anticoagulants have been evaluated in many clinical trials.[19-62]
- The efficacy of apixaban in patients with nonvalvular atrial fibrillation (AF) was evaluated in the AVERROES and ARISTOTLE trials.[19,23]
- In ARISTOTLE (N=18,201), patients were randomized to receive apixaban 5 mg twice daily or dose-adjusted warfarin (to target an International Normalized Ratio [INR] of 2.0 to 3.0). The incidence of stroke or systemic embolism, the primary endpoint, was significantly reduced in patients treated with apixaban compared to patients treated with warfarin (1.27 vs 1.60% per year; HR, 0.79; 95% CI, 0.66 to 0.95; *P*<0.001 for non inferiority and *P*=0.01 for superiority).
    - Treatment with apixaban was associated with a significantly lower incidence of major intracranial bleeding (*P*<0.001), and major bleeding at other locations (*P*=0.004) compared to warfarin treatment. There was no difference in the rate of major gastrointestinal bleeding with apixaban compared to warfarin (*P*=0.37). The rate of myocardial infarction (MI) was similar between the apixaban and warfarin treatment groups (*P*=0.37); however, apixaban treatment significantly reduced death from any cause compared to warfarin treatment (3.52 vs 3.94% per year; HR, 0.89; 95% CI, 0.80 to 0.998; *P*=0.047).[19]
- In AVERROES (N=5,599), patients were randomized to receive apixaban 5 mg twice daily or aspirin 81 to 324 mg once daily. The incidence of stroke or systemic embolism, the primary endpoint, was significantly reduced in patients treated with apixaban compared to patients treated with aspirin (1.6 vs 3.7% per year; hazard ratio [HR], 0.45; 95% confidence interval [CI], 0.32 to 0.62; *P*<0.001).
- There was no difference in major bleeding between the apixaban and aspirin treatment groups (*P*=0.57). The incidences of intracranial bleeding (*P*=0.69), extracranial bleeding (*P*=0.42), gastrointestinal bleeding (*P*=0.71), non gastrointestinal bleeding (*P*=0.22) and fatal bleeding (*P*=0.53) were similar between the treatment groups.[23]
- Approval of apixaban for use as prophylaxis of DVT and PE in patients who have undergone hip or knee replacement surgery, was established after being compared to enoxaparin in three large, multi-centered, double-blind, double-dummy, randomized control trials: ADVANCE-1, ADVANCE-2, and ADVANCE-3.[44-46]
    - In ADVANCE-1, the statistical criterion for the noninferiority of apixaban as compared with twice-daily administration of enoxaparin was not met. DVT, non-fatal PE, and all-cause death occurred in 104 of 1157 patients (9.0%) in the apixaban group, as compared with 100 of 1130

patients (8.8%) in the enoxaparin group (relative risk [RR], 1.02; 95% CI, 0.78 to 1.32; P=0.06 for noninferiority; difference in risk, 0.1%; 95% CI, –2.2 to 2.4; P<0.001).[44]
    - In ADVANCE-2, apixaban was had statistically significant reduction in risk compared to enoxaparin once-daily for prevention of all VTE and all-cause death (RR, 0.62; 95% CI, 0.51 to 0.74, one-sided P<0.0001 when tested for non-inferiority and for superiority). Absolute risk reduction was 9.3% (95% CI, 5.8% to 12.7%) in favor of apixaban (one-sided P<0.0001 for non-inferiority).[44]
    - In ADVANCE-1, There was a statistically significant increase in major and non-major bleeding for twice daily enoxaparin 30 mg compared to apixaban (adjusted difference in event rates according to type of surgery, -0.81%; 95% CI, -1.49% to −0.14%; P=0.053) as opposed to ADVANCE-2, where there was no difference in major bleeding rates between enoxaparin daily and apixaban (P=0.3014).[44,45]
    - In ADVANCE-3 there was a statistically significant reduction in asymptomatic or symptomatic DVT, nonfatal PE, or death from any cause with apixaban 2.5 mg twice dialy compared with enoxaparin 40 mg daily (RR with apixaban, 0.36; 95% CI, 0.22 to 0.54; one-sided P<0.001 for noninferiority and two-sided P<0.001 for superiority). The absolute risk reduction with apixaban was 2.5% (95% CI, 1.5% to 3.5%).[46]
- Approval of dabigatran etexilate mesylate for use in AF was based on the clinical evidence derived from the non inferiority, RE-LY trial (N=18,113). After a median follow-up of two years, dabigatran etexilate mesylate 110 mg twice-daily was associated with a similar rate of stroke and systemic embolism compared to warfarin (*P*=0.34), while dabigatran etexilate mesylate 150 mg twice-daily was associated with a significantly lower rate (*P*<0.001). Rates of major bleeding were similar between warfarin and dabigatran etexilate mesylate 150 mg twice-daily (*P*=0.31) but significantly less with dabigatran etexilate mesylate 110 mg twice-daily (*P*=0.003).[26]
    - No differences were observed between the two treatments with regard to death from any cause and pulmonary embolism (PE); however, the rate of MI was significantly higher (*P*=0.048 with dabigatran etexilate mesylate 150 mg vs warfarin) and the rate of hospitalization significantly lower (*P*=0.003 with dabigatran etexilate mesylate 110 mg vs warfarin) with dabigatran etexilate mesylate.[30]
    - A 2012 subgroup analysis of RE-LY demonstrated a nonsignificant increase in MI with dabigatran etexilate mesylate compared to warfarin, but other myocardial ischemic events were not increased. In addition, results revealed that treatment effects of dabigatran etexilate mesylate were consistent in patients at higher and lower risk of myocardial ischemic events.[23] In contrast, a meta-analysis published in 2012 demonstrated that dabigatran etexilate mesylate is associated with an increased risk of MI or acute coronary syndrome (ACS) in a broad spectrum of patients (e.g., stroke prophylaxis in AF, acute venous thromboembolism [VTE], ACS, short term prophylaxis of deep venous thrombosis [DVT]) compared to different controls (warfarin, enoxaparin, or placebo).[62]
- The RE-COVER study found dabigatran etexilate mesylate to be noninferior to warfarin in preventing recurrent VTE who had presented with acute symptoms of DVT or PE (P<0.001), with the RE-COVER II study also confirming the results (P<0.001).[47,48] Patients who participated in the RE-COVER or RE-COVER II study and received dabigatran etexilate mesylate and had additional risk factors could elect for long term VTE prophylaxis in two follow up studies, RE-MEDY or RE-SONATE. RE-MEDY was and active-control study whereas RE-SONATE was placebo-controlled. Dabigatran etexilate mesylate was found to be noninferior to warfarin and superior to placebo in long-term VTE prophylaxis (P=0.01 and P<0.001 respectively).[49]
- Approval of rivaroxaban for use in AF was based on the clinical evidence for safety and efficacy derived from the non inferiority, ROCKET-AF trial (N=14,264). Results demonstrated that rivaroxaban (15 or 20 mg/day) is non inferior to warfarin for the prevention of stroke or systemic embolism (*P*<0.001 for non inferiority), with no increased risk of major bleeding (*P*=0.44). Within ROCKET-AF, intracranial and fatal bleeding were significantly less frequent with rivaroxaban (*P*=0.02).[36]
    - In a subgroup analysis of ROCKET-AF evaluating the efficacy and safety of rivaroxaban among patients with and without previous stroke or transient ischemic attack, it was revealed that the relative efficacy and safety of rivaroxaban compared to warfarin was not different

between these two patient populations. Ultimately, results support the use of rivaroxaban as an alternative to warfarin for the prevention of recurrent as well as initial stroke in patients with AF.[37]

- Approval of rivaroxaban for prophylaxis of DVT was based on the clinical evidence for safety and efficacy derived from the global program of clinical trials known collectively as RECORD (1 [N=4,541], 2 [N=2,509], 3 [2,531], and 4 [N=3,148]). All four trials compared rivaroxaban to enoxaparin for thromboprophylaxis in patients undergoing total elective hip and knee replacement surgeries.[51-54]
  - In all four trials, rivaroxaban significantly reduced the risk of the primary composite endpoint of any DVT, nonfatal PE, or death from any cause compared to enoxaparin, with no increased risk of major bleeding, any bleeding, and hemorrhagic wound complications.
- The approval of rivaroxaban for the treatment of DVT and PE, and for the reduction in the risk of recurrence of DVT and PE was based on two open-label, non inferiority trials. In EINSTEIN-DVT, 3,449 patients with an acute, symptomatic, objectively confirmed proximal DVT without symptomatic PE received rivaroxaban 15 mg twice daily for three weeks followed by 20 mg once daily or enoxaparin 1 mg/kg subcutaneously twice daily plus warfarin or acenocoumarol adjusted to maintain an INR of 2.0 to 3.0. The occurrence of symptomatic, recurrent VTE was 2.1% in the rivaroxaban group and 3.0% in the standard therapy group (HR, 0.68; 95% CI, 0.44 to 1.04; *P*<0.001 for non inferiority and *P*=0.08 for superiority).[55]
  - Clinically relevant (first major or clinically relevant non major) bleeding was similar between the treatment groups (*P*=0.77). In a 12-month extension, EINSTEIN-EXT, symptomatic, recurrent VTE occurred in eight patients receiving rivaroxaban and 42 patients receiving placebo (1.3 vs 7.1%; HR, 0.18; 95% CI, 0.09 to 0.39; *P*<0.001).[55]
- In 4,832 patients with an acute, symptomatic PE, with or without symptomatic DVT (EINSTEIN-PE), there was a symptomatic recurrence of VTE in 50 patients treated with rivaroxaban compared to 44 patients treated with standard-therapy (HR, 1.12; 95% CI, 0.75 to 1.68; *P*=0.003 for non inferiority and *P*=0.57 for superiority).[56]
  - There was no difference between the rivaroxaban and standard therapy treatment groups with regard to major or clinically relevant non major bleeding (HR, 0.90; 95% CI, 0.76 to 1.07; *P*=0.23).[56]
- The FDA approval of edoxaban tosylate was based on two phase III, double-blind, multinational, randomized controlled clinical trials.
  - The second trial compared the efficacy and safety of edoxaban tosylate to warfarin in reducing the risk of stroke and systemic embolic events in adult patients with non-valvular AF. The annualized rate for occurrence of a first stroke (ischemic or hemorrhagic) or a systemic embolic event that occurred during treatment or within three days from the last dose taken was 1.50% with warfarin compared with 1.18% with high-dose edoxaban tosylate (HR, 0.79; 97.5% CI, 0.63 to 0.99; P<0.001) and 1.61% with low-dose edoxaban tosylate (HR, 1.07; 97.5% CI, 0.87 to 1.31; P=0.005). major bleeding during treatment was found to be 3.43% with warfarin compared with 2.75% with high-dose edoxaban tosylate (HR, 0.80; 95% CI, 0.71 to 0.91; P<0.001) and 1.61% with low-dose edoxaban tosylate (HR, 0.47; 95% CI, 0.41 to 0.55; P<0.001).[35]
  - The first study evaluated edoxaban tosylate was compared to warfarin in adult patients with acute venous thromboembolism. Results showed that there was a recurrence of venous thromboembolism in 3.2% of the edoxaban tosylate group as compared with 3.5% in the warfarin group (P<0.001). Edoxaban demonstrated superiority compared to warfarin for clinically relevant bleeding (8.5% compared with 10.3% for the warfarin group [P=0.004]). However, both treatment groups were similar in regards to major bleeding (P=0.35).[50]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[10-18]

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

· Other Key Facts:
- Rivaroxaban for use in atrial fibrillation:[4]
  - The approved package labeling for rivaroxaban acknowledges the low percentage of "time in International Normalized Ratio range" for patients randomized to warfarin within the ROCKET-AF trial as compared to other clinical trials, and states that it is unknown how rivaroxaban compares when patients are well controlled on warfarin.
  - Within the ROCKET-AF trial, an increased incidence of adverse clinical events were noted when patients were transitioned off of rivaroxaban to warfarin or to another vitamin K antagonist.
- The prescribing information for apixaban, dabigatran, edoxaban, and rivaroxaban contain a Black Box Warning regarding an increased risk of thromboembolic events following the discontinuation of treatment.[1-4]
- Apixaban has demonstrated a significant reduction in the risk of stroke and systemic embolism, major bleeding and all-cause mortality compared to warfarin in patients with atrial fibrillation.[19]
- Dabigatran etexilate mesylate 150 mg has demonstrated a significant reduction in the risk of stroke and systemic embolism compared to warfarin in patients with atrial fibrillation; the risk of major bleeding and all-cause mortality was similar between treatments.[26]
- Rivaroxaban was non inferior to warfarin with regard to the reduction in the risk of stroke and systemic embolism in patients with atrial fibrillation (per-protocol analysis) with a similar incidence of major bleeding.[36]

- Apixaban, dabigatran and rivaroxaban All three new oral anticoagulants are associated with a significant reduction in intracranial hemorrhage compared to warfarin.[19,26,36]
- Warfarin is available generically.[9]

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Therapeutic Class Overview
Insulins

Therapeutic Class

- **Overview/Summary:** This review will focus on the antidiabetic insulins, including human insulin products and synthetic insulin analogs.[1-17] Insulin products are Food and Drug Administration (FDA)-approved improve glycemic control in patients with diabetes mellitus (DM) type 1 and type 2. DM is a group of metabolic disorders with types 1 and 2 being the broadest categories. All categories of DM ultimately results in hyperglycemia, but the etiologies for each are distinct and may include reduced insulin secretion, decreased glucose utilization, or increased glucose production. Due to the metabolic dysregulation of DM, secondary pathophysiologic changes in multiple organ systems occur. Examples of severe complications that may occur include end-stage renal disease (ESRD), nontraumatic lower extremity amputation, and adult blindness. Additionally, it also predisposes the patient to cardiovascular disease.[18] Overall, there are a variety of oral and injectable antidiabetic agents currently available to treat diabetes. Available insulin products are summarized in Table 1. Insulin therapy is usually administered by subcutaneous injection, which allows for prolonged absorption and less pain compared to intramuscular injection.[1-17,19] Additionally, regular insulin is also formulated as an inhalation.[4] At least one formulation of all insulin products are supplied in multidose vials with only regular insulin not being formulated in a prefilled pen or syringe.[1-17] Inhaled insulin powder is formulated in disposable, single-use cartridges, known as Technosphere® which provided a more efficient inhalation device than what has been used in the past.[4] Another inhaled formulation of regular insulin, Exubera®, was previously FDA-approved; however, this agent was removed from the market in 2007 due to low patient and provider acceptance.[20] All insulin products have at least one formulation with a concentration of 100 units/mL (U-100). Two agents are also formulated with a higher concentration, regular insulin as 500 units/mL (U-500; Humulin® R U-500) and insulin glargine as 300 units/mL (U-300; Toujeo® SoloSTAR).[1-17]

Table 1. Current Medications Available in the Therapeutic Class[1-17]

Generic (Trade Name)	FDA-Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Products			
Insulin aspart (NovoLog®, NovoLog® FlexPen, NovoLog® PenFill)	To improve glycemic control in diabetes mellitus*	Cartridge: 100 units/mL Pen: 100 units/mL Vial: 100 units/mL	-
Insulin detemir (Levemir®, Levemir® FlexPen, Levemir® FlexTouch)	To improve glycemic control in diabetes mellitus*	Pen: 100 units/mL Vial: 100 units/mL	-
Insulin glargine (Lantus®, Lantus® SoloSTAR, Toujeo® SoloSTAR)	To improve glycemic control in diabetes mellitus*	Pen: 100 units/mL (Lantus® SoloSTAR) 300 units/mL (Toujeo® SoloSTAR) Vial:	-

Generic (Trade Name)	FDA-Approved Indications	Dosage Form/Strength	Generic Availability
		100 units/mL	
Insulin glulisine (Apidra®, Apidra® SoloSTAR)	To improve glycemic control in diabetes mellitus*	Pen: 100 units/mL Vial: 100 units/mL	-
Insulin lispro, human recombinant analog (Humalog®, Humalog® KwikPen)	To improve glycemic control in diabetes mellitus*	Cartridge: 100 units /mL Pen: 100 units /mL Vial: 100 units /mL	-
Insulin NPH (isophane), human recombinant (Humulin® N, Humulin® N U-100 Pen, Novolin® N, Novolin® N ReliOn)	To improve glycemic control in diabetes mellitus*	Pen: 100 units/mL Vial: 100 units/mL	-
Insulin regular, human recombinant (Afrezza®, Humulin® R, Humulin® R U-500, Novolin® R)	To improve glycemic control in diabetes mellitus* Treatment of diabetic patients with marked insulin resistance*,†	Inhalation powder (Afrezza®): 4 units/cartridge 8 units/cartridge Vial: 100 U/mL 500 U/mL(Humulin® R U-500)	-
Combination Products			
Insulin aspart/insulin aspart protamine (NovoLog® Mix 70/30, NovoLog® 70/30 Flex Pen)	To improve glycemic control in diabetes mellitus*	Pen: 70/30 units/mL Vial: 70/30 units/mL	-
Insulin lispro/insulin lispro protamine (Humalog® Mix 50/50, Humalog® Mix 75/25, Humalog® Mix 50/50 KwikPen, Humalog® Mix 75/25 KwikPen)	To improve glycemic control in diabetes mellitus*	Pen: 50/50 units/mL 75/25 units/mL Vial: 50/50 units/mL 75/25 units/mL	-
Insulin, regular/insulin, NPH, human recombinant (Humulin® 70/30, Humulin® 70/30 KwikPen, Humulin® 70/30 Pen, Novolin® 70/30, Novolin® 70/30 ReliOn)	To improve glycemic control in diabetes mellitus*	Pen: 70/30 units/mL Vial: 70/30 units/mL	-

FDA=Food and Drug Administration
*Includes diabetes mellitus type 1 and type 2. Generally, these agents have not been studied for the treatment of type 2 diabetes in pediatric patients. Additionally, some agents may carry an indication for use in pediatric patients, but have never been studied in that population.
†Humulin® R U-500 only

Evidence-based Medicine

- There are numerous clinical trials demonstrating the safety and efficacy of insulin products in the management of diabetes type 1 and 2.[21-142] Of note, only head-to-head or active-comparator trials have been included as insulin is a well-established treatment.
- The safety and efficacy of inhaled regular insulin (Afrezza®) in both diabetes type 1 and type 2. Clinical trials were 24 weeks each.[4,143,144]
    - For type 1 diabetes, inhaled regular insulin was non-inferior to insulin aspart for mean reduction in HbA_{1c}. However, it provided less HbA_{1c} reduction than insulin aspart (-0.4% vs -0.21%). On the other hand, there was a reduction in the rate of hypoglycemia (9.8 vs 14.0 events per subject month; P<0.0001) and less weight gain (−0.39 kg vs 0.93 kg; P=0.0102) with inhaled regular insulin.
    - For type 2 diabetes, mean reduction in HbA_{1c} was significantly greater in the insulin group compared to the placebo group (-0.82% vs -0.42%; 95% confidence interval [CI]: −0.57 to −0.23; P<0.0001).
- The safety and efficacy of insulin glargine U-300 (Toujeo®) was evaluated in four clinical trials. Each study compared insulin glargine U-300 to insulin glargine U-100 in an open label design over 26 weeks of therapy.
    - In all studies, insulin glargine U-300 was shown to be non-inferior to insulin glargine U-100. Additionally, the dose of basal glargine insulin required was higher in all studies for U-300 (requiring 11% to 17.5% more units). Generally, both U-100 and U-300 had similar rates of adverse events, including hypoglycemia and all three studies showed similar changes in weight.[12,71-73]
- Differences in safety and efficacy of insulin preparations are modest with slightly better improvement in in HbA_{1c} with the rapid-acting analogues compared to regular insulin.[44,45]
- Long-acting insulin analogs have been shown to be at least as effective as NPH insulin in HbA_{1c} reduction, with some studies showing a significant improvement associated with the long-acting insulin analogs compared with NPH insulin with similar rates of side effects.[64,102,103,105]
- When comparing the long-acting analogs head-to-head, several trials have demonstrated non-inferiority between the products in the same outcomes when used in the management of type 1 diabetes and as add-on therapy in type 2 diabetics.[46,47,75-77]
- When comparing the long-acting analogs head-to-head, several trials have demonstrated non-inferiority between the products in the same outcomes when used in the management of type 1 diabetes and as add-on therapy in type 2 diabetics.[46,47,75-77]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[145-155]
    - The goal of treatment for both type 1 and type 2 DM is to control hyperglycemia and reduce the risk of long-term complications.
    - For patients with type 1 DM, insulin therapy is required due to pathogenesis of the disease. The standard approach to therapy is a regimen that includes long-acting basal insulin and rapid-acting prandial insulin tailored to the individual.
    - For type 2 DM, there are many more options for therapy, including the insulin products, oral antidiabetic agents, and other injectable antidiabetic agents.
        - Metformin remains the cornerstone of most antidiabetic treatment regimens.
        - Patients with a high HbA_{1c} will likely require combination or triple therapy in order to achieve glycemic goals.
        - At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered.
    - For both conditions, the trend in treatment is toward a patient-centered approach focusing on patient needs, preferences and tolerances, individualized treatment, and flexibility in the

choice of drugs, the over-riding goal being to improve glycemic control while minimizing adverse effects.

- Other Key Facts:[1-17]
  - Insulin therapy is usually administered by subcutaneous injection. Regular insulin is also formulated as an inhalation. At least one formulation of all insulin products are supplied in multidose vials with only regular insulin not being formulated in a prefilled pen or syringe.[1-17]
  - All insulin products have at least one formulation with a concentration of 100 units/mL. Two agents are also formulated with a higher concentration, regular insulin as 500 units/mL (Humulin® R U-500) and insulin glargine as 300 units/mL (Toujeo® SoloSTAR).[1-17]
  - A Risk Evaluation and Mitigation Strategy (REMS) is required for this inhaled regular insulin and includes requirements for patient evaluation and testing prior to initiating therapy in order to ensure appropriate patient selection (e.g., avoiding this agent in patients with underlying chronic lung disease).
  - There are currently no generic formulations of insulin; however, there are several products available over-the-counter.

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Therapeutic Class Overview
Sedative Hypnotics

Therapeutic Class

- **Overview/Summary:**

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

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

Table 1. Current Medications Available in the Therapeutic Class[7-21]

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

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

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

Evidence-based Medicine

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

Key Points within the Medication Class

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

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

Other Key Facts:

- Currently, estazolam, eszopiclone, flurazepam, temazepam, triazolam, zaleplon and zolpidem (immediate-release and extended-release tablets) are available generically.[6]
- However; doxepin is available generically in higher doses that are approved for the treatment of depression and anxiety.[6]

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Therapeutic Class Overview
Beta-adrenergic antagonists (single-entity)

- **Therapeutic Class Overview/Summary:** The beta-adrenergic blocking agents (β-blockers) are Food and Drug Administration (FDA)-approved for the treatment of angina, arrhythmias, essential tremor, heart failure, hypertension, hypertrophic aortic stenosis, migraine prophylaxis, myocardial infarction, and pheochromocytoma.[1-26] The β-blockers differ with regards to their adrenergic-receptor blocking, membrane stabilizing and intrinsic sympathomimetic activities, as well as lipophilicity.[1-26] There are at least three distinct types of β receptors distributed throughout the body (β1, β2, and β3). β1-receptors are located predominantly in the heart and kidneys. β2-receptors are located in the lungs, gastrointestinal tract, liver, uterus, vascular smooth muscle, and skeletal muscle. β3-receptors are located in fat cells. β-blockers primarily exert their effects through a blockade of β1 and β2 receptor subtypes. Agents that have a greater affinity for β1 receptors are considered to be cardioselective. These agents may be safer in patients with asthma, chronic obstructive pulmonary disease, and peripheral vascular disease because they produce less inhibition of β2 receptors, which mediate vasoconstriction and bronchospasm. Cardioselectivity is dose dependent; therefore, β2 blockade can occur at higher doses. Carvedilol and labetalol also block α-adrenergic receptors.[27-28]

  Current clinical guidelines identify β-blockers as effective in many indications. Their place in therapy varies depending on indication and other patient specific factors. Specific treatment guidelines are summarized in Table 12.[29-61] The beta-adrenergic blocking agents that are included in this review are listed in Table 1 and comparative information on cardioselectivity is highlighted in Table 2. This review encompasses all dosage forms and strengths for the single-entity products. A significant majority of these agents are available as a generic product.

Table 1. Current Medications Available in the Therapeutic Class[1-26]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Acebutolol HCl (Sectral®*)	Management of ventricular premature beats; hypertension alone or in combination with other antihypertensives	Capsule: 200 mg 400 mg	a
Atenolol (Tenormin®*)	To decrease angina frequency and increase exercise tolerance due to coronary atherosclerosis; hypertension alone or in combination with other antihypertensives; hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality	Tablet: 25 mg 50 mg 100 mg	a
Betaxolol HCl (Kerlone®*)	Hypertension alone or in combination with other antihypertensives	Tablet: 10 mg 20 mg	a
Bisoprolol fumarate (Zebeta®*)	Hypertension alone or in combination with other antihypertensives	Tablet: 5 mg 10 mg	a
Carvedilol (Coreg®*)	Essential hypertension, alone or in combination with other antihypertensives; mild to severe chronic heart failure of ischemic or cardiomyopathic origin to increase survival and, also, to reduce the risk of hospitalizations; reduce cardiovascular mortality in clinically stable patients who have survived the acute phase	Tablet: 3.125 mg 6.25 mg 12.5 mg 25 mg	a

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
	of a myocardial infarction and have a left ventricular ejection fraction of ≤40% (with or without symptomatic heart failure)		
Carvedilol Phosphate (Coreg CR)	Essential hypertension, alone or in combination with other antihypertensives; mild to severe chronic heart failure of ischemic or cardiomyopathic origin to increase survival and, also, to reduce the risk of hospitalizations; reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of ≤40% (with or without symptomatic heart failure)	Extended-release capsule: 10 mg 20 mg 40 mg 80 mg	-
Esmolol (Brevibloc®*)	Intraoperative and Postoperative Tachycardia and/or Hypertension that occur during induction and tracheal intubation, during surgery, on emergence from anesthesia and in the postoperative period; Supraventricular Tachycardia or Noncompensatory Sinus Tachycardia, short term control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other emergent circumstances	Injection: 10 mg/mL IV solution (Brevibloc®): 10 mg/mL 20 mg/mL	a
Labetalol HCl (Trandate®*)	Hypertension alone or in combination with other antihypertensives (tablet); Hypertension, control of blood pressure in severe hypertension (injection)	Injection: 5 mg/mL Tablet: 100 mg 200 mg 300 mg	a
Metoprolol tartrate (Lopressor®*)	Angina, long-term maintenance treatment; Hypertension alone or in combination with other antihypertensives; Hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality	Injection: 5 mg/5 mL Tablet: 25 mg 50 mg 100 mg	a
Metoprolol succinate (Toprol XL®*)	Angina, long-term maintenance treatment; Hypertension alone or in combination with other antihypertensives; Stable, symptomatic (NYHA Class II or III) heart failure of ischemic, hypertensive, or cardiomyopathic origin; Hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality	Extended-release tablet: 25 mg 50 mg 100 mg 200 mg	a
Nadolol (Corgard®*)	Angina, long-term maintenance treatment; Hypertension alone or in combination with	Tablet: 20 mg	a

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
	other antihypertensives	40 mg 80 mg	
Nebivolol HCl (Bystolic®*)	Hypertension alone or in combination with other antihypertensives	Tablet: 2.5 mg 5 mg 10 mg 20 mg	-
Penbutolol sulfate (Levatol®)	Mild to moderate arterial hypertension alone or in combination with other antihypertensives	Tablet: 20 mg	-
Pindolol	Hypertension alone or in combination with other antihypertensives	Tablet: 5 mg 10 mg	a
Propranolol HCl (Hemangeol®, Inderal LA®*, Inderal XL®, Innopran XL®)	To decrease angina frequency and increase exercise tolerance due to coronary atherosclerosis (24-hour capsule); Persistent premature ventricular extrasystoles that impair the well-being of the patient and do not respond to conventional measures (injection); Short-term treatment of supraventricular tachycardia, including Wolff-Parkinson-White syndrome and thyrotoxicosis, to decrease ventricular rate (injection); To abolish tachyarrhythmias due to excessive catecholamine action during anesthesia when other measures fail (injection); To control ventricular rate in life-threatening digitalis-induced arrhythmias (injection); To control ventricular rate in patients with atrial fibrillation and a rapid ventricular response(tablet); Hypertension alone or in combination with other antihypertensives; Improves NYHA functional class in symptomatic patients with hypertropic subaortic stenosis (24-hour capsule); Reduce cardiovascular mortality in patients who have survived the acute phase of myocardial infarction and are clinically stable (tablet); Adjunct to alpha-adrenergic blockade to control blood pressure and reduce symptoms of catecholamine-secreting tumors (tablet); Familial or hereditary essential tremor (injection); Treatment of proliferating infantile hemangioma requiring systemic therapy (oral solution); Prophylaxis of migraine headache (24-hour capsule)	capsule: 60 mg 80 mg 120 mg 160 mg Injection: 1 mg/mL Oral solution: 20 mg/5 mL 40 mg/5 mL Oral Solution (Hemangeol®): 4.28 mg/mL Tablet: 10 mg 20 mg 40 mg 60 mg 80 mg	a
Sotalol HCl (Betapace®*, Betapace AF®*, Sotylize®,	Documented ventricular arrhythmias that in the judgement of the physician are life-threatening; Maintenance of normal sinus rhythm in patients with symptomatic atrial	Injection: 150 mg/10 mL Oral Solution	a

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Sorine®†)	fibrillation/atrial flutter who are currently in sinus rhythm	(Sotylize®): 5 mg/mL Tablet: 80 mg 120 mg 160 mg 240 mg	
Timolol Maleate	Hypertension alone or in combination with other antihypertensives; Reduce cardiovascular mortality and reinfarction in patients who have survived the acute phase of myocardial infarction and are clinically stable; Prophylaxis of migraine headache	Tablet: 5 mg 10 mg 20 mg	a

HCl=hydrochloride
* Generic available in at least one formulation
† Branded generic product

Evidence-based Medicine

- Despite the extensive experience with β-blockers in clinical practice, there have been no studies suggesting that any of these agents have major advantages or disadvantages in relation to the others for the treatment of many cardiovascular diseases. When any available β-blocker is titrated properly, it can be effective in patients with an arrhythmia, hypertension, or angina pectoris and other indications.[63-185]
- The safety and efficacy of sotalol hydrochloride oral solution (Sotylize®) was established using pre-existing clinical trial data used for the FDA-approval sotalol hydrochloride (Betapace®, Betapace AF®).[22-25]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - β-blockers as effective in many indications. Their place in therapy varies depending on indication and other patient specific factors.
- Other Key Facts:
  - β-blockers primarily exert their effects through a blockade of β1 and β2 receptor subtypes. Agents that have a greater affinity for β1 receptors are considered to be cardioselective.
    - These agents may be safer in patients with asthma, chronic obstructive pulmonary disease, and peripheral vascular disease.[27-28]
  - Carvedilol and labetalol also block α-adrenergic receptors.[27-28]

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Therapeutic Class Overview
Onychomycosis Agents

Therapeutic Class

Overview/Summary: This review will focus on the antifungal agents Food and Drug Administration (FDA)-approved for the treatment of onychomycosis.[1-9] Onychomycosis is a progressive infection of the nail bed which may extend into the matrix or plate, leading to destruction, deformity, thickening and discoloration. Of note, these agents are only indicated when specific types of fungus have caused the infection, and are listed in Table 1. Additionally, ciclopirox is only FDA-approved for mild to moderate onychomycosis without lunula involvement.[1] The mechanisms by which these agents exhibit their antifungal effects are varied. For ciclopirox (Penlac®) the exact mechanism is unknown. It is believed to block fungal transmembrane transport, causing intracellular depletion of essential substrates and/or ions and to interfere with ribonucleic acid (RNA) and deoxyribonucleic acid (DNA).[1] The azole antifungals, efinaconazole (Jublia®) and itraconazole tablets (Onmel®) and capsules (Sporanox®) works via inhibition of fungal lanosterol 14-alpha-demethylase, an enzyme necessary for the biosynthesis of ergosterol. By decreasing ergosterol concentrations, the fungal cell membrane permeability is increased, which results in leakage of cellular contents.[2,5,6] Griseofulvin microsize (Grifulvin V®) and ultramicrosize (GRIS-PEG®) disrupts the mitotic spindle, arresting metaphase of cell division. Griseofulvin may also produce defective DNA that is unable to replicate. The ultramicrosize tablets are absorbed from the gastrointestinal tract at approximately one and one-half times that of microsize griseofulvin, which allows for a lower dose of griseofulvin to be administered.[3,4] Tavaborole (Kerydin®), is an oxaborole antifungal that interferes with protein biosynthesis by inhibiting leucyl-transfer ribonucleic acid (tRNA) synthase (LeuRS), which prevents translation of tRNA by LeuRS.[7] The final agent used for the treatment of onychomycosis, terbinafine hydrochloride (Lamisil®), is an allylamine antifungal. While its mechanism is not known, it is asserted it probably exerts its effect by inhibiting the fungal enzyme squalene monooxygenase, which creates a deficiency in ergosterol, a component of fungal membranes necessary for normal growth.[8]

Table 1. Current Medications Available in the Therapeutic Class[1-8]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Ciclopirox (Penlac®)	Mild to moderate onychomycosis† of the finger or toenail without lunula involvement	Topical solution: 8%	-
Efinaconazole (Jublia®)	Onychomycosis† of the toenail	Topical solution: 10%	-
Griseofulvin microcrystalline (Grifulvin V®*)	Onychomycosis† of the finger or toenail; tinea corporis, tinea pedis, tinea cruris, tinea barbae, tinea capitis	Oral Suspension: 125 mg/5 mL Tablet: 500 mg	a
Griseofulvin ultramicrocrystalline (GRIS-PEG®*)	Onychomycosis† of the finger or toenail; tinea corporis, tinea pedis, tinea cruris, tinea barbae, tinea capitis	Tablet: 125 mg 250 mg	a
Itraconazole (Onmel®, Sporanox®*)	Onychomycosis† of the finger‡ or toenail§, Blastomycosis‡, Histoplasmosis‡, Aspergillosis‡	Capsule: 100 mg Tablet: 200 mg	a
Tavaborole (Kerydin®)	Onychomycosis† of the toenail	Topical solution: 5%	-
Terbinafine hydrochloride (Lamisil®*)	Onychomycosis† of the finger¶ or toenail¶	Tablet: 250 mg	a

*Generic available in at least one dosage form or strength
†Caused by Trichophyton rubrum (ciclopirox); caused by trichophyton rubrum and Trichophyton mentagrophytes (efinaconazole, itraconazole [Onmel®], tavaborole); caused by Trichophyton rubrum, Trichophyton tonsurans, Trichophyton mentagrophytes, Trichophyton interdigitalis, Trichophyton verrucosum, Trichophyton megnini, Trichophyton gallinae, Trichophyton crateriform, Trichophyton sulphureum, Trichophyton schoenleinii, Microsporum audouini, Microsporum canis, Microsporum gypseum and Epidermophyton floccosum (griseofulvin); causative pathogens not reported for itraconazole (Sporanox®) or terbinafine
‡Sporanox® tablets only
§Onmel® and Sporanox® tablets only
¶Lamisil® tablets only

Evidence-based Medicine

- Older agents such as itraconazole, griseofulvin and terbinafine HCl have been well studied. In head-to-head studies, terbinafine HCl and itraconazole provided an improved cure rate over griseofulvin microsize and ultramicrosize tablets.[9-13]
- Studies comparing terbinafine HCl to itraconazole have reported inconsistent results with numerous clinical trials reporting improved clinical and/or mycological cure rates with terbinafine HCl while several published studies have shown no difference between the agents.[13-28]
- The safety and efficacy of ciclopirox nail lacquer topical solution has been evaluated in two double-blind placebo-controlled trials which lasted for 48 weeks each. Both studies showed a significant improvement in mycological cure and culture results for ciclopirox compared with placebo (P<0.001 for both outcomes in both studies).[29]
- The safety and efficacy of once daily use of efinaconazole topical solution for the treatment of onychomycosis of the toenail were assessed in two 52-week vehicle-controlled study. The efinaconazole group had complete cure rates of 17.8% and 15.2% of compared to 3.3% and 5.5% in the vehicle group (P<0.001).[30]
- Itraconazole tablets were approved based on one 12 week, randomized, controlled study in patients with onychomycosis. It was compared to itraconazole capsules and placebo. At week-52, 22.3% of patients in the itraconazole tablets group had complete cure compared to 1.0% in the placebo group (P value not reported). The mycological and clinical cure rates were 44% and 6% and 26% and 3% in the itraconazole tablets and placebo groups, respectively (P value not reported). Efficacy results comparing itraconazole to itraconazole capsules were found to be similar (P value not reported).[5,31]
- The safety and efficacy of tavaborole for the treatment of onychomycosis of the toenail was assessed in two 52-week randomized controlled trials compared with vehicle solution. Complete cure rates in the two studies for tavaborole were 6.5% and 9.1% compared with 0.5% and 1.5% for the vehicle group. A greater proportion of patients in the tavaborole-treated groups experienced mycological cure and complete or almost complete cure compared to vehicle-treated groups (P values not reported).[5]

Key Points within the Medication Class

- Treatment guidelines for onychomycosis infections have not been updated recently, with the last update being in 2005.[32,33]
- According to Clinical Guidelines:[32,33]
  - Oral therapy is more effective, and should be utilized in more serious cases.
  - Combination therapy with an oral and topical agent may be useful in the more severe cases.
  - Oral terbinafine or itraconazole is recommended over griseofulvin due to a much higher cure rate.
  - Neither guideline mentions newer agents as they were not FDA-approved at the time of publication
- Other Key Facts:[1-8]
  - Treatment with topical therapy is longer than oral therapy. Oral therapy with terbinafine HCl or itraconazole is six to 12 weeks depending on indication compared with upwards of 48 weeks with topical therapies.
  - Limited systemic absorption with the topical agents provides reduced adverse effects, usually limited to local reactions.
  - Oral therapy is associated with more side effects and drug interactions that may limit use.

- In addition to a black-box warning for drug interactions, itraconazole has a black-box warning regarding its use in patients with congestive heart failure, which may have a negative inotropic effect.
- Itraconazole tablets (Onmel®) does not provide any clinical advantage over the generic 100 mg capsules other than reduced pill burden.
- Ciclopirox and griseofulvin are approved in pediatric patients (age ≥12 years and ≥2 years, respectively).
- No dosage adjustment is required for any renal or hepatic impairment for any agent; however, terbinafine HCl is not recommended in patients with creatinine clearance (CrCl) <50 mL/min.
- Terbinafine HCl and ciclopirox are pregnancy category B, while griseofulvin is X. Itraconazole, efinaconazole and tavaborole are listed as pregnancy category C; however, itraconazole tablets and capsules are contraindicated in pregnant patients or to women contemplating pregnancy.
- Other formulations of itraconazole (oral solution, Sporanox®), terbinafine HCl (granules, Lamisil®) and ciclopirox (gel, cream, lotion, suspension and shampoo) do not carry an FDA-approved indication for onychomycosis.
- Only griseofulvin microcrystalline, griseofulvin ultramicrocrystalline and terbinafine HCl are available generically.

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Therapeutic Class Overview
Anticonvulsants

Therapeutic Class

Overview/Summary: The anticonvulsants are Food and Drug Administration (FDA)-approved for the prevention and/or treatment of various seizure disorders either as monotherapy or adjunctive therapy. Some anticonvulsants are also FDA-approved for the prevention of migraines, and management of bipolar disorders, fibromyalgia, neuropathic pain and other non-seizure related conditions. The specific FDA-approved indications for each of these agents are outlined in Table 1.[1-48] Seizure disorders are classified into four major categories: partial seizures (seizures beginning locally), generalized seizures (bilaterally symmetrical and without local onset), unilateral seizures (seizures that are predominantly unilateral) and unclassified epileptic seizures (seizures that are unclassifiable because of incomplete data). Partial seizures are subdivided into those with elementary symptomatology, those with complex symptomatology, and those that are secondarily generalized. Partial seizures with elementary symptomatology include those with motor symptoms (e.g., Jacksonian seizures) or with autonomic symptoms. Partial seizures with complex symptomatology are also known as temporal lobe or psychomotor seizures. Generalized seizures include tonic-clonic (grand mal) seizures, absence (petit mal) seizures, myoclonic seizures and akinetic seizures. Two or more seizures that occur sequentially without full recovery of consciousness between the seizures or seizures that last more than 30 minutes are known as status epilepticus.[49]

Pharmacologic management of epilepsy should be individualized, and focused on controlling seizures, avoiding treatment-related adverse events and maintaining or restoring quality of life.[50] Prior to 1990, six major antiepileptic drugs were available for the treatment of various forms of epilepsy, including carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone and valproic acid. Over the past decade, many new chemical entities have become available in the United States. The newer antiepileptic drugs have better adverse event and drug interaction profiles, and they do not require serum concentration monitoring.[51-53] All of the anticonvulsants are FDA-approved for the treatment of various seizure disorders; however, these agents are primarily utilized in the treatment of partial, or focal, seizures and generalized tonic-clonic seizures. Currently there are several generic anticonvulsants available, and at least one generic agent is available within each anticonvulsant subclass.[1]

Table 1. Current Medications Available in Therapeutic Class[1-48]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Barbiturates			
Phenobarbital	Anticonvulsant (tablet), emergency control of certain acute convulsive episodes (injection), long term anticonvulsant for the treatment of generalized tonic-clonic and cortical focal seizures (injection), treatment of generalized and partial seizures (elixir), hypnotic, for short term treatment of insomnia (injection), preanesthetic (injection), sedative	Elixir: 20 mg/5 mL Injection: 65 mg/mL 130 mg/mL Tablet: 15 mg 16.2 mg 30 mg 32.4 mg 60 mg 64.8 mg 97.2 mg 100 mg	√
Primidone (Mysoline®*)	Control of grand mal, psychomotor, and focal epileptic seizures, used alone or	Tablet: 50 mg	√

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	concomitantly with other anticonvulsants	250 mg	
Benzodiazepines			
Clobazam (Onfi®)	Adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome in patients two years of age or older	Tablet: 5 mg 10 mg 20 mg	-
Clonazepam (Klonopin®*)	Treatment of Lennox-Gastaut Syndrome (petit mal variant), akinetic, and myoclonic seizures, alone or as adjunct therapy, treatment of panic disorder, with or without agoraphobia	Orally disintegrating tablet: 0.125 mg 0.25 mg 0.5 mg 1 mg 2 mg Tablet: 0.5 mg 1 mg 2 mg	√
Diazepam (Diastat®*)	Management of selected, refractory, patients with epilepsy, on stable regimens of antiepileptic drugs, who require intermittent use of diazepam to control bouts of increased seizure activity	Rectal gel: 2.5 mg 10 mg 20 mg	√
Hydantoins			
Ethotoin (Peganone®)	Control of generalized tonic-clonic and complex partial seizures	Tablet: 250 mg	-
Phenytoin (Phenytek®*, Dilantin®*)	Control of status epilepticus of the grand mal type (injection), control of generalized tonic-clonic and complex partial seizures (chewable tablet, extended-release capsule, suspension), prevention and treatment of seizures occurring during or following neurosurgery	Chewable tablet: 50 mg Extended-release capsule: 30 mg 100 mg 200 mg 300 mg Injection: 50 mg/mL Suspension: 125 mg/5 mL	√
Succinimides			
Ethosuximide (Zarontin®*)	Control of absence epilepsy	Capsule: 250 mg Syrup: 250 mg/5 mL	√
Methsuximide (Celontin®)	Control of absence seizures that are refractory to other drugs	Capsule: 300 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Anticonvulsants, Miscellaneous			
Carbamazepine (Carbatrol®*, Epitol®*, Equetro®, Tegretol®*, Tegretol XR®*)	Generalized tonic-clonic seizures, mixed seizure patterns, partial seizures with complex symptomatology, acute treatment of manic or mixed episodes associated with bipolar disorder (Equetro®), trigeminal neuralgia	Chewable tablet: 100 mg Extended-release capsule: 100 mg 200 mg 300 mg Extended-release tablet: 100 mg 200 mg 400 mg Suspension: 100 mg/5 mL Tablet: 200 mg	√
Divalproex (Depakote®*, Depakote ER®*)	Adjunctive therapy in patients with multiple seizure types, that include absence seizures (extended-release, delayed-release), monotherapy and adjunctive therapy of complex partial seizures and simple and complex absence seizures, acute treatment of the manic episodes associated with bipolar disorder (delayed-release), acute treatment of manic or mixed episodes associated with bipolar disorder (extended-release), prophylaxis of migraine headaches (extended-release, delayed-release)	Capsule (sprinkle): 125 mg Delayed-release tablet: 125 mg 250 mg 500 mg Extended-release tablet: 250 mg 500 mg	√
Eslicarbazepine (Aptiom®)	Adjunctive treatment of partial-onset seizures	Tablet: 200 mg 400 mg 600 mg 800 mg	-
Ezogabine (Potiga®)	Adjunctive therapy in the treatment of partial onset seizures	Tablet: 50 mg 200 mg 300 mg 400 mg	-
Felbamate (Felbatol®*)	Patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or liver failure is deemed acceptable in light of the benefits conferred by its use	Suspension: 600 mg/5 mL Tablet: 400 mg 600 mg	√

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Gabapentin (Neurontin®*)	Adjunctive therapy in the treatment of partial seizures, postherpetic neuralgia	Capsule: 100 mg 300 mg 400 mg Solution: 250 mg/5 mL Tablet: 600 mg 800 mg	√
Lacosamide (Vimpat®)	Adjunctive therapy in the treatment of partial seizures	Injection: 200 mg/20 mL Solution: 10 mg/mL Tablet: 50 mg 100 mg 150 mg 200 mg	-
Lamotrigine (Lamictal®*, Lamictal CD®*, Lamictal ODT® Lamictal XR®*)	Adjunctive therapy in the treatment of partial seizures, adjunctive therapy in the treatment of primary generalized tonic-clonic seizures, adjunctive therapy for seizures associated with Lennox–Gastaut syndrome (chewable and orally disintegrating tablets), monotherapy in patients with partial seizures who are receiving treatment with carbamazepine, phenobarbital, phenytoin, primidone, or valproate as the single antiepileptic drugs, maintenance treatment of bipolar disorder to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy (chewable and orally disintegrating tablets)	Chewable tablet: 2 mg 5 mg 25 mg Extended-release tablet: 25 mg 50 mg 100 mg 200 mg 250 mg 300 mg Orally disintegrating tablet: 25 mg 50 mg 100 mg 200 mg Tablet: 25 mg 50 mg 100 mg 150 mg 200 mg 250 mg	√

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Levetiracetam (Elepsia XR®, Keppra®*, Keppra XR®*)	Adjunctive therapy in the treatment of myoclonic seizures in patients with juvenile myoclonic epilepsy (injection, tablets), adjunctive therapy in the treatment of partial seizures, adjunctive therapy in the treatment of primary generalized tonic-clonic seizures (injection, tablets),	Extended-release tablet: 500 mg 750 mg Extended-release tablet (Elepsia XR®): 1,000 mg 1,500 mg Injection: 500 mg/5 mL Solution: 100 mg/mL Tablet: 250 mg 500 mg 750 mg 1,000 mg	√
Oxcarbazepine (Oxtellar XR®, Trileptal®*)	Monotherapy and adjunctive therapy in the treatment of partial seizures	Extended-release tablet: 150 mg 300 mg 600 mg Suspension: 300 mg/5 mL Tablet: 150 mg 300 mg 600 mg	√
Perampanel (Fycompa®)	Adjunctive therapy in the treatment of partial onset seizures†	Tablet: 2 mg 4 mg 6 mg 8 mg 10 mg 12 mg	-
Pregabalin (Lyrica®)	Adjunctive therapy in the treatment of partial seizures, fibromyalgia, neuropathic pain associated with diabetic peripheral neuropathy, neuropathic pain associated with spinal cord injury, postherpetic neuralgia	Capsule: 25 mg 50 mg 75 mg 100 mg 150 mg 200 mg 225 mg 300 mg Solution:	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		20 mg/mL	
Rufinamide (Banzel®)	Adjunctive therapy for seizures associated with Lennox–Gastaut syndrome	Suspension: 40 mg/mL Tablet: 200 mg 400 mg	-
Tiagabine (Gabitril®*)	Adjunctive therapy in the treatment of partial seizures	Tablet: 2 mg 4 mg 12 mg 16 mg	√
Topiramate (Qudexy XR®, Topamax®*, Trokendi XR®)	Adjunctive therapy in patients with partial onset or primary generalized tonic-clonic seizures, adjunctive therapy for seizures associated with Lennox–Gastaut syndrome, monotherapy (initial) in patients with partial onset or primary generalized tonic-clonic seizures, prophylaxis of migraine headaches	Capsule (sprinkle): 15 mg 25 mg Tablet: 25 mg 50 mg 100 mg 200 mg Extended-release capsule: 25 mg 50 mg 100 mg 150 mg 200 mg	√
Valproic acid (Depakene®* Stavzor®)	Adjunctive therapy in patients with multiple seizure types, that include absence seizures, monotherapy and adjunctive therapy of complex partial seizures and simple and complex absence seizures, acute treatment of the manic episodes associated with bipolar disorder (delayed-release), prophylaxis of migraine headaches (delayed-release)	Capsule: 250 mg Delayed-release capsule: 125 mg 250 mg 500 mg Solution: 250 mg/5 mL	√
Vigabatrin (Sabril®)	Adjunctive therapy for adult patients with refractory complex partial seizures who have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss (tablet), monotherapy for pediatric patients (one month to two years of age) with infantile spasms for whom the potential benefits outweigh the potential risk of vision loss (solution)	Solution (powder): 500 mg Tablet: 500 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Zonisamide (Zonegran®*)	Adjunctive therapy in the treatment of partial seizures	Capsule: 25 mg 50 mg 100 mg	√

*Generic available in at least one dosage form or strength.
†With or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

Evidence-based Medicine

- The safety and efficacy of Elepsia XR® (levetiracetam extended-release tablets) was established based on the clinical trials used to approve Keppra ER® (levetiracetam extended-release tablets).[19,48]
- Hancock et al conducted a meta-analysis of 14 randomized controlled trials which included infants and children with infantile spasms. Treatment with vigabatrin was associated with a complete cessation of spasms in 7/20 (35%) patients compared to 2/20 (10%) patients treated with placebo. A >70% reduction in the number of spasms was reported in 40% of patients treated with vigabatrin compared to 15% of patients treated with placebo.[54]
- Another meta-analysis by Hancock et al included trials that evaluated the safety and efficacy of felbamate, lamotrigine, rufinamide and topiramate in the treatment of Lennox-Gastaut Syndrome (LGS). While all of these agents demonstrated some efficacy, the optimum treatment of LGS remained uncertain as no single drug was highly efficacious. Felbamate, lamotrigine, rufinamide and topiramate may be helpful as add-on therapy.[55]
- The results of a study by Ng et al demonstrated that the mean percent reduction in weekly drop seizures was 41.2% with clobazam 0.25 mg/kg/day (P=0.0120), 49.4% with clobazam 0.5 mg/kg/day (P=0.0015) and 68.3% with clobazam 1.0 mg/kg/day (P<0.0001) compared to 12.1% for placebo.[55]
- In a study by Porter et al, treatment with ezogabine 600, 900 and 1,200 mg reduced the total monthly seizure frequency from baseline by 23, 29 and 35% compared to 13% with placebo (P<0.001 for all).[56] In a second study of patients with drug-resistant partial epilepsy, ezogabine 1,200 mg daily reduced the total monthly seizure frequency from baseline by 44.3% compared to 17.5% with placebo (P<0.001).[58]
- Perampanel is approved as adjunctive therapy in patients with partial onset seizures. In one study perampanel 8 or 12 mg significantly reduced seizure frequency compared to placebo (P=0.0261 and P=0.0158 for 8 and 12 mg, respectively); however, there was no significant difference in the proportion of patients who achieved a seizure reduction >50% from baseline compared to the placebo group.[59] Similar results were reported in a second study (P<0.001 and P=0.011 for 8 and 12 mg, respectively); however, more patients treated with perampanel 8 or 12 mg had a reduced seizure frequency >50% from baseline compared to placebo (P=0.002 and P<0.001 for 8 and 12 mg, respectively).[60] In a third study, treatment with perampanel 4 or 8 mg significantly reduced seizure frequency compared to placebo (P=0.003 and P<0.001 for 4 mg and 8 mg, respectively). Moreover, a greater proportion of patients treated with perampanel 4 or 8 mg achieved a reduction in seizure frequency >50% from baseline compared to placebo (P=0.013 and P<0.001 for 4 and 8 mg, respectively).[61]
- The most recent Food and Drug Administration-approved anticonvulsant, eslicarbazepine, was based on the results of three double-blind, multi-center, randomized, placebo-controlled trials. Each of these trials compared adjunctive treatment with eslicarbazepine to placebo in patients who were currently receiving one to three anti-epileptic drugs. In the first and second published trials, the investigators compared eslicarbazepine at a dose of 400, 800 and 1,200 mg once daily to placebo for 12 weeks.[62,63] In a pooled analysis of the three studies (third trial has not been published), the primary endpoint of seizure frequency per four weeks was 7.7 in the placebo group (N=406) compared to 7.3 with eslicarbazepine 400 mg (N=185; P=0.8136), 6.1 with 800 mg (N=375; P=0.0001) and 5.7 with 1,200 mg (N=352; P<0.0001). The proportion of patients who achieved a seizure reduction of at least 50% from baseline was 20.9% in the placebo group compared to 22.2% with eslicarbazepine 400 mg, 32.3% with 800 mg and 40.9% with 1,200 mg.[62-64] A fourth double-blind, multi-center, randomized, placebo-controlled trial compared adjunctive treatment with eslicarbazepine to placebo in patients who were currently receiving one to two anti-epileptic drugs. Investigators compared eslicarbazepine

at a dose of 800 and 1,200 mg once daily to placebo for 12 weeks. The primary endpoint of seizure frequency per four weeks was 7.3 in the placebo group (N=88) compared to 5.7 with eslicarbazepine 800 mg (N=85; P=0.048) and 5.5 with 1,200 mg (N=80; P=0.021). The proportion of patients who achieved a seizure reduction of at least 50% from baseline was 22.6% in the placebo group compared to 34.5% with eslicarbazepine 800 mg (P=0.106) and 37.7% with 1,200 mg (P=0.020).[65]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - The 2012 National Institute for Clinical Excellence guideline recommends carbamazepine and lamotrigine as first-line treatment of children, young people, and adults with newly diagnosed focal seizures (partial seizures). Levetiracetam, oxcarbazepine or sodium valproate should be offered if first-line therapies prove inadequate, and adjunctive therapy should be considered if a second well-tolerated antiepileptic also proves inadequate. Sodium valproate is recommended first-line for the treatment of children, young people, and adults with newly diagnosed generalized tonic-clonic focal seizures. Lamotrigine should be offered if sodium valproate proves inadequate, and carbamazepine and oxcarbazepine should be considered. Adjunctive therapy with clobazam, lamotrigine, levetiracetam, sodium valproate, or topiramate should be offered to all patients if first-line therapies are inadequate.[49]
  - Vigabatrin (oral solution) is Food and Drug Administration (FDA)-approved for the management of infantile spasm. According to the 2012 American Academy of Neurology medical management of infantile spasms guideline, there is insufficient evidence to support the use of agents other than adrenocorticotropic hormone and vigabatrin. Evidence suggests that adrenocorticotropic hormone may be preferred over vigabatrin for short-term management.[66]
  - Clobazam, clonazepam, lamotrigine, rufinamide and topiramate are FDA-approved for the management of Lennox Gastaut Syndrome. Sodium valproate is recognized as first-line, with lamotrigine recommended as adjunctive therapy if needed.[49]
  - Treatment guidelines recommend valproate and carbamazepine as potential beneficial options for the management of adults with a manic or mixed bipolar episode. Lamotrigine, topiramate, or gabapentin are unlikely beneficial in this clinical situation and oxcarbazepine may be considered for treatment. With regard to bipolar depression in adults, lamotrigine should be considered as a potential first-line option, and patients who do not respond to initial monotherapy should receive combination therapy with lithium.[67-71]
  - Divalproex, topiramate and valproic acid are FDA-approved for the prophylaxis of migraine headaches, and all should be offered for migraine prevention according to the 2012 guidelines from the American Academy of Neurology/American Headache Society. Furthermore, carbamazepine may be considered for migraine prevention as it is a possibly effective treatment, and lamotrigine is ineffective.[72]
  - According to the American Academy of Neurology, anticonvulsants, antidepressants, opioids and other pharmacologic agents (capsaicin, isosorbide dinitrate spray, and lidocaine patch) are potential treatment options for painful diabetic neuropathy. If clinically appropriate, pregabalin should be offered for treatment. Gabapentin and sodium valproate are other anticonvulsants that should be considered for treatment.[73]
  - According to the American Academy of Neurology, first-line therapies for the management of postherpetic neuralgia include tricyclic antidepressants, gabapentin, pregabalin, opioids, and topical lidocaine. At this time the use of these therapies for long-term management remains uncertain.[74]
  - The use of anticonvulsants in the management of fibromyalgia is not addressed in the European League Against Rheumatism guidelines.[75]
- Other Key Facts:
  - The majority of anticonvulsants are available in a generic formulation, and there is at least one generic agent available within each pharmacologic class.
  - Clobazam was approved by the FDA in 2011; however, this agent has been available internationally for several years for the treatment of anxiety and epilepsy.

- Ezogabine has a unique mechanism of action in that it may act as an anticonvulsant by reducing excitability through the stabilization of neuronal potassium channels in an "open" position.[34]
- Perampanel is a first-in-class anticonvulsant that works as a highly selective, non-competitive AMPA-type glutamate receptor antagonist.[76]
- The most recently FDA-approved anticonvulsant, eslicarbazepine, provides for another treatment option for patients with partial-onset seizures.

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Therapeutic Class Overview
Androgens (testosterone)

Therapeutic Class

- **Overview/Summary:** The topical testosterone products listed in Table 1 are approved by the Food and Drug Administration for testosterone replacement therapy in males with primary hypogonadism (congenital or acquired) or hypogonadotropic hypogonadism (congenital or acquired) with testosterone pellets also having an indication to stimulate puberty in carefully selected males with clearly delayed puberty.[1-10] There are few differences between the topical testosterone products with the exception of formulation and site of administration. Androderm® is the only testosterone product available as a transdermal patch. AndroGel®, Fortesta®, Natesto®, Testim®, and Vogelxo® are available in gel preparations, while Axiron® is formulated as a topical solution. These products are available as metered-dose pumps or single-use packets/tubes. Natesto® is the only nasal gel available in the form of a metered dose pump. Striant® is a mucoadhesive buccal tablet system that is placed on the gum for 12 hours and applied twice a day, once in the morning and once in the evening. Testopel® is an implantable pellet that consists of crystalline testosterone. It is a cylindrically shaped pellet, 3.2mm (1/8 inch) in diameter and approximately 8-9mm in length. When implanted subcutaneously, the pellet(s) slowly release the hormone over three to six months for a long acting androgenic effect. Androderm® is applied at night, while the topical gels and solution are generally applied in the morning.[1-10] A higher incidence of skin pruritus is associated with the transdermal patch compared to the topical gels; however, the use of hydrocortisone cream, may reduce skin irritations that develop.[1] The labeling of testosterone solution and gels, excluding testosterone nasal gel, include a Black Box Warning regarding the risk of virilization of female sexual partners that has been reported with male use of topical testosterone gels and solution.[2-7] The occlusive backing film on Androderm® prevents the partner from coming in contact with the active material in the system, and therefore the warning is not included on this product.[1] Currently, only AndroGel® has an A-rated generic formulation.

  Hypogonadism refers to a defect of the reproductive system resulting in a lack of gonad function.[12-16] Hypogonadism is classified based on the level of the defect within the reproductive axis. Primary hypogonadism results from a defect of the gonads and occurs when the serum testosterone concentration and/or sperm counts are below normal, and the serum luteinizing hormone (LH) and/or follicle-stimulating hormone (FSH) concentrations are above normal.[13] Secondary hypogonadism, known as hypogonadotropic hypogonadism, results from defects in the hypothalamus or pituitary. This occurs when the serum testosterone concentration and/or sperm counts are below normal, and the serum LH and/or FSH concentrations are normal or reduced.[13] Combined primary and secondary hypogonadism may occur and results in below-normal testosterone concentrations and variable LH and/or FSH concentrations, depending upon which clinical condition predominates.[15] Male hypogonadism may manifest as testosterone deficiency with or without infertility. Clinical signs and symptoms depend primarily on the age at the onset of the condition. Postpubertal hypogonadism usually results in slowly evolving clinical manifestations that may include a progressive decrease in muscle mass, loss of libido, impotence, oligospermia or azoospermia, poor concentration, and an increase in the risk of osteoporosis and fractures.[12-17]

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

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Testosterone (Androderm®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Androderm®: 2 mg/day patch 4 mg/day patch	-
Testosterone (AndroGel®*)	Hypogonadism in males, primary (congenital or acquired) and	AndroGel® 1%: Metered-dose pump:	a

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	hypogonadotropic hypogonadism in males (congenital or acquired)	12.5 mg testosterone/actuation Unit-dose packet: 50 mg testosterone/packet AndroGel® 1.62%: Metered-dose pump: 20.25 mg/actuation Unit-dose packet: 20.25 mg/packet	
Testosterone (Axiron®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Axiron®: Metered-dose pump: 30 mg/actuation	-
Testosterone (Fortesta®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Fortesta®: Metered-dose pump: 10 mg/actuation	-
Testosterone (Natesto®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Natesto®: Intranasal gel metered-dose pump: 5.5 mg/actuation	-
Testosterone (Striant®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Striant®: Buccal mucoadhesive system: 30 mg	-
Testosterone (Testim®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Testim® 1%: Unit-dose tubes: 50 mg/tube)	-
Testosterone (Testopel®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired); stimulate puberty in carefully selected males with clearly delayed puberty	Testopel®: Implantable pellet: 30 mg	-
Testosterone (Vogelxo®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Vogelxo®: Metered-dose pump: 12.5 mg/actuation Unit-dose packet: 50 mg/packet Unit-dose tube: 50 mg/tube	-

*A-rated generic available in at least one dosage form or strength

Evidence-based Medicine

- Topical and miscellaneous testosterone products have been evaluated in several clinical trials.[19-31]
- The efficacy of testosterone nasal gel was evaluated in an unpublished, 90-day, open-label, multicenter study of 306 hypogonadal men 18 years of age and older. Individuals were instructed to self-administer one spray of testosterone intranasally either two or three times daily. The primary endpoint assessed was the percentage of individuals with an average serum total testosterone concentration within the range of 300 to 1,050 ng/dL on Day 90. Of the 306 men in the study, results were only available for 73 hypogonadal men who had received the nasal gel three times daily. On Day 90, 90% of these individuals had an average concentration within the established normal range, 10% were below normal and no individuals were found to be above the desired range.[8]
- The safety and efficacy of Striant® (testosterone buccal tablet) was evaluated in a 12 week, open-label, multicenter, phase III clinical trial involving 98 hypogonadal men. At the conclusion of the trial, 86.6% of patients with sufficient data for full analysis had mean serum testosterone concentration values within the physiologic range. The mean (± standard deviation) serum testosterone concentration at the end of the study was 520 (±205) ng/dL compared with a mean of 149 (±99) ng/dL at baseline.[9]
- The clinical trials evaluating the safety and effectiveness that were used to obtain FDA approval of testosterone pellets are not available. However, a literature search identified a phase IV clinical trial by Kaminetsky et al. Mean testosterone significantly increased and luteinizing hormone (LH) levels significantly decreased from pre-implantation values at week one, week four and week 12 visits, and had returned to pre-implantation levels by week 24 ($P<0.001$ for mean testosterone and LH levels at week one, week four and week 12 visits; $P=0.58$ and $P=0.87$ for mean testosterone and LH at week 24 respectively). Prostate-specific antigen levels remained unchanged for the duration of the study.[19]
- Several clinical studies have shown that the transdermal patch and gels all restore serum testosterone concentrations to within normal limits and maintain sexual characteristics, sexual behavior, mood, and muscle development, and improve bone mineral density in hypogonadal men. The results of these head-to-head trials favored the use of the gel over the patch.[20-23]
- In an open-label study, Axiron® topical solution applied to the axilla provided a serum testosterone level in the normal range for 84.1% of patients after 120 days of treatment.[17] Results from a second open-label study reported that 76.2% of men achieved a mean serum testosterone level within the normal physiologic range following 35 days of treatment with Fortesta®.[27]
- In an open label extension study Kaufman et al evaluated efficacy of testosterone 1.62% gel up to one year of therapy.[30] Results from the study show that testosterone 1.62% is effective in replacement therapy with 78% (95% CI, 70.0% to 84.6%) and 87.0% (95% CI, 66.4% to 97.2%) of the different dosing regimens reaching therapeutic levels of testosterone.
- Blick et al evaluated the use of testosterone replacement therapy in human immunodeficiency virus infection/acquired immune deficiency syndrome (HIV/AIDS). In this prospective cohort study the effects of replacement therapy with testosterone 1% (Testim®) were evaluated in HIV/AIDS patients. During the twelve month study, but non-HIV/AIDS patients and HIV/AIDS cohorts had significant increases in total testosterone and free testosterone to within normal limits along with increased sexual function and improved and decreased antidepressant use. Body composition profiles improved significantly in men without HIV/AIDS ($P\leq0.05$) and remained stable in men with HIV/AIDS during the twelve months of follow-up.[31]
- A meta-analysis of 16 studies evaluating testosterone supplementation for the diagnosis or erectile dysfunction was conducted by Jain et al. The overall response rate was 57% ± 2.3% (203 of 356 cases). Among the studies with stratified results, 75 of 117 (64% ± 4%) men with a primary etiology responded and 53 of 120 (44% ± 2.9%) men with a secondary etiology responded, which was determined to be statistically significant ($P<0.001$).[32]

Key Points within the Medication Class

- According to Current Clinical Guidelines[13-16]:
  - Intramuscular and topical testosterone preparations are generally recommended for the management of hypogonadism in adult male patients.
  - The oral alkylated androgens are not recommended due to poor androgen effects, adverse lipid changes, and hepatic side effects, but may be considered when other agents are not suitable.
  - The selection of testosterone replacement therapy should be a joint decision between the patient and physician and should be made after consideration of patient preferences, the pharmacokinetic profiles of the respective agents, treatment burden and cost.
  - The short-acting preparations may be preferred over long-acting depot preparations when initiating treatment in patients with late-onset hypogonadism due to the potential development of an adverse event that may require rapid discontinuation of testosterone replacement therapy. Treatment guidelines do not recommend one topical preparation over another.

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Therapeutic Class Overview
Immunomodulators

Therapeutic Class

- **Overview/Summary:** This review will focus on oral and injectable immunomodulators. These agents are used for a variety of inflammatory and immunologic conditions which include: rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, juvenile/systemic idiopathic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis and several cryopyrin-associated periodic syndromes. Specific Food and Drug Administration (FDA)-approved indications for each agent are summarized in Table 1. These agents achieve their therapeutic effect via several different mechanisms of action. The majority of oral and injectable immunomodulators inhibit the effect of proinflammatory cytokines, specifically interleukins or tumor necrosis factor (TNF)-α. Interleukin (IL) inhibitors include anakinra (Kineret®), canakinumab (Ilaris®), rilonacept (Arcalyst®), secukinumab (Cosentyx®), tocilizumab (Actemra®), and ustekinumab (Stelara®) while the TNF-α inhibitors are adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®), golimumab (Simponi®, Simponi ARIA®), and infliximab (Remicade®). Abatacept (Orencia®) is a T-cell activation inhibitor, tofacitinib (Xeljanz®) is a Janus kinase inhibitor, and vedolizumab (Entyvio®) is an α4-β7 integrin receptor antagonist.[1-17]

  Generally, current consensus guidelines support the use of the TNF-blockers with respect to their FDA-approved indications and no one agent is preferred over another.[18-35] As more recent guidelines are published, the recommendations for use TNF-blockers earlier in therapy is becoming a more common occurance.[26,27,30] Given the paucity of clinical experience and long-term safety data, the 2013 European League against Rheumatism guidelines recommend that tofacitinib should primarily be used when biological treatment has failed.[18] Because the immunomodulators are biologic agents made from living organisms and are extremely difficult to duplicate, congress has struggled to create regulations to approve generic versions of these agents. Currently, none of the agents in this class are available generically; however, the recently upheld Patient Protection and Affordable Care provides a legal framework for regulatory approval of biosimilar drugs.[36]

Table 1. Current Medications Available in the Therapeutic Class[1-17]

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

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	syndrome; juvenile idiopathic arthritis	mg/mL)	
Certolizumab (Cimzia®)	Crohn's disease (adults only); rheumatoid arthritis (adults only); psoriatic arthritis (adults only); ankylosing spondylitis (adults only)	Prefilled syringe: 200 mg/mL Vial (powder for injection): 200 mg	-
Etanercept (Enbrel®)	rheumatoid arthritis (adults only); polyarticular juvenile idiopathic arthritis (age ≥2 years); psoriatic arthritis (adults only); ankylosing spondylitis (adults only); severe plaque psoriasis (adults only)	Prefilled "SureClick" autoinjector: 50 mg/mL Prefilled syringes: 25 mg/0.5 mL 50 mg/mL Vial (powder for injection): 25 mg	-
Golimumab (Simponi®, Simponi Aria®)	rheumatoid arthritis (Simponi® and Simponi Aria® [adults only]); psoriatic arthritis (Simponi® [adults only]); ankylosing spondylitis (Simponi® [adults only]); ulcerative colitis (Simponi® [adults only])	Prefilled "SmartJect" autoinjector: 50 mg/0.5 mL, 100 mg/mL Prefilled syringe: 50 mg/0.5 mL 100 mg/mL Single use vial*: 50 mg/4 mL	-
Infliximab (Remicade®)	Crohn's disease (age ≥6 years); ulcerative colitis (age ≥6 years); rheumatoid arthritis (adults only); ankylosing spondylitis (adults only); psoriatic arthritis (adults only), plaque psoriasis (adults only)	Single use vial: 100 mg	-
Rilonacept (Arcalyst®)	Cryopyrin-associated periodic syndromes – familial cold autoinflammatory syndrome or Muckle-Wells syndrome (age ≥12 years); juvenile idiopathic arthritis (age ≥12 years)	Vial: 220 mg (80 mg/mL)	-
Secukinumab (Cosentyx®)	Plaque Psoriasis (adults only)	Prefilled pen, syringe: 150 mg/mL Vial: 150 mg/mL	-
Tocilizumab (Actemra®)	Polyarticular juvenile idiopathic arthritis (age ≥ 2 years) ; systemic juvenile idiopathic arthritis (age ≥ 2 years); rheumatoid arthritis (adults only);	Prefilled syringe*: 162 mg/0.9 mL	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		Single use vial: 80 mg/4 mL 200 mg/10 mL 400 mg/20 mL	
Tofacitinib (Xeljanz®)	Rheumatoid arthritis (adults only)	Tablet: 5 mg	-
Ustekinumab (Stelara®)	Plaque psoriasis (adults only); psoriatic arthritis (adults only)	Prefilled syringe: 45 mg/0.5 mL 90 mg/mL Single use vial: 45 mg/0.5 mL 90 mg/mL	-
Vedolizumab (Entyvio®)	Crohn's disease (adults only); ulcerative colitis (adults only)	Single use vial: 300 mg/20 mL	-

*Only indicated for use in patients with rheumatoid arthritis.

Evidence-based Medicine

- The immunomodulators have been shown to be effective for their respective Food and Drug Administration (FDA)-approved indications, particularly in conditions where patients were unresponsive or refractory to traditional disease modifying antirheumatic drugs (DMARDs). Most research with these agents and FDA-approved indications (with the exception of ustekinumab) are for rheumatoid arthritis. In these trials, the immunomodulator were compared directly to placebo or traditional DMARD medications, either as monotherapy or in combination with a traditional DMARD. Consistently, immunomodulators have shown greater improvement in symptoms over the comparator.[41-137]
- The safety and efficacy of canakinumab in the treatment of systemic juvenile idiopathic arthritis was confirmed in two parallel clinical trials. At day 15 of the first trial, a total of 36 patients in the canakinumab group (84%), as compared with four in the placebo group (10%), had an adapted ACR30 response, which was sustained at day 29 (P<0.001). The second study concluded that There was a 64% relative reduction in the risk of flare for patients in the canakinumab group as compared to those in the placebo group (hazard ratio of 0.36; 95% CI: 0.17 to 0.75).[69]
- The safety and efficacy of secukinumab was evaluated in four multicenter, randomized, double-blind, placebo-controlled trials. The proportion of patients who achieved PASI 75 was statistically significantly greater in the secukinumab 300 mg group (81.6%, 77.1%, 75.9% and 86.7%) and secukinumab 150 mg group (71.6%, 67.0%, 69.5%, and 71.7%) compared with placebo (4.5%, 4.9%, 0%, 3.3%; P<0.001 for all secukinumab comparisons compared to placebo). In one of the trials, secukinumab 300 mg and 150 mg groups were compared to etanercept. Both secukinumab groups (77.1% and 67.0%) had a higher proportion of patients that achieved PASI 75 compared with etanercept (44%; P<0.001 for both secukinumab comparisons). Results were similar when IGA mod 2011 scores were compared.[5,76-78]
- To date, the majority of trials conducted have been placebo-controlled, with very few trials directly comparing two immunomodulators head-to-head for any of the FDA-approved indications. Those that have been conducted, most have shown comparable results. In one trial in rheumatoid arthritis patients who were either intolerant or were not candidates for methotrexate treatment, significantly greater improvements were observed in patients treated with tocilizumab compared to adalimumab.[118] In another trial in rheumatoid arthritis patients with inadequate response to methotrexate, similar responses were observed in patients treated with abatacept and adalimumab.[119,120] The inclusion of adalimumab arm in one phase 3 trial of tofacitinib allowed establishing relative safety and efficacy of tofacitinib; however, formal noninferiority comparison was not performed.[121] The few direct head-to-head trials available prevent clearly determining superiority of one agent over another.

- Recently anakinra was FDA-approved for neonatal-onset multisystem inflammatory disease, the only agent FDA-approved for this indication. The approval was based on the results of a single trial demonstrating sustained improvements in affected patients over 60 months.[135]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[18-35]
  - Support the use of the immunomodulators with respect to their Food and Drug Administration (FDA)-approved indications.
  - As more recent guidelines are published, the recommendations for use tumor necrosis factor-blockers earlier in therapy is becoming a more common occurance.[26,27,30] The adverse event profiles are similar across the class; however, routes of administration and dosing frequency may vary. In general, no one agent is preferred over another; however, given the paucity of clinical experience and long-term safety data, the use of tofacitinib for rheumatoid arthritis is recommended primarily after biological treatment has failed.[18]

- Other Key Facts:
  - None of the immunomodulators included in this review are available generically.
  - Dosing frequency and route of administration vary between products.
    - Tofacitinib is formulated as an oral tablet dosed twice daily.
    - Abatacept, golimumab (Simponi ARIA®), infliximab, tocilizumab (vial), and vedolizumab
      - Each is infused over 30 minutes, with the exception of infliximab which is infused over two hours.
    - Anakinra is administered subcutaneously, but requires more frequent (daily) administration.
  - Intravenous formulation of golimumab and subcutaneous formulation of tocilizumab are only indicated in the treatment of rheumatoid arthritis.
  - Anakinra is the only FDA-approved agent for neonatal-onset multisystem inflammatory disease. Canakinumab and rilonacept are the only FDA-approved agents for the treatment of familial cold autoinflammatory syndrome and Muckle-Wells syndrome.

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Tab: RxOutlook

Volume 2
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RxOutlook®

Recap: a monthly summary of pharmaceutical pipeline news, events, and trends

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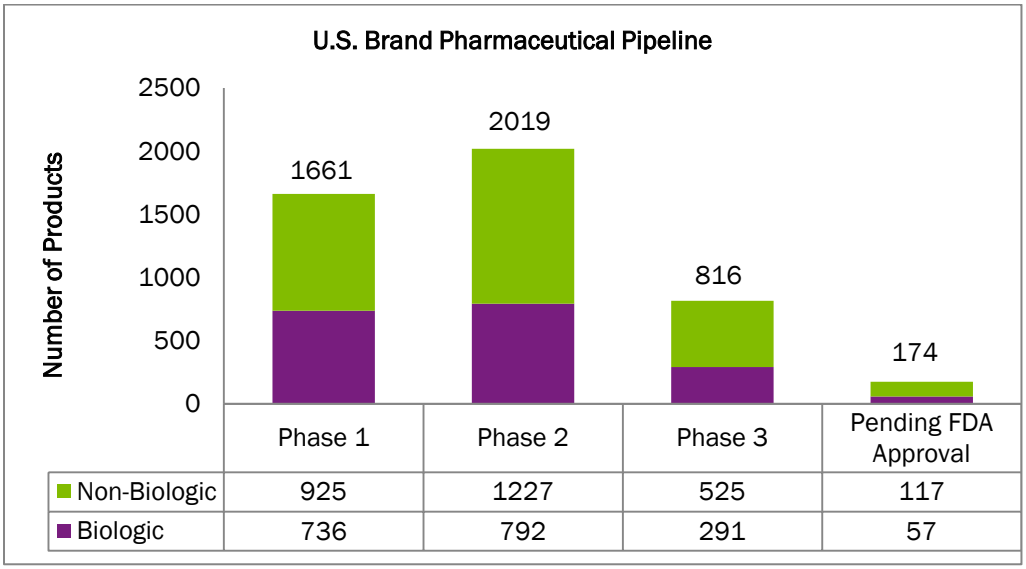
brand pipeline snapshot

- As of August 31, 2015, there are approximately 4,670 products either pending FDA approval or in phase 1, 2, or 3 of clinical development within the United States.



	Phase 1	Phase 2	Phase 3	Pending FDA Approval
Non-Biologic	925	1227	525	117
Biologic	736	792	291	57

Biologic = blood products, allergenics, recombinant peptides or proteins, monoclonal antibodies, vaccines, and cell or gene therapies (includes both specialty and non-specialty potentially designated products)

select pipeline & trend headlines

Pipeline-Related

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- Shionogi's Naldemedine Meets Primary Endpoint In Phase 3 Study For The Treatment Of Opioid-Induced Constipation
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- Allergan Confirms Generic NOXAFIL® Patent Challenge
- Phase 2 Study of Venetoclax in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia with 17p Deletion Meets Primary Endpoint
- ImmunoCellular Therapeutics Reaches Agreement with FDA on Special Protocol Assessment (SPA) for ICT-107 Phase 3 Registrational Trial in Glioblastoma
- Mylan Confirms First-to-File Patent Challenge Relating to ZYTIGA®
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- Novo Nordisk Completes Second and Final Phase 3a Trial with VICTOZA® (Liraglutide) as Adjunct Therapy to Insulin for People with Type 1 Diabetes (NN9211)
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- Novo Nordisk to Initiate Phase 3a Development of Oral Semaglutide, a Once-Daily Oral GLP-1 Analogue
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- CDC Releases Death Rate Estimates for Seven Conditions
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- Milliman Report: Understanding Biosimilars and Projecting the Cost Savings to Employers -- Update
- Washington Post: Alzheimer's grows on global scale as world societies age; The World Alzheimer Report 2015
- Aon: U.S. Specialty Pharmacy Cost Increases Expected to Jump to 23%
- Health Affairs Blog: Rising Cost Of Drugs: Where Do We Go From Here?

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- Medical Marketing & Media (MM&M): Drugs that Turn Cancer into a Chronic Disease Need New Marketing Strategies -- Report (may require free registration to access)
- Medical Marketing & Media (MM&M): Most Docs are in the Dark about Biosimilars -- Survey (may require free registration to access)
- Pfizer and Synthon Enter Into U.S. Commercialization Agreement for Potential Generic Treatment, Glatiramer Acetate, of Multiple Sclerosis
- AbbVie buys special review voucher for $350 million
- Fierce Pharma: The FDA has spoken on biosimilar names. But will its hybrid proposal work?; The FDA's Proposed Rule; The FDA's Draft Guidance

upcoming FDA approvals

Product Name (generic name) Company(ies)	Therapeutic Class	Route of Administration	Product Type	Potential Uses(s)	Anticipated FDA Approval Date (PDUFA)
TARCEVA (erlotinib) Astellas	Antineoplastics & Adjunctive Therapies	Oral	New Indication	Pediatric Ependymoma	2015-Aug 1 to 2015-Oct 31
(pegfilgrastim biosimilar) ApoBiologix / Apotex; Intas	Hematological Agents	Subcutaneous	Biosimilar	Neutropenia	2015-Aug 17 to 2015-Oct 16
(necitumumab) Eli Lilly	Antineoplastics & Adjunctive Therapies	Intravenous	New Molecular Entity	In Combintion with Gemcitabine and Cisplatin for the First-Line Treatment of Locally-Advanced or Metastatic Squamous Non-Small Cell Lung Cancer (NSCLC)[FT]	2015-Aug to 2015-Dec
SPIRIVA RESPIMAT (tiotropium bromide) Boehringer Ingelheim	Respiratory Agents	Inhalation	New Indication	Long-Term, Once-Daily, Add-On Maintenance Treatment of Asthma in Patients 12 Years of Age and Older Who Remain Symptomatic on at Least Inhaled Corticosteroids	2015-Aug 27 to 2015-Sep 3
(cariprazine) Allergan; Gedeon Richter	CNS Drugs	Oral	New Molecular Entity	Schizophrenia; Acute Treatment of Manic or Mixed Episodes Associated with Bipolar I Disorder	2015-Sep
FLUCELVAX (influenza virus vaccine) Novartis	Vaccines	Intramuscular	New Indication	Influenza Virus Infection Prevention in Patients >/= 4 Years of Age	2015-Sep to 2015-Oct
(rolapitant) OPKO; Tesaro	Gastrointestinal Agents	Oral	New Molecular Entity	Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV)	2015-Sep 5

Product Name (generic name) Company(ies)	Therapeutic Class	Route of Administration	Product Type	Potential Uses(s)	Anticipated FDA Approval Date (PDUFA)
DULAZA (acetylsalicylic acid) Flamel; NewHaven	Cardiovascular Agents	Oral	New Formulation	Secondary Prevention of Cardiovascular Disease	2015-Sep 5
KANUMA (sebelipase alfa) Synageva BioPharma	Endocrine & Metabolic Drugs	Intravenous	New Molecular Entity	Lysosomal Acid Lipase (LAL) Deficiency (Wolman Disease)[BT, FT, OD, PR]	2015-Sep 8
ARISTADA (aripiprazole lauroxil) Alkermes	CNS Drugs	Intramuscular	New Formulation	An Extended-Release Monthly Formulation for Schizophrenia	2015-Sep 11
MORPHABOND (morphine sulfate extended-release, abuse-deterrant) Inspirion Delivery Technologies; Trygg Pharma	Analgesics & Anesthetics	Oral	New Formulation	Extended-Release, Abuse-Deterrent Formulation for the Management of Pain Severe Enough to Require Daily, Around-the-Clock, Long-Term Opioid Treatment and for Which Alternative Treatment Options are Inadequate	2015-Sep 21
TEFLARO (ceftaroline fosamil) Allergan	Antiinfective Agents	Intravenous	New Indication	Concurrent Bacteremia in Patients with Acute Bacterial Skin and Skin Structure Infections (ABSSSIs) Caused by Susceptible Isolates of Staphylococcus aureus (including Methicillin-Susceptible and Resistant Isolates)	2015-Sep 21 to 2015-Sep 30
OPDIVO (nivolumab) Bristol Myers Squibb	Antineoplastics & Adjunctive Therapies	Intravenous	New Indication	In Combination with YERVOY (Ipilimumab) for the Treatment of Previously Untreated Advanced Melanoma[OD, PR]	2015-Sep 30
GRASTOFIL (filgrastim biosimilar) ApoBiologix / Apotex; Intas	Hematological Agents	Intravenous; Subcutaneous	Biosimilar	Neutropenia	2015-Sep 30 to 2015-Oct 30
STRENSIQ (asfotase alfa) Alexion	Endocrine & Metabolic Drugs	Subcutaneous	New Molecular Entity	Infantile- and Juvenile-Onset Hypophosphatasia (HPP)[BT, FT, OD]	2015-H2
(simoctocog alfa) Octapharma	Hematological Agents	Intravenous	New Formulation	Hemophilia A	2015-H2
REMSIMA; INFLECTRA (infliximab biosimilar) Celltrion; Hospira	Analgesics & Anesthetics	Intravenous	Biosimilar	Rheumatoid Arthritis (RA); Crohn's Disease (CD); Ulcerative Colitis (UC); Ankylosing Spondylitis (AS); Psoriasis; Psoriatic Arthritis (PsA) (seeking all REMICADE indications)	2015-H2
RIZAPORT (rizatriptan) RedHill; IntelGenx	Analgesics & Anesthetics	Sublingual	New Formulation	Oral Thin-Film Formulation for Treatment of Acute Migraines	2015-H2
NOCDURNA (desmopressin acetate) Ferring	Genitourinary Products	Sublingual	New Formulation; New Indication	Treatment of Nocturia Due to Nocturnal Polyuria in Adults Who Awaken Two or More Times Each Night to Void	2015-H2
BIOTHRAX (anthrax vaccine adsorbed) Emergent BioSolutions	Vaccines	Intramuscular	New Indication	To be Used in Combination with Antibiotics for Post-Exposure Prophylaxis (PEP) of Anthrax Disease in People with Suspected or Confirmed Exposure to Anthrax Spores[OD]	2015-H2
(oxycodone HCl IR) Purdue	Analgesics & Anesthetics	Oral	New Formulation	Immediate-Release, Abuse-Deterrent Formulation for the Management of Acute and Chronic Moderate to Severe Pain where the Use of an Opioid Analgesic is Appropriate	2015-H2
REXTORO (testosterone undecanoate) Clarus Therapeutics	Endocrine & Metabolic Drugs	Oral	New Formulation	Testosterone Replacement Therapy in Males for Conditions Associated with a Deficiency or Absence of Endogenous Testosterone: Primary Hypogonadism (Congenital or Acquired) and Hypogonadotropic Hypogonadism (Congenital or Acquired)	2015-H2

Product Name (generic name) Company(ies)	Therapeutic Class	Route of Administration	Product Type	Potential Uses(s)	Anticipated FDA Approval Date (PDUFA)
YONDELIS (trabectedin) Janssen	Antineoplastics & Adjunctive Therapies	Intravenous	New Molecular Entity	Treatment of Patients with Advanced Soft Tissue Sarcoma (STS), including Liposarcoma and Leiomyosarcoma Subtypes, who have Received Prior Chemotherapy Including an Anthracycline[OD, PR]	2015-H2
FERAHEME (ferumoxytol) AMAG	Hematological Agents	Intravenous	New Indication	Treatment of Iron Deficiency Anemia (IDA) in Adult Patients who have Failed or Could not Tolerate Oral Iron Treatment	2015-H2
HUMIRA (adalimumab) AbbVie	Analgesics & Anesthetics	Subcutaneous	New Indication	Moderate to Severe Hidradenitis Suppurativa[OD]	2015-H2
ONGLYZA (saxagliptin) AstraZeneca; Bristol Myers Squibb	Endocrine & Metabolic Drugs	Oral	Label Expansion	Label Expansion (Cardiovascular Outcomes) Based on SAVOR-TIMI 53 Study	2015-H2
BRILINTA (ticagrelor) AstraZeneca	Hematological Agents	Oral	Label Expansion	Cardiovascular Outcomes Data Based on PEGASUS-TIMI 54 Study (e.g., Reduced Risk of Cardiovascular Events with Dual Antiplatelet Therapy in Patients with Prior MI)	2015-Q3
PREVNAR 13 (pneumococcal polysaccharide conjugate vaccine [13-valent, adsorbed]) Pfizer	Vaccines	Intramuscular	New Indication	Use of PREVNAR 13 to include Adults 18 to 49 Years of Age for the Prevention of Invasive Disease Caused by 13 S. *pneumoniae* Strains	2015-Q3
ANTHIM (obiltoxaximab) Elusys Therapeutics	Antiinfective Agents	Intravenous; Intramuscular	New Molecular Entity	Prophylaxis and Treatment of Inhalational Anthrax[FT, OD]	2015-Q3 to 2016-Mar 20

BT=Breakthrough Therapy; FT=Fast-Track; PR=Priority Review; QIDP=Qualified Infectious Disease Product; OD=Orphan Drug

upcoming patent expirations/generic and biosimilar launches

Trade Name (generic name) Company(ies)	Therapeutic Use(s)	Estimated U.S. Sales	Anticipated Availability	Anticipated Launch Type	Comments
ADVICOR (niacin/lovastatin) AbbVie	Hyperlipidemia	$42 million	H2 2015	Exclusive	Per a settlement agreement, Teva may launch generic ADVICOR any time after September 20, 2013. It is unknown when or if Teva will launch its generic. Other generics are not expected to launch until March 2018.
ASACOL (mesalamine) Allergan	Ulcerative Colitis	$577 million	H2 2015	Exclusive with Authorized Generic	Generic availability applies to ASACOL 400 mg tablets. Brand name ASACOL 400 mg tablet has been discontinued; Allergan has released DELZICOL 400 mg that contains the same amount of mesalamine in a delayed-release capsule. Zydus will have an opportunity to launch generic ASACOL HD 800 mg in November 2015.
VIRACEPT (nelfinavir mesylate) ViiV Healthcare	Human Immunodeficiency Virus Infection	$51 million	H2 2015	Unknown	None
INVEGA (paliperidone extended-release) Janssen	Schizophrenia; Schizoaffective Disorder	$537 million	H2 2015	Competitive	Actavis received FDA approval of its generic INVEGA on August 3, 2015.
TRAVATAN Z (travoprost) Alcon	Glaucoma; Ocular Hypertension	$447 million	H2 2015	Exclusive	Alcon reached settlement agreements with Par, Actavis, and Wockhardt; terms have not been disclosed.

Trade Name (generic name) Company(ies)	Therapeutic Use(s)	Estimated U.S. Sales	Anticipated Availability	Anticipated Launch Type	Comments
NASONEX (mometasone furoate) Schering/Merck	Seasonal & Perennial Allergic Rhinitis; Nasal Polyps	$1.2 billion	H2 2015	Exclusive	An "at risk" launch is possible at any time if the FDA grants effective approval to Apotex's generic NASONEX product.
RENAGEL (sevelamer hydrochloride) Genzyme/Sanofi	Hyperphosphatemia Associated with Chronic Kidney Disease	$199 million	H2 2015	Unknown	Under a settlement agreement, Endo has permission to launch its generic RENAGEL as of March 16, 2014. Impax, Lupin, Sandoz, and InvaGen have permission to launch their generic RENAGEL on September 16, 2014.
ANDRODERM (testosterone) Allergan	Replacement Therapy in Males with Deficiency of Endogenous Testosterone	$84 million	H2 2015	Unknown	None
PREMPRO (conjugated estrogens / medroxyprogesterone acetate) Pfizer	Hormone Replacement Therapy	$221 million	H2 2015	Unknown	None
PREMPHASE (conjugated estrogens / medroxyprogesterone acetate) Pfizer	Hormone Replacement Therapy	$6 million	H2 2015	Unknown	None
WELCHOL (colesevelam hydrochloride) Daiichi Sankyo	Primary Hyperlipidemia; Type 2 Diabetes Mellitus	$574 million	H2 2015	Exclusive	Generic availability applies to oral tablets and granules for suspension. Oral tablets may launch as exclusive. Settlement agreement allows launch of generic WELCHOL beginning on March 2, 2015.
EMEND (aprepitant) Merck	Chemo-Associated Nausea & Vomiting; Prevention of Post-Op Nausea & Vomiting	$280 million	H2 2015	Exclusive	Generic availability applies to the oral formulation only. Sandoz received FDA approval for generic EMEND capsules on September 24, 2012. Patents will likely protect EMEND injection from generic competition until March 4, 2019 pending patent litigation.
OXYTROL (oxybutynin transdermal patch) Allergan	Overactive Bladder	$15 million	H2 2015	Exclusive	Teva received FDA approval of generic OXYTROL on March 4, 2014. Allergan reached a settlement agreement with Teva permitting launch of generic OXYTROL on April 26, 2015. An OTC product, OXYTROL for WOMEN, became available in September 2013 for the treatment of overactive bladder in women.
EPOGEN (epoetin alfa) Amgen	Anemia Associated with Cancer, Kidney Disease, and Zidovudine Treatment in Patients with Human Immunodeficiency Virus; Decrease Allogeneic Transfusions in Certain Surgeries	$2.4 billion	H2 2015	Biosimilar	In December 2014, Hospira announced its biosimilar submission for RETACRIT; reference products are EPOGEN and PROCRIT.
PROCRIT (epoetin alfa) Janssen	Anemia Associated with Cancer, Kidney Disease, and Zidovudine Treatment in Patients with Human Immunodeficiency Virus; Decrease Allogeneic Transfusions in Certain Surgeries	$1 billion	H2 2015	Biosimilar	In December 2014, Hospira announced its biosimilar submission for RETACRIT; reference products are EPOGEN and PROCRIT.
DAYTRANA (methylphenidate HCl transdermal system) Noven Therapeutics	Attention Deficit Hyperactivity Disorder	$103 million	September 2015	Exclusive	Per a settlement agreement, Actavis may market its generic DAYTRANA beginning on September 1, 2015, or earlier under certain circumstances.

Trade Name (generic name) Company(ies)	Therapeutic Use(s)	Estimated U.S. Sales	Anticipated Availability	Anticipated Launch Type	Comments
RITUXAN (rituximab) Genentech/Roche; Biogen Idec	Rheumatoid Arthritis; Non-Hodgkin's Lymphoma; Chronic Lymphocytic Leukemia; Granulomatosis with Polyangiitis (Wegener's Granulomatosis); Microscopic Polyangiitis	$3.4 billion	September 2015	Biosimilar	A pharmaceutical manufacturer planning to develop a biosimilar for RITUXAN will need to submit an abbreviated biologics license application (aBLA) through the biosimilar pathway.
NEUPOGEN (filgrastim) Amgen	Neutropenia; Peripheral Blood Stem Cell (PBSC) Mobilization	$1 billion	September 2015	Biosimilar	Sandoz's biosimilar, ZARXIO, received FDA approval on March 6, 2015. Due to ongoing litigation, the earliest launch may occur is September 2015. Apotex's biosimilar BLA for GRASTOFIL (reference product, NEUPOGEN) was accepted by the FDA on February 13, 2015.

recent FDA product filings/acceptances

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Route of Administration	Potential Use(s)	Anticipated FDA Approval Date (PDUFA)
(rociletinib) Clovis	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Oral	Treatment of Patients with Mutant Epidermal Growth Factor Receptor (EGFR) Non-Small Cell Lung Cancer (NSCLC) who have been Previously Treated with an EGFR-Targeted Therapy and have the EGFR T790M Mutation as Detected by an FDA Approved Test[BT, OD]	2016-Mar 30 (priority review)
KEYTRUDA (pembrolizumab) Merck	New Indication	Antineoplastics & Adjunctive Therapies	Intravenous	First-Line Treatment of Advanced Melanoma[BT, OD]	2015-Dec 18 (priority review)
HARVONI (sofosbuvir/ledipasvir) Gilead Sciences	New Indicaiton	Antiinfective Agents	Oral	Treatment of Genotypes 1 or 4 Chronic Hepatitis C Virus (HCV) Infection Among Patients Co-Infected with HIV (Based on the ION-4 Trial)	2015-Nov 15 (priority review)
HARVONI (sofosbuvir/ledipasvir) Gilead Sciences	New Indication	Antiinfective Agents	Oral	Treatment of Genotypes 4, 5, or 6 Chronic Hepatitis C Virus (HCV) Infection	2015-Nov 15 (priority review)
HARVONI (sofosbuvir/ledipasvir) Gilead Sciences	New Indication	Antiinfective Agents	Oral	Treatment of Chronic Hepatitis C Virus (HCV) Infection in Treatment-Experienced and Cirrhotic Patients	2015-Nov 15 (priority review)
BRINTELLIX (vortioxetine HCl) Lundbeck; Takeda	Label Expansion	CNS Drugs	Oral	Addition of Clinical Data Regarding the Effect of BRINTELLIX on Certain Aspects of Cognitive Dysfunction in Adults with Major Depressive Disorder (MDD)	2016-Mar 28 (standard review)
DEFITELIO (defibrotide) Jazz	New Molecular Entity	Hematological Agents	Intravenous	Severe Hepatic Veno-Occlusive Disease (VOD) Treatment in Patients Undergoing Hematopoietic Stem Cell Transplantation[OD]	2016-Jul 29 (standard review)
AUSTEDO (deutetrabenazine) Teva	New Formulation	Neuromuscular Drugs	Oral	Treatment of Chorea Associated with Huntington's Disease (HD)[OD]	2016-May 27 to 2016-Jun 28 (standard review)
DALVANCE (dalbavancin) Allergan	New Formulation	Antiinfective Agents	Intravenous	Single-Dose Regimen for Acute Bacterial Skin and Skin Structure Infections (ABSSSI)	2016-Jun 3 (standard review)
STIOLTO RESPIMAT (olodaterol / tiotropium bromide) Boehringer Ingelheim	Label Expansion	Respiratory Agents	Inhalation	Add Clinical Data Regarding the Effect of STIOLTO RESPIMAT on Quality of Life in Patients with Chronic Obstructive Pulmonary Disease (COPD) (based on OTEMTO study)	2016-Apr 1 to 2016-May 3 (standard review)

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Route of Administration	Potential Use(s)	Anticipated FDA Approval Date (PDUFA)
KEYTRUDA (pembrolizumab) Merck	New Indication	Antineoplastics & Adjunctive Therapies	Intravenous	First-Line Treatment of Unresectable or Metastatic Melanoma Patients	2015-Dec 19 (priority review)
BOTOX (onabotulinumtoxin A) Allergan	New Indication	Neuromuscular Drugs	Intramuscular	Lower Limb (involving Ankle and Toe Muscles) Spasticity in Adults	2016-Q1 (class 2 resubmission)
GILOTRIF (afatinib) Boehringer Ingelheim	New Indication	Antineoplastics & Adjunctive Therapies	Oral	Treatment of Advanced Squamous Cell Carcinoma of the Lung After First-Line Platinum-Based Chemotherapy[OD]	2016-Feb 11 to 2016-Mar 11 (standard review)
(etelcalcetide) Amgen	New Molecular Entity	Endocrine & Metabolic Drugs	Intravenous	Secondary Hyperparathyroidism in Patients with Chronic Kidney Disease (CKD) Receiving Dialysis	2016-Aug 25 (standard review)
PROBUPHINE (buprenorphine HCl sustained-release) Titan; Braeburn	New Formulation	Misc. Psychotherapeutic & Neurological Agents	Subcutaneous Implant	Subdermal Implant that Delivers Buprenorphine for 6 Months for the Maintenance Treatment of Opioid Dependence in Adults	2016-Mar 2 (if class 2 resubmission)
(testosterone undecanoate); LPCN-1021 Lipocine	New Formulation	Endocrine & Metabolic Drugs	Oral	Male Hypogonadism	2016-Jul 1 (standard review)
BROMSITE (bromfenanc) InSite Vision/QLT	New Formulation	Ophthalmic Agents	Intraocular	A Once Daily, Low Concentration (0.075%) Formulation for the Treatment of Inflammation and Prevention of Pain in Cataract Surgery	2016-Apr 10 (standard review)
(dronabinol) Insys Therapeutics	New Formulation	Gastrointestinal Agents	Oral	Orally Administered Liquid Formulation for the Treatment of Chemotherapy Induced Nausea and Vomiting (CINV) in Patients who have Failed to Respond Adequately to Conventional Antiemetic Treatments; and Anorexia Associated with Weight Loss in Patients with AIDS	2016-Apr 1 (standard review)
(mycobacterial cell wall-DNA complex); MCNA Bioniche Therapeutics; Telesta Therapeutics	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Intravesical	Treatment of Bladder Cancer After Failure of First-Line Bacillus Calmette-Guerin Live (BCG) Therapy[FT]	2016-Feb 27 (priority review)

BT=Breakthrough Therapy; FT=Fast-Track; QIDP=Qualified Infectious Disease Product; OD=Orphan Drug

products receiving FDA complete response letters (CRL) or refuse-to-file (RTF) letters

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Route of Administration	Potential Use(s)	Comments
XELPROS (latanoprost, BAK-free) Sun Pharma Advanced Research Co (SPARC)	New Formulation	Ophthalmic Agents	Intraocular	A Benzalkonium Chloride (BAC)-Free Formulation for Open-Angle Glaucoma and Ocular Hypertension	The FDA issued a CRL to SPARC's New Drug Application (NDA) for XELPROS. The FDA is seeking minor changes to the proposed labeling. SPARC hopes to address these requirements soon.

FDA/CDC advisory committee (AdCom) meeting announcements / outcomes

Trade Name (generic name) Company(ies)	Therapeutic Class	Route of Administration	Potential Use(s)	FDA Advisory Committee Meeting Date	Comments
(oxycodone HCl IR) Purdue	Analgesics & Anesthetics	Oral	Immediate-Release, Abuse-Deterrent Formulation for the Management of Acute and	09/10/2015	The FDA's Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory

Trade Name (generic name) Company(ies)	Therapeutic Class	Route of Administration	Potential Use(s)	FDA Advisory Committee Meeting Date	Comments
			Chronic Moderate to Severe Pain where the Use of an Opioid Analgesic is Appropriate		Committees will meet to discuss NDA 206830, oxycodone immediate-release tablets, submitted by Purdue, with the proposed indication of the management of moderate to severe pain where the use of an opioid analgesic is appropriate. It has been formulated with the intent to provide abuse-deterrent properties. The committees will be asked to discuss the potential safety risks and the potential effects on efficacy associated with the delayed peak concentration when taken with food, and the feasibility of labeling to be taken an empty stomach as a means to mitigate the potential risks. The committees will also be asked to consider whether the potential public health benefit of the product's abuse-deterrent properties are sufficient to outweigh the risk to patients who are prescribed the product for the management of pain.
XTAMPZA ER (oxycodone ER) Collegium	Analgesics & Anesthetics	Oral	Extended-Release, Abuse-Deterrent Formulation for Treatment of Moderate to Severe Chronic Pain	09/11/2015	The FDA's Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committees will meet to discuss the NDA 208090, oxycodone extended-release capsules for oral use, submitted by Collegium Pharmaceuticals, proposed for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative options are inadequate. The committees will be asked to discuss the potential safety risks and the potential effects on efficacy associated with the extent of the food effect, and potential fluctuations in oxycodone levels that may occur if the product is not taken consistently with the same amount of food. In addition, the committees will be asked to review and discuss whether the data characterizing the abuse-deterrent properties support the likelihood that this drug product will have a meaningful effect on abuse and whether potential benefits to the public from abuse-deterrent properties outweigh potential risks to patients from the effect of food.
Various	Various	Various	Various	09/16/2015	The FDA's Pediatric Advisory Committee (PAC) will meet to discuss pediatric-focused safety reviews for the following products: DUREZOL (difluprednate ophthalmic emulsion); phenylephrine hydrochloride ophthalmic solution; ZYLET (loteprednol etabonate and tobramycin ophthalmic suspension); BETHKIS (tobramycin inhalation solution); INTELENCE (etravirine); PREZISTA (darunavir); VIRAMUNE XR (nevirapine); EPIDUO (adapalene and benzoyl peroxide); EXJADE (deferasirox); DOTAREM (gadoterate meglumine);

Trade Name (generic name) Company(ies)	Therapeutic Class	Route of Administration	Potential Use(s)	FDA Advisory Committee Meeting Date	Comments
					FYCOMPA (perampanel); RECOTHROM (thrombin, topical [recombinant]); PREVNAR 13 (pneumococcal 13-valent conjugate vaccine [diphtheria CRM 197 protein]); PLEXIMMUNE; ELANA SURGICAL KIT (HUD); BERLIN HEART EXCOR PEDIATRIC VENTRICULAR ASSIST DEVICE (VAD); ENTERRA THERAPY SYSTEM; and CONTEGRA Pulmonary Valved Conduit.
(lesinurad) Ardea Biosciences; AstraZeneca	Analgesics & Anesthetics	Oral	Chronic Treatment of Patients with Gout	10/23/2015	The FDA's Arthritis Advisory Committee will meet to discuss NDA 207988, lesinurad oral tablets, submitted by Ardea Biosciences, Inc., for the treatment of hyperuricemia associated with gout, in combination with a xanthine oxidase inhibitor.
(enclomiphene citrate) Repros Therapeutics	Endocrine & Metabolic Drugs	Oral	Secondary Hypogonadism in Overweight Men	11/03/2015	The FDA's Bone, Reproductive, and Urologic Drugs Advisory Committee will discuss new drug application (NDA) 207959, enclomiphene citrate 12.5 mg and 25 mg capsules, submitted by Repros Therapeutics, Inc., for the proposed treatment of secondary hypogonadism in fertile men (men with more than 15 million sperm/mL, younger than 60 years of age with a Body Mass Index (BMI) over 25 kg/m^2).
BRIDION (sugammadex sodium) Merck	Neuromuscular Drugs	Intravenous	Reversal of Moderate or Deep Neuromuscular Blockade Induced by Rocuronium or Vecuronium	11/06/2015	Merck has stated that the FDA's Anesthetic and Analgesic Drug Products Advisory Committee will meet on November 6, 2015 to discuss the NDA for BRIDION.

products receiving special FDA review designations or statuses

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Current Development Status	Route of Administration	FDA Designation or Status Awarded	Use(s) Receiving Designation / Status
(veltuzumab) Immunomedics	New Molecular Entity	Hematological Agents	Phase 1/2	Subcutaneous; Intravenous	Orphan Drug	Treatment of Immune Thrombocytopenic Purpura
GILOTRIF (afatinib) Boehringer Ingelheim	New Indication	Antineoplastics & Adjunctive Therapies	Unknown	Oral	Orphan Drug	Treatment of Non-Small Cell Lung Cancer with Squamous Histology
(inecalcitol) Hybrigenics	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Phase 1	Oral	Orphan Drug	Treatment of Acute Myeloid Leukemia
(cannabidiol) GW	New Molecular Entity	Neuromuscular Agents	Discovery	Intravenous	Fast Track	Neonatal Hypoxic-Ischemic Encephalopathy (NHIE)
(butylidenephthalide) Everfront Biotech	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Unknown	Unknown	Orphan Drug	Treatment of Malignant Glioma
(varlitinib) Aslan	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Phase 2	Oral	Orphan Drug	Treatment of Cholangiocarcinoma
(daratumumab) Janssen	New Indication	Antineoplastics & Adjunctive Therapies	Unknown	Intravenous	Orphan Drug	Treatment of Follicular Lymphoma Treatment of Mantle Cell Lymphoma
(sodium valproate) The University of Birmingham	New Indication	CNS Drugs	Discovery	Oral	Orphan Drug	Treatment of Wolfram Syndrome

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Current Development Status	Route of Administration	FDA Designation or Status Awarded	Use(s) Receiving Designation / Status
ZEFTERA (ceftobiprole medocaril) Basilea; Johnson & Johnson	New Molecular Entity	Antiinfective Agents	Phase 3	Intravenous	Qualified Infectious Disease Product (QIDP)	Community Acquired Pneumonia; Acute Skin and Skin Structure Infections
ENVARSUS XR (tacrolimus (improved tablet formulation)) Veloxis	New Formulation	Assorted Classes	Approved	Oral	Orphan Drug	Prophylaxis of Organ Rejection in Patients Who Convert from Immediate-Release Tacrolimus
(amphotericin b (oral cochleate formulation)) Matinas BioPharma	New Formulation	Antiinfective Agents	Phase 1	Oral	Qualified Infectious Disease Product (QIDP) Fast Track	Treatment of Invasive Candidiasis
VL-2397; ASP-2397 Vical	New Molecular Entity	Antiinfective Agents	Discovery	Unknown	Qualified Infectious Disease Product (QIDP)	Treatment of Invasive Aspergillosis
(eteplirsen) Sarepta Therapeutics	New Molecular Entity	Neuromuscular Drugs	Pending Approval	Intravenous	Rare Pediatric Disease	Treatment of Duchenne Muscular Dystrophy (DMD) Amenable to Exon 51 Skipping
(firmacute eubacterial spores) Seres Therapeutics	New Molecular Entity	Antiinfective Agents	Phase 2	Oral	Orphan Drug	Prevention of Recurrent *Clostridium difficile* Infection (CDI) in Adults
(drisapersen) BioMarin	New Molecular Entity	Neuromuscular Drugs	Pending Approval	Subcutaneous	Rare Pediatric Disease	Treatment of Duchenne Muscular Dystrophy (DMD) Amenable to Exon 51 Skipping
RAXONE/CATENA (idebenone) Takeda; Santhera	New Molecular Entity	Neuromuscular Drugs	Phase 3	Oral	Rare Pediatric Disease	Duchenne Muscular Dystrophy (DMD)
COMETRIQ (cabozantinib) Exelixis	New Formulation; New Indication	Antineoplastics & Adjunctive Therapies	Phase 3	Oral	Breakthrough Therapy	Advanced Renal Cell Carcinoma (RCC) Treated With One Prior Therapy
(vocimagene amiretrorepvec + 5-flucytosine extended release) Tocagen	New Molecular Entity; New Combination	Antineoplastics & Adjunctive Therapies	Phase 2	Intravenous; Oral	Orphan Drug	Glioblastoma
(humanized monoclonal antibody of the IgG4 kappa isotype targeting CD47) Stanford University	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Discovery	Unknown	Orphan Drug	Treatment of Acute Myeloid (Myelogenous) Leukemia
(fostamatinib disodium) Rigel	New Molecular Entity	Hematological Agents	Phase 3	Oral	Orphan Drug	Treatment of Immune Thrombocytopenic Purpura
(adeno-associated virus serotype rh10 vector encoding the human factor IX gene); DTX-101 Dimension	New Molecular Entity	Hematological Agents	Discovery	Injection	Orphan Drug	Treatment of Hemophilia B
(sodium 2-hydroxylinoleate); ABTL-0812 Ability	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Phase 1	Oral	Orphan Drug	Treatment of Neuroblastoma
(secnidazole) Symbiomix	New Molecular Entity	Antiinfective Agents	Phase 3	Oral	Fast Track	Bacterial Vaginosis (BV)

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Current Development Status	Route of Administration	FDA Designation or Status Awarded	Use(s) Receiving Designation / Status
(obeticholic acid) Intercept	New Molecular Entity	Gastrointestinal Agents	Pending FDA Approval	Oral	Priority Review	Treatment of Primary Biliary Cirrhosis (PBC) in Combination with Ursodeoxycholic Acid (UDCA) in Adults with an Inadequate Response to UDCA or as Monotherapy in Adults Unable to Tolerate UDCA
CF-301 ContraFect	New Molecular Entity	Antiinfective Agents	Phase 1	Intravenous	Fast Track	Treatment of *Staph aureus* Bloodstream Infections, including MRSA
RESUNAB (ajulemic acid) Corbus	New Molecular Entity	Analgesics & Anesthetics	Phase 1	Oral	Fast Track	Systemic Sclerosis
(solithromycin) Cempra	New Molecular Entity	Antiinfective Agents	Phase 3	Oral; Intravenous	Fast Track	Community Acquired Bacterial Pneumonia (CABP)
OPDIVO (nivolumab) Bristol Myers Squibb	New Indication	Antineoplastics & Adjunctive Therapies	Phase 2	Intravenous	Orphan Drug	Treatment of Glioblastoma
(methotrexate oral solution) Silvergate	New Formulation; New Indication	Analgesics & Anesthetics	Discovery	Oral	Orphan Drug	Treatment of Oligoarticular Juvenile Idiopathic Arthritis (Persistent Oligoarthritis, Psoriatic Juvenile Idiopathic Arthritis, Enthesitis-Related Arthritis, or Undifferentiated Arthritis) and Polyarticular Juvenile Idiopathic Arthritis in Children 0 through 16 Years of Age

patent litigations/generic filings

Trade Name (generic name) Company(ies)	Generic Company(ies) Filer(s) or Defendant(s)	Therapeutic Class	Route of Administration	Use(s)	Patents Involved	Comments
VELCADE (bortezomib) Millenium/Takeda	Dr. Reddy's; Sun	Antineoplastics & Adjunctive Therapies	Intravenous	Multiple Myeloma; Mantle Cell Lymphoma	6,713,446; 6,958,319	Patent infringement lawsuit following a Paragraph IV certification as part of the defendants' filing of ANDAs to manufacture a generic version of Millenium's VELCADE.
ZOMETA (zolendronic acid) Novartis	Aurobindo	Endocrine & Metabolic Drugs	Intravenous	Hypercalcemia of Malignancy; Multiple Myeloma	8,324,189	Patent infringement lawsuit following a Paragraph IV certification as part of Aurobindo's filing of an ANDA to manufacture a generic version of Novartis' ZOMETA.
TREANDA (bendamustine hydrochloride) Cephalon	Fresenius	Antineoplastics & Adjunctive Therapies	Intravenous	Chronic Lymphocytic Leukemia; Indolent B-Cell Non-Hodgkin's Lymphoma	8,344,006	Patent infringement lawsuit following a Paragraph IV certification as part of Fresenius' filing of an ANDA to manufacture a generic version of Cephalon's TREANDA.

Trade Name (generic name) Company(ies)	Generic Company(ies) Filer(s) or Defendant(s)	Therapeutic Class	Route of Administration	Use(s)	Patents Involved	Comments
LYSTEDA (tranexamic acid) Ferring	Actavis	Hemtalogical Agents	Oral	Menorrhaggia; Bleeding Prophylaxis in Hemophilia A and B	9,060,939	Patent infringement lawsuit following a Paragraph IV certification as part of Actavis' filing of an ANDA to manufacture a generic version of Ferring's LYSTEDA.
AXIRON (testosterone) Lilly; Acrux	Lupin	Endocrine & Metabolic Drugs	External	Testosterone Replacement	8,435,944; 8,419,307; 8,177,449; 8,807,861; 8,993,520	Patent infringement lawsuit following a Paragraph IV certification as part of Lupin's filing of an ANDA to manufacture a generic version of Lilly's AXIRON.
TAMIFLU (oseltamivir phosphate) Roche/Genentech	Lupin	Antiinfective Agents	Oral	Prevention and Treatment of Influenza	5,763,483	Patent infringement lawsuit following a Paragraph IV certification as part of Lupin's filing of an ANDA to manufacture a generic version of Genentech's TAMIFLU.
APRISO (mesalamine, extended-release) Salix	Mylan	Gastrointestinal Agents	Oral	Ulcerative Colitis	6,551,620; 8,337,886; 8,496,965; 8,865,688	Patent infringement lawsuit following a Paragraph IV certification as part of Mylan's filing of an ANDA to manufacture a generic version of Salix's APRISO.
XYREM (sodium oxybate) Jazz	Actavis	Misc. Psychotherapeutic & Neurological Agents	Oral	Cataplexy; Daytime Sleepiness Associated with Narcolepsy	8,859,619; 8,952,062	Patent infringement lawsuit following a Paragraph IV certification as part of Actavis' filing of an ANDA to manufacture a generic version of Jazz's XYREM.
BRISDELLE (paroxetine mesylate) Noven	Priston	Psychotherapeutic and Neurological Agents - Miscellaneous	Oral	Treatment of Moderate to Severe Vasomotor Symptoms Associated with Menopause (VMS)	8,946,251	Declaratory judgment of non-infringement and invalidity in conjunction with Prinston's filing of an ANDA to manufacture a generic version of Noven's BRISDELLE.
ABILIFY (aripiprazole) Otsuka	Macleods	Antipsychotics / Antimanic Agents	Oral	Schizophrenia; Acute Treatment of Manic and Mixed Episodes associated with Bipolar I; Adjunctive Treatment of Major Depressive Disorder; Irritability Associated with Autistic Disorder; Treatment of Tourette's disorder	8,017,615; 8,580,796; 8,642,760; 8,759,350	Patent infringement lawsuit following a Paragraph IV certification as part of Macleods' filing of an ANDA to manufacture a generic version of Otsuka's ABILIFY.
LETAIRIS (ambrisentan) Gilead Sciences	SigmaPharma	Cardiovascular Agents - Miscellaneous	Oral	Treatment of Pulmonary Arterial Hypertension (PAH) (WHO Group 1) to Improve Exercise Ability and Delay Clinical Worsening	RE42,462	Patent infringement lawsuit following a Paragraph IV certification as part of SigmaPharm's filing of an ANDA to manufacture a generic version of Gilead's LETAIRIS.

Trade Name (generic name) Company(ies)	Generic Company(ies) Filer(s) or Defendant(s)	Therapeutic Class	Route of Administration	Use(s)	Patents Involved	Comments
PENNSAID (diclofenac sodium) Horizon	Taro; IGI; Amneal; Actavis; Lupin	Dermatologicals	External	Treatment of the Pain of Osteoarthritis of the Knee(s)	9,066,913	Patent infringement lawsuit in conjunction with defendants' filing of ANDAs to manufacture a generic version of Horizon's PENNSAID.

other/miscellaneous news

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Route of Administration	Current or Potential Use(s)	Comments
ENTYVIO (vedolizumab) Takeda	New Formulation	Gastrointestinal Agents	Subcutaneous	A Subcutaneous Formulation for Ulcerative Colitis or Crohn's Disease	Takeda plans to file a sBLA for a subcutaneous formulation of ENTYVIO for ulcerative colitis or Crohn's disease in 2016 or 2017.
(omarigliptin) Merck	New Molecular Entity	Endocrine & Metabolic Drugs	Oral	Type 2 Diabetes Mellitus (T2DM)	Merck plans to file a NDA for omarigliptin for T2DM by the end of 2015.
PROMACTA (eltrombopag olamine) Novartis	New Indication	Hematological Agents	Oral	Myelodysplastic Syndrome; Myelodysplastic Syndrome/Acute Myeloid Leukemia Associated Thrombocytopenia	Novartis plans to file a NDA for PROMACTA for myelodysplastic syndrome/acute myeloid leukemia associated thrombocytopenia in 2016 and for myelodysplastic syndrome in 2017.
(pediatric hexavalent combination vaccine) Merck	New Formulation	Vaccines	Intramuscular	Prevention of Invasive Disease Caused by *Haemophilus influenzae* Type b, Hepatitis B Virus (HBV) Infection, Diphtheria, Tetanus, Whooping Cough (Bordetella pertussis) and Polio (poliovirus types 1, 2, and 3)	Merck announced the FDA has extended the prescription drug user fee act (PDUFA) date for the pediatric hexavalent combination vaccine until sometime between November 6, 2015 and December 4, 2015.
(selumetinib) AstraZeneca	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Oral	Differentiated Thyroid Cancer	AstraZeneca plans to file a NDA for selumetinib for differentiated thyroid cancer in 2018.
(epinephrine) Adamis	New Formulation	Cardiovascular Agents	Subcutaneous; Intramuscular	Emergency Treatment of Allergic Reactions (Type 1) Including Anaphylaxis	After speaking to the FDA about its March 2015 complete response letter, Adamis plans to resubmit the NDA for epinephrine for treatment of allergic reactions by end of year 2015.
ENTRESTO (sacubitril / valsartan trisodium hemipentahydrate) Novartis	New Indication	Cardiovascular Agents	Oral	Heart Failure (Preserved Ejection Fraction [pEF])	Novartis plans to file a NDA for ENTRESTO for heart failure pEF in 2019.
(durvalumab) AstraZeneca	New Combination; New Indication	Antineoplastics & Adjunctive Therapies	Intravenous	In Combination with Tremelimumab for Second-Line Treatment of Squamous Cell Carcinoma of the Head and Neck (SSCHN) (PD-L1 Negative) (based on the CONDOR study)	AstraZeneca plans to file a sBLA for durvalumab + tremelimumab for the second-line treatment of SSCHN in 2017.

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Route of Administration	Current or Potential Use(s)	Comments
(durvalumab) AstraZeneca	New Combination; New Indication	Antineoplastics & Adjunctive Therapies	Intravenous	In Combination with Tremelimumab for the Treatment of 3rd Line Non-Small Cell Lung Cancer (NSCLC) (based on the ARCTIC study)	AstraZeneca plans to file a sBLA for durvalumab + tremelimumab for the third-line treatment of NSCLC in 2017.
OPANA ER (oxymorphone HCl) Endo	Label Expansion	Analgesics & Anesthetics	Oral	Abuse-Deterrant Labeling for Moderate-to-Severe Pain in Patients Requiring Continuous Pain Relief for an Extended Period	Endo plans to file supplemental data supporting abuse-deterrent labeling for OPANA ER in early 2016.
ITI-007 Intra-Cellular Therapies; Bristol-Myers Squibb	New Molecular Entity	CNS Drugs	Oral	Schizophrenia	Intra-Cellular plans to file a NDA for ITI-007 for schizophrenia in late 2016 or the first half 2017.
(venetoclax) AbbVie; Genentech/Roche	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Oral	Treatment of Chronic Lymphocytic Leukemia (CLL) in Previously Treated (Relapsed/Refractory) Patients with the 17p Deletion Genetic Mutation	AbbVie plans to file a NDA for venetoclax for treatment of CLL in previously treated patients with the 17p deletion generic mutation by the end of 2015.
OPDIVO (nivolumab) Bristol Myers Squibb	New Indication	Antineoplastics & Adjunctive Therapies	Intravenous	Previously Untreated Patients with Unresectable or Metastatic Melanoma	Bristol Myers Squibb (BMS) announced that the review date for OPDIVO in untreated advanced melanoma has been delayed by three months to November 27, 2015. BMS submitted additional data for review.
(naldemedine) Shionogi	New Molecular Entity	Gastrointestinal Agents	Oral	Alleviation of Opioid-Induced Adverse Events (Nausea, Emesis and Constipation)	Shionogi plans to file a NDA for naldemedine in the first quarter 2016.
NAMZARIC (memantine HCl ER / donepezil HCl) Allergan	New Strength	Misc. Psychotherapeutic & Neurological Agents	Oral	New Fixed-Dose Combinations for Treatment of Moderate to Severe Dementia of the Alzheimer's Type	Allergan plans to file a sNDA for additional fixed-dose combinations of NAMZARIC in 2015.
(damoctocog alfa pegol; recombinant human factor VIII) Bayer	New Formulation	Hematological Agents	Intravenous	Treament and Prevention of Bleeding Episodes Associated with Hemophilia A	Bayer plans to file a BLA for damoctocog alfa pegol for hemophilia A in mid 2017.
(necitumumab) Eli Lilly	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Intravenous	In Combintion with Gemcitabine and Cisplatin for the First-Line Treatment of Locally-Advanced or Metastatic Squamous Non-Small Cell Lung Cancer (NSCLC)	Eli Lilly announced that the FDA will make a decision on the pending NDA later this year. Originally the PDUFA date was for sometime in August 2015.
BERINERT (C1 esterase inhibitor [C1-INH], low volume) CSL Behring	New Formulation	Hematological Agents	Subcutaneous	Hereditary Angioedema (HAE)	CSL plans to file a NDA for BERINERT for HAE in second or third quarter 2016.
KAMRAB (human rabies immune globulin) Kamada	Biologic	Vaccines	Intramuscular	Passive, Transient Post-Exposure Prophylaxis Against Rabies Infection Administered After Exposure/Contact with an Animal Suspected of Being Infected with Rabies	Kamada announced that the results from the Phase 2/3 studies will now be released in fourth quarter 2015; and Kamada now plans to file a BLA for KAMRAB in first half 2016.
COMETRIQ (cabozantinib) Exelixis	New Formulation; New	Antineoplastics & Adjunctive Therapies	Oral	Advanced Renal Cell Carcinoma (RCC) Treated With One Prior Therapy	Based on the positive top-line results from the METEOR trial and productive dialogue with the FDA, Exelixis plans to complete its NDA

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Route of Administration	Current or Potential Use(s)	Comments
	Indication				submission for COMETRIQ in advanced RCC treated with one prior therapy prior to the end of 2015.
VICTOZA (liraglutide) Novo Nordisk	New Indication	Endocrine & Metabolic Drugs	Subcutaneous	Type 1 Diabetes Mellitus (T1DM)	Based on a risk/benefit assessment of the overall dataset from the two ADJUNCT trials, Novo Nordisk does not intend to submit an application to expand the label of VICTOZA for use inT1DM.
ARISTADA (aripiprazole lauroxil) Alkermes	New Formulation	CNS Drugs	Intramuscular	An Extended-Release Monthly Formulation for Schizophrenia	Alkermes announced that the FDA is not able to complete its review of ARISTADA by the August 22, 2015 PDUFA date. Alkermes is not required to submit any additional data. The delay should only be a few weeks.
KEYTRUDA (pembrolizumab) Merck	Full Approval for Accelerated Approval Products	Antineoplastics & Adjunctive Therapies	Intravenous	Treatment of Patients with Ipilimumab-Refractory Advanced Melanoma	The FDA has extended the action date for the sBLA for KEYTRUDA for the treatment of patients with ipilimumab-refractory advanced melanoma. The new action date is now December 24, 2015.

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Prepared by:
Valerie Taylor, PharmD
Clinical Pharmacist, Pipeline & Trend Surveillance; Drug Intelligence
Catamaran

Contributor/Reviewer:
Sherry Andes, PharmD, BCPS, BCPP, BCACP, CGP, PAHM
Sr. Manager, Pipeline & Trend Surveillance; Drug Intelligence
Catamaran