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NOTICE OF PUBLIC MEETING – PHARMACY AND THERAPEUTICS COMMITTEE

AGENDA

Date of Posting:	**August 24, 2016**
Date of Meeting:	**Thursday, September 22, 2016 at 1:00 PM**
Name of Organization:	**The State of Nevada, Department of Health and Human Services, Division of Health Care Financing and Policy (DHCFP), Pharmacy and Therapeutics Committee.**
Place of Meeting:	**Canyon Gate Country Club** **2001 Canyon Gate Drive** **Las Vegas, NV 89117** **Phone: (702) 363-0303** **Please check with staff to verify room location** **A visual and audio feed will also be broadcast via the internet for those who are unable to attend in person. See below for details.**
Webinar Event:	https://catamaranrx.webex.com/catamaranrx/onstage/g.php?MTID=e89a4188cfed0396b356f4b8c0dd78fe0 **Or** **www.webex.com, select "Join", enter Meeting Number 743 765 296, your name and email and then select, "Join"**
Event Number:	**743 765 296** **Follow the instructions that appear on your screen to join the teleconference. Audio will be broadcast over the internet (VoIP).**

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

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

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

AGENDA

1. Call to Order and Roll Call

2. Public Comment

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.

3. Administrative

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

B. Status Update by DHCFP
   1. Public Comment

4. Annual Review – Established Drug Classes

A. Analgesics: Opiate Agonists
   1. Public Comment
   2. Drug Class Review Presentation – OptumRx
   3. **For Possible Action**: Committee Discussion and Action
      a. Approve Clinical/Therapeutic Equivalency of Agents in Class
      b. Identify Exclusions/Exceptions for Certain Patient Groups
   4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx 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. Anti-infective Agents: Antivirals: Anti-hepatitis Agents: Polymerase Inhibitors/Combination
   1. Public Comment
   2. Drug Class Review Presentation – OptumRx
   3. **For Possible Action**: Committee Discussion and Action
      a. Approve Clinical/Therapeutic Equivalency of Agents in Class
      b. Identify Exclusions/Exceptions for Certain Patient Groups
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   5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

C. Anti-infective Agents: Antivirals: Anti-hepatitis Agents: Protease
   1. Public Comment
   2. Drug Class Review Presentation – OptumRx
   3. **For Possible Action**: Committee Discussion and Action
      a. Approve Clinical/Therapeutic Equivalency of Agents in Class
      b. Identify Exclusions/Exceptions for Certain Patient Groups
   4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
   5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

D. Biologic Response Modifiers: Multiple Sclerosis Agents: Oral
   1. Public Comment
   2. Drug Class Review Presentation – OptumRx
   3. **For Possible Action**: Committee Discussion and Action
      a. Approve Clinical/Therapeutic Equivalency of Agents in Class
      b. Identify Exclusions/Exceptions for Certain Patient Groups
   4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
   5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

E. Dermatological Agents: Topical Anti-infective: Topical Scabicides
   1. Public Comment
   2. Drug Class Review Presentation – OptumRx
   3. **For Possible Action**: Committee Discussion and Action

a. Approve Clinical/Therapeutic Equivalency of Agents in Class
b. Identify Exclusions/Exceptions for Certain Patient Groups

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

F. Electrolytic and Renal Agents: Phosphate Binding Agents
1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx 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. Gastrointestinal Agents: Antiemetics: Miscellaneous
1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

H. Hormones and Hormone Modifiers: Antidiabetic Agents: Dipeptidyl Peptidase-4 Inhibitors
1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups

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

J. Hormones and Hormone Modifiers: Antidiabetic Agents: Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors
1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx 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. Ophthalmic Agents: Antiglaucoma Agents: Ophthalmic Prostaglandins
1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy

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

L. Ophthalmic Agents: Ophthalmic Anti-infective/Anti-inflammatory Combinations: Ophthalmic Quinolones
   1. Public Comment
   2. Drug Class Review Presentation – OptumRx
   3. **For Possible Action**: Committee Discussion and Action
      a. Approve Clinical/Therapeutic Equivalency of Agents in Class
      b. Identify Exclusions/Exceptions for Certain Patient Groups
   4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
   5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

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

N. Respiratory Agents: Respiratory Beta-Agonists: Long-Acting Respiratory Beta-Agonist
   1. Public Comment
   2. Drug Class Review Presentation – OptumRx
   3. **For Possible Action**: Committee Discussion and Action
      a. Approve Clinical/Therapeutic Equivalency of Agents in Class
      b. Identify Exclusions/Exceptions for Certain Patient Groups
   4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
   5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

O. Respiratory Agents: Respiratory Beta-Agonists: Short-Acting Respiratory Beta-Agonist
   1. Public Comment
   2. Drug Class Review Presentation – OptumRx
   3. **For Possible Action**: Committee Discussion and Action
      a. Approve Clinical/Therapeutic Equivalency of Agents in Class
      b. Identify Exclusions/Exceptions for Certain Patient Groups
   4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
   5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

P. Toxicology Agents: Substance Abuse Agents: Mixed Opiate Agonists/Antagonists
   1. Public Comment
   2. Drug Class Review Presentation – OptumRx
   3. **For Possible Action**: Committee Discussion and Action
      a. Approve Clinical/Therapeutic Equivalency of Agents in Class
      b. Identify Exclusions/Exceptions for Certain Patient Groups
   4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
   5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

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

A. Analgesics: Opiate Agonists - Abuse Deterrent
   1. Public Comment
   2. Drug Class Review Presentation – OptumRx
   3. **For Possible Action**: Committee Discussion and Action
      a. Approve Clinical/Therapeutic Equivalency of Agents in Class
      b. Identify Exclusions/Exceptions for Certain Patient Groups
   4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx 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. Biologic Response Modifiers: Multiple Sclerosis Agents: Injectable
   1. Public Comment
   2. Drug Class Review Presentation – OptumRx
   3. **For Possible Action**: Committee Discussion and Action
      a. Approve Clinical/Therapeutic Equivalency of Agents in Class
      b. Identify Exclusions/Exceptions for Certain Patient Groups
   4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
   5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

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

D. Genitourinary Agents: Benign Prostatic Hyperplasia (BPH) Agents:5-Alpha Reductase Inhibitors
   1. Public Comment
   2. Drug Class Review Presentation – OptumRx
   3. **For Possible Action**: Committee Discussion and Action
      a. Approve Clinical/Therapeutic Equivalency of Agents in Class
      b. Identify Exclusions/Exceptions for Certain Patient Groups
   4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx 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. Hormones and Hormone Modifiers: Antidiabetic Agents: Insulins (Vials, Pens and Inhaled)
   1. Public Comment
   2. Drug Class Review Presentation – OptumRx

3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

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

G. Psychotropic Agents: ADHD Agents
1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx 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. Psychotropic Agents: Antipsychotics: Atypical Antipsychotics – Oral
1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups

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

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

J. Respiratory Agents: Respiratory Long-Acting Antimuscarinic/Long-Acting Beta-Agonist Combinations
1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

6. ANNUAL REVIEW – DRUG CLASSES WITHOUT PROPOSED CHANGES

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

A. Analgesics: Analgesic/Miscellaneous: Neuropathic Pain/Fibromyalgia Agents

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

EE. Dermatological Agents: Topical Analgesics
FF. Dermatological Agents: Topical Antiinfectives: Acne Agents: Topical, Benzoyl Peroxide, Antibiotics and Combination Products
GG. Dermatological Agents: Topical Antiinfectives: Impetigo Agents: Topical
HH. Dermatological Agents: Topical Antiinfectives: Topical Antifungals (onychomycosis)
II. Dermatological Agents: Topical Antiinfectives: Topical Antivirals
JJ. Dermatological Agents: Topical Antiinflammatory Agents: Immunomodulators: Topical
KK. Dermatological Agents: Topical Antineoplastics: Topical Retinoids
LL. Gastrointestinal Agents: Antiemetics: Serotonin-receptor antagonists/Combo
MM. Gastrointestinal Agents: Antiulcer Agents:H2 blockers
NN. Gastrointestinal Agents: Antiulcer Agents: Proton Pump Inhibitors (PPIs)
OO. Gastrointestinal Agents: Gastrointestinal Anti-inflammatory Agents
PP. Gastrointestinal Agents: Gastrointestinal Enzymes
QQ. Genitourinary Agents: Benign Prostatic Hyperplasia (BPH) Agents: Alpha-Blockers
RR. Genitourinary Agents: Bladder Antispasmodics
SS. Hematological Agents: Anticoagulants: Injectable
TT. Hematological Agents: Anticoagulants: Oral
UU. Hematological Agents: Erythropoiesis-Stimulating Agents
VV. Hematological Agents: Platelet Inhibitors
WW. Hormones and Hormone Modifiers: Androgens
XX. Hormones and Hormone Modifiers:Antidiabetic Agents: Alpha-Glucosidase Inhibitors/Amylin analogs/Misc.
YY. Hormones and Hormone Modifiers: Antidiabetic Agents: Biguanides
ZZ. Hormones and Hormone Modifiers: Antidiabetic Agents: Meglitinides
AAA. Hormones and Hormone Modifiers: Antidiabetic Agents: Sulfonylureas
BBB. Hormones and Hormone Modifiers: Antidiabetic Agents: Thiazolidinediones
CCC. Hormones and Hormone Modifiers: Pituitary Hormones: Growth hormone modifiers
DDD. Hormones and Hormone Modifiers: Progestins for Cachexia
EEE. Musculoskeletal Agents: Antigout Agents
FFF. Musculoskeletal Agents: Bone Resorption Inhibitors: Bisphosphonates

GGG. Musculoskeletal Agents: Bone Resorption Inhibitors: Nasal Calcitonins
HHH. Musculoskeletal Agents: Restless Leg Syndrome Agents
III. Musculoskeletal Agents: Skeletal Muscle Relaxants
JJJ. Neurological Agents: Alzheimer's Agents
KKK. Neurological Agents: Anticonvulsants: Barbiturates
LLL. Neurological Agents: Anticonvulsants: Benzodiazepines
MMM. Neurological Agents: Anticonvulsants: Hydantoins
NNN. Neurological Agents: Anti-Migraine Agents: Serotonin-Receptor Agonists
OOO. Neurological Agents: Antiparkinsonian Agents: Non-ergot Dopamine Agonists
PPP. Ophthalmic Agents: Antiglaucoma Agents: Carbonic Anhydrase Inhibitors/Beta-Blockers
QQQ. Ophthalmic Agents: Ophthalmic Antiinfectives: Ophthalmic Macrolides
RRR. Ophthalmic Agents: Ophthalmic Antihistamines
SSS. Ophthalmic Agents: Ophthalmic Anti-inflammatory Agents: Ophthalmic Corticosteroids
TTT. Ophthalmic Agents: Ophthalmic Anti-inflammatory Agents: Ophthalmic Nonsteroidal Anti-inflammatory Drugs (NSAIDs)
UUU. Otic Agents: Otic Antiinfectives: Otic Quinolones
VVV. Psychotropic Agents: Antidepressants: Other
WWW. Psychotropic Agents: Antidepressants: Selective Serotonin Reuptake Inhibitors (SSRIs)
XXX. Psychotropic Agents: Anxiolytics, Sedatives, and Hypnotics
YYY. Psychotropic Agents: Psychostimulants: Narcolepsy Agents
ZZZ. Respiratory Agents: Nasal Antihistamines
AAAA. Respiratory Agents: Respiratory Antiinflammatory Agents: Leukotriene Receptor Antagonists
BBBB. Respiratory Agents: Respiratory Antiinflammatory Agents: Nasal Corticosteroids
CCCC. Respiratory Agents: Respiratory Antiinflammatory Agents: Phosphodiesterase Type 4 Inhibitors
DDDD. Respiratory Agents: Respiratory Corticosteriod/Long-Acting Beta-Agonist Combinations
EEEE. Toxicology Agents: Antidotes: Opiate Antagonists

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

8. Closing Discussion

A. Public comments on any subject.

B. Date and location of the next meeting.

1. Discussion of the time of the next meeting.

C. Adjournment.

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

Notice of this meeting will be available on or after the date of this notice at the DHCFP Web site www.dhcfp.nv.gov, Carson City Central office and Las Vegas DHCFP. The agenda posting of this meeting can be viewed at the following locations: Nevada State Library; Carson City Library; Churchill County Library; Las Vegas Library; Douglas County Library; Elko County Library; Lincoln County Library; Lyon County Library; Mineral County Library; Tonopah Public Library; Pershing County Library; Goldfield Public Library; Eureka Branch Library; 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 meeting materials will be mailed to you. Requests and/or written comments may be sent to Ellen Felsing at the Division of Health Care Financing and Policy, 1100 E. William Street, Suite 101, Carson City, NV 89701, at least 3 days before the public hearing.

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

Analgesics 3
Analgesic/Miscellaneous 3
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Opiate Agonists - Abuse Deterrent 3
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Antihistamines 4
H1 blockers 4
Anti-infective Agents 4
Aminoglycosides 4
Antivirals 4
Cephalosporins 5
Macrolides 6
Quinolones 6
Autonomic Agents 6
Sympathomimetics 6
Biologic Response Modifiers 6
Immunomodulators 6
Multiple Sclerosis Agents 6
Cardiovascular Agents 7
Antihypertensive Agents 7
Antilipemics 9
Dermatological Agents 10
Antipsoriatic Agents 10
Topical Analgesics 10
Topical Anti-infectives 10
Topical Antiinflammatory Agents 11
Topical Antineoplastics 11
Electrolytic and Renal Agents 11
Phosphate Binding Agents 11
Gastrointestinal Agents 11
Antiemetics 11
Antiulcer Agents 12
Gastrointestinal Anti-inflammatory Agents 12
Gastrointestinal Enzymes 12
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Benign Prostatic Hyperplasia (BPH) Agents 12
Bladder Antispasmodics 13
Hematological Agents 13
Anticoagulants 13
Erythropoiesis-Stimulating Agents 13
Platelet Inhibitors 13
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Androgens 14

Antidiabetic Agents 14
Pituitary Hormones 16
Progestins for Cachexia 16
Musculoskeletal Agents 16
Antigout Agents 16
Bone Resorption Inhibitors 16
Restless Leg Syndrome Agents 16
Skeletal Muscle Relaxants 17
Neurological Agents 17
Alzheimers Agents 17
Anticonvulsants 17
Anti-Migraine Agents 19
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Ophthalmic Agents 19
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Otic Agents 21
Otic Antiinfectives 21
Psychotropic Agents 21
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Antidepressants 22
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Anxiolytics, Sedatives, and Hypnotics 22
Psychostimulants 23
Respiratory Agents 23
Nasal Antihistamines 23
Respiratory Anti-inflammatory Agents 23
Respiratory Antimuscarinics 24
Respiratory Beta-Agonists 24
Respiratory Corticosteriod/Long-Acting Beta-Agonist Combinations 24
Respiratory Long-Acting Antimuscarinic/Long-Acting Beta-Agonist Combinations 24
Toxicology Agents 24
Antidotes 24
Substance Abuse Agents 24

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

Preferred Products	PA Criteria	Non-Preferred Products
IBUPROFEN TAB NEW		DUEXIS® TAB NEW
INDOMETHACIN CAP NEW		ETODOLAC CAP NEW
KETOROLAC TAB NEW		ETODOLAC TAB NEW
MELOXICAM TAB NEW		ETODOLAC ER TAB NEW
NABUMETONE TAB NEW		INDOMETHACIN CAP ER NEW
NAPROXEN SUSP NEW		KETOPROFEN CAP NEW
NAPROXEN TAB NEW		MEFENAMIC ACID CAP NEW
NAPROXEN DR TAB NEW		MELOXICAM SUSP NEW
PIROXICAM CAP NEW		NAPRELAN® TAB CR NEW
SULINDAC TAB NEW		NAPROXEN TAB CR NEW
		OXAPROZIN TAB NEW
		TIVORBEX® CAP NEW
		VIMOVO® TAB NEW
		ZIPSOR® CAP NEW
		ZORVOLEX® CAP NEW
Antihistamines		
H1 blockers		
Non-Sedating H1 Blockers		
CETIRIZINE D OTC CETIRIZINE OTC LORATADINE D OTC LORATADINE OTC	A two week trial of one of these drugs is required before a non- preferred drug will be authorized.	ALLEGRA® CLARITIN® CLARINEX® DESLORATADINE FEXOFENADINE SEMPREX® XYZAL®
Anti-infective Agents		
Aminoglycosides		
Inhaled Aminoglycosides		
BETHKIS® KITABIS® PAK TOBI PODHALER® TOBRAMYCIN NEBULIZER		
Antivirals		
Alpha Interferons		
PEGASYS® PEGASYS® CONVENIENT PACK PEG-INTRON® and REDIPEN		

Preferred Products	PA Criteria	Non-Preferred Products
Anti-hepatitis Agents		
Polymerase Inhibitors/Combination Products		
HARVONI® SOVALDI® VIEKIRA PAK®	**PA required: (see below)** http://dhcfp.nv.gov/uploadedFiles/dhcfpnvgov/content/Resources/AdminSupport/Manuals/MSMCh1200Packet6-11-15(1).pdf https://www.medicaid.nv.gov/Downloads/provider/Pharmacy_Announcement_Viekira_2015-0721.pdf	
Protease Inhibitors		
INCIVEK® VICTRELIS® OLYSIO®	**PA required** https://www.medicaid.nv.gov/Downloads/provider/FA-75.pdf	
Ribavirins		
RIBAVIRIN		RIBASPHERE RIBAPAK® MODERIBA® REBETOL®
Anti-Herpetic Agents		
ACYCLOVIR FAMVIR® VALCYCLOVIR		
Influenza Agents		
AMANTADINE TAMIFLU® RIMANTADINE RELENZA®		
Cephalosporins		
Second-Generation Cephalosporins		
CEFACLOR CAPS and SUSP CEFACLOR ER CEFUROXIME TABS and SUSP CEFPROZIL SUSP		CEFTIN® CECLOR® CECLOR CD® CEFZIL
Third-Generation Cephalosporins		
CEFDINIR CAPS and SUSP CEFPODOXIME TABS and SUSP		CEDAX® CAPS and SUSP CEFDITOREN OMNICEF® SPECTRACEF® SUPRAX® VANTIN®

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

	Preferred Products	PA Criteria	Non-Preferred Products
Specific Symptomatic Treatment			
	AMPYRA® QL	PA required	
Cardiovascular Agents			
Antihypertensive Agents			
Angiotensin II Receptor Antagonists			
	DIOVAN® DIOVAN HCTZ® LOSARTAN LOSARTAN HCTZ		ATACAND® AVAPRO® BENICAR® CANDESARTAN COZAAR® EDARBI® EDARBYCLOR® EPROSARTAN HYZAAR® IRBESARTAN MICARDIS® TELMISARTAN TEVETEN® VALSARTAN
Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors)			
	BENAZEPRIL BENAZEPRIL HCTZ CAPTOPRIL CAPTOPRIL HCTZ ENALAPRIL ENALAPRIL HCTZ EPANED® £ LISINOPRIL LISINOPRIL HCTZ RAMIPRIL	£ PREFERRED FOR AGES 10 AND UNDER ‡ NONPREFERRED FOR OVER 10 YEARS OLD	ACCURETIC® EPANED® ‡ FOSINOPRIL MAVIK® MOEXIPRIL QUINAPRIL QUINARETIC® TRANDOLAPRIL UNIVASC®

Preferred Products	PA Criteria	Non-Preferred Products
Beta-Blockers		
ACEBUTOLOL ATENOLOL ATENOLOL/CHLORTH BETAXOLOL BISOPROLOL BISOPROLOL/HCTZ BYSTOLIC®* CARVEDILOL LABETALOL METOPROLOL (Regular Release) NADOLOL PINDOLOL PROPRANOLOL PROPRANOLOL/HCTZ SOTALOL TIMOLOL	*Restricted to ICD-10 codes J40-J48	SOTYLIZE®
Calcium-Channel Blockers		
AFEDITAB CR® AMLODIPINE CARTIA XT® DILTIA XT® DILTIAZEM ER DILTIAZEM HCL DYNACIRC CR® EXFORGE® EXFORGE HCT® FELODIPINE ER ISRADIPINE LOTREL® NICARDIPINE NIFEDIAC CC NIFEDICAL XL NIFEDIPINE ER NISOLDIPINE ER TAZTIA XT® VERAPAMIL VERAPAMIL ER		

Preferred Products	PA Criteria	Non-Preferred Products
Direct Renin Inhibitors		
TEKAMLO® TEKTURNA® TEKTURNA HCT® VALTURNA®		AMTURNIDE®
Vasodilators		
Inhaled		
VENTAVIS® TYVASO®		
Oral		
LETAIRIS® ORENITRAM® SILDENAFIL TRACLEER®		ADCIRCA® ADEMPAS® OPSUMIT® REVATIO ®
Antilipemics		
Bile Acid Sequestrants		
COLESTIPOL CHOLESTYRAMINE WELCHOL®		QUESTRAN®
Cholesterol Absorption Inhibitors		
ZETIA®		
Fibric Acid Derivatives		
FENOFIBRATE FENOFIBRIC GEMFIBROZIL LIPOFEN®		ANTARA® FENOGLIDE® FIBRICOR® 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®

Preferred Products	PA Criteria	Non-Preferred Products
Niacin Agents		
NIASPAN® (Brand only) NIACIN ER (ALL GENERICS)		NIACOR®
Omega-3 Fatty Acids		
LOVAZA® VASCEPA®		OMEGA-3-ACID OMTRYG®
Dermatological Agents		
Antipsoriatic Agents		
Topical Vitamin D Analogs		
CALCIPOTRIENE		CALCITENE® DOVONEX® CREAM SORILUX® TACLONEX® VECTICAL®
Topical Analgesics		
LIDOCAINE LIDOCAINE HC LIDOCAINE VISCOUS VOLTAREN® GEL		EMLA® FLECTOR® LIDODERM® QL LIDAMANTLE® PENNSAID®
Topical Anti-infectives		
Acne Agents: Topical, Benzoyl Peroxide, Antibiotics and Combination Products		
ACANYA® NEW AZELEX® 20% cream BENZACLIN® BENZOYL PEROXIDE (2.5, 5 and 10% only) CLINDAMYCIN ONEXTON GEL® NEW	PA required if over 21 years old	ACZONE GEL® NEW BENZOYL PEROXIDE AEROSOL NEW CLINDAMYCIN AEROSOL NEW CLINDAMYCIN/BENZOYL PEROXIDE GEL DUAC CS® ERYTHROMYCIN ERYTHROMYCIN/BENZOYL PEROXIDE SODIUM NEW SODIUM SULFACETAMIDE / SULFUR SULFACETAMIDE NEW
Impetigo Agents: Topical		
MUPIROCIN OINT		ALTABAX® CENTANY® MUPIROCIN CREAM

Preferred Products	PA Criteria	Non-Preferred Products
Topical Antifungals (onychomycosis)		
CICLOPIROX SOLN TERBINAFINE TABS	PA required	JUBLIA® KERYDIN® PENLAC® ITRACONAZOLE
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 PROTOPIC® QL	Prior authorization is required for all drugs in this class	TACROLIMUS
Topical Antineoplastics		
Topical Retinoids		
RETIN-A MICRO®(Pump and Tube) TAZORAC® ZIANA®	Payable only for recipients up to age 21.	ADAPALENE GEL AND CREAM ATRALIN® AVITA® DIFFERIN® EPIDUO® TRETINOIN TRETIN-X® VELTIN®
Electrolytic and Renal Agents		
Phosphate Binding Agents		
CALCIUM ACETATE ELIPHOS® FOSRENOL® RENAGEL® RENVELA®		AURYXIA ® PHOSLO® PHOSLYRA® SEVELAMER CARBONATE VELPHORO®
Gastrointestinal Agents		
Antiemetics		
Miscellaneous		
Diclegis® Emend®		

Preferred Products	PA Criteria	Non-Preferred Products
Serotonin-receptor antagonists/Combo		
GRANISETRON QL ONDANSETRON QL	PA required for all medication in this class	AKYNZEO® ANZEMET® QL KYTRIL® QL SANCUSO® ZOFRAN® QL ZUPLENZ® QL
Antiulcer Agents		
H2 blockers		
FAMOTIDINE RANITIDINE RANITIDINE SYRUP*	*PA not required for < 12 years	
Proton Pump Inhibitors (PPIs)		
NEXIUM® CAPSULES NEXIUM® POWDER FOR SUSP* PANTOPRAZOLE	PA required if exceeding 1 per day *for children ≤ 12 yrs.	ACIPHEX® DEXILANT® LANSOPRAZOLE OMEPRAZOLE OTC TABS PREVACID® PRILOSEC® PRILOSEC® OTC TABS PROTONIX®
Gastrointestinal Anti-inflammatory Agents		
ASACOL® SUPP BALSALAZIDE® CANASA® DELZICOL® MESALAMINE ENEMA SUSP PENTASA® SULFASALAZINE DR SULFASALAZINE IR		APRISO® ASACOL HD® COLAZAL® GIAZO® LIALDA ®
Gastrointestinal Enzymes		
CREON® ZENPEP®		PANCREAZE® PANCRELIPASE PERTZYE® ULTRESA® VIOKACE®
Genitourinary Agents		
Benign Prostatic Hyperplasia (BPH) Agents		
5-Alpha Reductase Inhibitors		
AVODART® FINASTERIDE		JALYN® PROSCAR®

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

Preferred Products	PA Criteria	Non-Preferred Products
Hormones and Hormone Modifiers		
Androgens		
ANDROGEL® ANDRODERM®	**PA required** **PA Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-72.pdf	AXIRON® FORTESTA® NATESTO® STRIANT® TESTIM® TESTOSTERONE GEL VOGELXO®
Antidiabetic Agents		
Alpha-Glucosidase Inhibitors/Amylin analogs/Misc.		
ACARBOSE (Precose®) GLYSET® PRECOSE® SYMLIN® (PA required)		CYCLOSET®
Biguanides		
FORTAMET® GLUCOPHAGE® GLUCOPHAGE XR® METFORMIN EXT-REL (Glucophage XR®) GLUMETZA® METFORMIN (Glucophage®) RIOMET®		
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®

Preferred Products	PA Criteria	Non-Preferred Products
Insulins (Vials, Pens and Inhaled)		
APIDRA® HUMALOG® HUMULIN® LANTUS® LEVEMIR ® NOVOLIN® NOVOLOG®		AFREZZA® HUMALOG® U-200 TOUJEO SOLO® 300 IU/ML
Meglitinides		
NATEGLINIDE (Starlix®) PRANDIMET® PRANDIN® STARLIX®		
Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors		
FARXIGA® INVOKAMET® INVOKANA® XIGDUO XR®		GLYXAMBI® JARDIANCE® SYNJARDY®
Sulfonylureas		
AMARYL® CHLORPROPAMIDE DIABETA® GLIMEPIRIDE (Amaryl®) GLIPIZIDE (Glucotrol®) GLUCOTROL® GLUCOVANCE® GLIPIZIDE EXT-REL (Glucotrol XL®) GLIPIZIDE/METFORMIN (Metaglip®) GLYBURIDE MICRONIZED (Glynase®) GLYBURIDE/METFORMIN (Glucovance®) GLUCOTROL XL® GLYBURIDE (Diabeta®) GLYNASE® METAGLIP® TOLAZAMIDE TOLBUTAMIDE		

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

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

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

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

Preferred Products	PA Criteria	Non-Preferred Products
Ophthalmic Antihistamines		
ALAWAY® BEPREVE® KETOTIFEN PAZEO® ZADITOR OTC®		AZELASTINE ALOMIDE ALOCRIL ELESTAT® EMADINE® EPINASTINE LASTACRAFT® OPTIVAR® PATADAY® PATANOL®
Ophthalmic Anti-infectives		
Ophthalmic Macrolides		
ERYTHROMYCIN OINTMENT		
Ophthalmic Quinolones		
BESIVANCE® CIPROFLOXACIN MOXEZA® OFLOXACIN® VIGAMOX®		CILOXAN® ZYMAXID®
Ophthalmic Anti-infective/Anti-inflammatory Combinations (NEW CLASS)		
NEO/POLY/DEX NEW PRED-G® NEW SULF/PRED NA PHOS SOLN NEW TOBRADEX® OINT NEW TOBRA/DEXAMETH SUSP NEW ZYLET® SUSP NEW		BLEPHAMIDE® NEW MAXITROL® NEW NEO/POLY/BAC/HC OINT NEW NEO/POLY/HC SUSP NEW TOBRADEX® SUSP NEW TOBRADEX® ST SUSP NEW
Ophthalmic Anti-inflammatory Agents		
Ophthalmic Corticosteroids		
ALREX® DEXAMETHASONE DUREZOL® FLUOROMETHOLONE LOTEMAX® PREDNISOLONE		FLAREX® FML® FML FORTE® MAXIDEX® OMNIPRED® PRED FORTE® PRED MILD® VEXOL®

Preferred Products	PA Criteria	Non-Preferred Products
Ophthalmic Nonsteroidal Anti-inflammatory Drugs (NSAIDs)		
DICLOFENAC FLURBIPROFEN ILEVRO® KETOROLAC NEVANAC®		ACULAR® ACULAR LS® ACUVAIL® BROMDAY® BROMFENAC® PROLENSA®
Otic Agents		
Otic Anti-infectives		
Otic Quinolones		
CIPRODEX® OFLOXACIN		
Psychotropic Agents		
ADHD Agents		
ADDERALL XR® AMPHETAMINE SALT COMBO IR DEXMETHYLPHENIDATE DEXTROAMPHETAMINE SA TAB DEXTROAMPHETAMINE TAB DEXTROSTAT® FOCALIN XR® INTUNIV® METADATE CD® METHYLIN® METHYLIN ER® METHYLPHENIDATE METHYLPHENIDATE ER (All forms generic extended release) METHYLPHENIDATE SOL PROCENTRA® QUILLIVANT® XR SUSP RITALIN LA® STRATTERA® VYVANSE®	**PA required for entire class** **Children's Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-69.pdf **Adult Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-68.pdf	ADDERALL® AMPHETAMINE SALT COMBO XR CONCERTA® DAYTRANA® DESOXYN® DEXEDRINE® DEXTROAMPHETAMINE SOLUTION FOCALIN® KAPVAY® METADATE ER® RITALIN®

Preferred Products	PA Criteria	Non-Preferred Products
Antidepressants		
Other		
BUPROPION BUPROPION SR BUPROPION XL DULOXETINE* MIRTAZAPINE MIRTAZAPINE RAPID TABS PRISTIQ® TRAZODONE VENLAFAXINE (ALL FORMS)	PA required for members under 18 years old * PA required *No PA required if ICD-10 - M79.1; M60.0-M60.9; M61.1.*	APLENZIN® BRINTELLIX® CYMBALTA®* DESVENLAFAXINE FUMARATE EFFEXOR® (ALL FORMS) FETZIMA® FORFIVO XL® KHEDEZLA® VIIBRYD® WELLBUTRIN®
Selective Serotonin Reuptake Inhibitors (SSRIs)		
CITALOPRAM ESCITALOPRAM FLUOXETINE PAROXETINE PEXEVA® SERTRALINE	PA required for members under 18 years old	CELEXA® FLUVOXAMINE QL LEXAPRO® LUVOX® PAXIL® PROZAC® SARAFEM® ZOLOFT®
Antipsychotics		
Atypical Antipsychotics - Oral		
ABILIFY® 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	ARIPIPRAZOLE CLOZARIL® FAZACLO® GEODON® INVEGA® PALIPERIDONE REXULTI® RISPERDAL® SEROQUEL® ZYPREXA®
Anxiolytics, Sedatives, and Hypnotics		
ESTAZOLAM FLURAZEPAM ROZEREM® * TEMAZEPAM TRIAZOLAM ZOLPIDEM	*(PA not required for ICD-10 code G47.0 and F51.0)	AMBIEN® AMBIEN CR® BELSOMRA® DORAL® ESZOPICLONE EDLUAR® HETLIOZ® INTERMEZZO® LUNESTA® SILENOR®

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

Preferred Products	PA Criteria	Non-Preferred Products
Respiratory Antimuscarinics		
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 NEBULIZER® STRIVERDI RESPIMAT®
Short-Acting Respiratory Beta-Agonist		
ALBUTEROL NEB/SOLN PROVENTIL® HFA PROAIR® HFA XOPENEX® HFA* QL XOPENEX® Solution* QL	* PA required	LEVALBUTEROL MAXAIR AUTOHALER® PROAIR RESPICLICK® VENTOLIN HFA®
Respiratory Corticosteriod/Long-Acting Beta-Agonist Combinations		
ADVAIR DISKUS® ADVAIR HFA® DULERA® SYMBICORT®		BREO ELLIPTA®
Respiratory Long-Acting Antimuscarinic/Long-Acting Beta-Agonist Combinations		
ANORO ELLIPTA® STIOLTO RESPIMAT®		
Toxicology Agents		
Antidotes		
Opiate Antagonists		
EVZIO ® NALOXONE NARCAN® NASAL SPRAY		
Substance Abuse Agents		
Mixed Opiate Agonists/Antagonists		
BUNAVAIL® SUBOXONE® ZUBSOLV®	PA required for class	BUPRENORPHINE/NALOXONE

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

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

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

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

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

(b) Antirejection medications for organ transplants;

(c) Antihemophilic medications; and

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

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

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

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

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

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

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

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

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

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

(b) Maintains continuous eligibility for Medicaid; and

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

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

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

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

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

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

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

(c) Anticonvulsant medications;

(d) Antirejection medications for organ transplants;

(e) Antidiabetic medications;

(f) Antihemophilic medications; and

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

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

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

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

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

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

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

Definition of "Therapeutic Alternative"

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

Appendix D – Quantity Limits (effective May 16, 2016)

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

Appendix D – Quantity Limits (effective May 16, 2016)

Brand Name	Generic Name	Strength	Dosage Form	Limit
Quillichew XR®	Methylphenidate ER	20mg 30mg 40mg	Chew Tab	30 tabs/30 days
Quillivant XR®	Methylphenidate ER	25mg	Oral Susp	360 ml/30 days
Ritalin LA®	Methylphenidate ER	10mg 20mg 30mg 40mg 60mg	Capsule	30 caps/30 days
Ritalin SR®	Methylphenidate ER	10mg 20mg	Tablets	30 tabs/30 days
Strattera®	Atomoxetine	10mg 18mg 25mg 40mg 60mg 80mg 100mg	Capsule	60 caps/30 days
Vyvanse®	Lisdexamfetamine	10mg 20mg 30mg 40mg 50mg 60mg 70mg	Capsule	30 caps/30 days
Analgesics				
Celebrex® (COX-II)	Celecoxib	All Strengths	Capsule	400mg per day
Lidoderm®	Lidocaine	5%	Transdermal patch	90 patches per rolling 30 days
Toradol	Ketorolac	10mg	Tablet	20 tablets per 6 months
Acetaminophen containing products		All Strengths	All	3,000mg Acetaminophen per day
Anticoagulants				
Lovenox®	Enoxaparin	30mg/0.3ml	Solution for Injection	18ml/Rx
Lovenox®	Enoxaparin	40mg/0.4ml	Solution for Injection	24ml/Rx
Lovenox®	Enoxaparin	60mg/0.6ml	Solution for Injection	36ml/Rx
Lovenox®	Enoxaparin	80mg/0.8ml	Solution for Injection	48ml/Rx
Lovenox®	Enoxaparin	100mg/ml	Solution for Injection	60ml/Rx
Lovenox®	Enoxaparin	120mg / 0.8ml	Solution for Injection	48ml/Rx

Appendix D – Quantity Limits (effective May 16, 2016)

Brand Name	Generic Name	Strength	Dosage Form	Limit
Lovenox®	Enoxaparin	150mg/ml	Solution for Injection	60ml/Rx
Pradaxa®	Dabigatran	75mg and 150mg	Capsule	60 tabs/30 days
Antiemetics				
Aloxi®	Palonosetron HCL	0.25mg/5ml	Solution for Injection	35 mls/30 days
Anzemet®	Dolasetron	50 mg	Tablet	4 tabs/Rx
Anzemet®	Dolasetron	100 mg	Tablet	2 tabs/Rx
Anzemet®	Dolasetron	20mg/ml	Solution for Injection	35 mls/30 days
Cesamet®	Nabilone	1 mg	Capsule	180 caps/30 days
Kytril®	Granisetron	1 mg	Tablet	2 tabs/Rx
Kytril®	Granisetron	1 mg/5 ml, 30 ml per bottle	Oral Solution	1 bottle/Rx
Sancuso®	Granisetron transdermal	3.1 mg/24 hr (7 day patch)	Transdermal patch	1 patch/Rx
Zofran®	Ondansetron	4 mg	Tablet and ODT	12 tabs/Rx
Zofran®	Ondansetron	8 mg	Tablet and ODT	6 tabs/Rx
Zofran®	Ondansetron	24 mg	Tablet	1 tab/Rx
Zofran®	Ondansetron	4 mg/5 ml, 50 ml per bottle	Oral Solution	1 bottle/Rx
Zofran®	Ondansetron	2mg/ml	Solution for Injection	350 mls/30 days
Zofran®	Ondansetron	4mg/2ml	Solution for Injection	6 mls/claim
Zofran®	Ondansetron	40mg/20ml	Solution for Injection	20 mls/claim
Zuplenz®	Ondansetron	4 mg	Dissolving Film	12 films/Rx
Zuplenz®	Ondansetron	8 mg	Dissolving Film	6 films/Rx
Emend®	Aprepitant	80mg	Capsule	2 caps/Rx
Emend®	Aprepitant	125mg	Capsule	1 cap/Rx
Zofran®	Ondansetron	4mg	ODT	12 tabs/Rx
Zofran®	Ondansetron	8mg	ODT	6 tabs/Rx
Antimigraine Agents				
Amerge®	Naratriptan	1mg	Tablet	9 tabs/month
Amerge®	Naratriptan	2.5mg	Tablet	9 tabs/month
Axert®	Almotriptan	6.25mg	Tablet	6 tabs/month
Axert®	Almotriptan	12.5mg	Tablet	6 tabs/month
Frova®	Frovatriptan	2.5mg	Tablet	9 tabs/month
Imitrex®	Sumatriptan	25mg	Tablet	18 tabs/month

Appendix D – Quantity Limits (effective May 16, 2016)

Brand Name	Generic Name	Strength	Dosage Form	Limit
Imitrex ®	Sumatriptan	50mg	Tablet	9 tabs/month
Imitrex ®	Sumatriptan	100mg	Tablet	9 tabs/month
Imitrex®	Sumatriptan	6mg	Injection Kit	4 injections/month
Imitrex®	Sumatriptan	5mg	Nasal Spray	12 units/month
Imitrex®	Sumatriptan	20mg	Nasal Spray	6 units/month
Maxalt®	Rizatriptan	5mg	Tablet	12 tabs/month
Maxalt	Rizatriptan	10mg	Tablet	12 tabs/month
Maxalt-MLT	Rizatriptan	5mg	ODT	12 tabs/month
Maxalt-MLT	Rizatriptan	10mg	ODT	12 tabs/month
Zomig®	Zolmitriptan	2.5mg	Tablet	12 tabs/month
Zomig®	Zolmitriptan	5mg	Tablet	6 tabs/month
Zomig-ZMT	Zolmitriptan	2.5mg	ODT	12 tabs/month
Zomig-ZMT	Zolmitriptan	5 mg	Nasal Spray	12 tabs/month
Chemotherapy Agents				
Avastin®	Bevacizumab	100mg/4ml	Solution for Injection	12 mls/claim
Avastin®	Bevacizumab	400mg/16ml	Solution for Injection	32 mls/claim
	Bleomycin Sulfate	All Strengths	Vial	30 vials/7 days
	Cytarabine	20mg/ml 5ml vial	Solution for Injection	15 mls/claim
	Cytarabine	20mg/ml 50ml vial	Solution for Injection	250 mls/claim
Herceptin®	Trastuzumab	440mg vial	Solution for Injection	3 vials/claim
Lupron®	Leuprolide Acetate Kit	All Strengths	Solution for Injection	2 kits/30 days
Navelbine®	Vinorelbine Tartrate	All Strengths	Solution for Injection	36 mls/30 days
Taxol	Paclitaxel	100mg/16.7 ml	Solution for Injection	50.1mls/claim
Taxol	Paclitaxel	150mg/25ml	Solution for Injection	75mls/claim
Taxol	Paclitaxel	30mg/5ml	Solution for Injection	15mls/claim
Taxol	Paclitaxel	300mg/50ml	Solution for Injection	150mls/claim
Diabetic Supplies				
	Lancets			200 lancets/month
	Alcohol Swabs			200 swabs/month
	Battery for Monitor			1 battery/year
	Blood Glucose Monitor			1 meter every 2 years
	Blood Glucose Strips			200 strips/month
	Insulin Syringes			100 syringes/month
	Keto-Stix			100 strips/month

Appendix D – Quantity Limits (effective May 16, 2016)

Brand Name	Generic Name	Strength	Dosage Form	Limit
	Control Solution			1 solution set/month
Erythropoiesis Stimulating Agents				
Aranesp®	Darbepoetin Alfa	All Strengths	Solution for Injection	1500 mcg/30 days or 3 ML per claim
Epogen®/Procrit®	Epoetin Alfa	All Strengths	Solution for Injection	500,000 units/30 days or 3 ML per claim
Neulasta®	Pegfilgrastim	6mg/0.6ml	Solution for Injection	1.2 mls/7 days
Omontys®	Peginesatide	10mg/ml	Solution for Injection	3 ML per claim
Omontys®	Peginesatide	20mg/2ml	Solution for Injection	4 ML per claim
Hepatitis C Agents				
Daklinza®	Daclatasvir		Tablet	14 days supply first fill, 28 tabs per rolling 25 days on subsequent fills
Harvoni®	Ledipasvir-Sofosbuvir		Tablet	14 days supply first fill, 28 tabs per rolling 25 days on subsequent fills
Incivek®	Telaprevir	375 mg	Tablet	168 tabs per rolling 25 days
Olysio®	Simprevir		Capsule	14 days supply first fill, 28 caps/rolling 25 days on subsequent fills
Sovaldi®	Sofosbuvir		Capsule	14 days supply first fill, 28 caps/rolling 25 days on subsequent fills
Technivie®	Ombitasvir / Paritaprevir / Ritonavir		Tablet	14 days supply first fill, 2 boxes of tablets, 56/28 days
Victrelis®	Boceprevir	200 mg	Capsule	336 caps per rolling 25 days
Viekira Pak®	Ombitas-Paritapre-Riton-Dasab		Pack	14 days supply first fill, 1 pack/28 days
Multiple Sclerosis Agents				
Copaxone®	Glatiramer Acetate	20mg	Solution for Injection	30 ml/30 days

Appendix D – Quantity Limits (effective May 16, 2016)

Brand Name	Generic Name	Strength	Dosage Form	Limit
Rebif®	Interferon Beta-1A	All Strengths	Solution for Injection	6 vials/Rx
Ampyra®	dalfampridine	10mg	Tablet	60 tabs/30 days
Opioids				
Actiq®	Fentanyl	All Strengths	Lozenge	120 lozenges per rolling 30 days
Avinza®	Morphine Sulfate	All Strengths	Capsule	1 capsule/day
Butrans®	Buprenorphine transdermal patch	All Strengths	Transdermal patch	4 patches/30 days
Demerol	Meperidine Hydrochloride	All Strengths	Solution for Injection	30 mls/day
Duragesic®	Fentanyl	All Strengths	Transdermal patch	1 patch every 3 days
Duragesic	Fentanyl	All Strengths	Patch	1 patch every 2 days if failure to achieve pain relief is documented and clinical notes are provided to the clinical call center.
Exalgo®	Hydromorphine ER	All Strengths	Tablet	1 tablet per day
Fentora®	Fentanyl	All Strengths	Buccal tablet	120 tabs per rolling 30 days
Hysingla® ER	Hydrocodone ER	All Strengths	Tablet	1 tablet per day
Kadian®	Morphine Sulfate	All Strengths	Capsule	2 caps/day
MS Contin	Morphine Sulfate	All Strengths	Tablet	3 tabs/day
Nucynta® ER	Tapentadol ER	All Strengths	Tablet	2 tablets/day
Opana® ER	Oxymorphone ER	All Strengths	Tablet	2 tablets/day
OxyContin®	Oxycodone	All Strengths	Tablet	3 tabs/day
Stadol®	Butorphanol	All Strengths	Nasal Spray	2 per rolling 30 days
Xartemis® XR	Oxycodone/APAP ER	All Strengths	Tablet	4 tabs/day
Zohydro® ER	Hydrocodone ER	All Strengths	Tablet	2 tabs/day
Oral Contraceptives				
Oral Contraceptives	All Products	All Strengths	Tablet	28 tablets (when provided in a physician's office)
Respiratory				
Daliresp®	Roflumilast	500mcg	Tablet	30 tabs/25 days
Duoneb	Ipratropium/Albuterol	0.5-2.5mg / 3ml	Nebulizer Solution	360 ml/month
Flovent®	Fluticasone	100mcg	Rotadisk	1 inhaler/month
Flovent®	Fluticasone	250mcg	Rotadisk	1 box/month
Flovent®	Fluticasone	50mcg	Rotadisk	1 box/month

Appendix D – Quantity Limits (effective May 16, 2016)

Brand Name	Generic Name	Strength	Dosage Form	Limit
Serevent® Diskus®	Salmeterol	50mcg	Diskus	1 box (60 inhalations per month)
Xopenex®	Levalbuterol	(All Strengths)	Nebulizer Solution	4 boxes (288ml) per month
Xopenex	Levalbuterol	0.31 and 0.63mg		Every 6 hours (see monthly max above)
Xopenex	Levalbuterol	1.25mg		Every 8 hours (see monthly max above)
Sedative/Hypnotics				
Ambien®	Zolpidem	5mg and 10mg	Tab	30 tabs/30 days
Ambien CR®	Zolpidem ER	6, 6.25, 12, 12.5mg	Tab CR	30 tabs/30 days
Belsomra®	Suvorexant	5, 10, 15 and 20mg	Tab	30 tabs/30 days
Dalmane®	Flurazepam	15mg and 30mg	Capsule	30 caps/30 days
Doral®	Quazepam	15mg	Tab	30 tabs/30 days
Edluar®	Zolpidem	5mg and 10mg	SL Tab	30 tabs/30 days
Halcion	Triazolam	0.125 and 0.25 mg	Tab	30 tabs/30 days
Hetlioz®	Tasimelteon	20mg	Capsule	30 caps/30 days
Intermezzo®	Zolpidem	1mg and 3mg	SL tab	30 tabs/30 days
Prosom®	Estazolam	1mg and 2mg	Tab	30 tabs/30 days
Restoril®	Temazepam	7, 7.5, 15, 22, 22.5, and 30mg	Capsule	30 caps/30 days
Rozerem®	Ramelteon	8mg	Tab	30 tabs/30 days
Silenor®	Doxepin	3mg and 6mg	Tab	30 tabs/30 days
Sonata®	Zaleplon	5mg and 10mg	Capsule	30 caps/30 days
Zolpimist®	Zolpidem	5mg	Oral Spray	1 Unit/30 days
Buprenorphine/ Naloxone				
Subutex®	Buprenorphine	2mg	SL Tab	90 tabs/30 days
Subutex®	Buprenorphine	8mg	SL Tab	60 tabs/30 days
Suboxone®	Buprenorphine/ Naloxone	2mg/0.5mg	SL Tab/Film	90 tabs/30 days
Suboxone®	Buprenorphine/ Naloxone	4mg/1mg	SL Tab/Film	30 tabs/30 days
Suboxone®	Buprenorphine/ Naloxone	8mg/2mg	SL Tab/Film	60 tabs/30 days

Appendix D – Quantity Limits (effective May 16, 2016)

Brand Name	Generic Name	Strength	Dosage Form	Limit
Suboxone®	Buprenorphine/ Naloxone	12mg/3mg	SL Tab/Film	30 tabs/30 days
Zubsolv®	Buprenorphine/ Naloxone	1.4mg/0.36 mg	SL Tab	90 tabs/30 days
Zubsolv®	Buprenorphine/ Naloxone	5.7mg / 1.4mg	SL Tab	60 tabs/30 days
Miscellaneous				
Adenocard	Adenosine	All Strengths	Solution for Injection	255 ml/30 days
Benadryl®	Diphenhydramine HCL	All Strengths	Solution for Injection	5 mls/day
Botox®	Onabotulinumtoxina	All Strengths	Solution for Injection	4 vials/30 days
Brilinta®	ticagrelor	All Strengths	Tablet	60 tabs/25 days
Colcrys®	Colchicine	0.6mg	Tablet	90 tabs/30 days - FMF 60 tabs/30 days - Chronic Gout
Corlanor®	Ivabradine	5mg 7.5mg	Tablet	60 tabs/30 days
Crestor®	Rosuvastatin	10mg	Tablet	2 tabs/day
Crestor®	Rosuvastatin	20mg	Tablet	1 tab/day
Depo-Provera	Medroxyprogesterone	150 mg	Solution for Injection	2 ml/3 months
Duexis®	Ibuprofen/famotidine	800/26.6mg	Tablet	3 tabs/day
Effient®	Prasugrel		Tablet	30 tabs/30 days
Elidel®	Pimecrolimus	1%	Tube	30 GM per rolling 30 days with a 25% tolerance for refills
Entresto®	Sacubitril/Valsartan	24-26mg 49-51mg 97-103mg	Tablets	60 tabs/30 days
Haldol®	Haloperidol Decanoate	All Strengths	Solution for Injection	20 ml/30 days
Jublia®	Efinaconazole	10%	Topical Solution	1 bottle/30 days
Kalydeco™	Ivacaftor	50 mg 75mg 150mg	Tablet Packets	60 tabs or packs/25 days
Kerydin®	Tavaborole	5%	Topical Solution	1 bottle/30 days
Lamisil® Granules	Terbinafine	125mg 187.5mg	Granules Packet	60 packs/30 days
Makena®	Hydroxyprogesterone Caproate	250mg/ml	Solution for Injection	1 vial/30 days

Appendix D – Quantity Limits (effective May 16, 2016)

Brand Name	Generic Name	Strength	Dosage Form	Limit
Mitigare®	Colchicine	0.6mg	Tablets	60 tabs/30 days
Nuvigil®	Armodafinil	50mg 150mg 200mg 250mg	Tablet	1 tablet per day
Onmel®	Itraconazole	200mg	Tablet	30 tabs/30 days
Orkambi®	Lumacaftor/Ivacator	200-125mg	Tablet	112 tabs/28 days
Phenergan/Codeine	Promethazine/Codeine	6.25-10 mg/5 ml	Syrup	120 ml/fill, 3 fills per rolling 12 months
Phenergan VC/Codeine	Promethazine VC/Codeine	6.25-10 mg/5 ml	Syrup	120 ml/fill, 3 fills per rolling 12 months
Praluent®	Alirocumab	75mg 150mg	Pen/Syringe	2 pens/syringes per rolling 28 days
Protopic®	Tacrolimus	All Strengths	Tube	30 gm per rolling 30 days with a 25% tolerance for refills
Provigil®	Modafinil	100mg 200mg	Tablet	1 tablet per day
Regranex®	Becaplermin	0.01%	Tube	15 gm tube per claim, 2 tubes in lifetime
Repatha®	Evolocumab	140mg/ml	Pen/Syringe	3 pens/syringes per rolling 28 days
Smoking Cessation Products				180 days/year
Solu-Medrol®	Methylprednisolone	All Strengths	Solution for Injection	12 ml/30 days
Synagis®	Palivizumab	100mg	Vial	4 vials/Rx
Versed	Midazolam Hydrochloride	All Strengths	Solution for Injection	100 mls/day
	Triamcinolone Acetonide	All Strengths	Solution for Injection	16 mls/30 days
	Blood Factor per unit (Antihemophilic Factor, Human or Recombinant)	All Strengths	Unit	10,000 units/day
Xolair®	Omalizumab	150mg	Vial	6 vials/28 days
Xyrem®	Sodium oxybate	500mg/ml	Solution	540 ml/30 days

BRIAN SANDOVAL
Governor

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RICHARD WHITLEY, MS
Director

MARTA JENSEN
Acting Administrator

Nevada Medicaid
Pharmacy and Therapeutics
Draft Meeting Minutes

The Division of Health Care Financing and Policy (DHCFP) Pharmacy and Therapeutics Committee held a public meeting on March 24, 2016 beginning at **1:00 p.m.** at the following location:

Spring Preserve
Desert Living Center
333 S. Valley View Blvd
Las Vegas, NV 89107
702-822-7700

Committee Members Present:
Mark Decerbo, Pharm.D.; Shamim Nagy, MD; Weldon Havins, MD; Adam Zold, Pharm.D.; Evelyn Chu, Pharm.D.; David Fluitt, RPh; Mike Hautekeet, Pharm.D.

Committee Members Absent:
Bill Evans, MD; Joseph Adashek, MD

Others Present:
DHCFP:
Mary Griffith, RN, Pharmacy Services Specialist; Susanne M. Sliwa, Deputy Attorney General;

HPES:
Beth Slamowitz, Pharm.D.

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

Others:
Jeff Buel, J&J; Sergio Gonzalez, Takeda; Dr. Robert Lynn Hornee; Krystal Joy, Otsuka; Samantha Min, Otsuka; Yurri Yamamoto, Alkermes; Melissa Walsh, Novartis; Kriby Consier, Novartis; Jennifer Lauper,

MBS; Charissa Anne, J&J; Mary Kay Queener, J&J; Gregg A Gittus, Akermes; Colin Carey, Eli Lilly; Mark Shaw, Allergan; Sean M, Allergan; Kathy Moore, Otsuka; Cynthia Kouske, Otsuka; Kerry Kostman Bonilla, AstraZeneca; Gin Yun, AstraZeneca; Ann Nelson, Vertex; James Kotusky, Gilead; Deron Grothe, Teva; Bob G, Lundbeck; Sandy Sierawski, Pfizer; Contessa Fincher, Teva

Others via teleconference:
Laurie Kelly, Optum; Rob Bigham, Shire; Ann Nelson, Vertex; Lovell Robinson, Abbvie; John Pruett; Philip Walsh, Sunovion; Dr. Charles Costas; Kim Brown; Ken Ley; Deborah Campanella

AGENDA

1. Call to Order and Roll Call

Meeting called to order at 1:15 PM.

Roll Call:

Kevin Whittington, OptumRx

Carl Jeffery,

Mary Griffith

Mike Hautekeet

Evelyn Chu

Mark Decerbo

Adam Zold

Weldon Havins

Shamin Nagy

Susanne M. Sliwa

Beth Slamowitz

David Fluitt

Public Comment

Shamim Nagy, Chair: Calls for public comment.

2. Administrative

A. **For Possible Action:** Review and approve meeting Minutes from December 3, 2015

Shamim Nagy, Chair: We need a motion for approval of the minutes from the last meeting.

Weldon Havins: So moved.

Adam Zold: Second.

Voting: Ayes across the board, the motion carries.

B. Status Update by DHCFP

1. Public Comment

Mary Griffith: Coleen Lawrence is working in the Director's office for the Director of Health and Human Services. Interim CPT chief is Marti Cote. We have a permanent person starting soon, Shannon Sprout. She has been with the State for a long time.

From CMS on covered outpatient drugs as a result of the ACA, the biggest change is how we reimburse 340b providers. We are prohibited from exceeding the ceiling price, even though we don't know what it is. That is one of the things we are working through.

We do have the WebEx up, so please talk clearly if you are going to give public comment.

Weldon Havins: What is a 340b provider?

Mary Griffith: A 340b provider is a federal program where certain clinics in Nevada get drug discounts from the manufacture. We don't collect rebates on these claims. It started to expand with ACA. It doesn't impact this group, but it does impact DHCFP.

Shamim Nagy, Chair: Public comment? None.

3. Established Drug Classes

A. Respiratory Long-Acting Anti-muscarinic/Long-Acting Beta-Agonist Combinations

Shamim Nagy, Chair: Moving to the established class of drugs. The respiratory long-acting anti-muscarinic/long-acting beta-agonist combinations.

Carl Jeffery: We anticipated a new product on the market by the time of the meeting, but it is not yet available. We ask the chair to bypass this agenda topic.

B. Acne Agents: Topical, Benzoyl Peroxide, Antibiotics and Combination Products

Shamim Nagy, Chair: acne agents. Any public comment? No.

Carl Jeffery: We have a new product on the market in this class, generic dapsone, or Aczone is the trade name for it. The Duac CS is no longer on the market. We wanted to review this class with the Committee. I am not going to spend a lot of time on the clinical side with this class. Most of these have been on the market for a long time and are well known. The anti-infectives are well established in the guidelines in the treatment of acne, and it is not different with the dapsone. These are all categorized as anti-infectives. The guidelines recommend adding benzoyl peroxide with the clindamycin and erythromycin so there is not as much drug resistance. The safety and efficacy is well known and are shown to be more effective than placebo. Sulfacetamide of note was available on the market before the 1962 FDA classification and was never shown to be safe and effective. It is widely used, but it is not approved. Aczone was approved based on two studies. Shown to be safe and more effective over vehicle alone. Another study looked at adolescent females vs. adult females and it was shown it was more effective in the adults, but the researches were not sure why. There are several dosage forms available. Optum recommends the Committee consider these clinically and therapeutically equivalent.

Adam Zold: I motion that they are therapeutically equivalent.

Weldon Havins: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: We want to shuffle this around a little. Aczone we recommend be non-preferred, and move sulfacetamide to non-preferred since it is not FDA approved. There are some new products, Onexton and Acanya are newer combination products to be preferred. A couple new aerosol products on the market. They shouldn't be first line, so we are recommending these be non-preferred.

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

Michael Hautekeet: Second.

Voting: Ayes across the board, the motion carries.

4. Proposed New Drug Classes

A. Ophthalmic Anti-infective/Anti-inflammatory Combinations

Shamim Nagy, Chair: The next class, ophthalmic anti-infective/anti-inflammatory combinations.

Public comment? None.

Carl Jeffery: This is a new class we would like to propose adding to the PDL. We have the individual products on the list now, but would like to add the combinations. A couple newer products, Pred G, Zylet, they are all combinations of well-known products that have been out for years. Most are available generically, just the Pred-G and the Zylet do not have generics. The Zylet has tobramycin and a newer steroid that is in Alrex. Optum recommends these be considered clinically and therapeutically equivalent.

Weldon Havins: I move these drugs be considered clinically and therapeutically equivalent.

Michael Hautekeet: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: Our recommendation is shown on the screen. The Pred-G and Zylet are the two brand names available as preferred. The Tobradex ointment, sulfa/prednisone and the Neo/Poly/Dexamethasone are all widely used. But the one that might get some pushback is the Tobradex suspension as it is widely used and this may not be a popular decision. Having Zylet which is the same ingredient, we are hoping to push some utilization to that medication.

Weldon Havins: The Tobradex suspension is also available as a generic.

Carl Jeffery: Right, we have the generic listed as non-preferred as well.

Weldon Havins: I think this is a commonly used medication, I hate to see it not available. I move that we move the generic Tobramycin dexamethasone be move to preferred. And that the preferred drug list be accepted.

Adam Zold: Second.

Voting: Ayes across the board, the motion carries.

B. Injectable Long-Acting Atypical Antipsychotics

Shamim Nagy, Chair: The next class is long-acting injectable atypical antipsychotics. Optum wanted to make a comment before we open to public comment?

Carl Jeffery: Thank you. I know there will be public comment for this class, to make sure everyone is on the same field. We have to cover them, but there are some limitations, on or before June 30, 2010. I understand the way this is interpreted is that if the product was on the market before June 30, 2010, the Committee cannot make them non-preferred. If the product came on the market after that date, the Committee has the option to make it non-preferred. Also, the exception criteria, recipients discharged from an acute mental health facility have up to 90 day to see a provider. They will be given an approval for 90 regardless if preferred or non-preferred. That is across the board and is how the oral atypical antipsychotics are being handled.

Mary Griffith: As of April, we will have a public hearing on some other changes, that 90 days will be increased to 6 months.

Carl Jeffery: The other exclusion criteria, in order for a member to get a non-preferred medication, they only need to try one preferred. The other classes require two trials. I would like to make sure we keep the comments in line with our objective here and not get sidetracked with PA process or what the call center does.

Shamim Nagy, Chair: Public comment?

Samantha Min: My name is Samantha Min, I am a Pharm.D. with the Medical Affairs Department with Otsuka and I want to talk today about Abilify Maintena. I want to first review our position on open access. Reviews studies showing different medications work differently for different patients. Formulary restrictions more likely to be hospitalized and have higher costs. Otsuka supports open access to all medication. She presented indications and trials of Abilify Maintena, adverse events and black boxed warning. I ask for Abilify Maintena to be available unrestricted.

MaryKay Queener: My name is MaryKay Queener, I'm a Pharm.D. with Johnson and Johnson. I also support open access and support Invega Trinza and Consta on the preferred drug list.

Weldon Havins: So you are in favor of having these on the preferred drug list?

Mary Kay Queener: I am.

Robert Horne: I am Dr. Robert Horne. I was previously on the P&T. I'm asking today this class not be removed from the excluded list. He presented on two studies involving, fewer hospitalizations and readmissions with long-acting injectable antipsychotics. The problem is if you put all of these on, next year they don't have to be all preferred. If they continue to be excluded, then we don't have to worry about it becoming non-preferred at some point. We don't want to be in a position of having to use Haldol or Prolixin like some MCOs. I think it would be best for psychiatrists to use what is best for the individual patient, we know our patient's better. Please allow us to continue to use the best medication at the time for that patient by excluding these medications from the preferred drug list.

Weldon Havins: Dr. Horne, is it your impression that all these drugs are on the excluded drug list.

Robert Horne: I know there is some controversy about what is excluded, but I think these are all excluded. I don't think they should all be excluded.

Weldon Havins: Do you think they should be moved to the excluded list?

Robert Horne: Yes.

Weldon Havins: Is it your understanding that if they are on the preferred drug list they have to fail on some other drug to use these?

Robert Horne: For the patient for one of the two MCO's, they have to fail Prolixin or Haldol.

Mary Griffith: This criteria is for fee for service only, this will not affect MCO coverage.

Robert Horne: I understand that, if it comes off the excluded list and added to the preferred drug list, it can be moved to non-preferred the following year. I don't want to see that happen and the only way I know to make sure it doesn't happen is if they all stay on the excluded list.

Weldon Havins: But you are aware if they were on the preferred drug that psychiatrists could use these without any drug failure.

Robert Horne: Right, for the next year, but what I'm saying is I have seen many times something that is preferred on the list and be non-preferred the next year.

Weldon Havins: But to do that it would have to come before this Committee.

Robert Horne: Yes, but it comes up every year.

Weldon Havins: Potentially.

Robert Horne: So I would just like to see it not to be able to happen for the benefit of my patients. Thank you.

Dr. Gellifen: I'm the Director of Mental Health. We sent a letter yesterday for the Committee, I just wanted to make sure the Committee saw the letter and ask for any questions.

Carl Jeffery: He is referring to the letter from Dr. Gellifin, you should have a copy. Dr. Gellifin, I do not see any questions from the Committee at this time.

Dr. Gellifen: Thank you. I just want to request to not have any restriction to this class of medications as expressed in the letter.

Shamim Nagy, Chair: Any other public comment?

Carl Jeffery: We talked about the exclusion criteria and the Committee I think understands the ramification. We have the injectable atypical antipsychotics, they are all available orally as well and you can see the indications for each listed on the screen. What really separates these products is the half-life. On the screen lists the number of days for the half-life. There have been a lot of trials showing they are safe and effective, they are used quite a bit. They are established in numerous trials. The clinical guidelines do not have a preference for one single agent. The Zyprexa is part of a limited distribution due to some special administration requirements and a black box warning. When looking at practice guidelines, they have not been updated for a while, they say these agents are good for patients having a hard time with compliance. That is really where they fall into therapy according to these guidelines. This slide shows the brand and generic names of each of the injectable product. Optum recommends these products be considered clinically and therapeutically equivalent.

Weldon Havins: The list you presented highlighted in yellow, are those currently part of the excluded list?

Carl Jeffery: The initial screen showed that we wanted to make all the products preferred.

Weldon Havins: That wasn't my questions, currently are these on the list of excluded?

Carl Jeffery: I don't know that excluded is the right word, they are not included in any category, so there is no PA restriction for preferred or non-preferred right now.

Weldon Havins: So a psychiatrist writing for one of these currently does not have any restrictions?

Carl Jeffery: Right, the only limitation is the DUR board added criteria for the Invega Trinza. It follows the approved labeling.

Weldon Havins: Since we have had testimony for them to remain excluded, is there a compelling reason to move them to the preferred drug list?

Carl Jeffery: It gives the Committee the ability down the road to evaluate new products and if there are some products that come on the market that are subpar or have some limitations in use then the Committee can drive utilization to other agents. As the Committee, your first priority is to make sure everything on the preferred side is clinically appropriate and is the best therapy. If there is a product released in the future that is substandard, the Committee can drive the utilization to the better agents.

Weldon Havins: But we are not considering those drugs now, we are considering these currently available. Several clinical psychiatrists believe they should remain in the current status as they are now. Is there a compelling need to move them to the preferred drug?

Carl Jeffery: It is in the interest of the state to have these on the PDL and down the road we can drive utilization.

Weldon Havins: Couldn't we address that down the road.

Carl Jeffery: Yes, for any changes we propose to the PDL needs to come to this Committee first.

Mark Decerbo: For the exclusion criteria, is it the dosage form or the molecule? They don't appear like they meet the excluded list. Is this a unique example or are there other examples around?

Carl Jeffery: My understanding is it is by dosage form, so it would be the long-acting injectable agents. There are only three that were introduced after the date, the Invega Trinza, Aristada and Abilify Maintena.

Mary Griffith: To clarify, there is not a list of drugs that are excluded. If there is a category that is not listed on the PDL, then they are not subject to the same criteria as a listed class. If we are adding the class to the PDL, there is going to be more scrutiny, and if listed as non-preferred it

will require a PA. So it isn't a list, it is just when something is added to the PDL. It is the Committee's responsibility to decide what is preferred and non-preferred.

Weldon Havins: I understand, as I read the screen, I don't see where it lists the oral antipsychotic medications. I see "antipsychotic medications".

Mary Griffith: We do have the drug class.

Carl Jeffery: I don't have the orals listed.

Weldon Havins: This is from the legislature, they did not distinguish between the injectables and oral agents. I move we keep them in the same class as they are now until there is a compelling reason to change their status.

Mark Decerbo: Second. I work with USP along with CMS that works with the Part D formularies, there are six protected classes which antipsychotics are one. This is one category where I would endorse a protected status, while I do not have any issue with putting them all on the PDL, thinking for the future and different compositions of the Committee and what changes may come from that. That is my main hesitation.

Mary Griffith: Did we do the therapeutic equivalency vote for this yet?

Weldon Havins: No, but we don't have to go there if we are voting this way. We don't want them on the list at all.

Beth Slamowitz: For clarification, is it still possible that if these are added as a class, that the DUR Board can make decisions for criteria to be placed on those products for safety reasons. The DUR Board can still add restrictions, so just by not adding this class, there could still be PA requirements from the DUR Board added.

Weldon Havins: That is out of the scope of this Committee.

Beth Slamowitz: Correct, I want to make sure that is understood by the public as well.

Voting: Ayes across the board, the motion carries.

C. Oral Non-steroidal Anti-inflammatory Drugs (NSAIDs)

Shamim Nagy, Chair: Next is Oral Non-steroidal anti-inflammatory drugs. Any public comment?

Carl Jeffery: This is our last class. This is a new class of medications. This is the NSAIDS, these have been out for years. We are seeing manufacturers bringing new forms out after tweaking old formulations a little. We would like to push utilization to the more well-known, established medications in this class. Looking at the list, there really are not any new molecules. The literature available is old and there isn't really studies showing one is better than the other.

A few of the new agents compare to Celebrex and they are shown to be non-inferior. The advantage of the newer agents is it works just a little faster. The three new products are ground down to a very fine powder in theory absorbing a little faster. The other two I will point out is Duexis and Vimovo, they are combination products where the DUR Board has placed criteria on them. All the NSAIDS have a black-box warning. There is supposed to be a big study coming out later this year showing the results of cardiovascular effects. Optum recommends the products listed be considered clinically and therapeutically equivalent.

Mark Decerbo: I move this list be accepted as clinically and therapeutically equivalent.

Adam Zold: Second.

Voting: Ayes across the board.

Carl Jeffery: We came up with the preferred list by drawing a line between the brands and generics. We included the highly used medications. This gives the availability of the higher used products.

Mark Decerbo: We didn't have this as a class before?

Carl Jeffery: No, up until recently all the products were generic.

Evelyn Chu: I make the motion we accept the list of preferred products as presented.

Weldon Havins: Second.

Voting: Ayes across the board, the motion carries.

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

Carl Jeffery: Your binders have some new drug information. Hepatitis C agents are coming. Please let us know if there are other classes you think should be included in the future.

Weldon Havins: Is there a list of HIV medications?

Carl Jeffery: For prophylaxis? We are excluded from having HIV medications as a class on the PDL.

6. Closing Discussion

Shamim Nagy, Chair: Any public comment? Date and location of the next meeting?

Carl Jeffery: June 23rd, does this location work?

Shamim Nagy, Chair: Meeting adjourned.

Meeting adjourned at 2:20 pm.

F. Transdermal Fentanyl

Therapeutic Class: Analgesics, Narcotic
Last Reviewed by the DUR Board: January 22, 2015

Transdermal fentanyl, a narcotic agonist analgesic, is indicated in the management of chronic pain in patients requiring continuous opioid analgesia for pain that cannot be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics or PRN dosing with short-acting opioids. Transdermal fentanyl is subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the Social Security Act and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

Because serious or life-threatening hypoventilation could occur, fentanyl transdermal is contraindicated in management of acute or postoperative pain, mild or intermittent pain responsive to PRN or non-opioid therapy, or in doses exceeding 25 mcg/hr at the initiation of opioid therapy. Therefore, patients must meet the following criteria in order to gain prior authorization approval:

a. Patient cannot be managed by lesser means such as acetaminophen-opioid combinations, nonsteriodal analgesics, or PRN dosing with short-acting opioid.

b. Patient requires continuous opioid administration.

c. Prescribers are encouraged to check the Nevada State Board of Pharmacy's Prescription Monitoring Program (PMP) prior to prescribing narcotic analgesics. Refer to the PMP website at http://bop.nv.gov/links/PMP/.

d. If transitioning from another opioid, daily morphine equivalent doses are used to calculate the appropriate fentanyl patch dose.

1. Morphine 60-134 mg/day PO; Initial Transdermal Fentanyl dose 25 mcg/hr.

2. Morphine 135-224 mg/day PO; initial Transdermal Fentanyl dose 50 mcg/hr.

3. Morphine 225-314 mg/day PO; initial Transdermal Fentanyl dose 75 mcg/hr.

4. Morphine 315-404 mg/day PO; initial Transdermal Fentanyl dose 100 mcg/hr.

5. Morphine 405-494 mg/day PO; initial Transdermal Fentanyl dose 125 mcg/hr.

6. Morphine 495-584 mg/day PO; initial Transdermal Fentanyl dose 150 mcg/hr.

7. Morphine 585-674 mg/day PO; initial Transdermal Fentanyl dose 175 mcg/hr.

8. Morphine 675-764 mg/day PO; initial Transdermal Fentanyl dose 200 mcg/hr.

9. Morphine 765-854 mg/day PO; initial Transdermal Fentanyl dose 225 mcg/hr.

10. Morphine 855-944 mg/day PO; initial Transdermal Fentanyl dose 250 mcg/hr.

11. Morphine 945-1034 mg/day PO; initial Transdermal Fentanyl dose 275 mcg/hr.

12. Morphine 1035-1124 mg/day PO; initial Transdermal Fentanyl dose 300 mcg/hr.

2. Prior Authorizations

Prior approval will be given for a 12 month time period.

Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

Q. Long-Acting Narcotics

Therapeutic Class: Analgesics, Narcotic
Last Reviewed by DUR Board: July 30, 2009

Long-Acting Narcotics are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the Social Security Act and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

Indications: Management of moderate-to-severe pain when continuous around-the-clock analgesic is needed for an extended period of time. Medications:

a. Oxycontin (including generic); MS Contin (including generic); Avinza; Kadian; Oramorph.

1. No prior authorization is required for diagnosis of terminal cancer.

b. Please Note: The use of Long – Acting Narcotics for acute/short term treatment of pain not within the quantity limits will not be approved.

Approval will be for a three month time limit.

2. Prior Authorization Guidelines:

The prior authorization must be initiated by the prescriber. The approved Payment Authorization Request (PAR) must be available if requested.

Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

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 1.[1-19] 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.[20] 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.[20] 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).[20] 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.[21]

  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.[21] 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.[22]

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.[22]

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.[22,23]

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.[24]

According to the FDA abuse and misuse of prescription opioid products has created a serious and growing public health problem. The FDA considers the development of abuse-deterrent products a priority. As outlined in their guidance for evaluation and labeling, “abuse-deterrent properties” are defined as those properties shown to meaningfully deter abuse, even if they do not fully prevent abuse. The FDA elected to use the term “abuse-deterrent” rather than “tamper-resistant” because the latter term refers to, or is used in connection with, packaging requirements applicable to certain classes of drugs, devices, and cosmetics. Abuse-deterrent technologies should target known or expected routes of abuse relevant to the proposed product. The FDA has provided several categories for abuse-deterrent formulations. Categories include physical/chemical barriers, agonist/antagonist combinations, aversion (adding a product that has an unpleasant effect if manipulated or is used at a higher than recommended dose), delivery systems, new molecular entities/prodrugs, a combination of these methods, or a novel approach (encompasses approaches or technologies not currently captured in previous categories).[25]

Buprenorphine buccal film is formulated using bioerodible mucoadhesive (BEMA®) technology. BEMA® is a film formulation that consists of a water-soluble polymer that adheres to the buccal mucosa. The film dissolves over approximately 30 minutes into the buccal mucosa, leaving behind no residual film. Delivery into the buccal mucosa enhances the bioavailability of buprenorphine, as it bypasses gastrointestinal absorption and first-pass metabolism.[1]

Hysingla ER® (hydrocodone extended-release [ER]) tablets are resistant to crushing, breaking and dissolution using different solvents, and the tablets still retain some ER properties after tampering. Attempts to dissolve the tablets result in the formation of a viscous gel, which may cause difficulty passing through a hypodermic needle.[5] In addition, the tablets appear to be associated with less “drug liking”

based upon results reported from two unpublished clinical abuse potential studies conducted in a small number of non-dependent recreational opioid users.[26]

There are currently two formulation of oxycodone ER which are considered abuse deterrent, OxyContin® and Xtampza ER®. OxyContin® utilizes the RESISTEC® technology that employs a combination of polymer and processing that gives tablet hardness, imparts viscosity when dissolved in aqueous solutions and resists increased drug release rate when mixed with alcoholic beverages.[10] Results from trials support that, the reformulated oxycodone ER is able to resist crushing, breaking, extraction and dissolution in small volumes using a variety of tools and solvents.[28-29] Xtampza ER® utilizes DETERx technology, which is designed to provide adequate pain control while maintaining its drug release profile after being subjected to common methods of manipulation, including chewing and crushing.[30,31]

Originally approved by the FDA in 2009, Embeda® (morphine sulfate/naltrexone hydrochloride) was voluntarily recalled from the market in March 2011 due to stability issues with the manufacturing process.[32] Subsequently, in November 2013, the FDA approved a manufacturing supplement for the product after the stability concerns were addressed through the manufacturing process. The abuse deterrent formulation of Embeda® (morphine sulfate/naltrexone hydrochloride) was granted FDA approval in October 2014, making it the third ER opioid analgesic to obtain this designation and the first among the morphine ER products.[33] Embeda® (morphine sulfate/naltrexone hydrochloride) capsules contain pellets consisting of morphine sulfate with a sequestered core of naltrexone hydrochloride at a ratio of 100:4.[18] If morphine sulfate/ naltrexone hydrochloride is crushed, chewed, or dissolved up to 100% of the sequestered naltrexone is released, reversing the effects of morphine, potentially precipitating withdrawal in opioid tolerant individuals, and increasing the risk of overdose and death.[33]

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

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Buprenorphine (Belbuca®, 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.	Buccal Film (Belbuca®): 75 µg 150 µg 300 µg 450 µg 600 µg 750 µg 900 µg 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 37.5 µg/hour 50 µg/hour 62.5 µg/hour 75 µg/hour 87.5 µg/hour 100 µg/hour	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
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 treatment options are inadequate.	Capsule, extended release (Zohydro ER®): 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‡	✔
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	✔
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‡	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		Capsule, extended release: 10 mg 20 mg 30 mg 40 mg 50 mg 60 mg 80 mg 100 mg‡ 200 mg‡ Tablet, extended release: 15 mg 30 mg 60 mg 100 mg‡ 200 mg‡	
Oxycodone (OxyContin®*, Xtampza 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 in adults (all formulations) and in opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent (extended release tablet).¶	Capsule, extended release (Xtampza ER®): 9 mg 13.5 mg 18 mg 27 mg 36 mg Tablet, extended release (OxyContin®): 10 mg 15 mg 20 mg 30 mg 40 mg 60 mg‡ 80 mg‡	✔ #
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	✔
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	Tablet, extended release: 50 mg 100 mg 150 mg 200 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	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.	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/ Acetaminophen (Xartemis XR®)	For the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate	Biphasic tablet, 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® or Xtampza ER® >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.[5,36]
- The efficacy and safety of buprenorphine buccal film was evaluated in three phase III clinical trials. However one of the clinical trials, which is currently not published, did not show a significant difference between buprenorphine and placebo.[1] The other two studies evaluated patients who had a diagnosis of chronic low back pain in a randomized withdrawal design. The first study evaluated opioid-naïve patients while the second study evaluated opioid-experienced patients. The double-blind treatment phase for both studies was 12 weeks.[1,38,39] In the first study, the increase in mean (standard deviation [SD]) pain intensity scores on the NRS from baseline to week 12 for buprenorphine buccal film (0.94 [1.85]) was significantly lower than that of patients who received placebo (1.59 [2.04]; P=0.0012).[38] The increase in mean (SD) pain intensity scores on the NRS from baseline to week 12 for buprenorphine buccal film was significantly less than that of placebo (0.88 [1.79] versus 1.92 [1.87], respectively; P<0.00001).[39]
- 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.[49-51]
- 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).[52]

- 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.[53] In a noninferiority analysis of a hydromorphone ER compared to oxycodone ER, two agents provided similar pain relief in the management of osteoarthritic pain.[54]
- 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.[58,59]
- 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.[61] 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).[62]
- 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.[32]
- Morphine/naltrexone has demonstrated significantly better pain control compared to placebo in patients with osteoarthritis pain.[65]
- Oxycodone ER (OxyContin®) has demonstrated significantly greater efficacy compared to placebo for the treatment of neuropathic pain and chronic refractory neck pain.[66-68] 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.[69]
- The FDA-approval of oxycodone ER (Xtampza ER®) was based upon an enriched-enrollment, randomized-withdrawal, double-blind, placebo-controlled, parallel group, study was conducted in patients with persistent, moderate-to-severe chronic lower back pain, with inadequate pain control from their prior therapy (n=740). Following the titration phase, 389 subjects met the study randomization criteria of adequate analgesia and acceptable tolerability and entered the randomized, double-blind maintenance phase. Patients were randomized at a ratio of 1:1 into a 12-week double-blind maintenance phase with their fixed stable dose of oxycodone ER (Xtampza ER® or matching placebo. There was a significant difference in pain reduction as assessed by average pain intensity favoring the oxycodone ER group when compared to placebo from randomization baseline to week 12 (0.29 vs. 1.85 ;P<0.0001).[71]
- 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. [72,73] 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.[72] In another trial, oxymorphone ER demonstrated greater efficacy for the relief of osteoarthritis pain compared to placebo.[74]
- 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).[76] 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).[77] 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).[75]

- 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).[83]
- 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%).[84]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - The current clinical guidelines regarding the use of opioids recognize their established efficacy in the treatment of moderate to severe pain. None of the available agents are distinguished from the others in the class, and recommendations for treatment are made for the class as a whole.[86-98]
    - Guidelines published by Centers for Disease Control and Prevention's (CDC) opioid use in the management of chronic pain recommend physicians start with immediate-release (IR) opioids and reserve ER formulations for severe, continuous pain that IR opioids cannot treat.[86]
    - Physicians should prescribe the lowest effective dose and carefully reassess benefits and risks when considering a dose of ≥50 morphine milligram equivalents (MME) while avoiding increasing opioid doses to ≥90 MME unless justified.[86]
    - Optimal analgesic selection will depend on the patient's pain intensity, any current analgesic therapy, and concomitant medical illness. ER products are generally similar and selection should be based on clinical or patient-specific factors.[87]

- Other Key Facts:[1-19]
    - Products currently available as a generic include fentanyl patches, hydromorphone ER tablets, methadone (all formulations), morphine ER (all formulations), oxycodone ER tablets and oxymorphone ER tablets.
    - There are currently several abuse deterrent ER opioids approved by the FDA. These include buprenorphine sublingual film (Belbuca®), oxycodone ER (OxyContin®, Xtampza ER®) and hydrocodone ER (Zohydro ER®, Hysingla ER®) as well as morphine sulfate/naltrexone (Embeda®).
    - Oxymorphone ER (Opana ER®) and hydromorphone ER (Exalgo®) have also been formulated with abuse deterrent properties, however they are classified as abuse deterrent by the FDA.
    - All long-acting opioids are pregnancy category C, with the exception of oxycodone.
    - Only fentanyl transdermal system (age 2 to 17 years) and oxycodone ER tablets (age 11 and older) are approved for use in children
    - Tapentadol is contraindicated with monoamine oxidase inhibitors; although, caution should be used when used in combination with any long-acting opioid.
    - 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.
- Frequency of dosing varies by agent:
  - Buprenorphine patch: once every seven days
  - Fentanyl transdermal system: once every 72 hours
  - Hydromorphone ER (Exalgo®), hydrocodone ER (Hysingla ER®) and morphine ER (Avinza®): once daily
  - Morphine ER (Kadian®) and morphine/naltrexone (Embeda®): once or twice daily
  - Morphine ER (MS Contin®) and all methadone formulations: twice or three times daily
  - All remaining long-acting agents: twice daily
- Avinza® (morphine) and Xartemis XR® (oxycodone/acetaminophen) are the only long-acting opioids with a maximum daily dose.
  - Avinza® (morphine): 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): max dose is limited to four tablets per day, and/or if taking other acetaminophen products, a maximum of 4,000 mg/day[19]
- 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]
  - Morphine ER capsules (Avinza®, Kadian®), morphine/naltrexone capsules (Embeda®) and oxycodone ER capsules (Xtampza ER®) can be opened and the pellets sprinkled on applesauce and then swallowed whole.[11,12,15,18]
  - Kadian® pellets can also be placed in water and used through a gastrostomy tube.
  - Xtampza® may be opened and administered through a gastrostomy or nasogastric tube.
  - Avinza®, Kadian®, and Embeda® pellets should not be used thorough a nasogastric tube.
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HH. Anti-Hepatitis Agents – Protease Inhibitor Agents

Therapeutic Class: Anti-Hepatitis Agents-Protease Inhibitors
Last Reviewed by the DUR Board: January 22, 2015

Victrelis® (boceprevir), Incivek® (telaprevir), and Olysio® (simeprevir) are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the Social Security Act and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

Approval will be given if the following criteria are met and documented:

a. Victrelis® (boceprevir)

1. For treatment initiation (treatment weeks 5 through 28), the recipient must have all of the following:

a. The recipient has a diagnosis of chronic hepatitis C genotype 1 infection; and

b. The recipient will be treated with peginterferon alfa and ribavirin for four weeks prior to starting Victrelis® (boceprevir) and will continue peginterferon alfa and ribavirin for the entire duration of treatment with Victrelis® (boceprevir); and

c. The recipient has not received a previous course of therapy with Incivek® (telaprevir), Olysio® (simeprevir) or Victrelis® (boceprevir) unless the drug is being switched due to an adverse event with the alternative drug.

2. For treatment continuation for treatment weeks 28 through 36, the recipient must have one of the following:

a. The recipient is treatment-naïve and their HCV-RNA level was detectable at treatment week eight and undetectable at treatment week 24; or

b. The recipient is a previous partial responder or a relapser to peginterferon alfa and ribavirin and their HCV-RNA was undetectable at treatment week eight and treatment week 24.

3. For treatment continuation for treatment weeks 28 through 48, the recipient must have one of the following:

a. The recipient has a diagnosis of chronic hepatitis C genotype 1 with compensated cirrhosis and their HCV-RNA was detectable at treatment week 24; or

b. The recipient had a <2-$\log_{10}$ HCV-RNA drop by treatment week 12 on prior treatment with peginterferon alfa and ribavirin and HCV-RNA on triple therapy is undetectable at treatment week 24; or

c. The recipient is treatment-naïve and poorly interferon responsive based on <1-$\log_{10}$ decline in HCV-RNA at treatment week four following lead-in therapy with peginterferon alfa.

b. Incivek® (telaprevir)

1. For treatment initiation (weeks one through eight) the recipient must have all of the following:

a. The recipient has a diagnosis of chronic hepatitis C genotype 1 infection; and

b. The recipient will be treated with concomitant peginterferon alfa plus ribavirin; and

c. The recipient has not received a previous course of therapy with Incivek® (teaprevir), Olysio® (simeprevir) or Victrelis® (boceprevir) unless the drug is being switched due to an adverse event with the alternative drug.

2. For treatment continuation for treatment weeks nine through 12:

a. The recipient is treatment-naïve and their HCV-RNA level was <1000 IU/mL at treatment week four.

c. Olysio® (simeprevir)

1. For treatment initiation (treatment weeks one through eight), the recipient must meet all of the following:

a. The recipient has a diagnosis of chronic hepatitis C genotype 1 infection; and

b. The recipient will be treated with concomitant peginterferon alfa plus ribavirin; and

c. The recipient has not received a previous course of therapy with Incivek® (telaprevir), Olysio® (simeprevir), or Victrelis® (boceprevir) unless the drug is being switched due to an adverse event with the alternative drug; and

d. The recipient has been pre-screened and does not test positive for the 1A NS3 Q80K polymorphism.

2. For treatment continuation for treatment weeks nine through 12, the recipient must have one of the following:

a. The recipient is treatment-naïve, and their HCV-RNA level was <25 IU/mL at treatment week four; or

b. The recipient is a previous prior relapser and their HCV-RNA level was <25 IU/mL at treatment week four; or

c. The recipient is a partial or a null-responder to previous therapy of interferon and ribavirin alone (no other HCV protease inhibitors) and their HCV-RNA was <25 IU/mL at treatment week four.

3. The initial prescription for Olysio, with peginterferon alfa and ribavirin must be for a two week supply. Subsequent refills can be up to 34 days.

2. Prior Authorization Guidelines:

a. Victrelis® (boceprevir)

1. Initial prior authorization will be for 24 weeks (through treatment week 28).

2. For recipients meeting criteria for continuation treatment for treatment weeks 28 through 36, a prior authorization may be renewed once for an additional eight weeks.

3. For recipients meeting criteria for continuation treatment for treatment weeks 28 through 44, a prior authorization may be renewed once for an additional 24 weeks.

b. Incivek® (teleprevir) and Olysio® (simeprevir)

1. Initial prior authorization approval will be for eight weeks.

2. For recipients meeting criteria for continuation treatment for treatment weeks nine through 12, a prior authorization approval may be renewed once for an additional four weeks.

c. Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

Therapeutic Class Overview
Direct Acting Hepatitis C Antivirals and Combinations

Overview/Summary:
The direct acting hepatitis C antiviral and combination products are all Food and Drug Administration (FDA)-approved for the treatment of chronic hepatitis C virus (HCV) infection; although, differences in indications exist relating to use in specific genotypes, with certain combination therapies and other patient factors.[1-9] Daklinza® (daclatasvir) is a once-daily NS5A inhibitor indicated for use with an NS5B polymerase inhibitor Sovaldi® (sofosbuvir) for 12 weeks in the treatment of patients with chronic hepatitis C virus (HCV) genotype 3 infection. It is the first Food and Drug Administration (FDA)-approved all-oral regimen for the HCV genotype 3 infection that does not require co-administration of interferon or ribavirin.[1] Technivie® (ombitasvir/paritaprevir/ ritonavir) in combination with ribavirin is the first interferon-free Food and Drug Administration (FDA)-approved drug for the treatment of HCV genotype 4 infection.[7]

HCV is an enveloped ribonucleic acid virus that is transmitted through exposure with infected blood and is the most common bloodborne infection in the United States, with an estimated prevalence of 3.2 million people chronically infected. Chronic HCV develops in 70 to 85% of HCV-infected persons and is associated with significant morbidity (e.g., cirrhosis, hepatocellular carcinoma [HCC]) and is the leading cause of liver transplantation.[10-12] The average annual incidence rate of HCC in the U.S. between 2001 and 2006 was 3.0 per 100,000 people, with 48% to cases attributed to HCV.[11] These agents act via several different mechanisms of action to exert their therapeutic effect.[1-9] Daclatasvir (Daklinza) binds to the N-terminus of NS5A, a nonstructural protein encoded by HCV, and inhibits both viral ribonucleic acid (RNA) replication and virion assembly.[1] Simeprevir (Olysio®) works via inhibition of the HCV NS3/4A protease of HCV genotype 1a and 1b, thus preventing replication of HCV host cells.[2] Similarly, sofosbuvir (Sovaldi®) inhibits HCV NS5B polymerase which also prevents the replication of HCV host cells, however, it is active against multiple genotypes of HCV.[3] The combination products that include direct acting hepatitis C antivirals include ledipasvir/sofosbuvir (Harvoni®), ombitasvir/paritaprevir/ritonavir (Technivie®), and ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira Pak®), elbasvir/grazoprevir (Zepatier®) and sofosbuvir/velpatasvir (Epclusa®). Grazoprevir and paritaprevir inhibit NS3/4A protease, dasabuvir inhibits NS5B polymerase and elbasvir, ledipasvir, ombitasvir and velpatasvir specifically inhibit HCV non-structural protein NS5A. Ritonavir, when used in Technivie® and Viekira Pak®, is used as a boosting agent that increases the peak and trough plasma drug concentrations of paritaprevir along with overall drug exposure; it has no direct effect on the hepatitis C virus.[4-8] Specific indications for each of the direct acting hepatitis C antiviral agents are listed in Table 1.

Efficacy of these agents have been established in multiple clinical trials with numerous clinical trials still underway.[13-47] Generally, therapy is determined by clinical guidelines developed by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America and International Antiviral Society (IDSA) rather than the FDA-approved labels of these agents.[48] The newer combination regimens that include direct hepatis C antivirals are preferred over older pegylated interferon-based regimens (including those containing older protease inhibitors) due to a higher sustained virologic response (SVR) rate, improved side effects profile, and reduced pill burden. However, many different regimens with direct-acting agents or combinations, which may or may not also include ribavirin or pegylated interferon, are recommended based on HCV genotype, previous treatment experience and certain special populations. Each of the direct HCV antivirals is recommended as part of at least one first-line regimen.[48-50] Currently, there are no generic direct-acting antivirals available.

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

Generic (Trade Name)	FDA Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agents			
Daclatasvir (Daklinza®)	Treatment of chronic HCV genotype 3 infection in adults as part of a combination antiviral regimen	Tablet: 30 mg 60 mg	-
Simeprevir (Olysio®)	Treatment of chronic HCV genotype 1,4	Capsule: 150	-

Generic (Trade Name)	FDA Approved Indications	Dosage Form/Strength	Generic Availability
	infection in adults as part of a combination antiviral regimen	mg	
Sofosbuvir (Sovaldi®)	Treatment of chronic HCV genotype 1, 2, 3, and 4 infection in adults as part of a combination antiviral regimen	Tablet: 400 mg	-
Combination Products			
Elbasvir/grazoprevir (Zepatier®)	Treatment of chronic HCV genotype 1 and 4 infection in adults as part of a combination antiviral regimen	Tablet: 50/100 mg	-
Ledipasvir/sofosbuvir (Harvoni®)	Treatment of chronic HCV genotype 1, 4, 5, and 6 infection in adults as part of a combination antiviral regimen	Tablet: 90/400 mg	-
Ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira Pak®)	Treatment of chronic HCV genotype 1 infection in adults as part of a combination antiviral regimen	Tablet (dasabuvir): 250 mg Tablet (ombitasvir/ paritaprevir/ ritonavir): 12.5/75/50 mg	-
Ombitasvir/paritaprevir/ ritonavir (Technivie®)	Treatment of chronic HCV genotype 4 infection in adults as part of a combination antiviral regimen	Tablet: 12.5/75/50 mg	-
Sofosbuvir/velpatasvir (Epclusa®)	Treatment of chronic HCV genotypes 1, 2, 3, 4, 5 or 6 in adults	Tablet: 400 mg/100 mg	-

FDA=Food and drug administration, HCV=hepatitis C virus

Evidence-based Medicine

- Clinical trials have demonstrated the safety and efficacy of the direct acting hepatitis C antivirals in various genotypes and regimens.[13-47] Overall, data from clinical trials support the FDA-approved indications and dosing recommendations for these agents.
- The FDA approval of daclatasvir was based on the results of ALLY-3, an open-label study evaluating 12 week regimen of daclatasvir 60 mg plus sofosbuvir 400 mg in treatment-naive and treatment-experienced patients with chronic HCV genotype 3 infection. The primary endpoint was the SVR at post treatment week 12 (SVR12). High SVR12 rates were observed among patients without cirrhosis: 97% (73/75) and 94% (32/34) in treatment-naïve and treatment-experienced patients, respectively. In contrast, SVR12 rates in cirrhotic patients were much lower: 58% (11/19) and 69% (9/13) in treatment-naïve and treatment-experienced patients, respectively.[33]
    - An ongoing randomized phase III study is evaluating a combination of daclatasvir, sofosbuvir and ribavirin for 12 or 16 weeks to determine whether the addition of ribavirin or extending treatment duration improved SVR rates in cirrhotic patients with HCV genotype 3 infection.[34]
- The efficacy of simeprevir in patients with HCV genotype 1 infection was evaluated in several unpublished studies, including two phase III trials in treatment-naïve patients (QUEST 1 and QUEST 2), one phase III trial in patients who relapsed after prior interferon-based therapy (PROMISE).[2]
    - In the pooled analysis of QUEST 1 and QUEST 2, a greater proportion of patients in the simeprevir group achieved SVR at 12 weeks (SVR12) compared to control group (80 vs 50%; P value not reported).[2]
- The safety and efficacy of simeprevir in combination with sofosbuvir with or without ribavirin for the treatment of hepatitis C genotype 1 was evaluated in the COSMOS trial. Cohort 1 included prior null responders with METAVIR scores F0 to F2 and Cohort 2 included prior null responders and treatment-naïve patients with METAVIR scores F3 to F4.[2,27]
    - SVR at 12 weeks post therapy (SVR12) was achieved in 92% of the patients in the the intention to treat (ITT) population. SSVR12 for Cohort 1 and Cohort 2 were 90% (95% CI, 81

to 96) and 94% (95% CI, 87 to 98), respectively. The results were not significantly altered by use of ribavirin, duration of treatment, or treatment history (no P values reported). [20]

- The FDA approval of sofosbuvir was based on the results of five phase III trials (N=1,724) in HCV mono-infected patients (genotypes 1 to 6) and one unpublished phase III trial (N=223) in HCV/HIV-1 co-infected patients (HCV genotype 1, 2 or 3).[13,31,32]
    - All trials utilized SVR12 as the primary endpoint and overall, these studies showed that sofosbuvir provided a significant improvement in SVR12 compared with control in both treatment-naïve and treatment-experienced patients.[13,31,32]
    - Sofosbuvir was not specifically studied in treatment-experienced patients with HCV genotype 1 infection. According to the prescribing information, the estimated response rate in patient who previously failed treatment with peginterferon alfa and ribavirin is 71%. This is based on the observed response rate in patients from the NEUTRINO study.[13]
- The FDA-approval of elbasvir/grazoprevir was based on two placebo-controlled trials and four uncontrolled phase II and III clinical trials in 1,401 patients with genotype HCV genotype 1, 4, or 6 chronic HCV with compensated liver disease (C-EDGE TN, C-EDGE COINFECTION, C-SURFER, C-SCAPE, C-EDGE TE, and C-SALVAGE). All clinical trials evaluated SVR12 as the primary endpoint. Elbasvir/grazoprevir was administered once daily in all trials and ribavirin, if received, was dosed by weightd.[4,14-20]
    - After 12 weeks to therapy, SVR12 rates in C-EDGE TN were 91.7% (genotype 1a), 98.5% (genotype 1b), 100% (genotype 4), and 80% (genotype 6). SVR12 was achieved in 97.1% of cirrhotic patients and 93.9% (231/246) of noncirrhotic patients.[14] After 12 weeks to therapy, SVR12 rates in C-EDGE COINFECTION (HIV-coinfection) were 96.5% (genotype 1a), 95.5% (genotype 1b), 96.4% (genotype 4), and 100% (genotype 6) with 100% of cirrhotic patients. All 35 patients with cirrhosis achieved SVR12.[15] The SVR12 rate after 12 weeks of therapy in C-SURFER (chronic kidney disease) was 99.1%.[16] The overall SVR12 rate in C-SALVAGE (genotype 1, previously failed ≥4 weeks of peginterferon alfa and ribavirin combined with a protease inhibitor [boceprevir, telaprevir, or simeprevir]) was 96.2% overall, including 91.2% in patients with baseline NS3 resistance, and 94.1% (32/34) in cirrhotic patients.[17,18] C-WORTHY (N=471) was a phase II, randomized, parallel-group, multicenter, open-label study comparing grazoprevir plus elbasvir with or without ribavirin in different patient populations (20 arms total) with chronic HCV genotype 1 infection. SVR12 rates ranged from 80% to 100%.[19,20]
- The FDA approval of combination ledipasvir/sofosbuvir was based on the results of three phase III trials (N=1,518) in HCV mono-infected subjects with genotype 1 infection who had compensated liver disease. Treatment duration was fixed in each trial and was not guided by subjects' HCV RNA levels.[20,21,25]
    - ION-1 evaluated treatment-naïve patients include patients with cirrhosis; ION-2 evaluated patients with or without cirrhosis who failed previous therapy with an interferon-based regimen including those containing an HCV protease inhibitor; ION-3 evaluated non-cirrhotic, treatment-naïve patients.[21,22,26]
    - All studies showed that ledipasvir/sofosbuvir significantly improved SVR12 rate compared to control. [21,22,26]
- The FDA approval of ombitasvir/paritaprevir/ritonavir and dasabuvir was based on the results of six randomized, multicenter, clinical trials (N=2,308) in HCV patients with genotype 1, including one trial exclusively in patients with cirrhosis and mild hepatic impairment (Child-Pugh A). All studies included at least one treatment arm with ribavirin, while several studies included treatment arms without ribavirin.[23-25,28,29]
    - Study populations for each of the studies include treatment-naïve, non-cirrhotic adults with HCV genotype 1 infection (SAPPHIRE-I), treatment-naïve, non-cirrhotic adults with HCV genotype 1b and HCV genotype 1a infections (PEARL-III and PEARL-IV, respectively), treatment-naïve or previously treated with peginterferon alfa and ribavirin cirrhotic adults with HCV genotype 1 infection (TURQUOISE-II), noncirrhotic adults with HCV genotype 1 infection who either relapsed or were nonresponders to prior peginterferon alfa and ribavirin therapy (SAPPHIRE-II) and finally, non-cirrhotic adults with HCV genotype 1b infection who either relapsed or were nonresponders to prior peginterferon alfa and ribavirin therapy (PEARL-II). [23-25,28,29]

  - Overall, SVR12 rates were high and significantly improved compared with control after 12 weeks of therapy. [23-25,28,29] Only TURQUOISE-II evaluated patients beyond 12 weeks of therapy and found there was no difference between 12 weeks of therapy compared with 24 weeks of therapy (P=0.09).[25]
- The FDA-approval of ombitasvir/paritaprevir/ritonavir in the treatment of HCV genotype 4 was based on the results of an open-label, randomized, multicenter phase IIb PEARL-I study, which evaluated ombitasvir/paritaprevir/ritonavir with or without ribavirin and no cirrhosis. Patients were either treatment-naïve or treatment experienced (prior failure of peginterferon alfa and ribavirin). In treatment-naive patients, the SVR12s were 100% (42/42) in the ribavirin-containing regimen and 90.9% (40/44) in the ribavirin-free regimen. In the treatment-naive group without ribavirin, on-treatment virologic breakthrough was reported in one patient (2%), two patients (5%) experienced post-treatment relapse, and one patient (2%) was lost to follow-up. All 49 treatment-experienced patients in the ribavirin-containing group achieved SVR12.[35]
  - AGATE-I is an ongoing phase III study evaluating ombitasvir/paritaprevir/ritonavir with ribavirin for 12, 16 or 24 weeks in cirrhotic patients with HCV genotype 4 infection, including treatment-naïve patients and those who have failed peginterferon alfa and ribavirin or sofosbuvir-containing regimens.[36]
  - TURQUOISE-CPB is another ongoing phase III study evaluating ombitasvir/paritaprevir/ritonavir with ribavirin for 24 weeks in patients with HCV genotype 4 infection and decompensated cirrhosis.[37]
  - Several other studies are planned or recruiting patients to evaluate ombitasvir/paritaprevir/ritonavir with or without ribavirin in less well studied subpopulations with HCV genotype 4 infection, including severe renal disease, children (three to 17 years old), and status post successful treatment of early stage hepatocellular carcinoma.[38-41]
- The FDA-approval of sofosbuvir/velpatasvir was based on the results of four phase III studies (ASTRAL-1, ASTRAL-2, ASTRAL-3, and ASTRAL-4) in patients with HCV genotype 1 through 6.
  - ASTRAL-1 (N=706) was a phase III, randomized, double-blind, placebo-controlled study evaluating sofosbuvir/velpatasvir 400 mg/100 mg once daily for 12 weeks in adult patients with chronic HCV genotype 1, 2, 4, 5, or 6 infection. Overall, SVR12 rate in the sofosbuvir/velpatasvir group of 99% (618/624) was higher than the prespecified benchmark rate of 85% (P<0.001). [42]
  - ASTRAL-2 (N=266) and ASTRAL-3 (N=552) were two phase III, randomized, open-label studies comparing sofosbuvir/velpatasvir 400 mg/100 mg once daily for 12 weeks to sofosbuvir 400 mg plus weight-based ribavirin for 12 weeks (ASTRAL-2) or 24 weeks (ASTRAL-3) in adult patients with chronic HCV genotype 2 and HCV genotype 3 infections, respectively. Among patients with HCV genotype 2, the overall SVR12 rate in the 12-week sofosbuvir/velpatasvir group was 99% (133/134) as compared to 94% (124/132) in the 12-week sofosbuvir/ribavirin (P=0.02). Among patients with HCV genotype 3, the overall SVR12 rate in the 12-week sofosbuvir/velpatasvir group was 95% (264/277) as compared to 80% (221/275) in the 24-week sofosbuvir/ribavirin group (P<0.001).[43]
  - ASTRAL-4 (N=267) was a phase III, randomized, open-label study evaluating sofosbuvir/velpatasvir 400 mg/100 mg once daily for 12 weeks (with or without ribavirin) or 24 weeks in adult patients with chronic HCV genotype 1, 2, 4, or 6 infection and decompensated cirrhosis (Child-Turcotte-Pugh class B). Overall SVR12 rates were 83% (75/90), 94% (82/87), and 86% (77/90) among patients who received sofosbuvir/velpatasvir for 12 weeks, sofosbuvir/velpatasvir and ribavirin for 12 weeks, and sofosbuvir/velpatasvir for 24 weeks, respectively.[44]
  - Other trials are ongoing and full results have not been published. Sofosbuvir/velpatasvir has been evaluated in treating HCV/HIV coinfection in patients with genotypes 1 through 4 (ASTRAL-5), in patients with genotypes 1 through 3 and previous sofosbuvir/velpatasvir failures and in patients undergoing liver transplant.[45-47]

Key Points within the Medication Class

- American Association for the Study of Liver Diseases, Infectious Diseases Society of America and International Antiviral Society-USA have included all current treatments in their guideline.[48]

- Old standards of therapy, including pegylated interferon alfa and ribavirin dual therapy and pegylated interferon alfa, ribavirin along with a protease inhibitor triple therapy are no longer recommended.
- Current, first-line therapies recommended in the new guidelines include all-oral combination therapies, each of which generally has at least one polymerase inhibitor and one other direct-acting agent that acts via a different mechanism of action.
- Each of the new HCV direct acting antivirals are recommended as part of a first-line regimen for at least one genotype and/or patient population.[48]
- Depending on genotype, previous treatment-experience and special populations, the recommended regimens and durations of treatment vary due to differences in efficacy provided by clinical trials.
    - For genotype 1, five regimens with similar efficacy are recommended. Duration and addition of ribavirin depend on cirrhosis status and/or previous treatment failures.
        - Daclatasvir 60 mg daily (QD) + sofosbuvir 400 mg QD ± ribavirin for 12 to 24 weeks
        - Ledipasvir/sofosbuvir 90/400 mg QD ± ribavirin for 12 to 24 weeks
        - Ombitasvir/ paritaprevir/ritonavir 25/150/100 mg QD + dasabuvir 250 mg twice-daily (BID) ± ribavirin for 12 to 24 weeks
        - Sofosbuvir 400 mg QD + simeprevir 150 mg QD for 12 to 24 weeks
        - Elbasvir/grazoprevir 50/100 mg QD ± ribavirin for 12 to 16 weeks
        - Sofosbuvir/velpatasvir 400 mg/100mg QD for 12 weeks
    - For genotype 2:
        - Daclatasvir 60 mg QD + sofosbuvir (400 mg) QD ± ribavirin for 12 to 24 weeks
        - Sofosbuvir/velpatasvir 400 mg/100mg QD ± ribavirin for 12 weeks
    - For genotype 3:
        - Daclatasvir (60 mg) and sofosbuvir (400 mg) ± ribavirin for 12 to 24 weeks
        - Sofosbuvir/velpatasvir 400 mg/100mg QD ± ribavirin for 12 weeks
    - For Genotype 4:
        - Ledipasvir/sofosbuvir 90/400 mg QD ± ribavirin for 12 to 24 weeks
        - Ombitasvir/ paritaprevir/ritonavir 25/150/100 mg+ ribavirin for 12 weeks
        - Elbasvir/grazoprevir 50/100 mg QD ± ribavirin for 12 to 16 weeks
        - Sofosbuvir/velpatasvir 400 mg/100mg QD for 12 weeks
    - Genotype 5 and 6:
        - Ledipasvir/sofosbuvir 90/400 mg QD for 12 weeks
        - Sofosbuvir/velpatasvir 400 mg/100mg QD for 12 weeks
    - In patients that fail a sofosbuvir, daclatasvir, ledipasvir/sofosbuvir, or paritaprevir/ritonavir/ombitasvir plus dasabuvir, it is recommended to defer therapy if they have minimal liver disease; guidelines do not offer a specific regimen for recipients with extensive liver disease, but recommend resistance-testing. They recommend treatment for at least 24 weeks with ribavirin, if not contraindicated.[48]

- Other Key Facts:
    - There are also disparities between the FDA-approved indications and first-line recommendations according to the AASLD-IDSA guidelines.[1-8,48]
    - Prior to initiating therapy with simeprevir (in combination with sofosbuvir) in cirrhotic patients with genotype 1a, they should be screened for the presence of NS3 Q80K polymorphism. Alternative therapy should be considered if this polymorphism is present.[2]
    - When prescribing ombitasvir/paritaprevir/ritonavir or ombitasvir/paritaprevir/ritonavir/dasabuvir, screening for drugs that should not be coadministered is recommended due to many, often severe, drug interactions.[5,6]
    - Dose of daclatasvir must be adjusted when given with strong CYP3A inhibitors (30 mg QD) and moderate CYP3A inducers (90 mg QD).[1]
    - Testing for NS5A-associated resistance is recommended prior to treatment with sofosbuvir, elbasvir/grazoprevir, ledipasvir/sofosbuvir and sofosbuvir/velpatasvir for several patient populations. [48]

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CC. Ampyra® (dalfampridine)

Therapeutic Class: Agents for the treatment of Neuromuscular Transmission Disorder
Last Reviewed by the DUR Board: July 25, 2013

Ampyra® (dalfampridine) is subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the Social Security Act and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

Approval for Ampyra® (dalfampridine) will be given if all of the following criteria are met and documented:

a. Ampyra® (dalfampridine)

The recipient must meet all of the following:

1. The recipient must have a diagnosis of Multiple Sclerosis ; and

2. The medication is being used to improve the recipient's walking speed; and

3. The medication is being prescribed by or in consultation with a neurologist; and

4. The recipient is ambulatory and has an EDSS score between 2.5 and 6.5; and

5. The recipient does not have moderate to severe renal dysfunction (CrCL >50 ml/min); and

6. The recipient does not have a history of seizures; and

7. The recipient is not currently pregnant or attempting to conceive.

2. Prior Authorization Guidelines

a. Initial Prior Authorization approval will be for three months.

b. Requests for continuation of therapy will be approved for one year.

c. Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

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) and include alemtuzumab (Lemtrada®), daclizumab (Zinbryta®), glatiramer acetate (Copaxone®, Glatopa®), interferon β (IFNβ)-1b (Betaseron®, Extavia®), intramuscular (IM) IFNβ-1a (Avonex®), subcutaneous (SC) IFNβ-1a (Rebif®), SC peginterferon β-1a (Plegridy®) along with the oral products dimethyl fumarate (Tecfidera®), fingolimod (Gilenya®) and teriflunomide (Aubagio®).[1-14] Both IFNβ-1b and IM IFNβ-1a are also FDA-approved for the treatment of patients experiencing a first clinical episode with magnetic resonance imaging (MRI) evidence of multiple sclerosis (MS), which is often referred to as a clinically isolated syndrome.[7,8,10] The exact mechanisms of action of daclizumab, dimethyl fumarate, teriflunomide, the INFs and glatiramer acetate are unknown or not completely understood but are likely due to their antiproliferative and immuno-modulatory effects.[2,3,5-12]

  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.[16-17] There are four clinical subtypes of MS: RRMS, primary progressive (PPMS), progressive relapsing (PRMS), and secondary progressive (SPMS).[16-19] The most common form is RRMS, characterized by acute relapses followed by partial or full recovery.[17,19] Patients with PPMS have a continuous and gradual decline in function without evidence of acute attacks. Patients with PRMS also have a continuous decline in function while experiencing occasional attacks. Finally, SPMS begins as RRMS, but as time progresses the attack rate declines and patients experience a gradual deterioration.[19]

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

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Alemtuzumab (Lemtrada)	Relapsing-remitting multiple sclerosis*		-
Daclizumab (Zinbryta®)	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: 0.5 mg	-
Glatiramer acetate (Copaxone®**, Glatopa®††)	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	Relapsing-remitting multiple sclerosis¶, treatment of first clinical episode with	Prefilled syringe: 30 µg	-

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Administration Pack®)	magnetic resonance imaging features consistent with multiple sclerosis	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.
#Treatment of patients with relapsing forms of multiple sclerosis in patients who have an inadequate response to two or more drugs indicated for the treatment of multiple sclerosis.
**Generic available in at least one dosage form or strength.
††Glatopa® is considered a biosimilar to reference product Copaxone®

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.
- The FDA-approval of daclizumab was based on the results of two randomized double-blind studies in adults with a diagnosis of relapsing MS (RMS). Both utilized the primary endpoint of annualized relapse rate (ARR). The first study evaluated 1,841 patients over 96 to 144 weeks who were randomized to either daclizumab 150 mg every four weeks or to IFN β-1a 30 µg weekly. Both groups received a placebo matching the other treatment arm. The ARR was significantly reduced in the daclizumab arm (0.216) compared with the IFN β-1a group (0.393) representing a relative reduction of 45% (P<0.0001).[2,33] The second study, SELECT, evaluated a total of 621 patients over 52 weeks who were randomized to daclizumab 150 mg every four weeks, daclizumab 300 mg every four weeks or placebo. The ARR was significantly lower in both the daclizumab 150 mg group (0.21) and the daclizumab 300 mg group (0.23) compared to the placebo group (0.46; P<0.001 for both).[2,34]
- 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).[37,61] 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).[61]
- 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).[38]
- The FREEDOMS II trial had similar results, with fingolimod providing a lower ARR over 24 months compared to placebo.[87]
- 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).[43] 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.[44]

- 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).[56] In an unpublished extension study, ARR remained low after five years and the adverse event rates were similar to those reported in previous trials.[57,58]
- The TOWER study showed that over one year teriflunomide had a lower ARR than placebo.[88]
- 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).[89]
- 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.[103,104]
- 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). [105]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - The approach to treating MS includes: the management of symptoms, treatment of acute relapses, and utilization of disease-modifying therapies to reduce the frequency and severity of relapses, and delay disease and disability progression.[14,16,19,22]
    - IFNβ products or glatiramer acetate are recommended as first-line therapy in patients with RRMS.[18,19]
    - The Association of British Neurologists also recommend either of the oral agents as potential first-line options.[18]
    - Due to its adverse effect profile, fingolimod is sometimes recommended as a second-line option.[19,20] NICE recommends use of fingolimod only if patients have an unchanged or increased relapse rate, or ongoing severe relapses compared to the previous year despite treatment with IFNβ.[20]
    - Consensus guidelines do not recommend a change of therapy in patients positive for neutralizing antibodies who are responding to IFN therapy, noting that neutralizing antibodies disappear with continued treatment in the majority of patients.[18,23-25]
    - A change of therapy may be considered in patients experiencing a suboptimal response or intolerable adverse effects.[26,28,29]
    - Data suggests a significant reduction in relapse rate and a delay in disease and disability progression in patients switching from IFNβ to glatiramer acetate therapy or vice versa due to poor response.[26,28,29]
- Other Key Facts:
    - A biosimilar version of Copaxone® (glatiramer acetate 20 mg/mL) was recently approved by the FDA and is marked under the trade name Glatopa®. There are no other generic MS products available, including other strengths of glatiramer acetate.[1-14]
    - 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®.[5,6]

- Alemtuzumab must be administered by a healthcare professional.
- Alemtuzumab and daclizumab are available only through restricted access programs. Both are associated with causing serious autoimmune disorders. In addition, alemtuzumab has been associated with life threatening infusion reactions as well as increased risk of malignancy.[1,2]

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MM. Natroba® (spinosad)

Therapeutic Class: Topical Antiparasitics
Last Reviewed by the DUR Board: July 26, 2012

Natroba® (spinosad) is subject to prior authorization.

1. Coverage and Limitations

Authorization will be given if the following criteria are met and documented:

a. The recipient has experienced an allergy or adverse event with a permethrin or pyrethrin-containing pediculicide product; or

b. The recipient has experienced a treatment failure with a permethrin or pyrethrin-containing pediculicide product despite a full course of treatment (two applications); or

c. The recipient has a contraindication to treatment with permethrin or pyrethrin-containing pediculicide product.

2. Prior Authorization Guidelines

a. Prior authorization approval will be for the date of service only.

b. Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

Therapeutic Class Overview
Scabicides and Pediculicides

Therapeutic Class

- **Overview/Summary:** The agents indicated for the management of scabies and head lice are listed in Table 1. The skin and mucous membrane scabicides and pediculicides are approved to treat pediculosis and scabies.[1-10] Pediculosis is a transmissible infection, which is caused by three different kinds of lice depending on the location: head (*Pediculus humanus capitis*), body (*Pediculus humanus corporis*) and pubic region (*Phthirus pubis*). Pediculosis is often asymptomatic; however, itching may occur due to hypersensitivity to lice saliva.[11] Scabies is also a transmissible skin infection caused by the mite *Sarcoptes scabiei.* Mites burrow into the skin and lay eggs, which when hatched, will crawl to the skin's surface and begin to make new burrows. The most common clinical manifestation of scabies is itching, which is due to a hypersensitivity reaction to the mite or mite excrement.[12] When treating scabies and lice, the goal of therapy is to eradicate the parasite. Benzyl alcohol inhibits lice from closing their respiratory spiracles, which causes the lice to asphyxiate.[3] Crotamiton has scabicidal and antipruritic actions; however, the exact mechanism of action is unknown.[4] Lindane is a central nervous system stimulant, which causes convulsions and death of the arthropod.[1,2] Malathion is an organophosphate agent, which inhibits cholinesterase activity.[5] Permethrin disrupts the sodium channel current, which leads to delayed repolarization and paralysis of the arthropod.[1,2] Spinosad causes neuronal excitation, which leads to paralysis and death.[6] The suspension also contains an unspecified amount of benzyl alcohol. Retreatment with benzyl alcohol and permethrin is required after seven to 10 days to eradicate the infestation. The newest agent in the class ivermectin, is pediculicidal but not ovicidal and it is approved as a single application product only.[7] Lindane, malathion, permethrin, spinosad, and piperonyl butoxide and pyrethrins products are available generically, while permethrin, and piperonyl butoxide and pyrethrins products are also available over-the-counter.

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
Single-Entity Agents			
Benzyl alcohol (Ulesfia®)	Treatment of head lice	Lotion: 5% (227 g/bottle)	-
Crotamiton (Eurax®)	Treatment of scabies	Cream: 10% (2 oz/ tube) Lotion: 10% (2 oz/bottle, 16 oz/bottle)	-
Ivermectin (Sklice®)	Treatment of head lice	Lotion: 0.5% (4 oz/tube)	-
Lindane*	Treatment of head and pubic lice	Shampoo: 1% (2 oz/bottle)	✔
Malathion (Ovide®*)	Treatment of head lice	Lotion: 0.5% (2 oz/ bottle)	✔
Permethrin*† (Acticin®, Nix Complete Lice System®*†, Nix Crème Rinse®*†)	Treatment of head lice and scabies	Cream: 5% (2 oz/tube) Liquid: 1% (2 oz/bottle) Lotion: 1% (2 oz/bottle, 4	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		oz/bottle)	
Spinosad (Natroba®*)	Treatment of head lice	Topical Suspension: 0.9% (4 oz/bottle)	✔
Combination Products			
Piperonyl butoxide and pyrethrins*† (Licide Complete Lice Treatment Kit®*†, Pronto®*†, RID®*†)	Treatment of head, body and pubic lice	Gel: 4/0.33% (each kit) Shampoo: 4/0.33% (each kit) Solution: 4/0.33% (each kit)	✔

*Generic available in one dosage or strength.
†Over-the-counter product is available in at least one dosage form or strength.

Evidence-based Medicine

- In two, randomized, active-controlled trials in patients with an active head lice infestation, a greater proportion of patients were lice-free 14 days following treatment with spinosad alone compared to patients who received permethrin plus nit combing (P<0.001 for both trials).[13]
- The combined results of two identical, vehicle-controlled trials (N=765) in patients six months and older with head lice showed that significantly more patients treated with ivermectin lotion were lice-free on day two (94.9 vs 31.3%), day eight (85.2 vs 20.8%) and remained lice-free through day 15 (73.8 vs 17.6%; P<0.001 for each day) compared to the vehicle group.[14]
- In two studies comparing benzyl alcohol to its vehicle, the absolute difference in treatment success rate in study one was 71.4% in favor of benzyl alcohol (95% confidence interval [CI], 61.8 to 85.7) and 48.8% (95% CI, 31.1 to 62.0) in study two, again in favor of benzyl alcohol. Benzyl alcohol was associated with a lower risk of treatment failure in both studies (P<0.001 for both).[15]
- For the treatment of lice, permethrin has demonstrated a higher rate of treatment success compared to lindane, following a single application.[16-19] Compared to the combination of pyrethrins and piperonyl butoxide, permethrin was more efficacious several days following treatment; however, one study found the agents to be equally effective at 14 days following treatment (P>0.01).[20,21] In multiple studies, malathion has been reported to be pediculicidal and ovicidal when compared to permethrin.[22,23]
- In studies comparing various topical agents for the treatment of scabies, a higher cure rate has been demonstrated with permethrin compared to crotamiton and lindane.[24-29] In the largest study completed (N=467), Schultz et al reported that there was a trend towards a higher cure rate with permethrin treatment compared to lindane; however, the difference was not statistically significant.[25]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Permethrin and pyrethrin products are recommended for treatment of scabies and lice, despite increasing resistance in the United States. These agents are available over-the-counter without a prescription.[29,30]
  - Malathion 0.5% can be used in people who are ≥24 months of age when resistance to permethrin or pyrethrins is documented or when treatment with these products fails despite their correct use. Due to the high alcohol concentration of the product it is highly flammable.[29,30]
  - Permethrin is the most studied pediculicide and is the least toxic to humans. Permethrin is less allergenic than pyrethrins and does not cause allergic reactions in individuals with plant allergies.[30]
  - Lindane has low ovicidal activity (30 to 50% of eggs are not killed), and resistance has been reported worldwide for many years. For these reasons, it should be used cautiously. The Food

and Drug Administration (FDA) has warned that incorrect use of lindane can be neurotoxic and its use should be restricted to patients for whom prior treatments have failed or in those patients who cannot tolerate safer medications. [29,30]
    - Lindane should not be used to treat premature infants, persons with the human immunodeficiency virus, seizure disorders, women who are pregnant or breast-feeding, persons who have very irritated skin or sores where the lindane will be applied, infants, children, the elderly, and persons who weigh <110 pounds. [29,30]
    - Permethrin is the drug of choice for the treatment of scabies. Two (or more) applications may be necessary to eliminate all mites, particularly when treating crusted (Norwegian) scabies.
    - Crotamiton is approved for the treatment of scabies in adults but is frequently associated with treatment failure.[31]
    - Lindane is not recommended as a first-line therapy for the treatment of scabies due to its potential for toxicity with frequent or incorrect use. Lindane should be restricted to patients who have failed recommended therapies or who cannot tolerate recommended treatments.[31]
- Other Key Facts:
    - Several first-line therapies are available generically in at least one strength or formulation.[1]
    - According to the manufacturer, spinosad is the first FDA-approved head lice treatment that does not require nit combing following treatment.[33]
    - Ivermectin is approved for use as a single application only and is not indicated for retreatment.[7]
    - Reasons for treatment failure with the topical scabicide and pediculicide products include misdiagnosis, noncompliance, failure to follow instructions correctly, not enough pediculicide applied, reinfestation, and resistance. If resistance is suspected, retreatment should be with a different chemical entity than initially used.[34]

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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	✔
Ferric citrate (Auryxia®)	Control serum phosphorus in patients with chronic kidney disease on dialysis.	Tablet: 210 mg	
Lanthanum carbonate (Fosrenol®)	Reduce phosphate with end stage renal disease.	Tablet, chewable: 500 mg 750 mg 1,000 mg Oral Powder: 750 mg 1,000 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Sevelamer carbonate (Renvela®)	Control serum phosphorus in patients with chronic kidney disease on dialysis.	Powder for oral suspension: 0.8 g 2.4 g 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-analyses 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.
    - 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
Neurokinin-1 (NK1) Receptor Antagonists and Combinations

Therapeutic Class Overview/Summary:
This review will focus on miscellaneous antiemetics, which includes doxylamine succinate/pyridoxine hydrochloride (Diclegis®) as well as the neurokin-1 (NK_1) receptor antagonists/combinations. NK_1 antagonists are all Food and Drug Administration (FDA)-approved for the prevention of chemotherapy-induced nausea and vomiting (CINV).[1-5] Single-entity NK_1 antagonists include: aprepitant (Emend®), its prodrug fosaprepitant dimeglumine (Emend®), and rolapitant hydrochloride (Varubi®). There is a single NK_1 antagonist combination product currently available, netupitant/palonosetron (Akynzeo®). With this combination, netupitant, the NK_1 antagonist is co-formulated with palonosetron, a serotonin type-3 (5-HT_3) receptor antagonist. In addition to CINV, aprepitant is FDA-approved for the prevention of post-operative nausea and vomiting in adults.[1-4] Differences in anti-emetic effect for the acute and delayed phases of CINV exist between NK_1 antagonists and are summarized in Table 2. Doxylamine/pyridoxine is FDA-approved for the treatment of nausea and vomiting of pregnancy.[5]

As the pathophysiology of CINV is not completely understood, the exact mechanisms by which NK_1 antagonists exert there antiemetic effects are not known. NK_1 is a broadly distributed receptor located in both the central and peripheral nervous systems. One proposed mechanism of NK_1 antagonists is by depressing the substance P mediated response in the central nevous system by blocking activation of NK_1 in areas of the brain responsible for chemoreception. Decreased activation of NK_1 by substance P reduces the emetic reflex. A second proposed mechanism is the blockade of peripheral NK_1 receptors located on the vagal terminals of the gut. It is hypothesized that peripheral blockade may decrease the intensity of the signal transmitted to the central nervous system, thus decreasing the overall emetic reflex.[1-4,6,7] 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.[5,8,9]

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

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Aprepitant (Emend®)	Prevention of acute and delayed CINV associated with initial and repeat courses of HEC, Prevention of CINV associated with initial and repeat courses of MEC, Prevention of PONV	Capsule: 40 mg 80 mg 125 mg Capsule, Dose Pack: 125 and 80 mg Oral Suspension: 125 mg/5 mL	-
Fosaprepitant dimeglumine (Emend®)	Prevention of acute and delayed CINV associated with initial and repeat courses of HEC, Prevention of delayed CINV associated with initial and repeat courses of MEC	Vial: 150 mg	-
Rolapitant hydrochloride	Prevention of delayed CINV	Tablet:	-

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
(Varubi®)	associated with initial and repeat courses of HEC, Prevention of delayed CINV associated with initial and repeat courses of MEC and prevention of delayed CINV associated with combination of anthracycline and cyclophosphamide	90 mg	
Doxylamine succinate/pyridoxine hydrochloride (Diclegis®)	Treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management	Delayed-release tablet: 10 mg/10 mg	-
Netupitant/palonosetron (Akynzeo®)	Prevention of acute and delayed CINV associated with initial and repeat courses of HEC, Prevention of acute and delayed CINV associated with initial and repeat courses of cancer chemotherapy not considered highly emetogenic	Capsule: 300/0.5 mg	-

Other abbreviations: CINV=chemotherapy-induced nausea and vomiting, HEC=highly emetogenic cancer chemotherapy, MEC=moderately emetogenic cancer chemotherapy, PONV=post-operative nausea and vomiting

Evidence-based Medicine

- The safety and efficacy of the miscellaneous antiemetics have been evaluated in several clinical trials for their FDA-approved indications.[15-51] Aprepitant, being an older, more established agent has had more extensive review. Results of these trials are similar to those used by the FDA for approval.[19-36] There are currently no clinical trials that compare NK_1 antagonists to one-another.
- The approval of rolapitant (Varubi®) was based on the efficacy and safety in preventing CINV in patients receiving anthracycline combination therapy, MEC, or HEC with a cisplatin-based regimen in three clinical trials. The primary endpoint in both HEC studies was complete response (CR) in the delayed phase (defined as 25 to 120 hours post administration of chemotherapy) of CINV. Results of the showed a greater proportion of individuals treated with the rolapitant arm had a statistically significant CR compared with the placebo control group in HEC-1: (192 [73%] compared to 153 [58%]; P=0.0006). However, in HEC-2, this was statistically significant: (rolapitant [70%] compared to placebo control group [62%]; P=0.0426).[39,40] In the third trial, the antiemetic effect of rolapitant was evaluated in MEC. The primary endpoint of CR in the delayed phase of CINV showed a greater proportion of individuals treated with the rolapitant arm had a statistically significant CR compared with the placebo control group: (475 [71%] compared to 410 [62%]; P=0.0002).[39,41]
- The approval of netupitant/palonosetron (Akynzeo®) was based on the efficacy and safety in preventing CINV in patients receiving MEC or HEC. Both trials were double-blind, randomized, double-dummy, multicenter, parallel-group studies of netupitant/palonosetron given as a single oral dose 60 minutes before administration of chemotherapy in combination with dexamethasone. CR in the delayed phase was statically significant in HEC and MEC for patients who received netupitant/palonosetron (P=0.032 and P=0.01, respectively).[42,43]
- FDA-approval of doxylamine succinate/pyridoxine hydrochloride (Diclegis®) was based on a single double-blind, randomized, multi-center, placebo-controlled study that evaluated 298 pregnant adult women with nausea and vomiting in the gestational age range of 7 to 14 weeks. Patients were randomized to 14 days of placebo or doxylamine/pyridoxine (two to four tablets daily). Mean change from baseline was -4.8 points in the symptom domain (Pregnancy Unique-Quantification of Emesis) score at day 15 in the doxylamine/pyridoxine group compared to -3.9 points in the placebo group (P=0.006). For the Quality of Life domain, mean change from baseline was 2.8 points at day 15 in the

doxylamine/pyridoxine group compared to -1.8 points in the placebo group (P=0.005).[50] A second study compared a five-day course of low-dose ondansetron to low-dose doxylamine/pyridoxine. The study concluded that ondansetron provided a statistically significant reduction in the nausea and vomiting (P=0.019 and P=0.049, respectively).[51]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - It is recommended that antiemetic therapy be initiated before the administration of chemotherapy and then continued throughout the period when delayed emesis may occur. Choice of antiemetic regimen depends primarily on the emetogenic potential and the risk of delayed CINV associated with the chemotherapy agents. The period of risk for CINV may be up to three days after administration of highly emetogenic chemotherapy (HEC) and at least two days after moderately emetogenic chemotherapy (MEC).[10]
  - For the prevention of CINV post-HEC, triple therapy with a 5-HT_3 receptor antagonist, dexamethasone, and a NK_1 receptor antagonist is recommended.[10-11]
  - The updated 2015 National Comprehensive Cancer Network (NCCN) guidelines do not currently recommend one specific regimen over another.[10]
  - For the prevention of CINV post-MEC, a 5-HT_3 receptor antagonist and dexamethasone is recommended, with a NK_1 receptor antagonist being optional.[10-12]
  - Guidelines generally recommend palonosetron as the preferred 5-HT_3 receptor antagonist for the prevention CINV associated with MEC. Adjunctive therapies include with lorazepam, an H_2 receptor antagonist or a proton pump inhibitor.[10-12]
  - The Pediatric Oncology Group of Ontario in 2012 recommend aprepitant in combination with granisetron and dexamethasone in children 12 years of age or older who will be receiving HEC and in which the antineoplastics are not known to or suspected of interacting with aprepitant. Dual therapy with ondansetron or granisetron and dexamethasone is recommended if the antineoplastic agents interact with aprepitant.[13]
  - Several guidelines have not yet been updated to include netupitant/palonosetron and/or rolapitant.[11-13]
  - According to the Obstetrician-Gynecologists Clinical Management Guideline for Nausea and Vomiting of Pregnancy, more severe cases should be treated with pyridoxine monotherapy first-line. If monotherapy is inadequate, guidelines recommend pyridoxine in combination with doxylamine. If combination therapy failed, promethazine or dimenhydrinate can be substituted for doxylamine. Other third-line options include metoclopramide, ondansetron, trimethobenzamide or methylprednisolone.[14]

- Other Key Facts:
  - Doxylamine/pyridoxine is the only FDA-approved agent for the treatment of nausea and vomiting of pregnancy.
  - All NK_1 antagonists are formulated as either an oral capsule or tablet, with the exception of fosaprepitant, which is an intravenous injection. Aprepitant is also formulated as an oral suspension.[1-4]
  - For HEC, fosaprepitant, rolapitant, and netupitant/palonosetron are given only on day one as a single dose, while aprepitant is given for three days.[1-4]
  - Doxylamine/pyridoxine is initially given once daily at bedtime (two tablets) but may be increased to twice daily (one tablet in the morning and two tablets at bedtime). The maximum dose is two tablets in the morning and two tablets at bedtime (four tablets/day).[5]
  - All NK_1 antagonists are associated with drug interactions to some extent. Of particular concern are drug interactions with agents that are either substrates of CYP3A4 or inhibit/induce CYP3A4. Dose adjustments and contraindications may apply based on the concurrent agent.[1-4]
  - Aprepitant oral suspension and capsules are the only NK_1 antagonist currently approved by the FDA for use in pediatric patients.[1-4]

- Both the FDA-approved label and clinical guidelines do not recommend aprepitant for patients less than 12 years of age, however, the oral suspension has been shown to be safe and effective in patients 6 months of age and older.[1,13]
- Due to its co-formulation, netupitant/palonosetron carries the associated warnings of palonosetron, including a risk for serotonin syndrome.[4]

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Therapeutic Class Review
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Therapeutic Class

- **Overview/Summary:** A significant advancement in the management of type 2 diabetes has been the development of incretin-based therapies. This novel therapeutic approach is important as type 2 diabetics have been shown to have an impaired incretin response.[1] Currently, there are two classes of incretin-based therapies available: the dipeptidyl pepetidase-4 (DPP-4) inhibitors and the glucagon-like peptide-1 receptor agonists, or incretin mimetics. The DPP-4 inhibitors include alogliptin, linagliptin, saxagliptin, and sitagliptin, which are all available as single-entity agents (alogliptin [Nesina®], linagliptin [Tradjenta®], saxagliptin [Onglyza®], and sitagliptin [Januvia®]) or in fixed-dose combination products (alogliptin/metformin [Kazano®], alogliptin/pioglitazone [Oseni®], linagliptin/empagliflozin [Glyxambi®], linagliptin/metformin [Jentadueto®], saxagliptin/metformin [Kombiglyze ER®], and sitagliptin/metformin [Janumet®, Janumet XR®]).[2-12] The DPP-4 inhibitors are Food and Drug Administration (FDA)-approved as adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes. Single-entity and combination agents containing alogliptin are available for use either as monotherapy or in combination with other antidiabetic agents. The fixed-dose combination products are available for use when treatment with both drug components is appropriate.[2-12]

  The DPP-4 inhibitors reversibly block the DPP-4 enzyme, which is responsible for the rapid degradation of endogenous incretin hormones. These hormones are produced by the gastrointestinal tract in response to meals and are involved in the regulation of insulin. The antidiabetic actions of endogenous incretin hormones include the enhancement of meal-stimulated insulin secretion, decreased glucagon secretion, improvements in β cell function, and slowing of gastric emptying. Through their effect on these hormones, the DPP-4 inhibitors primarily target post-prandial glucose and have also been shown to decrease fasting plasma glucose.[13,14] In general, the DPP-4 inhibitors are associated with a favorable side effect profile and also have a weight neutral effect compared to other antidiabetic agents commonly used in the management of type 2 diabetes. Compared to sulfonylureas, the risk of hypoglycemia associated with the DPP-4 inhibitors is low due to the glucose-dependent nature of incretin hormone activity. In addition, the DPP-4 inhibitors have not been associated with the same increased risk of cardiovascular disease that has been observed with the use of thiazolidinediones (TZDs). The DPP-4 inhibitors improve the function of β cells and although TZDs and metformin treat insulin resistance, these agents do not address the progressive decline in β cell function that is observed in patients with type 2 diabetes.[13-15]

  The DPP-4 inhibitors are available as fixed-dose combination products with metformin. Metformin, a biguanide, improves glucose tolerance in type 2 diabetics by lowering both basal and postprandial plasma glucose. Specifically, the actions of metformin result in decreased hepatic glucose production, decreased intestinal absorption of glucose, and improvement in insulin sensitivity via increased peripheral glucose uptake and utilization.[6-10] Additionally, alogliptin is available in a fixed-dose combination with pioglitazone. Pioglitazone is a TZD, an agonist for peroxisome proliferator-activated receptor-gamma (PPARγ).[11] PPAR receptors are found in adipose, skeletal muscle, and liver tissue and activation of these receptors modulates transcription of insulin response genes that control glucose and lipid metabolism, providing an overall effect of increasing insulin sensitivity in muscle and adipose tissue while inhibiting hepatic gluconeogenesis.[2,11] Linagliptin is available as a fixed-dose combination with empagliflozin (Glyxambi®).[12] Empagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor and improves glycemic control by producing glucosuria. This is accomplished by inhibiting SGLT2 and increasing urinary glucose excretion.[12] The net effect is an increase excretion of glucose from the body and normalization of plasma glucose levels.[12] Overall, the DPP-4 inhibitors are significantly more effective compared to placebo in reducing glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose, and post-prandial glucose, with no major effect on body weight. Combination therapy with a DPP-4 inhibitor and metformin consistently demonstrates improved benefits in glycemic control over monotherapy with either a DPP-4 inhibitor or metformin; limited within class head-to-head trials have been conducted.[16-63,65-68,76,77]

Two meta-analyses revealed that DPP-4 inhibitors are not associated with an increased risk of cardiovascular events or cancer compared to placebo or other antidiabetic agents, respectively.[37,61] However, a recent clinical trial suggested an increased risk of heart-failure with saxagliptin compared to placebo.[38] In April 2016, the FDA added heart failure warnings to the labeling of medications containing saxagliptin and alogliptin.[65]

With regards to the specific DPP-4 inhibitor agents, all single-entity agents are available for once-daily dosing.[2-5] Three fixed-dose combination products contain metformin immediate-release (alogliptin/metformin [Kazano®], linagliptin/metformin [Jentadueto®] and sitagliptin/metformin [Janumet®]) which are available for twice-daily dosing.[6,7,9] One fixed-dose combination product (alogliptin/pioglitazone [Oseni®]) contains pioglitazone and is dosed once daily.[11] Two fixed-dose combination products contain metformin extended-release (ER) (saxagliptin/metformin ER [Kombiglyze XR®] and sitagliptin/metformin ER [Janumet XR®]), and because of the metformin ER component, these products are available for once-daily dosing.[8,10] The fixed-dose combination product containing linagliptin and empagliflozin (Glyxambi®) is also available for once-daily dosing.[12] Single-entity linagliptin is the only agent within the class that does not require renal and hepatic dosing.[3] The fixed-dose combination of alogliptin/pioglitazone [Oseni®] carries a boxed warning regarding the risk of use in patients with congestive heart failure as the TZD component may cause or exacerbate congestive heart failure in some patients.[11] Furthermore, because of the metformin component in certain fixed-dose combination products, caution is recommended with both renal and hepatic dysfunction.[6-10] In addition, these products all have a boxed warning regarding the risk of lactic acidosis due to metformin accumulation.[6-10] Currently, alogliptin, alogliptin/metformin, and alogliptin/pioglitazone are available generically.[2,6,11]

Table 1. Medications Included Within the Therapeutic Class Review[2-12]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Alogliptin (Nesina®)	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 6.25 mg 12.5 mg 25 mg	✔
Linagliptin (Tradjenta®)	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 5 mg	-
Saxagliptin (Onglyza®)	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 2.5 mg 5 mg	-
Sitagliptin (Januvia®)	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 25 mg 50 mg 100 mg	-
Combination Products			
Alogliptin/ metformin (Kazano®)	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet (alogliptin/ metformin): 12.5/500 mg 12.5/1,000 mg	✔
Alogliptin/ pioglitazone (Oseni®)	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2	Tablet (alogliptin/ pioglitazone): 12.5/15 mg	✔

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
	diabetes	12.5/30 mg 12.5/45 mg 25/15 mg 25/30 mg 25/45 mg	
Linagliptin/ empagliflozin (Glyxambi®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes*	Tablet (linagliptin/ empagliflozin): 5/10 mg 5/25 mg	-
Linagliptin/ metformin (Jentadueto®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes†	Tablet (linagliptin/ metformin): 2.5/500 mg 2.5/850 mg 2.5/1,000 mg	-
Saxagliptin/ metformin (Kombiglyze XR®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes‡	Tablet (saxagliptin/ metformin ER): 5/500 mg 2.5/1,000 mg 5/1,000 mg	-
Sitagliptin/ metformin (Janumet®, Janumet XR®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes§	Tablet (sitagliptin/ metformin): 50/500 mg 50/1,000 mg Tablet (sitagliptin/ metformin ER): 50/500 mg 50/1,000 mg 100/1,000 mg	-

*When treatment with both linagliptin and empagliflozin is appropriate.
†When treatment with both linagliptin and metformin is appropriate.
‡When treatment with both saxagliptin and metformin extended-release is appropriate.
§When treatment with both sitagliptin and metformin or metformin extended-release is appropriate.
ER=extended-release, XR=extended-release

Evidence-based Medicine

- Clinical trials have demonstrated the safety and efficacy of the dipeptidyl peptidase-4 (DPP-4) inhibitors in the management of type 2 diabetes.[16-63,65-68,76,77] Of note, there have been minimal clinical efficacy or safety trials conducted with any of the DPP-4 inhibitor fixed-dose combination products; bioequivalence of these products with co-administration of the individual drug components has been demonstrated for all tablet strengths.[6-12] Available trials evaluating the fixed-dose combination of sitagliptin/metformin support its efficacy and safety in the management of type 2 diabetes. Specifically, combination therapy was associated with significantly improved glycemic control compared to metformin monotherapy.[57]
- In studies, alogliptin was associated with significant decreases in HbA_{1c} from baseline as monotherapy compared to placebo. In addition, in studies with metformin or pioglitazone combination therapy with alogliptin, significant decreases in HbA_{1c} were observed and more patients reached specific HbA_{1c} goals compared to the monotherapy comparator. As an add-on therapy in patients already being treated with metformin, pioglitazone, metformin/pioglitazone, glipizide or insulin therapy, the additions of alogliptin demonstrated significant improvements in HbA_{1c} from baseline compared to placebo.[16-23]
- Overall, linagliptin is more effective compared to placebo in decreasing HbA_{1c} and fasting plasma glucose (FPG) as monotherapy or as add-on therapy to other antidiabetic agents in type 2 diabetics

not achieving glycemic goals. In addition, more patients achieved glycemic goals (HbA_{1c} <7.0%) with linagliptin compared to placebo.[24-27] Combination therapy with linagliptin and pioglitazone has been shown to be more efficacious in terms of reducing HbA_{1c} compared to pioglitazone monotherapy.[53]
- Similar results were achieved with saxagliptin when compared to placebo.[29-36] In addition, combination therapy with saxagliptin and metformin was "superior" to monotherapy with either agent in observed reductions in HbA_{1c}, FPG, and post-prandial glucose (PPG), and a significantly greater proportion of patients achieved glycemic goals with combination therapy.[55,56]
- Similar to the results of clinical trials evaluating other DPP-4 inhibitors, sitagliptin is consistently more efficacious in improving glycemic control compared to placebo, and combination therapy with sitagliptin and metformin is more efficacious than monotherapy with either agent.[40-51]
- In a single head-to-head trial, saxagliptin demonstrated non-inferiority to sitagliptin in reducing HbA_{1c}. However, a significantly greater proportion of patients achieved an HbA_{1c} ≤6.5% and achieved significant reductions in FPG with sitagliptin compared to saxagliptin.[52] While the beneficial effects of the DPP-4 inhibitors in improving HbA_{1c}, FPG, and PPG compared to placebo are well established, observed improvements in body weight and β cell function with these agents are not consistent.[16-63,64]
- In general, meta-analyses and systematic reviews evaluating incretin-based therapies, including the DPP-4 inhibitors, support the results observed in randomized-controlled trials evaluating these agents.[37,54,62-64,65-68] Two meta-analyses revealed that DPP-4 inhibitors are not associated with an increased risk of cardiovascular events or cancer compared to placebo or other antidiabetic agents, respectively.[37,61]

Key Points within the Medication Class
- According to Current Clinical Guidelines for the management of type 2 diabetes:[69-73,78-80]
    - Metformin remains the cornerstone of most antidiabetic treatment regimens.
    - Additionally, 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.
    - The DPP-4 inhibitors are recommended as a potential second-line treatment option to be added in combination with metformin in patients not achieving glycemic goals.
    - Clinical guidelines note a lower rate of hypoglycemia and an established efficacy and safety profile when used in combination with metformin as advantages associated with the DPP-4 inhibitors compared to other classes of antidiabetic agents.
    - Patients who are not appropriate for initial therapy with metformin may be initiated on another oral antidiabetic agent, such as a sulfonylurea/glinide, pioglitazone, or a DPP-4 inhibitor, and in occasional cases where weight loss is seen as an essential aspect of therapy, initial therapy with an incretin mimetic may be useful. Among all current clinical guidelines, preference of one DPP-4 inhibitor over another is not stated.
- Other Key Facts:
    - All single-entity agents are available for once-daily dosing.[2-5]
    - Single-entity linagliptin is the only agent within the class that does not require renal and hepatic dosing.[3]
    - The metformin component in certain fixed-dose combination products requires caution in patients with renal and hepatic dysfunction.[6-10]
    - The DPP-4 inhibitors are associated with low risk of hypoglycemia and is weight neutral when used as monotherapy.[2-12]
    - DPP-4 inhibitors improve the function of β cells in the pancreas.[1-13-15]

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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[1-5]

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).[7-12]
    - 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).[12]
- 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).[14]
- 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.[30,37] In a single trial, liraglutide significantly decreased HbA_{1c} compared to exenatide. Furthermore, liraglutide significantly decreased FPG while exenatide significantly decreased PPG.[45]
- 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).[38]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Type 2 diabetes: [60-66]
        - 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. [60-66]

- 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[3-9]

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‡	Tablet: 10 mg/5 mg 25 mg/5 mg:	-

Empagliflozin/metformin (Synjardy®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes§	Tablet: 5/500 mg 5/1000 mg 12.5/500 mg 12.5/1000 mg	-

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

Evidence-based Medicine

- Each agent has been studied as monotherapy and dual and triple therapy compared to placebo and active controls and combinations of placebo and active controls.
- As monotherapy, patients randomized to canagliflozin 100 or 300 mg daily compared to patients randomized to placebo had a statistically significant improvement in HbA_{1c}. Both doses also resulted in a greater proportion of patients achieving an HbA_{1c} <7.0%, significant reductions in FPG and post prandial glucose (PPG), and in percent body weight reduction compared to placebo. There were also small decreases from baseline in systolic blood pressure relative to placebo (P values not reported).[10]
- 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).[12]
- 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}.[14]
- 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.[15]
- There have been no clinical efficacy studies conducted with empagliflozin/metformin combination tablets. FDA-approval of empagliflozin/metformin ER was based on previous studies conducted with the bioequivalent single-entity agents.[9] The safety and efficacy of empagliflozin added to metformin was evaluated in a double-blind, placebo-controlled study of patients with type 2 DM inadequately controlled on at least 1,500 mg of metformin per day (N=637). At week 24, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA_{1c} (-0.7% and -0.8% vs. 0.1%, respectively; P<0.0001 for both comparisons), FPG (-20 mg/dL and -22 mg/dL vs. 6 mg/dL, respectively; P values not reported) and body weight (-2.5 kg and -2.9 kg vs. -0.5 kg, respectively; P<0.001 for both comparisons) compared with placebo.[24] In addition, the safety and efficacy of empagliflozin was evaluated in an active-control study versus glimepiride (in combination with metformin). The study was a double-blind, active-controlled, non-inferiority design of patients with type 2 DM inadequately controlled on metformin monotherapy (N=1,545). At week 52, empagliflozin 25 mg daily meet the non-inferiority criteria for lowering HbA_{1c} compared to glimepiride (-0.7% vs. -0.7%). There was a greater reduction in FPG and body weight with empagliflozin 25 mg compared to glimepiride;

however the significance was not reported (-19 mg/dL vs. -9 mg/dL and -3.9 kg vs. 2 kg; P values not reported).[25]

- 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).[32] 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).[33]
- Similar results were observed when comparing sodium glucose co-transport 2 agents in combination for the treatment of diabetes mellitus.[17-31]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[34-41]
    - Metformin remains the cornerstone of most antidiabetic treatment regimens.
    - Patients with high glycosylated hemoglobin (HbA_{1c}) will likely require combination or triple therapy in order to achieve glycemic goals.
        - Uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered.
        - The role of sodium-glucose co-transporter 2 (SGLT2) inhibitors are addressed in several available treatment guidelines and are recommended as a potential alternative to metformin in patients who cannot receive that agent or as a part of two- or three-drug regimens in combination with other antidiabetic agents in patients not achieving glycemic goals.[35,38-39]

- Other Key Facts:
    - Canagliflozin is formulated with metformin in a single tablet (Invokamet®). Empagliflozin is formulated with linagliptin in a single tablet (Glyxambi®) and with metformin in a single tablet (Synjardy®). Dapagliflozin is formulated with metformin as a single extended-release tablet (Xigduo XR®).[6-9]
    - All products are dosed once daily, with the exception of canagliflozin/metformin and empagliflozin/metformin, which are dosed twice dialy.[3-9]
    - 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
Ophthalmic Prostaglandin Analogues

Therapeutic Class

- **Overview/Summary:** Glaucoma is an optic neuropathy that causes gradual degeneration of the cells making up the optic nerve. It is the leading cause of blindness and second leading cause of vision loss in the world.[1] Four distinct types of glaucoma include primary open-angle, acute angle-closure, secondary and congenital. Patients with open-angle glaucoma initially experience peripheral visual field loss, followed by central field loss, which may progress to irreversible blindness if untreated. The exact etiology of open-angle glaucoma is unknown. Major risk factors for developing open-angle glaucoma include advanced age, African or Hispanic/Latino descent, elevated intraocular pressure (IOP), family history of glaucoma or a central corneal thickness of less than 545 micrometers.[2-3] Other possible risk factors that have been investigated include low ocular systolic perfusion pressure, low systolic blood pressure, cardiovascular disease, hypertension, diabetes mellitus and hypothyroidism.[1,3-6]

- IOP is the one major risk factor for glaucoma that is treatable. Available evidence suggests that lowering IOP inhibits or reduces the progression of optic nerve damage.[1-3,7] Treatment may be initiated in patients with a raised IOP despite having no visual field loss or optic nerve damage. An IOP greater than 22 mm Hg is generally considered to be elevated and would be treated by most clinicians; however, this number varies according to screening methods, risk factors and disease progression.[7] The target IOP should be individualized based on their response to therapy and disease progression. There is no consensus target IOP below which further visual loss and optic nerve damage will be prevented.[2,3]

Table 1. Current Medications Available in the Therapeutic Class[9-14]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Bimatoprost (Lumigan®)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension	Ophthalmic solution: 0.01% (2.5, 5, 7.5 mL) 0.03% (2.5, 5, 7.5 mL)	-
Latanoprost (Xalatan®*)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension	Ophthalmic solution: 0.005% (2.5 mL)	✔
Tafluprost (Zioptan®)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension	Ophthalmic solution: 0.0015% (30 or 90 0.3 mL single-use containers)	-
Travoprost (Travatan Z®)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension	Ophthalmic solution: 0.004% (2.5, 5 mL)	-
Unoprostone	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension	Ophthalmic solution: 0.015%	-

*Available generically in one dosage form or strength.

Evidence-based Medicine

- Many clinical trials have evaluated the safety and efficacy of the ophthalmic prostaglandin analogues for the reduction of intraocular pressure (IOP) in patients with glaucoma or ocular hypertension.[18-59]
- Ophthalmic bimatoprost appears to have the greatest efficacy in reducing IOP; however, trials have not consistently demonstrated a difference in IOP reduction between ophthalmic travoprost and ophthalmic latanoprost.[18,20,21,25,28,30,31,35,36]

- Available trials suggest that ophthalmic tafluprost may have a similar IOP-lowering effect as ophthalmic latanoprost but less than ophthalmic travoprost.[49-52]
- Results from one trial demonstrated a significantly lower incidence of ocular irritation/burning, tearing, itching, dry eye sensation and conjunctival hyperemia when switched from ophthalmic latanoprost to ophthalmic tafluprost as well as ophthalmic tafluprost also significantly reduced IOP compared to baseline treatment with ophthalmic latanoprost (16.4 vs 16.8 mm Hg; P=0.049).[48]
- A meta-analysis of 11 randomized control trials showed significant reductions in IOP with ophthalmic latanoprost compared to ophthalmic timolol (P<0.001).[38]
- The ophthalmic prostaglandin analogues have consistently demonstrated comparable or greater efficacy when compared to combination therapy.[33,34,39-42]
- The safety and efficacy of unoprostone isopropyl for lowering IOP in patients with glaucoma or ocular hypertension was established in six, six-month randomized controlled clinical studies. Patients had a mean baseline intraocular pressure of 23 mmHg, and unoprostone isopropyl lowered intraocular pressure by approximately 3 to 4 mmHg throughout the day. Unoprostone isopropyl appeared to lower intraocular pressure without affecting cardiovascular or pulmonary function.[14] A review of all clinical trial data suggests unoprostone may not be as efficacious as other prostanoids; however, it is effective for IOP reduction both as monotherapy and adjunctive therapy with timolol. In addition, unoprostone has decreased affinity for the prostaglandin F2α receptor, which may explain its well tolerated ocular and systemic side effect profile compared with other prostanoids.[59]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[1-3,7,8]
    - The current treatment of glaucoma focuses on decreasing IOP by one of three methods: laser therapy, surgery or medical intervention.
    - Medical intervention is generally used as initial therapy prior to laser or surgical treatment. Medical intervention includes five classes of ophthalmic drugs used for the long-term management of glaucoma: alpha-$_2$ adrenergic agonists, β adrenergic antagonists, carbonic anhydrase inhibitors, parasympathomimetics and prostaglandin analogues.
    - These treatments reduce IOP by either decreasing the amount of aqueous humor produced by the ciliary body or by increasing uveoscleral outflow.
    - Current guidelines by the American Academy of Ophthalmology and American Optometric Association recommend ophthalmic β adrenergic antagonists and prostaglandin analogues as first-line pharmacologic therapy in patients with elevated IOP. Combination or monotherapy with agents from an alternative pharmacologic class is recommended for patients that experience intolerable adverse events or who do not achieve the optimal IOP reduction with first-line agents.
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- Other Key Facts:
    - Latanoprost is the only ophthalmic prostaglandin analogue that is available generically.[9]
    - Tafluprost is the only preservative-free ophthalmic prostaglandin product and is only available in single-use containers.[13]
    - Bimatoprost and latanoprost are formulated with benzalkonium chloride, an agent associated with ocular irritation/inflammation in some patients. Travoprost is formulated with sofZia, an ionic buffer containing borate, sorbitol, propylene glycol, and zinc.[9-14]

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Therapeutic Class Overview
Ophthalmic Fluoroquinolones

Therapeutic Class

- **Overview/Summary:** This review will focus on the ophthalmic fluoroquinolone antibiotics. These agents are used for the treatment of bacterial conjunctivitis and corneal ulcers caused by susceptible isolates.[1-8] Conjunctivitis occurs worldwide and affects all ages, social strata, and both genders. This infection rarely causes permanent visual loss or structural damage and mild cases may be self-limited, as many cases will resolve without treatment in immunocompetent individuals. The most common causative pathogens seen with bacterial conjunctivitis include *Staphylococcus* aureus, *Streptococcus pneumonia*, *Haemophilus influenza*, and *Moraxella catarrhalis*.[9] Major clinical features of bacterial conjunctivitis include redness and discharge in one eye, although it can be bilateral. Patients eye(s) will often be "stuck shut" in the morning. Purulent discharge continues throughout the day and is thick, globular and may be yellow, white or green in color, which may help distinguish between viral and allergic conjunctivitis which usually has watery discharge.[9] Fluoroquinolone antibiotics act via direct inhibition of bacterial DNA synthesis, preventing the action of DNA gyrase and topoisomerase IV, which blocks DNA replication and eventually leads to damage to bacterial DNA and cell death.[10] Currently, ofloxacin, levofloxacin, gatifloxacin and ciprofloxacin hydrochloride (solution) are available generically.

  These ophthalmiac quinolones include besifloxacin, ciprofloxacin hydrochloride, gatifloxacin, levofloxacin, moxifloxacin hydrochloride, and ofloxacin. They are all indicated for the treatment of bacterial conjunctivitis.[1-8] In addition, ciprofloxacin solution and ofloxacin have the indication to treat corneal ulcers caused by susceptible isolates.[2,8] All medications are formulated as drops (either solution or suspension) with only ciprofloxacin hydrochloride being formulated as an ointment (Ciloxan®).[3] Although generally considered equally effective, differences in resistance exist, with fewer gram-positive cocci being resistant to gatifloxacin and moxifloxacin hydrochloride than other fluoroquinolones.[13] Frequency and duration of therapy varies depending on specific agents. Treatment for bacterial conjunctivitis with besifloxacin and moxifloxacin hydrochloride is usually dosed twice or three times daily, while the others are generally prescribed every two to four hours.[1-8] Most ophthalmic quinolones are indicated for use in patients one year of age or older, however, moxifloxacin hydrochloride (Moxeza®) is indicated for use in children four months of age and older and ciprofloxacin hydrochloride ointment is only indicated for use in children two years of age or older.[1-8]

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

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Besifloxacin ophthalmic (Besivance®)	Treatment of bacterial conjunctivitis	Ophthalmic suspension: 0.6% (5 mL)	-
Ciprofloxacin hydrochloride ophthalmic (Ciloxan®*)	Treatment of bacterial conjunctivitis; treatment of corneal ulcers (solution)	Ophthalmic ointment: 0.3% (3.5 g) Ophthalmic solution: 0.3% (2.5, 5, 10 mL)	✔
Gatifloxacin ophthalmic (Zymaxid®*)	Treatment of bacterial conjunctivitis	Ophthalmic solution: 0.5% (2.5 mL)	✔
Levofloxacin ophthalmic	Treatment of bacterial conjunctivitis; treatment of corneal ulcers	Ophthalmic solution: 0.5% (5 mL)	✔
Moxifloxacin hydrochloride ophthalmic (Moxeza®, Vigamox®)	Treatment of bacterial conjunctivitis	Ophthalmic solution: 0.5% (3 mL)	-

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Ofloxacin ophthalmic (Ocuflox®*)	Treatment of bacterial conjunctivitis; treatment of corneal ulcers	Ophthalmic solution: 0.3% (5, 10 mL)	✔

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

Evidence-based Medicine

- Clinical trials have demonstrated that ophthalmic fluoroquinolones are effective in treating and providing relief of conjunctivitis and corneal ulcers in pediatric and adult patients.[15-40]
- Several studies comparing ophthalmic fluoroquinolones to either placebo or vehicle have concluded that these medications resulted in significantly higher clinical resolution rates at days one through five.[15-20]
- Head-to-head trials evaluating the efficacy of ophthalmic antibiotics for the treatment of bacterial conjunctivitis have found that no one medication was inferior to another.[21-30]
- In one trial, significantly more patients in the ophthalmic moxifloxacin group had complete resolution of ocular signs and symptoms at 48 hours when compared to patients treated with ophthalmic polymyxin B sulfate/trimethoprim (P=0.001).[22] One study found levofloxacin 0.5% to have statistically greater microbial eradication in pediatric patients two to 11 years of age with bacterial conjunctivitis (P≤0.032) compared to ofloxacin 0.3% in, but not in any other pediatric age group..[26] In a seven day trial, a higher percentage of patients receiving levofloxacin had microbial eradication at the final visit compared to patients receiving ofloxacin (P=0.034);however, clinical cure rates were similar between the two treatments (P value not reported).[27] In a small meta-analysis, moxifloxacin was found to be associated with fewer drop-outs for treatment failure (P=0.002) compared to ofloxacin.[28]
- In patients with a diagnosis of corneal ulcer, ophthalmic ciprofloxacin hydrochloride was shown to be efficacious treatment options.[31,32] Specifically, in one trial of patients with a diagnosis of infectious keratitis ophthalmic ciprofloxacin had a shorter average time to healing as compared to ophthalmic cefazolin sodium fortified with gentamicin sulfate, although this was not found to be significant (P value not reported).[32]
- A number of studies consisted of patients with multiple diagnoses such as blepharitis, blepharoconjunctivitis, bacterial conjunctivitis and blepharitis, keratoconjunctivitis, or symptoms of surface ocular infections. These studies found that the ophthalmic formulations of ciprofloxacin, gentamicin sulfate, ofloxacin, tobramycin solution, and polymyxin B sulfate/trimethoprim were efficacious in resolving or curing multiple ocular infections. No significant differences were observed in any study with regard to cure rates, decline in bacterial counts, bacterial eradication or reduction of bacteria, microbial improvement or overall improvement. [34-39]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Use of ophthalmic antibiotics is associated with earlier clinical and microbiological remission when compared to placebo. Therapy for severe conjunctivitis disease be based on culture and sensitivity, but if that is not available or if mild disease is present, empiric therapy is considered appropriate.[9,11-13]
    - The selection of an ophthalmic antibiotics for bacterial conjunctivitis is typically empirical, and the most convenient or least expensive ophthalmic antibiotic is typically effective for most cases of conjunctivitis.[11]
    - Although effective, ophthalmic quinolones are generally regarded as second-line agents for routine bacterial conjunctivitis because of resistance and cost concerns.[9,11,12]
    - Ophthalmic quinolones are the considered the treatment of choice for corneal ulcers and for infections caused by pseudomonas.[9,13]
    - The recommended ophthalmic antibiotics for treatment of keratitis vary depending on organism identified. Empiric therapy is often utilized and includes ophthalmic quinolones[13]
    - Fewer gram-positive cocci are resistant to gatifloxacin and moxifloxacin hydrochloride than other fluoroquinolones[13]

  - Single-drug therapy using an ophthalmic fluoroquinolone has been shown to be as effective as combination therapy with ophthalmic antibiotics that are fortified by increasing their concentration over commercially available topical antibiotics.[13]
- Other Key Facts:
  - Ofloxacin, levofloxacin, gatifloxacin and ciprofloxacin hydrochloride (solution) are available generically.
  - Only ciprofloxacin hydrochloride is formulated as an ointment.[3]
  - Moxeza® (moxifloxacin) is dosed twice daily while besifloxacin and Vigamox® (moxifloxacin) are dosed three times a day. The remaining agents are dosed every two or every four hours while awake.[1-8]
  - Most ophthalmic quinolones are indicated for use in patients one year of age or older; however, moxifloxacin hydrochloride (Moxeza®) is indicated for use in children four months of age and older and ciprofloxacin hydrochloride ointment is only indicated for use in children two years of age or older.[1-8]

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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	✔
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®): 100 µg 200 µg	-

* 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.
Asmanex HFA®: In patients 12 years of age and older.
** Asmanex Twisthaler®: In patients four 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]
  - 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]
  - 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:
  - None of the inhaled corticosteroid products are indicated for the relief of acute bronchospasm[1-10]
  - Currently, budesonide suspension for nebulization is the only generic product available within the therapeutic class.

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Therapeutic Class Overview
Long-Acting Inhaled β2-Agonists (Single Entity)

Therapeutic Class

- **Overview/Summary:** Respiratory β_2-agonists are primarily used to treat reversible airway disease. The long-acting β_2-agonists (LABAs) are all Food and Drug Administration (FDA)-approved for chronic obstructive pulmonary disease with some agents also being approved for asthma maintenance therapy and exercise-induced asthma/bronchospasm.[1-7] Respiratory β_2-agonists act preferentially on the β_2-adrenergic receptors. Activation of these receptors on airway smooth muscle leads to the activation of adenylyl cyclase and an increase in intracellular cyclic-3',5'-adenosine monophosphate (cyclic AMP). The increase in cyclic AMP leads to activation of protein kinase A and the inhibition of myosin phosphorylation resulting in lower intracellular ionic calcium and smooth muscle relaxation. Increased cyclic AMP levels also inhibit the release of mediators from mast cells in the airways.[1-6] The respiratory β_2-agonists can be divided into two categories: short-acting and long-acting. Only the inhaled long-acting β_2-agonists will be covered in this review and they include: arformoterol, formoterol, indacaterol salmeterol, and the newest agent olodaterol. Respiratory β_2-agonists elicit a similar biologic response in patients suffering from reversible airway disease, but differ in their dosing requirements, pharmacokinetic parameters and potential adverse events.[1-6] Guidelines do not recommend one long-acting agent over another.[8-11] In addition, head-to-head clinical trials have been inconclusive to determine "superiority" of any one agent .[12-60] There are currently no generic formulations for the LABAs.

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
Arformoterol (Brovana®)	Bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment	Solution for nebulization: 15 µg (2 mL)	-
Formoterol (Foradil®, Perforomist®)	Asthma (including nocturnal asthma) and bronchospasm prevention as concomitant therapy with a long-term asthma control medication†; bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment‡ exercise-induced bronchospasm prophylaxis, acute†	Capsule for inhalation: 12 µg Solution for nebulization: 20 µg/2 mL	-
Indacaterol (Arcapta Neohaler®)	Bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment§	Capsule for inhalation: 75 µg	-
Olodaterol (Striverdi Respimat®)	Bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment§	Solution for inhalation (breath activated, metered-dose inhaler): 2.5 µg	-
Salmeterol (Serevent Diskus®)	Asthma (including nocturnal asthma) and bronchospasm prevention as concomitant therapy with a long-term asthma control medication; bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment‡;	Dry powder inhaler: 50 µg (28 or 60 inhalations)	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment		

COPD=chronic obstructive pulmonary disease
*Generic available in at least one dosage form or strength.
†Dry powder inhaler only
‡Twice-daily
§Once-daily

Evidence-based Medicine

- Clinical trials have demonstrated the efficacy long-acting β_2-agonists in providing relief from asthma, COPD exacerbations and exercise induced asthma .[12-61]
- Salmeterol and formoterol have been found to improve FEV_1 in patients with mild to moderate asthma who require persistent use of SABAs. In a meta-analysis by Salpeter et al, salmeterol and formoterol both demonstrated an increase in severe exacerbations that required hospitalization, life threatening exacerbations and asthma-related deaths in adults and children alike when compared to placebo.[13]
- A systematic review concluded that in patients with COPD, there was no difference in rate of mild exacerbation between patients treated with an ICS or LABA (odds ratio, 1.63; 95% confidence interval [CI], 0.49 to 5.39) or in the rate of moderate or severe COPD exacerbations (relative risk, 0.96; 95% CI, 0.89 to 1.02).[42]
- Overall, data from published clinical trials demonstrate that treatment with indacaterol consistently results in significantly higher mean trough FEV_1 after 12 weeks of treatment compared to placebo, formoterol, salmeterol and tiotropium. Patients treated with indacaterol also achieved significant improvements in COPD symptoms, as well as health-related quality of life compared to those treated with placebo.[42-52]
- The safety and efficacy of olodaterol were evaluated in eight unpublished placebo- and/or active-controlled confirmatory clinical trials in patients with COPD. Results from four 48-week studies showed 5 µg olodaterol provided significant improvements in FEV_1 and FEV_1 $AUC_{0\text{-}3hr}$ at weeks 12 and 24 when compared with placebo (no P value provided). In addition, four 6-week cross-over studies showed that FEV_1 $AUC_{0\text{-}12hr}$ and FEV_1 $AUC_{12\text{-}24hr}$ was significantly improved with olodaterol when compared with placebo at the conclusion of the studies (no P value provided). No data was provided showing the results of the active comparators (formoterol and/or tiotropium) or whether the results were significantly different than olodaterol or not.[4]
- Two replicate, double-blind, placebo-controlled, multicenter, randomized studies evaluated FEV_1 $AUC_{0\text{-}3}$ and trough FEV_1 after 12 weeks of therapy after adding olodaterol (via Respimat® inhaler) to COPD patients being treated with tiotropium 18 µg via HandiHaler®. There was a significant improvement in both FEV_1 $AUC_{0\text{–}3}$ and trough FEV_1 responses without a significant increase in side effects when olodaterol was added to tiotropium. The mean difference in FEV_1 $AUC_{0\text{–}3}$ in ANHELTO 1 and 2 respectively were 0.117 L and 0.106 L ($P<0.001$ for both). Mean difference in FEV_1 responses were 0.062 L and 0.040 L ($P<0.001$ and $P=0.0029$).[57]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Short-acting β_2-agonists are recommended for patients in all stages of asthma, for symptomatic relief of reversible airway disease and for exercise-induced bronchospasm.[8,9]
  - Short-acting β_2-agonists should be used on an as-needed or "rescue" basis. [8,9]
  - In the chronic management of asthma, the long-acting β_2-agonists should be used as add-on therapy in patients not adequately controlled on an inhaled corticosteroid. [8,9]
  - Long-acting β_2-agonists should not be used as monotherapy for the long-term control of asthma. [8,9]
  - Long-acting β_2-agonists can be used for exercise-induced bronchospasm and provide a longer period of coverage compared to short acting β_2-agonists. [8,9]

  - Long-acting β_2-agonists have a role in the treatment of chronic obstructive pulmonary disease (COPD), for patients who remain symptomatic even with current treatment with short-acting bronchodilators. [8,9]
  - Long-acting β_2-agonists can be added to other COPD treatment regimens, including an anticholinergic agent, in efforts to decrease exacerbations.[10,11]
- Other Key Facts:
  - The role of the short- and long-acting respiratory β_2-agonists in the treatment of asthma and COPD has been well established.
  - Studies have failed to consistently demonstrate significant differences between products.
  - None of the long-acting respiratory β_2-agonists are currently available generically.

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U. Xopenex® (Levalbuterol)

Therapeutic Class: Beta Adrenergic Agents
Last Reviewed by the DUR Board: July 26, 2012

Xopenex® is subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the Social Security Act and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

   a. Authorization only for recipients experiencing side effects on one other beta-adrenergic agent of any formulation.

   b. Authorization for patients whose cardiovascular status is considered to be in severe deteriorating condition.

2. Prior Authorization Guidelines

   Prior Authorization forms are available at:
   http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

Therapeutic Class Overview
Short-acting β2-Agonists

Therapeutic Class

- **Overview/Summary:** Respiratory short acting β_2-agonists (SABAs) are Food and Drug Administration (FDA)-approved indications include asthma, chronic obstructive pulmonary disease, exercise-induced bronchospasm (EIB), and/or and reversible bronchospasm. Respiratory β_2-agonists act preferentially on the β_2-adrenergic receptors. Activation of these receptors on airway smooth muscle leads to the activation of adenylyl cyclase and an increase in intracellular cyclic-3',5'-adenosine monophosphate (cyclic AMP). The increase in cyclic AMP leads to activation of protein kinase A and the inhibition of myosin phosphorylation resulting in lower intracellular ionic calcium and smooth muscle relaxation. Increased cyclic AMP levels also inhibit the release of mediators from mast cells in the airways.[1-15] The β_2-agonists can be divided into two categories: short-acting and long-acting. The short-acting respiratory β_2-agonists consist of albuterol (ProAir HFA®, ProAir RespiClick®, Proventil HFA®, Proventil HFA®, Ventolin HFA®), levalbuterol (Xopenex®, Xopenex HFA®), metaproterenol and terbutaline. Respiratory β_2-agonists elicit a similar biologic response in patients suffering from reversible airway disease, but differ in their dosing requirements, pharmacokinetic parameters and potential adverse events.[1-15] As a result of the Clean Air Act and the Montreal Protocol on Substances that Deplete the Ozone Layer, the FDA made the decision to end production, marketing and sale of all albuterol metered dose inhalers (MDIs) containing chlorofluorocarbons (CFCs) as their propellant by December 31, 2008. These inhalers were replaced by MDIs which use hydrofluoroalkanes (HFAs). There is no difference in the safety or efficacy of the HFA inhalers compared to the CFC inhalers; however, there may small differences in taste and/or feel with the HFA inhalers. The deadline for removal of the pirbuterol (Maxair®) CFC inhaler is December 31, 2013.[16]

Table 1. Current Medications Available in the Therapeutic Class[1-15]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Short-Acting β_2-agonists			
Albuterol (AccuNeb®*, ProAir HFA®, ProAir RespiClick®, Proventil HFA®, Ventolin HFA®, VoSpire ER®*)	Relief of bronchospasm in patients with asthma†,‖, treatment or prevention of bronchospasm in patients with reversible obstructive airway disease†‡§, prevention of exercise-induced bronchospasm†‡	Dry Powder Inhaler: 90 µg Meter dose aerosol inhaler (HFA): 120 µg albuterol sulfate# Solution for nebulization: 0.63 mg 1.25 mg 2.5 mg 0.5% concentrated solution (3 mL unit dose vials) Sustained-release tablet: 4 mg 8 mg Syrup:	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		2 mg/5 mL Tablet: 2 mg 4 mg	
Levalbuterol (Xopenex®*, Xopenex HFA®)	Treatment or prevention of bronchospasm in patients with reversible obstructive airway disease†	Meter dose aerosol inhaler (HFA): 59 µg¶ Solution for nebulization: 0.31 mg 0.63 mg 1.25 mg (3 mL vials)	✔
Metaproterenol*	Prevention and treatment of asthma and reversible bronchospasm, which may occur in association with bronchitis and emphysema	Syrup: 10 mg/5 mL Tablet: 10 mg 20 mg	✔
Terbutaline*	Prevention and treatment of asthma and reversible bronchospasm, which may occur in association with bronchitis and emphysema	Injection: 1 mg/mL (2 mL vial) Tablet: 2.5 mg 5 mg	✔

*Generic available in at least one dosage form or strength.
†Inhalation solution.
‡Metered-dose inhaler.
§Dry powder inhaler.
‖Oral formulations.
¶Delivering 45 µg levalbuterol base.
#Delivering 108 µg of albuterol (90 µg albuterol base).

Evidence-based Medicine

- Clinical trials have demonstrated the efficacy SABAs in providing relief from reversible bronchospasms and EIA.[21-41]
- Safety and efficacy of albuterol dry powder inhaler (ProAir Respiclick®) was evaluated in two 12-week randomized, double-blind, placebo-controlled studies. Forced expiratory volume in one second (FEV_1) was significantly improved with albuterol dry powder inhaler compared with placebo (no P value reported).[7]
- In clinical trials that comparing albuterol to levalbuterol, inconsistent results have been reported and have not consistently demonstrated improved outcomes with levalbuterol compared to albuterol. Moreover, studies have shown no significant differences between the two agents in the peak change in FEV_1 or the number and incidence of adverse events.[21-31]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Short-acting β_2-agonists are recommended for patients in all stages of asthma, for symptomatic relief of reversible airway disease and for exercise-induced bronchospasm.[17-20]
  - Short-acting β_2-agonists should be used on an as-needed or "rescue" basis. [17-20]

  - Anticholinergics may also be used for the treatment of acute exacerbations but are considered less effective than SABAs.[17-20]
  - The addition of a systemic corticosteroid may be required if patients do not respond immediately to treatment with a SABA or if the exacerbation is severe.[17-20]
  - The use of LABAs to treat acute symptoms or exacerbations of asthma is not recommended.[17]
- Other Key Facts:
  - Studies have failed to consistently demonstrate significant differences between products.
  - Albuterol oral solution, oral tablets, and solution for nebulization, levalbuterol solution for nebulization, metaproterenol oral solution and oral tablets, and terbutaline oral tablets and solution for injection are available generically.
  - There are currently branded albuterol hydrofluoroalkanes (HFA) inhalers and one dry-powder inhaler; however, no generic equivalents are available.

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BB. Buprenorphine/Naloxone (Suboxone®)

Therapeutic Class: Narcotic Withdrawal Therapy Agents
Last Reviewed by the DUR Board: July 25, 2013

Buprenorphine/Naloxone (Brand Suboxone®) and Buprenorphine (Brand Subutex®) are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the Social Security Act and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

Nevada Medicaid encourages recipients to participate in formal substance abuse counseling and treatment.

Approval will be given if all of the following criteria are met and documented:

a. Buprenorphine/Naloxone (Suboxone®)

The recipient must meet all of the following:

1. The recipient has a diagnosis of opioid dependence; and

2. The recipient is 16 years of age or older; and

3. There is documentation that the recipient has honored all of their office visits; and

4. The medication is being prescribed by a physician with a Drug Addiction Treatment Act (DATA) of 2000 waiver who has a unique "X" DEA number.

b. Buprenorphine (Subutex®) (for female recipients):

The recipient must meet all of the following:

1. There is documentation that the recipient is pregnant or there is documentation the recipient is breastfeeding an infant who is dependent on methadone or morphine; and

2. The recipient has a diagnosis of opioid dependence; and

3. The recipient is 16 years of age or older; and

4. There is documentation that the recipient has honored all of their office visits; and

5. The medication is being prescribed by a physician with a Drug Addiction Treatment Act (DATA) of 2000 waiver who has a unique "X" DEA number.

2. Prior Authorization Guidelines

a. Prior Authorization approval will be for one year.

b. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

ZZ. Vivitrol® (naltrexone)

Therapeutic Class: Opioid Dependence Agents
Last Reviewed by DUR Board: April 23, 2015

Vivitrol® (naltrexone®) is subject to prior authorizations based on the Application of Standards in Section 1927 of the Social Security Act and/or approved by the DUR Board.

1. Coverage and Limitations

Approval will be given if the following criteria are met and documented:

a. The drug is being used for an FDA approved indication; and

b. Recipients must be given the Naloxone Challenge Test prior to administration to assure recipient is opiate free before initiation of therapy; and

c. The drug must be delivered directly to the prescriber's office; and

d. The drug is only to be administered once per month.

2. Prior Authorization Guidelines

a. Prior Authorization approvals will be for six months.

b. Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

Therapeutic Class Overview
Opioid Dependence Agents

Overview/Summary:
This review will focus on the agents used for the treatment of opioid dependence, which includes both partial opioid agonists and opioid antagonists. These agents are used alone or in combination for the treatment of opioid use disorder with several agents used for the reversal of opioid overdose.[1-10] Buprenorphine, buprenorphine/naloxone (Bunavail®, Suboxone®, Zubsolv®) and naltrexone (ReVia®, Vivitrol®) are all 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] Naloxone (Evzio®, Narcan®) is used for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.[8-10] Products which contain buprenorphine are classified as Schedule III controlled substances.[11] Other formulations of buprenorphine, buccal film (Belbuca®), injectable (Buprenex®) and transdermal patch (Butrans®) are FDA-approved for use in the management of pain and will not be discussed within this review.[12-14] Buprenorphine, buprenorphine/naloxone sublingual tablets, naltrexone tablets and naloxone prefilled syringes are currently available as generic products.

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).[1,4-7] Compared to full opioid agonists, partial agonists bind to the μ-opioid receptor at a higher degree while activating the receptor to a lesser degree. Partial opioid agonists reach a ceiling effect at higher doses and will displace full opioid agonists from the μ-opioid receptor. Although buprenorphine is associated with significant respiratory depression when used intravenously, or by patients with concomitant benzodiazepine or alcohol abuse, it is associated with a lower abuse potential, a lower level of physical dependence and is safer in overdose when compared to full opioid agonists.[15] During buprenorphine administration, opioid-dependent patients experience positive subjective opioid effects which are limited by ceiling effect.[4-7]

Naloxone and naltrexone are μ-opioid receptor antagonists.[2-10] 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.[11] Similarly, when naloxone alone is administered to a patient via intravenous, intramuscular, nasal or subcutaneous routes, reversal of opioid-related effects is expected. This includes respiratory and/or nevous system depression.[8-10]

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.[15] Transitioning patients to buprenorphine/naloxone as early as possible to minimize potential diversion associated with buprenorphine monotherapy is also reccomended.[15] Veterans Health Administration and American Psychiatric Association guidelines outline a similar strategy with methadone and buprenorphine first line.[16-17] Only the American Psychiatric Association guidelines recommend naltrexone use as an alternative regimen.[17] Naloxone is recommended as an appropriate emergency pharmacologic intervention for instances of opioid overdose.[16] Additionally, The Substance Abuse and Mental Health Services Administration and American Medical Association are among some of the prominent medical organizations and advocacy groups that recognize naloxone as standard care for pharmacologic treatment of opioid overdose.[18,19]

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
Single Entity Agents			
Buprenorphine‖	Opioid dependence, treatment induction*,†; opioid dependence, treatment maintenance*,†	Sublingual tablet: 2 mg 8 mg	✔
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	✔
Naloxone (Evzio®, Narcan®)	Opioid overdose§	Auto-injector solution (Evzio®): 0.4 mg/0.4 mL Nasal Spray (Narcan®) Prefilled syringe: 0.4 mg/mL 2 mg/2 mL	✔
Combination Product			
Buprenorphine/naloxone‖ (Bunavail®, Suboxone®, Zubsolv®)	Opioid dependence, treatment induction† (Suboxone® film); opioid dependence, treatment maintenance†	Buccal film (Bunavail®): 2.1/0.3 mg 4.2/0.7 mg 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.
§As manifested by respiratory and/or central nervous system depression.
‖Generic available in at least one dosage form or strength.

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.[22-32,43-50]
- 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.[24,33-40]
- 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).[60]
- 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.[61]
- Evzio® (naloxone injection), Narcan® (naloxone nasal spray), buprenorphine buccal film (Bunavail®) and buprenorphine/naloxone tablet (Zubsolv®) were FDA-approved via the 505(b)(2) pathway, which allows a manufacturer to compare a new product to a previously-approved drug (or drugs) and utilize data from studies that were performed on the reference drug. These medications have not been specifically studied in clinical trials evaluating their efficacy. Clinical and safety data for these medications is based on previously approved reference products.[5,7,9,10,62]

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.[15]
    - 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.[15]
    - Naloxone is recommended as an appropriate emergency pharmacologic intervention for instances of opioid overdose.[16]
    - Naltrexone is generally reserved as an alternative regimen after buprenorphine-containing products and methadone.[17]
- Other Key Facts:
    - Buprenorphine is available as a sublingual tablet; buprenorphine/naloxone is available as a sublingual tablet (Zubsolv®), sublingual film (Suboxone®) and buccal film (Bunavail®); naltrexone is available as a tablet (ReVia®) and extended-release suspension for injection (Vivitrol®); and naloxone is available as a prefilled syringe, nasal spray (Narcan®) and auto-injector (Evzio®)[1-10]
    - 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.[20]
    - 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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F. Transdermal Fentanyl

Therapeutic Class: Analgesics, Narcotic
Last Reviewed by the DUR Board: January 22, 2015

Transdermal fentanyl, a narcotic agonist analgesic, is indicated in the management of chronic pain in patients requiring continuous opioid analgesia for pain that cannot be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics or PRN dosing with short-acting opioids. Transdermal fentanyl is subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the Social Security Act and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

Because serious or life-threatening hypoventilation could occur, fentanyl transdermal is contraindicated in management of acute or postoperative pain, mild or intermittent pain responsive to PRN or non-opioid therapy, or in doses exceeding 25 mcg/hr at the initiation of opioid therapy. Therefore, patients must meet the following criteria in order to gain prior authorization approval:

a. Patient cannot be managed by lesser means such as acetaminophen-opioid combinations, nonsteriodal analgesics, or PRN dosing with short-acting opioid.

b. Patient requires continuous opioid administration.

c. Prescribers are encouraged to check the Nevada State Board of Pharmacy's Prescription Monitoring Program (PMP) prior to prescribing narcotic analgesics. Refer to the PMP website at http://bop.nv.gov/links/PMP/.

d. If transitioning from another opioid, daily morphine equivalent doses are used to calculate the appropriate fentanyl patch dose.

1. Morphine 60-134 mg/day PO; Initial Transdermal Fentanyl dose 25 mcg/hr.

2. Morphine 135-224 mg/day PO; initial Transdermal Fentanyl dose 50 mcg/hr.

3. Morphine 225-314 mg/day PO; initial Transdermal Fentanyl dose 75 mcg/hr.

4. Morphine 315-404 mg/day PO; initial Transdermal Fentanyl dose 100 mcg/hr.

5. Morphine 405-494 mg/day PO; initial Transdermal Fentanyl dose 125 mcg/hr.

6. Morphine 495-584 mg/day PO; initial Transdermal Fentanyl dose 150 mcg/hr.

7. Morphine 585-674 mg/day PO; initial Transdermal Fentanyl dose 175 mcg/hr.

8. Morphine 675-764 mg/day PO; initial Transdermal Fentanyl dose 200 mcg/hr.

9. Morphine 765-854 mg/day PO; initial Transdermal Fentanyl dose 225 mcg/hr.

10. Morphine 855-944 mg/day PO; initial Transdermal Fentanyl dose 250 mcg/hr.

11. Morphine 945-1034 mg/day PO; initial Transdermal Fentanyl dose 275 mcg/hr.

12. Morphine 1035-1124 mg/day PO; initial Transdermal Fentanyl dose 300 mcg/hr.

2. Prior Authorizations

Prior approval will be given for a 12 month time period.

Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

Q. Long-Acting Narcotics

Therapeutic Class: Analgesics, Narcotic
Last Reviewed by DUR Board: July 30, 2009

Long-Acting Narcotics are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the Social Security Act and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

Indications: Management of moderate-to-severe pain when continuous around-the-clock analgesic is needed for an extended period of time. Medications:

a. Oxycontin (including generic); MS Contin (including generic); Avinza; Kadian; Oramorph.

1. No prior authorization is required for diagnosis of terminal cancer.

b. Please Note: The use of Long – Acting Narcotics for acute/short term treatment of pain not within the quantity limits will not be approved.

Approval will be for a three month time limit.

2. Prior Authorization Guidelines:

The prior authorization must be initiated by the prescriber. The approved Payment Authorization Request (PAR) must be available if requested.

Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

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 1.[1-19] 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.[20] 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.[20] 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).[20] 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.[21]

  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.[21] 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.[22]

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.[22]

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.[22,23]

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.[24]

According to the FDA abuse and misuse of prescription opioid products has created a serious and growing public health problem. The FDA considers the development of abuse-deterrent products a priority. As outlined in their guidance for evaluation and labeling, “abuse-deterrent properties” are defined as those properties shown to meaningfully deter abuse, even if they do not fully prevent abuse. The FDA elected to use the term “abuse-deterrent” rather than “tamper-resistant” because the latter term refers to, or is used in connection with, packaging requirements applicable to certain classes of drugs, devices, and cosmetics. Abuse-deterrent technologies should target known or expected routes of abuse relevant to the proposed product. The FDA has provided several categories for abuse-deterrent formulations. Categories include physical/chemical barriers, agonist/antagonist combinations, aversion (adding a product that has an unpleasant effect if manipulated or is used at a higher than recommended dose), delivery systems, new molecular entities/prodrugs, a combination of these methods, or a novel approach (encompasses approaches or technologies not currently captured in previous categories).[25]

Buprenorphine buccal film is formulated using bioerodible mucoadhesive (BEMA®) technology. BEMA® is a film formulation that consists of a water-soluble polymer that adheres to the buccal mucosa. The film dissolves over approximately 30 minutes into the buccal mucosa, leaving behind no residual film. Delivery into the buccal mucosa enhances the bioavailability of buprenorphine, as it bypasses gastrointestinal absorption and first-pass metabolism.[1]

Hysingla ER® (hydrocodone extended-release [ER]) tablets are resistant to crushing, breaking and dissolution using different solvents, and the tablets still retain some ER properties after tampering. Attempts to dissolve the tablets result in the formation of a viscous gel, which may cause difficulty passing through a hypodermic needle.[5] In addition, the tablets appear to be associated with less “drug liking”

based upon results reported from two unpublished clinical abuse potential studies conducted in a small number of non-dependent recreational opioid users.[26]

There are currently two formulation of oxycodone ER which are considered abuse deterrent, OxyContin® and Xtampza ER®. OxyContin® utilizes the RESISTEC® technology that employs a combination of polymer and processing that gives tablet hardness, imparts viscosity when dissolved in aqueous solutions and resists increased drug release rate when mixed with alcoholic beverages.[10] Results from trials support that, the reformulated oxycodone ER is able to resist crushing, breaking, extraction and dissolution in small volumes using a variety of tools and solvents.[28-29] Xtampza ER® utilizes DETERx technology, which is designed to provide adequate pain control while maintaining its drug release profile after being subjected to common methods of manipulation, including chewing and crushing.[30,31]

Originally approved by the FDA in 2009, Embeda® (morphine sulfate/naltrexone hydrochloride) was voluntarily recalled from the market in March 2011 due to stability issues with the manufacturing process.[32] Subsequently, in November 2013, the FDA approved a manufacturing supplement for the product after the stability concerns were addressed through the manufacturing process. The abuse deterrent formulation of Embeda® (morphine sulfate/naltrexone hydrochloride) was granted FDA approval in October 2014, making it the third ER opioid analgesic to obtain this designation and the first among the morphine ER products.[33] Embeda® (morphine sulfate/naltrexone hydrochloride) capsules contain pellets consisting of morphine sulfate with a sequestered core of naltrexone hydrochloride at a ratio of 100:4.[18] If morphine sulfate/ naltrexone hydrochloride is crushed, chewed, or dissolved up to 100% of the sequestered naltrexone is released, reversing the effects of morphine, potentially precipitating withdrawal in opioid tolerant individuals, and increasing the risk of overdose and death.[33]

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

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Buprenorphine (Belbuca®, 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.	Buccal Film (Belbuca®): 75 µg 150 µg 300 µg 450 µg 600 µg 750 µg 900 µg 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 37.5 µg/hour 50 µg/hour 62.5 µg/hour 75 µg/hour 87.5 µg/hour 100 µg/hour	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
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 treatment options are inadequate.	Capsule, extended release (Zohydro ER®): 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‡	✔
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	✔
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‡	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		Capsule, extended release: 10 mg 20 mg 30 mg 40 mg 50 mg 60 mg 80 mg 100 mg‡ 200 mg‡ Tablet, extended release: 15 mg 30 mg 60 mg 100 mg‡ 200 mg‡	
Oxycodone (OxyContin®*, Xtampza 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 in adults (all formulations) and in opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent (extended release tablet).¶	Capsule, extended release (Xtampza ER®): 9 mg 13.5 mg 18 mg 27 mg 36 mg Tablet, extended release (OxyContin®): 10 mg 15 mg 20 mg 30 mg 40 mg 60 mg‡ 80 mg‡	✔ #
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	✔
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	Tablet, extended release: 50 mg 100 mg 150 mg 200 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	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.	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/ Acetaminophen (Xartemis XR®)	For the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate	Biphasic tablet, 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® or Xtampza ER® >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.[5,36]
- The efficacy and safety of buprenorphine buccal film was evaluated in three phase III clinical trials. However one of the clinical trials, which is currently not published, did not show a significant difference between buprenorphine and placebo.[1] The other two studies evaluated patients who had a diagnosis of chronic low back pain in a randomized withdrawal design. The first study evaluated opioid-naïve patients while the second study evaluated opioid-experienced patients. The double-blind treatment phase for both studies was 12 weeks.[1,38,39] In the first study, the increase in mean (standard deviation [SD]) pain intensity scores on the NRS from baseline to week 12 for buprenorphine buccal film (0.94 [1.85]) was significantly lower than that of patients who received placebo (1.59 [2.04]; P=0.0012).[38] The increase in mean (SD) pain intensity scores on the NRS from baseline to week 12 for buprenorphine buccal film was significantly less than that of placebo (0.88 [1.79] versus 1.92 [1.87], respectively; P<0.00001).[39]
- 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.[49-51]
- 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).[52]

- 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.[53] In a noninferiority analysis of a hydromorphone ER compared to oxycodone ER, two agents provided similar pain relief in the management of osteoarthritic pain.[54]
- 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.[58,59]
- 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.[61] 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).[62]
- 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.[32]
- Morphine/naltrexone has demonstrated significantly better pain control compared to placebo in patients with osteoarthritis pain.[65]
- Oxycodone ER (OxyContin®) has demonstrated significantly greater efficacy compared to placebo for the treatment of neuropathic pain and chronic refractory neck pain.[66-68] 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.[69]
- The FDA-approval of oxycodone ER (Xtampza ER®) was based upon an enriched-enrollment, randomized-withdrawal, double-blind, placebo-controlled, parallel group, study was conducted in patients with persistent, moderate-to-severe chronic lower back pain, with inadequate pain control from their prior therapy (n=740). Following the titration phase, 389 subjects met the study randomization criteria of adequate analgesia and acceptable tolerability and entered the randomized, double-blind maintenance phase. Patients were randomized at a ratio of 1:1 into a 12-week double-blind maintenance phase with their fixed stable dose of oxycodone ER (Xtampza ER® or matching placebo. There was a significant difference in pain reduction as assessed by average pain intensity favoring the oxycodone ER group when compared to placebo from randomization baseline to week 12 (0.29 vs. 1.85 ;P<0.0001).[71]
- 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. [72,73] 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.[72] In another trial, oxymorphone ER demonstrated greater efficacy for the relief of osteoarthritis pain compared to placebo.[74]
- 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).[76] 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).[77] 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).[75]

- 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).[83]
- 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%).[84]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - The current clinical guidelines regarding the use of opioids recognize their established efficacy in the treatment of moderate to severe pain. None of the available agents are distinguished from the others in the class, and recommendations for treatment are made for the class as a whole.[86-98]
    - Guidelines published by Centers for Disease Control and Prevention's (CDC) opioid use in the management of chronic pain recommend physicians start with immediate-release (IR) opioids and reserve ER formulations for severe, continuous pain that IR opioids cannot treat.[86]
    - Physicians should prescribe the lowest effective dose and carefully reassess benefits and risks when considering a dose of ≥50 morphine milligram equivalents (MME) while avoiding increasing opioid doses to ≥90 MME unless justified.[86]
    - Optimal analgesic selection will depend on the patient's pain intensity, any current analgesic therapy, and concomitant medical illness. ER products are generally similar and selection should be based on clinical or patient-specific factors.[87]

- Other Key Facts:[1-19]
    - Products currently available as a generic include fentanyl patches, hydromorphone ER tablets, methadone (all formulations), morphine ER (all formulations), oxycodone ER tablets and oxymorphone ER tablets.
    - There are currently several abuse deterrent ER opioids approved by the FDA. These include buprenorphine sublingual film (Belbuca®), oxycodone ER (OxyContin®, Xtampza ER®) and hydrocodone ER (Zohydro ER®, Hysingla ER®) as well as morphine sulfate/naltrexone (Embeda®).
    - Oxymorphone ER (Opana ER®) and hydromorphone ER (Exalgo®) have also been formulated with abuse deterrent properties, however they are classified as abuse deterrent by the FDA.
    - All long-acting opioids are pregnancy category C, with the exception of oxycodone.
    - Only fentanyl transdermal system (age 2 to 17 years) and oxycodone ER tablets (age 11 and older) are approved for use in children
    - Tapentadol is contraindicated with monoamine oxidase inhibitors; although, caution should be used when used in combination with any long-acting opioid.
    - 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.
- Frequency of dosing varies by agent:
  - Buprenorphine patch: once every seven days
  - Fentanyl transdermal system: once every 72 hours
  - Hydromorphone ER (Exalgo®), hydrocodone ER (Hysingla ER®) and morphine ER (Avinza®): once daily
  - Morphine ER (Kadian®) and morphine/naltrexone (Embeda®): once or twice daily
  - Morphine ER (MS Contin®) and all methadone formulations: twice or three times daily
  - All remaining long-acting agents: twice daily
- Avinza® (morphine) and Xartemis XR® (oxycodone/acetaminophen) are the only long-acting opioids with a maximum daily dose.
  - Avinza® (morphine): 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): max dose is limited to four tablets per day, and/or if taking other acetaminophen products, a maximum of 4,000 mg/day[19]
- 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]
  - Morphine ER capsules (Avinza®, Kadian®), morphine/naltrexone capsules (Embeda®) and oxycodone ER capsules (Xtampza ER®) can be opened and the pellets sprinkled on applesauce and then swallowed whole.[11,12,15,18]
  - Kadian® pellets can also be placed in water and used through a gastrostomy tube.
  - Xtampza® may be opened and administered through a gastrostomy or nasogastric tube.
  - Avinza®, Kadian®, and Embeda® pellets should not be used thorough a nasogastric tube.
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CC. Ampyra® (dalfampridine)

Therapeutic Class: Agents for the treatment of Neuromuscular Transmission Disorder
Last Reviewed by the DUR Board: July 25, 2013

Ampyra® (dalfampridine) is subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the Social Security Act and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

Approval for Ampyra® (dalfampridine) will be given if all of the following criteria are met and documented:

a. Ampyra® (dalfampridine)

The recipient must meet all of the following:

1. The recipient must have a diagnosis of Multiple Sclerosis ; and

2. The medication is being used to improve the recipient's walking speed; and

3. The medication is being prescribed by or in consultation with a neurologist; and

4. The recipient is ambulatory and has an EDSS score between 2.5 and 6.5; and

5. The recipient does not have moderate to severe renal dysfunction (CrCL >50 ml/min); and

6. The recipient does not have a history of seizures; and

7. The recipient is not currently pregnant or attempting to conceive.

2. Prior Authorization Guidelines

a. Initial Prior Authorization approval will be for three months.

b. Requests for continuation of therapy will be approved for one year.

c. Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

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) and include alemtuzumab (Lemtrada®), daclizumab (Zinbryta®), glatiramer acetate (Copaxone®, Glatopa®), interferon β (IFNβ)-1b (Betaseron®, Extavia®), intramuscular (IM) IFNβ-1a (Avonex®), subcutaneous (SC) IFNβ-1a (Rebif®), SC peginterferon β-1a (Plegridy®) along with the oral products dimethyl fumarate (Tecfidera®), fingolimod (Gilenya®) and teriflunomide (Aubagio®).[1-14] Both IFNβ-1b and IM IFNβ-1a are also FDA-approved for the treatment of patients experiencing a first clinical episode with magnetic resonance imaging (MRI) evidence of multiple sclerosis (MS), which is often referred to as a clinically isolated syndrome.[7,8,10] The exact mechanisms of action of daclizumab, dimethyl fumarate, teriflunomide, the INFs and glatiramer acetate are unknown or not completely understood but are likely due to their antiproliferative and immuno-modulatory effects.[2,3,5-12]

  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.[16-17] There are four clinical subtypes of MS: RRMS, primary progressive (PPMS), progressive relapsing (PRMS), and secondary progressive (SPMS).[16-19] The most common form is RRMS, characterized by acute relapses followed by partial or full recovery.[17,19] Patients with PPMS have a continuous and gradual decline in function without evidence of acute attacks. Patients with PRMS also have a continuous decline in function while experiencing occasional attacks. Finally, SPMS begins as RRMS, but as time progresses the attack rate declines and patients experience a gradual deterioration.[19]

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

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Alemtuzumab (Lemtrada)	Relapsing-remitting multiple sclerosis*		-
Daclizumab (Zinbryta®)	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: 0.5 mg	-
Glatiramer acetate (Copaxone®**, Glatopa®††)	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	Relapsing-remitting multiple sclerosis¶, treatment of first clinical episode with	Prefilled syringe: 30 µg	-

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Administration Pack®)	magnetic resonance imaging features consistent with multiple sclerosis	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.
#Treatment of patients with relapsing forms of multiple sclerosis in patients who have an inadequate response to two or more drugs indicated for the treatment of multiple sclerosis.
**Generic available in at least one dosage form or strength.
††Glatopa® is considered a biosimilar to reference product Copaxone®

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.
- The FDA-approval of daclizumab was based on the results of two randomized double-blind studies in adults with a diagnosis of relapsing MS (RMS). Both utilized the primary endpoint of annualized relapse rate (ARR). The first study evaluated 1,841 patients over 96 to 144 weeks who were randomized to either daclizumab 150 mg every four weeks or to IFN β-1a 30 µg weekly. Both groups received a placebo matching the other treatment arm. The ARR was significantly reduced in the daclizumab arm (0.216) compared with the IFN β-1a group (0.393) representing a relative reduction of 45% (P<0.0001).[2,33] The second study, SELECT, evaluated a total of 621 patients over 52 weeks who were randomized to daclizumab 150 mg every four weeks, daclizumab 300 mg every four weeks or placebo. The ARR was significantly lower in both the daclizumab 150 mg group (0.21) and the daclizumab 300 mg group (0.23) compared to the placebo group (0.46; P<0.001 for both).[2,34]
- 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).[37,61] 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).[61]
- 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).[38]
- The FREEDOMS II trial had similar results, with fingolimod providing a lower ARR over 24 months compared to placebo.[87]
- 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).[43] 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.[44]

- 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).[56] In an unpublished extension study, ARR remained low after five years and the adverse event rates were similar to those reported in previous trials.[57,58]
- The TOWER study showed that over one year teriflunomide had a lower ARR than placebo.[88]
- 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).[89]
- 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.[103,104]
- 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). [105]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - The approach to treating MS includes: the management of symptoms, treatment of acute relapses, and utilization of disease-modifying therapies to reduce the frequency and severity of relapses, and delay disease and disability progression.[14,16,19,22]
    - IFNβ products or glatiramer acetate are recommended as first-line therapy in patients with RRMS.[18,19]
    - The Association of British Neurologists also recommend either of the oral agents as potential first-line options.[18]
    - Due to its adverse effect profile, fingolimod is sometimes recommended as a second-line option.[19,20] NICE recommends use of fingolimod only if patients have an unchanged or increased relapse rate, or ongoing severe relapses compared to the previous year despite treatment with IFNβ.[20]
    - Consensus guidelines do not recommend a change of therapy in patients positive for neutralizing antibodies who are responding to IFN therapy, noting that neutralizing antibodies disappear with continued treatment in the majority of patients.[18,23-25]
    - A change of therapy may be considered in patients experiencing a suboptimal response or intolerable adverse effects.[26,28,29]
    - Data suggests a significant reduction in relapse rate and a delay in disease and disability progression in patients switching from IFNβ to glatiramer acetate therapy or vice versa due to poor response.[26,28,29]
- Other Key Facts:
    - A biosimilar version of Copaxone® (glatiramer acetate 20 mg/mL) was recently approved by the FDA and is marked under the trade name Glatopa®. There are no other generic MS products available, including other strengths of glatiramer acetate.[1-14]
    - 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®.[5,6]

- Alemtuzumab must be administered by a healthcare professional.
- Alemtuzumab and daclizumab are available only through restricted access programs. Both are associated with causing serious autoimmune disorders. In addition, alemtuzumab has been associated with life threatening infusion reactions as well as increased risk of malignancy.[1,2]

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Therapeutic Class Overview
Fibric Acid Derivatives

Therapeutic Class

- **Overview/Summary:** The fibric acid derivatives are agonists of the peroxisome proliferator activated receptor α (PPARα). Activation of PPARα increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein CIII. The resulting decrease in triglycerides (TG) produces an alteration in the size and composition of low-density lipoprotein cholesterol (LDL-C) from small, dense particles to large buoyant particles. There is also an increase in the synthesis of high-density lipoprotein cholesterol (HDL-C), as well as apoprotein AI and AII.[1-10] The major action of this class of medications is to reduce TG. The fibric acid derivatives can decrease TG by 20 to 50% and increase HDL-C by 10 to 35%. They also lower LDL-C by 5 to 20%; however, in patients with hypertriglyceridemia, LDL-C may increase with the use of fibric acid derivatives.[11]

  Several fenofibrate products are currently available, including micronized and non-micronized formulations. The different fenofibrate formulations are not equivalent on a milligram-to-milligram basis. Micronized fenofibrate is more readily absorbed than non-micronized formulations, which allows for a lower daily dose. Fenofibrate (micronized and non-micronized formulations), fenofibric acid, and gemfibrozil are available generically in at least one dosage form and/or strength.[12] Fenofibrate and fenofibric acid are Food and Drug Administration (FDA)-approved for the adjunctive treatment of primary hypercholesterolemia or mixed dyslipidemias, as well as an adjunctive treatment for hypertriglyceridemia. Gemfibrozil is FDA-approved for the treatment of hypertriglyceridemia and to reduce the risk of developing coronary heart disease (CHD) in select patients.[13] Gemfibrozil has demonstrated a reduction in the risk of fatal and nonfatal myocardial infarction (MI) for primary prevention, as well as a reduction in CHD death and nonfatal MI and stroke for secondary prevention. Clinical trial results demonstrating that the fibric acid derivatives, as a class, reduce CHD incidence is less robust than that with statin therapy.[11]

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
Fenofibrate (Antara®*, Fenoglide®, Lipofen®, Lofibra®*, Tricor®*, Triglide®)	Adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia. Adjunctive therapy to diet to reduce elevated LDL-C, total cholesterol, TG and apolipoprotein B, and to increase HDL-C in patients with primary hypercholesterolemia or mixed dyslipidemia.	Capsule: 50 mg (Lipofen®) 150 mg (Lipofen®) Capsule, Micronized: 30 mg (Antara®) 43 mg (Antara®) 67 mg (Lofibra®) 90 mg (Antara®) 130 mg (Antara®) 134 mg (Lofibra®) 200 mg (Lofibra®) Tablet: 40 mg (Fenoglide®) 48 mg (Tricor®) 50 mg (Triglide®) 54 (Lofibra®) 120 mg (Fenoglide®) 145 mg (Tricor®) 160 mg (Lofibra®, Triglide®)	✔

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/ Strength	Generic Availability
Fenofibric acid (Fibricor®*, Trilipix®†)	Adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fibricor®).‡ Adjunctive therapy to diet to reduce elevated LDL-C, total cholesterol, TG and apolipoprotein B, and to increase HDL-C in patients with primary hypercholesterolemia or mixed dyslipidemia.	Delayed-release capsule: 45 mg (Trilipix®) 135 mg (Trilipix®) Tablet: 35 mg (Fibricor®) 105 mg (Fibricor®)	✔
Gemfibrozil (Lopid®*)	Treatment of adult patients with very high elevations of serum TG levels who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them. Reducing the risk of developing CHD only in Type IIb patients without history of or symptoms of existing CHD who have had an adequate response to weight loss, dietary therapy, exercise and other pharmacologic agents and who have the following triad of lipid abnormalities: low HDL-C levels in addition to elevated LDL-C and elevated TG.	Tablet: 600 mg	✔

CHD=coronary heart disease, HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, TG=triglycerides
*Generic is available in at least one dosage form and/or strength.
†Choline fenofibrate.
‡Indicated for therapy in patients with triglycerides ≥500 mg/dL.

Evidence-based Medicine

- In general, the fibric acid derivatives consistently demonstrate greater efficacy compared to placebo in the management of hypercholesterolemia and hypertriglyceridemia.[14-18]
- The addition of fibric acid derivatives to other well established lipid lowering agents has been shown to be safe and resulted in additional improvements in lipid profile compared to each drug given as monotherapy.[16-28]
- The five year, placebo-controlled FIELD trial (N=9,975) demonstrated that fenofibrate did not significantly reduce the risk of the combined primary outcome of coronary events (CHD), death or nonfatal myocardial infarction (MI) in patients with type 2 diabetes. When individual endpoints were analyzed, fenofibrate significantly reduced nonfatal MI by 24% (hazard ratio [HR], 0.76; P=0.010), but a nonsignificant increase in CHD mortality (HR, 1.19; P=0.22) was observed.[29] Similar results were observed in the ACCORD trial (N=5,518) which evaluated the efficacy of fenofibrate on reducing the risk of major cardiovascular events in high risk type 2 diabetics.[30]
- In the five year, Helsiniki Heart Study (N=4,081), a primary prevention trial, gemfibrozil demonstrated a significant 34% (P<0.02) reduction in the incidence of cardiac events but demonstrated no effect on all-cause mortality.[31] After 8.5 years of follow up, all-cause mortality was numerically higher with gemfibrozil, but the increase did not meet significance.[32] In a secondary prevention component of the Helsinki Heart Study, there was no difference between gemfibrozil and placebo in the incidence of fatal and nonfatal MI and cardiac death.[33]
- A meta-analysis of 10 randomized controlled trials (N=36,489) evaluated fibric acid derivatives for the primary and secondary prevention of cardiovascular events and demonstrated that treatment tended to increase all-cause mortality (odds ratio [OR], 1.07; P=0.08) and was associated with a significant increase in noncardiovascular mortality (OR, 1.16; P=0.004). No effect of fibric acid derivatives was observed for cardiovascular mortality (OR, 0.98; P=0.68). When the individual fibric acid derivatives were analyzed, the odds of cardiovascular mortality were significantly lower with gemfibrozil (OR, 0.77; P=0.05).[34]

- A second meta-analysis of 18 randomized controlled trials (N=45,058) demonstrated no effect on all-cause mortality (relative risk [RR], 1.00; P=0.918), cardiovascular mortality (RR, 0.97; P=0.582) or sudden death (RR, 0.89; P=0.190). An increased risk of noncardiovascular mortality was noted; however, this finding did not reach significance (RR, 1.10; P=0.063).[35]
- Fenofibric acid was added to rosuvastatin in patients with chronic kidney disease and it was shown that there was a significantly greater decrease in median percent TGs compared to rosuvastatin alone after eight weeks (P<0.001) and 16 weeks (P<0.001) along with an increase in HDL-C over the same time periods (P<0.001).[36]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Therapeutic lifestyle changes remain an essential modality in the management of patients with hypercholesterolemia.[37-46]
    - In general, hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are considered first line therapy for decreasing low density lipoprotein cholesterol (LDL-C) levels.
    - Due to increased muscle side effects including rhabdomyolysis, gemfibrozil is not recommended to be used in a combination with statins.[43]
    - Fibric acid derivatives are typically reserved for the treatment of hypertriglyceridemia, to reduce the risk of pancreatitis, or for an isolated low high density lipoprotein cholesterol.[37,40]
    - Fibric acid derivatives can be considered in patients with coronary heart disease who have low levels of LDL-C and atherogenic dyslipidemia, or in combination with a statin in patients who have elevated LDL-C and atherogenic dyslipidemia.[37] Since the publication of these guidelines, the FD) requested the discontinuation of the marketing of Trilipix® indicated as an adjunct to diet in combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD (coronary heart disease) or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal. This decisions was based on the FDA's conclusion that the totality of the scientific evidence no longer supports the conclusion that a drug-induced reduction in TG and/or increase in HDL-C levels in statin-treated patients results in a reduction in the risk of cardiovascular events.[47]
    - The National Institute for Health and Clinical Excellence (NICE) guidelines recommend non-routine use of fibrates if intolerant to statins as monotherapy and recommend against the use of niacin, bile acid sequestrants, and omega-3 fatty acids or any combination of a stains plus either a fibrate, niacin, bile acid sequestrants, or omega-3 fatty acids for primary or secondary prevention of coronary vascular disease due to lack of evidence.[44]

- Other Key Facts:
    - Gemfibrozil (Lopid®) is the only fibric acid derivative approved for reducing the risk of developing coronary heart disease in select patients.[10]
    - Currently, all fibric acid derivatives are available generically in at least one dosage form and/or strength.[12]

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Therapeutic Class Overview
Benign Prostatic Hyperplasia (BPH) Treatments

Therapeutic Class

- **Overview/Summary:** The agents approved for the treatment of signs and symptoms of benign prostatic hyperplasia (BPH) will be the focus of this review. The α-adrenergic blockers including, alfuzosin, doxazosin, silodosin, tamsulosin, and terazosin, reduce smooth-muscle tone in the prostate and bladder neck decreasing lower urinary tract symptoms (LUTS) secondary to BPH. Alfuzosin, silodosin and tamsulosin are selective to the α-adrenergic receptors located in the prostate and therefore are only Food and Drug Administration (FDA) approved for BPH, whereas doxazosin and terazosin also inhibit α-adrenergic receptors found in the vascular smooth muscle and are additionally indicated for hypertension.[1-6] The 5-α reductase inhibitors, dutasteride and finasteride, act by blocking the conversion of testosterone to dihydrotestosterone and in turn suppress the growth of the prostate. making them appropriate treatment options for LUTS associated with overall prostatic enlargement.[7,8] Jalyn® (dutasteride/tamsulosin) is a combination of both an α-adrenergic blocker and a 5-α reductase inhibitors.[9] The final drug approved for use in BPH is the phosphodiesterase-5 inhibitor, tadalafil. The exact mechanism for reducing BPH symptoms is unknown.[10] Note that even though doxazosin and terazosin are FDA-approved for use in the treatment of hypertension, tadalafil is FDA-approved for use in the treatment of erectile dysfunction and pulmonary arterial hypertension, and finasteride is FDA-approved for alopecia, they are not included in this review. Jalyn® (dutasteride/tamsulosin) is a combination of both an α-adrenergic blocker and a 5-α reductase inhibitors.[9] Another drug approved for use in BPH is the phosphodiesterase-5 inhibitor, tadalafil. The exact mechanism for reducing BPH symptoms is unknown.[10] Although doxazosin and terazosin are FDA-approved for use in the treatment of hypertension, tadalafil is FDA-approved for use in the treatment of erectile dysfunction and pulmonary arterial hypertension, and finasteride is FDA-approved for alopecia, they are not included in this review.

  Clinical manifestations of BPH include LUTS (frequency of urination, nocturia, hesitancy, urgency, and weak urinary stream). The appearance and progression of symptoms is usually slow, over a couple of years, with a poor correlation between symptoms and the presence of an enlarged prostate on rectal exam.[11] Disease prevalence and the occurrence of symptoms are age dependent, with an initial onset of disease occurring patients greater than 50 years of age.[11] Current treatment guidelines acknowledge that not all men with histological evidence of BPH will develop bothersome LUTS and not all patients with BPH and LUTS actually have prostate enlargement, one of the main features of symptomatic disease. Additionally, prostate enlargement may exist in the absence of LUTS.[12-13]

Table 1. Current Medications Available in the Therapeutic Class[1-10,14]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Alfuzosin hydrochloride (Uroxatral®)	Treatment of signs and symptoms of benign prostatic hyperplasia	Tablet, extended release: 10 mg	✔
Doxazosin mesylate (Cardura®,¶, Cardura XL®)	Treatment of signs and symptoms of benign prostatic hyperplasia#; treatment of hypertension*	Tablet, extended release: 4 mg 8 mg Tablet: 1 mg 2 mg 4 mg 8 mg	✔

Dutasteride (Avodart®)	Treatment of signs and symptoms of benign prostatic hyperplasia†,‡	Capsule: 0.5 mg	✔
Finasteride (Proscar®)	Treatment of signs and symptoms of benign prostatic hyperplasia†,§	Tablet: 5 mg	✔
Silodosin (Rapaflo®)	Treatment of signs and symptoms of benign prostatic hyperplasia	Capsule: 4 mg 8 mg	-
Tadalafil (Cialis®, Adcirca®)	Treatment of signs and symptoms of benign prostatic hyperplasia, treatment of erectile dysfunction**	Tablet: 2.5 5 10¶ 20¶	-
Tamsulosin hydrochloride (Flomax®)	Treatment of signs and symptoms of benign prostatic hyperplasia†	Capsule: 0.4 mg	✔
Terazosin hydrochloride	Treatment of signs and symptoms of benign prostatic hyperplasia,	Capsule: 1 mg 2 mg 5 mg 10 mg	✔
Combination Products			
Dutasteride/tamsulosin hydrochloride (Jalyn®)	Treatment of signs and symptoms of benign prostatic hyperplasia†, treatment of hypertension††	Capsule: 0.5 mg/0.4 mg	✔

*Immediate-release formulation only.
†In men with an enlarged prostate, to improve symptoms, reduce the risk of acute urinary retention and reduce the risk of the need for BPH-related surgery.
‡To treat symptomatic BPH in men with an enlarged prostate in combination with tamsulosin.
§To reduce the risk of symptomatic progression of BPH in combination with doxazosin.
#Doxazosin indicated for both the urinary outflow obstruction and obstructive and irritative symptoms associated with BPH.
¶Generic available in at least one dosage form or strength.
**** When used with finasteride to initiate BPH treatment, such use is recommended for up to 26 weeks.
†† In men with an enlarged prostate.

Evidence-based Medicine[15-67]

- FDA-approval of silodosin was based on two clinical trials where it was compared to placebo and demonstrated its efficacy in decreasing the International Prostate Symptom Score (IPSS) and improving general quality of life scores. In a pooled analysis of these two clinical trials, the mean change in total IPSS at baseline was -6.40 (±6.63) and -3.50 (±5.84) for the silodosin and placebo groups, respectively with an adjusted mean difference reported as -2.8 (P<0.0001). The maximum urinary flow rate (Q_{max}) at endpoint was 2.6 mL/second (standard deviation [SD]±4.43) in the silodosin group and 1.5 mL/ second (SD±4.36) in the placebo group; corresponding to an adjusted mean group difference of 1.0 mL/ second (P=0.0007).[16]
- The safety and efficacy of tadalafil for BPH has been evaluated in multiple studies. These studies. Tadalafil consistently showed significantly better improvement in IPSS compared to placebo.[18-25] One study evaluated men with BPH who had comorbid erectile dysfunction. Tadalafil was associated with statistically significant improvements in both internation index of erectile function (IIEF) scores and total IPSS (P<0.001 for both).[25]
- Studies comparing the α-adrenergic blocking agents to each. Although some trials have suggested superiority one agent over another, most studies, have tended toward non-inferiority within the α-blockers related to reducing IPSS.[26-46]
    - A Cochrane review has evaluated tamsulosin in comparison to other α-adrenergic blocking agents. It was concluded that tamsulosin was as effective as other α-adrenergic blockers in improving LUTS and urinary flow rates. Dizziness, rhinitis and abnormal ejaculation occurred

significantly more frequently than placebo and withdrawal was reported more often with higher doses of tamsulosin. Additionally, terazosin use was associated with a higher rate of discontinuation than low dose tamsulosin.[37]
    - A second Cochrane review evaluated terazosin to other α blockers, finasteride alone or in combination with terazosin and placebo. Terazosin was comparable to tamsulosin in improving IPSS (40% vs 43%), and more effective than finasteride (38% vs 20%) or placebo (38% vs 17%) in improving American Urological Association Symptom Score (AUA-SS). Peak urinary flow rates were similar among α blockers and higher with terazosin (22%) over finasteride (15%) and placebo (11%).[38]
    - A meta-analysis by Djavan et al of α-adrenergic blocking agents (alfuzosin, doxazosin, tamsulosin, and terazosin) in men with LUTS suggestive of benign prostatic obstruction did not identify any difference among agents in improving total urinary symptom scores or Q_{max}. However, alfuzosin and tamsulosin were better tolerated than doxazosin and terazosin.[39]
- Similar to the α-blocking agents, the 5-α reductase inhibitors have been compared to one another in a number of clinical trials, with mixed results. Dutasteride was shown to be non-inferior to finasteride for reducing prostate volume, post-void volume, and American Urological Association Symptom Score (AUA-SS).[47-50]
- Head-to-head trials between 5-α reductase inhibitors and α blockers have also been conducted.[51-62]
    - When compared to finasteride, tamsulosin showed comparable effect on urinary symptom scores at study end point (24 weeks and 1 year)[51,52], however a benefit was found with tamsulosin at earlier assessment (4 weeks) in both IPSS and Q_{max}.[51]
    - Tamsulosin in combination with dutasteride has been found to be associated with a greater benefit in IPSS and Q_{max} than each agent alone. As expected tamsulosin use resulted in a much lower decrease in prostate volume as compared to combination therapy (0.00%±0.84% and 26.90%±0.62%, respectively; P<0.001).[53,]
    - Four large, long-term trials comparing doxazosin, finasteride, each agent alone and in combination, and placebo.[58-61] Rates of nocturia were significantly reduced with monotherapy and combination treatment compared to placebo.[59]
    - Men with moderate to enlarged prostate glands benefited most from combination therapy (P<0.05), however doxazosin therapy alone was as effective as combination therapy for decreasing the risk of progression in men without an enlarged prostate.[60]
    - Doxazosin monotherapy and in combination with finasteride was associated with significantly greater improvements in Q_{max} and IPSS. Differences between finasteride alone and placebo did not reach statistical significane.[61]
    - Terazosin use alone and in combination with finasteride was associated with significantly greater reductions in symptom scores and greater increases in Q_{max} compared to finasteride monotherapy or placebo. Differences among combination therapy and terazosin monotherapy did not reach statistical significance, nor did difference between finasteride and placebo.[62]
- Studies have been conducted evaluating the safety and efficacy of combination therapy with two agents from different classes.[63-66]
    - A retrospective analysis showed that combination therapy with finasteride and an α-blocking agent significantly improved IPSS in patients with severe BPH symptoms, but was not statistically different from monotherapy in the same population.[63]
    - A meta-analysis conducted by Gacci et al found that a phosphodiesterase-5 inhibitor and α blocker combination therapy significantly improved IPSS, IIEF score and Q_{max} compared to a blockers alone (P<0.05, P<0.0001 and P<0.0001, respectively).[64]
    - Tadalafil 5 mg once daily coadministered with finasteride 5 mg for 12 weeks resulted in an IPSS total score improvement that was significantly better than finasteride/placebo (P=0.001).[66]
- A systematic review of alfuzosin studies showed a greater improvement in the primary outcome (IPSS) over placebo (weighted mean difference, -1.8 points; 95% confidence interval [CI], -2.49 to -1.11); however, when compared to other α-blockers (doxazosin, tamsulosin), doxazosin use was associated with the most favorable change from baseline IPSS. Alfuzosin alone and in combination with finasteride showed a greater improvement in LUTS compared to finasteride alone.

Key Points within the Medication Class

- According to Current Clinical Guidelines:[12,13]
  - Watchful waiting is recommended for mild symptoms of BPH (AUA symptom score <8) and patients with moderate or severe symptoms (AUA symptom score ≥8) who are not bothered by their symptoms.[12,13]
  - α blockers are considered first line; their rapid onset of action, good efficacy, and low rate and severity of adverse events, followed by a 5- α reductase inhibitor
    - The older, less costly, generic α-blockers remain reasonable treatment choices.
  - PDE-5 inhibitors reduce moderate-to-severe (storage and voiding) LUTS in men with or without erectile dysfunction.[13].
  - Combination therapy is an appropriate and effective treatment for patients with LUTS associated with demonstrable prostatic enlargement based on volume measurement, prostate specific antigen level as a proxy for volume, and/or enlargement on digital rectal exam.[12]
- Other Key Facts:
  - Alfuzosin, doxazosin immediate-release, tamsulosin, terazosin, dutasteride, and finasteride are available generically in standard formulations. The doxazosin sustained-release tablet (Cardura XL®), silodosin (Rapaflo®), and tadalafil (Cialis®) are not currently available generically.
  - Finasteride (Propecia®) is also available as a 1 mg tablet for the treatment of alopecia. Tadalafil (Adcirca®) is available as a 20 mg tablet for the treatment of pulmonary hypertension.[14]
  - 5-α reductase inhibitors are pregnancy category X; women who are pregnant or who could be pregnant should avoid handling dutasteride and dutasteride/tamsulosin capsules along with crushed finasteride tablets.[1-10]
  - Administration considerations:[1-5,7-10]
    - Alfuzosin, doxazosin extended-release, dutasteride, tamsulosin and dutasteride/ tamsulosin should all be swallowed whole and not crushed, chewed, or cut.
    - Doxazosin immediate-release, finasteride, and tadalafil tablets may be crushed.
    - Silodosin capsules can be opened and the powder sprinkled on applesauce.

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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.[1-18] 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.[19] 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.[1-18,20] Additionally, regular insulin is also formulated as an inhalation.[4] At least one formulation of all insulin products are supplied in multidose vials, with the exception of insulin degludec.[1-18] 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.[21] All insulin products have at least one formulation with a concentration of 100 units/mL (U-100). Several 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) and insulin degludec (Tresiba®) and insulin lispro (Humalog U-200®).[1-18]

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

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 degludec (Tresiba®)	To improve glycemic control in diabetes mellitus*	Pen: 100 units/mL 200 units/mL	-
Insulin detemir (Levemir®, 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	-

Generic (Trade Name)	FDA-Approved Indications	Dosage Form/Strength	Generic Availability
		(Toujeo® SoloSTAR) Vial: 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 (Humalog®, Humalog® KwikPen, Humalog® U-200 KwikPen)	To improve glycemic control in diabetes mellitus*	Cartridge: 100 units/mL Pen: 100 units/mL 200 units/mL Vial: 100 units/mL	-
Insulin NPH (isophane), (Humulin® N, Humulin® N KwikPen, Novolin® N, Novolin® N ReliOn)	To improve glycemic control in diabetes mellitus*	Pen: 100 units/mL Vial: 100 units/mL	-
Insulin regular (Afrezza®, Humulin® R, Humulin® R U-500, Humulin® R U-500 KwikPen, Novolin® R)	To improve glycemic control in diabetes mellitus* Treatment of diabetic patients with marked insulin resistance*,†	Inhalation powder (Afrezza®): 4 units/cartridge Inhalation powder pack (Afrezza®): 4 units-8 units 8 units-12 units Vial: 100 U/mL 500 U/mL (Humulin® R U-500, Humulin® R U-500 KwikPen)	-
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 (Humulin® 70/30, Humulin®	To improve glycemic control in diabetes mellitus*	Pen: 70/30 units/mL	-

Generic (Trade Name)	FDA-Approved Indications	Dosage Form/Strength	Generic Availability
70/30 KwikPen, Humulin® 70/30 Pen, Novolin® 70/30, Novolin® 70/30 ReliOn)		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.[22-157] Of note, only head-to-head or active-comparator trials have been included as insulin is a well-established treatment.
- The efficacy and safety of insulin degludec was evaluated in the BEGIN clinical trial program. This included multiple 26-week and 52-week clinical trials with several trials being extended to 78 or 104 weeks in order to gather additional long-term safety and efficacy data. Insulin degludec once-daily injection was evaluated in both insulin-naïve and insulin-experienced adults with type 1 and 2 diabetes who had inadequate blood sugar control at trial entry.[13,47-49,75-81]
    - Hemoglobin A1c (HbA1c) reduction was in line with reductions achieved with insulin glargine and insulin detemir (-0.3 to -0.6% decrease from baseline in type 1 DM and -1.0% to -1.5% decrease from baseline in type 2 DM).[13,47-49,75-81]
    - In addition, the agent was associated with a lower risk of hypoglycemia compared to insulin glargine.[13,47-49,75-81]
    - A meta-analysis of four of these trails demonstrated a lower rate of overall and nocturnal hypoglycemia in type 1 and 2 DM.[82]
    - A concentrated formulation of insulin degludec (200 units/mL) was compared to the standard formulation of insulin glargine with similar results.[83]
- The safety and efficacy of inhaled regular insulin (Afrezza®) in both diabetes type 1 and type 2. Clinical trials were 24 weeks each.[4,156,157]
    - 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.[12,84-86]
- 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.[45,46]
- 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.[68,115,116,118]

- 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.[50,51,88-90]
- 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.[50,51,88-90]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[158-168]
    - 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:[1-18]
    - 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.[1-18]
    - All insulin products have at least one formulation with a concentration of 100 units/mL.[1-18]
    - 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
Anticonvulsants

Therapeutic Class

Overview/Summary: The anticonvulsants class encompasses over 20 different chemical entities including barbiturates, benzodiazepines, hydantoins, succinimides, and miscellaneous anticonvulsants. These agents are Food and Drug Administration (FDA)-approved for the prevention and/or treatment of various seizure disorders either as monotherapy or adjunctive therapy. The goals of epilepsy management are to control seizures, avoid treatment side effects and maintain or restore patients' quality of life. Anticonvulsants work by various mechanisms of action to achieve these treatment goals, often by stabilizing neuronal membranes in the brain to reduce seizure activity and to elevate the seizure threshold. Some anticonvulsants are also FDA-approved for the prevention of migraines and the management of bipolar disorder, fibromyalgia, neuropathic pain, along with other non-seizure conditions.[1,2] The specific FDA-approved indications for each of these agents are outlined in Table 1.[3-49] Seizure disorders can be organized into three major categories: generalized seizures, focal seizures, and unknown. Generalized seizures are subdivided into tonic-clonic (in any combination), absence, myoclonic, clonic, tonic, and atonic seizures types. Absence seizures are further divided into typical, atypical, and absence with special features (myoclonic absence, eyelid myoclonia) while myoclonic seizures are further divided into myoclonic, myoclonic atonic, and mycolonic. Epileptic spasms fall into the unknown seizure category. However, based on FDA-approved labeling, seizures are more commonly referred to as partial (or focal) seizures and generalized tonic-clinical seizures.[50]

Pharmacologic management of epilepsy should be individualized, and focused on controlling seizures, avoiding treatment-related adverse events and maintaining or restoring quality of life. Prior to 1990, six major antiepileptic drugs were available for the treatment of various forms of epilepsy, including carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone (metabolized to phenobarbital) and valproic acid. Over the past two decades, many new chemical entities or formulations have become available in the United States. Some advantages of the newer antiepileptic drugs include more favorable adverse event profile, drug interaction profiles and ability to treat without the requirement of serum concentration monitoring.[51-53] Anticonvulsants are primarily used for their FDA-approved indications; however, in instances of severe and refractory seizure disorders, anticonvulsants may be used off-label for seizure types that are non-FDA approved. Currently there are several generic anticonvulsants available, and at least one generic agent is available within each anticonvulsant subclass.[1] Many anticonvulsants contained within this class review, such as pregabalin and lacosamide, are controlled substances. Anticonvulsants are available in a varity of formulations, which include: immediate release, delayed-release, and extended-release capsules or tablets; sprinkle capsules; chewable tablets; orally disintegrating tablets; solutions or suspensions; and injections.[3-49]

Table 1. Current Medications Available in Therapeutic Class[1-49]

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	√

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		60 mg 64.8 mg 97.2 mg 100 mg	
Primidone (Mysoline®*)	Control of grand mal, psychomotor, and focal epileptic seizures, used alone or concomitantly with other anticonvulsants	Tablet: 50 mg 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	Control of absence epilepsy	Capsule:	√

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
(Zarontin®*)		250 mg Syrup: 250 mg/5 mL	
Methsuximide (Celontin®)	Control of absence seizures that are refractory to other drugs	Capsule: 300 mg	-
Anticonvulsants, Miscellaneous			
Brivaracetam (Briviact®)	Adjunctive therapy in the treatment of partial seizures	Tablet: 10 mg 25 mg 50 mg 75 mg 100 mg Oral solution: 10 mg/mL Injection: 50 mg/5 mL	-
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:	√

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		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	√
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	Chewable tablet: 2 mg 5 mg 25 mg Extended-release tablet: 25 mg 50 mg 100 mg 200 mg 250 mg	√

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	treated for acute mood episodes with standard therapy (chewable and orally disintegrating tablets)	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	
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	√

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
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: 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	Capsule: 250 mg Delayed-	√

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	complex absence seizures, acute treatment of the manic episodes associated with bipolar disorder (delayed-release), prophylaxis of migraine headaches (delayed-release)	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	-
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 anticonvulsants, as monotherapy and as adjunct therapy, have been evaluated in numerous clinical trials for their respective FDA-approved indications. Selected trials have evaluated the use of anticonvulsants for the treatment of various seizures disorders as well as non-seizure disorders.[54-198]
- 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).[20,49]
- 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.[55]
- 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.[145]
- 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.[125]
- 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).[55] 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).[70]
- 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.[87] 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).[88] 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).[89]

- Eslicarbazepine was evaluated in 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.[64,65] 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.[64-66] 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).[67]

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.[199]
    - 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.[200]
    - 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.[199]
    - 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.[201-205]

  - 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.[206]
  - 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.[207]
  - 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.[208]
  - The use of anticonvulsants in the management of fibromyalgia is not addressed in the European League Against Rheumatism guidelines.[209]
- 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.[35]
  - Perampanel is a first-in-class anticonvulsant that works as a highly selective, non-competitive AMPA-type glutamate receptor antagonist.[210]
  - The most recently FDA-approved anticonvulsant, eslicarbazepine, provides for another treatment option for patients with partial-onset seizures.

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C. Agents used for the treatment of Attention Deficit Disorder (ADD)/Attention Deficit Hyperactivity Disorder (ADHD)

Therapeutic Class: ADHD/ADD Agents
Last Reviewed by the DUR Board: January 24, 2008

Agents, both stimulants and non-stimulants used for the treatment of ADD/ADHD are subject to prior authorization for pediatric, adolescent, and adult clients that meet the criteria for coverage.

1. Coverage and Limitations

Approval for medications will be given at the therapeutics class level if the following criteria is met and documented:

a. General Criteria (Children and Adults)

1. Only one long-acting agent at a time may be used for the treatment of ADD/ADHD (applies to the entire ADD/ADHD/Stimulant Class); a 30-day transitional overlap in therapy will be allowed.

2. The following two criteria's must be met and documented in the recipient's medical record for adult and pediatric recipients.

a. The decision to medicate for ADD or ADHD must be based on problems that are persistent and sufficiently severe to cause functional impairment in one or more of the following social environments: school, home, work or with peers; and

b. Before treatment with pharmacological methods is instituted, other treatable causes have been ruled out.

b. Children (up to age 18 years)

In addition to the general criteria above, the following conditions apply and must be documented in the recipient's medical record.

1. Prescriptions for ADD/ADHD medications do not require prior authorizations for children five years of age, up to eighteen years of age, if the following conditions apply:

a. The medication is prescribed by a psychiatrist; and

b. An ICD code for Attention Deficit Disorder with or without Hyperactivity is documented on the prescription.

2. In all other cases, prior authorization is required. The following is required for prior authorization.

a. An initial evaluation or examination has been done within the past 12 months by the treating physician, pediatrician, psychiatrist or neurologist documenting the developmental history, physical evaluation, medical history or a primary neurological diagnosis and all of the following:

1. School information, Standardized Teachers Rating Scales testing reports such as Test of Variables of Attention (TOVA), achievement test, neuropsychological testing if indicated, Conner's scale, speech and language evaluation;

2. Diagnosis and symptoms of ADD or ADHD, presence or absence-child behavior checklist, development and context of symptoms and resulting impairment, including school, family and peers, diagnostic symptoms of possible alternate or comorbid psychiatric diagnosis, history of psychiatric, psychological pediatric or neurological treatment for ADD or ADHD; and

3. Family history including diagnosis of ADD and ADHD, tic disorder, substance abuse disorder, conduct disorder, personality disorder and other anxiety disorders, past or present family stressors, crises, any abuse or neglect, interview with parent(s) or guardian(s).

c. Adults (18 years and above) In addition to the general criteria above, the following must be present and documented in the recipient's medical record:

1. An initial evaluation-complete psychiatric assessment, present and past, diagnostic symptoms of ADD or ADHD, history of development and context of symptoms and resulting past and present impairment, including academic achievement, learning disorder evaluation, and

2. One of the following:

a. Medical history, medical or primary neurological diagnosis, identify medication(s) that could be causing symptoms (e.g. Phenobarbital, steroids), or;

b. History of other psychiatric disorder(s) and treatment, or;

c. Diagnostic symptoms of ADD and ADHD presence or absence, possible alternate comorbid psychiatric diagnosis (especially:

personality disorder, mood disorder, depression or mania, anxiety disorder, dissociative disorder, tic disorder including Tourette's disorder and substance abuse disorder); or

d. Family history including diagnosis of ADD or ADHD, tic disorder, substance abuse disorder, conduct disorder, personality disorder, mood disorder and anxiety disorder, possible family stressors, any history of abuse or neglect.

3. Prior Authorization will be given for a one year time period.

Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

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

Therapeutic Class Overview/Summary:
This review will focus on the agents used in the treatment of attention deficit/hyperactivity disorder (ADHD). These agents come from a variety of drug classes and are summarized in Table 1.[1-27] ADHD is a common psychiatric disorder often diagnosed during childhood; however, children with ADHD may continue to manifest symptoms into adulthood.[28,29] The core symptoms of ADHD utilized in the diagnosis of the disorder include hyperactivity, impulsivity and inattention. There are three subtypes of ADHD, including a predominantly inattentive subtype, a predominantly hyperactive-impulsive subtype and a combined subtype in which both symptoms are displayed.[28,29] Untreated, or undertreated, ADHD is associated with adverse sequelae, including delinquent behavior, antisocial personality traits, substance abuse and other comorbidities[29]. There are several central nervous system agents that are Food and Drug Administration (FDA)-approved for the treatment of ADHD, including the cerebral stimulants (amphetamines and methylphenidate derivatives), as well as atomoxetine (Strattera®), clonidine extended-release (Kapvay®) and guanfacine extended-release (Intuniv®).[1-27] Due to the potential for abuse, the cerebral stimulant agents are classified as Schedule II controlled substances.[1-24] Atomoxetine, clonidine extended-release and guanfacine extended-release are not classified as controlled substances.[25-27] Clonidine and guanfacine extended-release formulations are approved for use as both adjunctive therapy with stimulant medications and as monotherapy.[26,27]

Most ADHD agents and stimulants are currently available generically. Agents that are available only as a brand name product include: lisdexamfetamine capsules (Vyvanse®), amphetamine tablets (Evekeo®), orally disintegrating tablets (Adzenys XR-ODT®), and extended-release suspension (Dyanavel XR®), atomoxetine capsules (Strattera®), methylphenidate patch (Daytrana®), extended release chewable tablet (Quillichew®), and extended-release suspension (Quillivant XR®). Aptensio XR® (methylphenidate extended-release capsule) is also available only as a brand name product; however, other extended-release biphasic capsules are available generically.[31]

Current consensus clinical guidelines for the treatment of children and adolescents with ADHD recommend that stimulants are highly effective for reducing core symptoms of ADHD in children.[29,30,32] Although initial therapy with atomoxetine or extended-release formulations of clonidine and guanfacine may reduce core symptoms of ADHD, there is less evidence to support their use compared to stimulants. The selection of therapy should be based on comorbid conditions, adverse event profiles, compliance issues, risk of drug diversion and patient/parent preference.[33] Stimulants, particularly methylphenidate, are recommended as first-line therapy in adult patients with ADHD.[30,34] Consensus guidelines also list theses agents as options in the treatment of narcolepsy.[35-37]

Table 1. Current Medications Available in the Therapeutic Class[1-27]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines			
Amphetamine (Adzenys XR-ODT®, Dyanavel XR®, Evekeo®)	Treatment of ADHD, narcolepsy†, exogenous obesity†	Extended-release suspension 2.5 mg/mL Tablet: 5 mg 10 mg	-
Amphetamine/dextroamphetamine salts (Adderall®*, Adderall XR®*)	Treatment of ADHD, narcolepsy‡	Capsule: 5 mg 10 mg 15 mg	✔

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
		20 mg 25 mg 30 mg Extended-release orally disintegrating tablet: 3.1 mg 6.3 mg 9.4 mg 12.5 mg 15.7 mg 18.8 mg Tablet: 5 mg 7.5 mg 10 mg 12.5 mg 15 mg 20 mg 30 mg	
Dextroamphetamine (ProCentra®*, Dexedrine®*, Dexedrine Spansule®*, 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	✔
Lisdexamfetamine (Vyvanse®)	Treatment of ADHD, binge eating disorder§	Capsule: 10 mg 20 mg 30 mg 40 mg 50 mg 60 mg 70 mg	-
Methamphetamine (Desoxyn®*)	Treatment of ADHD, exogenous obesity	Tablet: 5 mg	✔
Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous			
Dexmethylphenidate (Focalin®*, Focalin XR®*)	Treatment of ADHD	Extended-release capsule: 5 mg 10 mg	✔

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
		15 mg 20 mg 25 mg 30 mg 35 mg 40 mg Tablet: 2.5 mg 5 mg 10 mg	
Methylphenidate (Aptensio XR®, Concerta®*, Daytrana®, Metadate CD®*, Metadate ER®*, Methylin®*, Methylin ER®*, Quillichew ER®, Quillivant XR®, Ritalin®*, Ritalin LA®*, Ritalin SR®*)	Treatment of ADHD, narcolepsy‖	Chewable tablet: 2.5 mg 5 mg 10 mg Extended-release capsule (Aptensio XR®) 10 mg 15 mg 20 mg 30 mg 40 mg 50 mg 60 mg Extended-release capsule (Metadate CD®, generic): 10 mg 20 mg 30 mg 40 mg 50 mg 60 mg Extended-release capsule (Ritalin LA®, generic): 10 mg 20 mg 30 mg 40 mg Extended-release chewable tablet: 20 mg 30 mg 40 mg Extended-release	✔

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
		suspension: 25 mg/ 5 mL Extended-release tablet (Concerta®, generic): 18 mg 27 mg 36 mg 54 mg Extended-release tablet (Metadate ER®, generic): 10 mg 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) 15 mg/9 hours (1.6 mg/hour) 20 mg/9 hours (2.2 mg/hour) 30 mg/9 hours (3.3 mg/hour)	
Central α-Agonists			
Clonidine extended-release (Kapvay®*)	Treatment of ADHD	Extended-release tablet: 0.1 mg 0.2 mg	✔
Guanfacine extended-release (Intuniv®*)	Treatment of ADHD	Extended-release tablet: 1 mg 2 mg 3 mg 4 mg	✔
Central Nervous System Agents-Miscellaneous			

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Atomoxetine (Strattera®)	Treatment of ADHD	Capsule: 10 mg 18 mg 25 mg 40 mg 60 mg 80 mg 100 mg	-

ADHD=attention deficit hyperactivity disorder
*Generic available in at least one dosage form or strength.
†Evekeo®
‡Adderall®
§For use in moderate to severe binge eating disorder. Not indicated for weight loss or treatment of obesity.
‖Metadate ER®, Methylin®, Ritalin® and Ritalin SR®

Evidence-based Medicine

- The attention deficit/hyperactivity disorder (ADHD) agents and stimulants have demonstrated the safety and efficacy for their Food and Drug Administration (FDA)-approved indications.[39-132]
- Overall, there is insufficient evidence to suggest that one ADHD agent and stimulant is more efficacious than another for the treatment of ADHD. [39-132]
- Limited data exists to demonstrate the efficacy of a variety of cerebral stimulants and atomoxetine in the adult population. [44,46,52-54, 62,63,71,90,93,98,99,101,104,113,114,116]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Current consensus clinical guidelines for the treatment of children and adolescents with ADHD recommend that stimulants are highly effective for reducing core symptoms of ADHD in children.[29,30,32]
  - Although initial therapy with atomoxetine or extended-release formulations of clonidine and guanfacine may reduce core symptoms of ADHD, there is less evidence to support their use compared to stimulants. The selection of therapy should be based on comorbid conditions, adverse event profiles, compliance issues, risk of drug diversion and patient/parent preference.[33]
  - Stimulants, particularly methylphenidate, are recommended as first-line therapy in adult patients with ADHD.[31,34]

- Other Key Facts:
  - At least one short-, intermediate-, and long-acting stimulant is available generically.[29]

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Therapeutic Class Overview
Oral Atypical (Second-Generation) Antipsychotics

Therapeutic Class Overview/Summary:
This overview will focus on the atypical antipsychotics, which are also known as second-generation antipsychotics (SGAs).[1-16] While several atypical antipsychotics are formulated as long-acting injections, these formulations will not be covered in this review. Antipsychotic medications have been used for over fifty years to treat schizophrenia and a variety of other psychiatric disorders.[17] Schizophrenia is believed to be caused by an increase in the cerebral activity of dopamine D_2 in the mesolimbic and/or mesocortical regions of the brain. Antipsychotic medications exert their effect in part by blocking D_2 receptors. It is the blockade of these receptors in the mesolimbic pathway that is believed to contribute to desired antipsychotic effects, especially improvement of positive symptoms associated with the disorder.[18]

In addition to blocking D_2 receptors in the mesolimbic pathway, FGAs also block D_2 receptors in the mesocortical, tuberoinfundibular, and nigrostriatal pathways.[18] D_2 blockade in these other pathways is thought to be responsible for the hyperprolactinemia and extrapyramidal symptoms (EPS) associated with this class.[19] FGAs may be characterized according to their affinity for the D_2 receptor. Low potency antipsychotics, such as chlorpromazine and thioridazine, are more sedating and associated with a higher incidence of anticholinergic side effects. Fluphenazine, haloperidol, pimozide, thiothixene, and trifluoperazine are high potency antipsychotics that are less sedating but associated with a higher incidence of EPS. The medium potency antipsychotics (loxapine, molindone, and perphenazine) possess a moderate risk of EPS and anticholinergic side effects.[20] With the exception of pimozide, all FGAs are indicated for use in the treatment of schizophrenia. FGAs are effective in the treatment of positive symptoms of schizophrenia, which include agitation, aggression, delusions, and hallucinations. Negative symptoms of schizophrenia which include avolition, anhedonia, alogia, affective flattening, and social withdrawal, do not respond as well to this antipsychotic class.[19] Pimozide is indicated only for the suppression of motor and phonic tics in patients with Tourette's disorder.

The term "atypical antipsychotic" was introduced in 1989 when clozapine was approved for use by the Food and Drug Administration (FDA). Originally, this term referred to an antipsychotic with a low risk of EPS.[18] As a class, SGAs or atypical antipsychotics are more selective in targeting the mesolimbic D_2 pathway. They also block or partially block serotonin $(5\text{-HT})_{2A}$ and 5-HT_{1A} receptors and have a greater affinity for 5-HT_2 receptors than D_2 receptors.[18,20] These differences in neuropharmacologic activity are associated with a lower risk of EPS and tardive dyskinesia; the risks vary with the specificity of each agent for D_2 and serotonin receptors.[18,20] Atypical antipsychotics have a more favorable outcome in the treatment of the negative symptoms of schizophrenia.[18] The SGAs are comprised of nine separate chemical entities, each with a unique neuropharmacologic and adverse event profile, mechanism of action, and chemical structure. The SGAs are aripiprazole, asenapine, brexpiprazole clozapine, cariprazine, iloperidone, lurasidone, olanzapine, paliperidone, pimavanserin, quetiapine, risperidone and ziprasidone.

Although in some respects the SGAs are safer and better tolerated than the FGAs, they are still associated with a number of serious risks and side effects. For this reason, the FDA has required various warnings to be inserted in the manufacturers' product information for these agents. All agents have a black box waring regarding an increased risk of death when used in the treatment of psychosis and behavioral problems in elderly patients with dementia. Most of the deaths that prompted the addition of the warning were due to cardiac-related events (e.g., heart failure or sudden death) or infection.[21] Of note, atypical antipsychotics are not FDA-approved for this indication. With the exception of pimavanserin, all atypical antipsychotics bear a warning that alerts prescribers and patients to the risk of hyperglycemia and other metabolic changes.[1-16] Aripiprazole, brexpiprazole, lurasidone and quetiapine carry a black box warning regarding suicidality and antidepressant drugs.[1,3,9,13,14] Ziprasidone also has a warning concerning QTc interval prolongation; however, all of the SGAs can increase the QTc interval to some degree.[16]

Due to the potential side-effect risks associated with these medications, any off-label use deserves close attention. Data published in peer-reviewed journals and in national and international guidelines support the use of SGAs as a treatment option for certain off-label uses. In many of these scenarios, SGAs are reserved for patients who are refractory to other first-line treatment modalities, including both pharmacotherapy and psychotherapy, and used in adjunction to mainstream therapies, as part of a multimodal approach.

Over the past 20 years, antipsychotic use in children and adolescents has grown. In the United States, the frequency of prescribing an antipsychotic agent increased from 8.6 per 1000 children in 1996 to 39.4 per 1000 children in 2002. According to a survey of national trends in the outpatient use of antipsychotics in children and adolescents, only 14.2% of antipsychotic prescriptions in children were for patients diagnosed with psychotic disorders.[24] Indications commonly associated with antipsychotic prescribing in pediatric patients include psychosis, schizophrenia, bipolar disorder, aggressive and disruptive behavior, and tic disorders. Off-label indications with limited available evidence for the use of atypical antipsychotics in children and adolescents include autistic spectrum disorders, major depressive disorder, anxiety disorders, and eating disorders. At this time, risperidone and aripiprazole are FDA-approved for the management of children and adolescents with autism (aged 5 to 16 and 6 to 17 years, respectively). Moreover, the following agents are indicated for the treatment of schizophrenia in adolescents: aripiprazole, olanzapine, paliperidone, quetiapine, and risperidone. Aripiprazole, asenapine, olanzapine, quetiapine and risperidone are FDA-approved for the treatment of manic or mixed bipolar I disorder in children and adolescents. None of the other available atypical antipsychotic agents are currently indicated for use in pediatric patients.[1-16]

Concerns have also been raised about the risks of combination therapy with the antipsychotics, which can multiply the risks of dangerous adverse events. The practice of polypharmacy is not supported by well-designed clinical trials published in the peer-reviewed literature. However, national and international consensus guidelines consider this approach in patients with treatment-refractory illness.

Table 1. Current Medications Available in Therapeutic Class[1-16]

Generic Name (Trade name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Aripiprazole (Abilify®*, Abilify Discmelt®*)	Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults; acute or maintenance treatment of manic or mixed episodes associated with bipolar I disorder in children and adolescents aged 10 to 17 years; adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with bipolar I disorder with or without psychotic features in adults and in pediatric patients aged 10 to 17 years; maintenance treatment of manic or mixed episodes associated with bipolar I disorder in adults; treatment of agitation associated with bipolar I disorder, manic or mixed in adults; acute and maintenance treatment of schizophrenia in adults; treatment of agitation associated with schizophrenia in adults; treatment of schizophrenia in adolescents aged 13 to 17; treatment of schizophrenia in adults; adjunctive treatment to antidepressants for major depressive disorder in adults; irritability associated with autistic disorder in children and adolescents aged six to 17 years	Injection: 7.5 mg/mL Orally disintegrating tablet: 10 mg 15 mg Oral solution: 1 mg/mL Tablet: 2 mg 5 mg 10 mg 15 mg 20 mg 30 mg	✔

Generic Name (Trade name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Asenapine (Saphris®)	Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults or adolescents (10 to 17 years of age); adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with bipolar I disorder; acute and maintenance treatment of schizophrenia in adults	Sublingual tablet: 2.5 mg 5 mg 10 mg	-
Brexpiprazole (Rexulti®)	Adjunctive treatment to antidepressants for major depressive disorder in adults; treatment of schizophrenia in adults	Tablet: 0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg	-
Cariprazine (Vraylar®)	Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults; treatment of schizophrenia	Capsule: 1.5 mg 3 mg 4.5 mg 6 mg Capsule, dose-pack: 1.5/3 mg	-
Clozapine (Fazaclo ODT®*, Clozaril®*, Versacloz®)	Reduction in the risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorder in adults; treatment-resistant schizophrenia in adults	Orally disintegrating tablet: 12.5 mg 25 mg 100 mg 150 mg 200 mg Tablet: 25 mg 50 mg 100 mg Suspension: 50 mg/mL	✔
Iloperidone (Fanapt®)	Treatment of schizophrenia in adults	Tablet: 1 mg 2 mg 4 mg 6 mg 8 mg 10 mg 12 mg Dose Pack: 1/2/4/6 mg	-
Lurasidone	Treatment of schizophrenia in adults, treatment	Tablet:	-

Generic Name (Trade name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
(Latuda®)	of depressive episodes associated with bipolar disorder in adults	20 mg 40 mg 80 mg 60 mg 120 mg	
Olanzapine (Zyprexa®*, Zyprexa Zydis®*)	Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults; acute or maintenance treatment of manic or mixed episodes associated with bipolar I disorder in children and adolescents aged 10 to 17 years; adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with bipolar I disorder; maintenance treatment of manic or mixed episodes associated with bipolar I disorder in adults; treatment of agitation associated with bipolar I disorder, manic or mixed in adults; treatment of agitation associated with bipolar I mania in adults; treatment of depressive episodes associated with bipolar disorder in adults; acute and maintenance treatment of schizophrenia in adults; treatment of agitation associated with schizophrenia in adults; treatment of schizophrenia in adolescents aged 13 to 17; adjunctive treatment to antidepressants for major depressive disorder in adults	Injection: 10 mg vials Orally disintegrating tablet: 5 mg 10 mg 15 mg 20 mg Tablet: 2.5 mg 5 mg 7.5 mg 10 mg 15 mg 20 mg	✔
Paliperidone (Invega®*)	Acute and maintenance treatment of schizophrenia in adults; treatment of schizophrenia in adolescents aged 12 to 17; treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers and/or antidepressants in adults	Extended-release tablet: 1.5 mg 3 mg 6 mg 9 mg	✔
Pimavanserin (Nuplazid®)	Hallucinations and delusions associated with Parkinson's disease psychosis	Tablet: 17 mg	-
Quetiapine (Seroquel®*, Seroquel XR®)	Maintenance treatment of bipolar I disorder as adjunct therapy to lithium or divalproex in adults; treatment of acute manic episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex in adults; treatment of acute manic episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex in children and adolescents aged 10 to 17 years; treatment of manic or mixed episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex in adults; treatment of depressive episodes associated with bipolar disorder in adults; acute and maintenance treatment of schizophrenia in adults; treatment of schizophrenia in adolescents aged 13 to 17; treatment of schizophrenia in adults; adjunctive treatment to antidepressants for major	Extended-release tablet: 50 mg 150 mg 200 mg 300 mg 400 mg Tablet: 25 mg 50 mg 100 mg 200 mg 300 mg 400 mg	✔

Generic Name (Trade name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	depressive disorder in adults		
Risperidone (Risperdal®*, Risperdal M-Tab®*)	Adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar I disorder; maintenance treatment of bipolar I disorder as adjunct therapy to lithium or valproate in adults; short-term treatment of acute manic or mixed episodes associated with bipolar I disorder in adults and in children and adolescents aged 10 to 17 years; short-term treatment of acute mixed or manic episodes associated with bipolar I disorder in combination with lithium or valproate in adults; acute and maintenance treatment of schizophrenia in adults; treatment of schizophrenia in adolescents aged 13 to 17; irritability associated with autistic disorder in children and adolescents aged five to 16 years	Orally disintegrating tablet: 0.25 0.5 mg 1 mg 2 mg 3 mg 4 mg Oral solution: 1 mg/mL Tablet: 0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg	✔
Ziprasidone (Geodon®*)	Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults; maintenance treatment of bipolar I disorder as adjunct therapy to lithium or valproate in adults; treatment of acute manic or mixed episodes associated with bipolar disorder; treatment of agitation associated with schizophrenia in adults; treatment of schizophrenia in adults	Capsule: 20 mg 40 mg 60 mg 80 mg Injection: 20 mg/mL	✔

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

Evidence-based Medicine

- The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) was a large, multi-center study initiated by the National Institute of Mental Health to examine the effectiveness of second generation antipsychotics (SGAs) compared to first generation antipsychotics (FGAs) in patients with chronic schizophrenia.[48-50] Among the unexpected outcomes was the finding that, with the exception of clozapine, the SGAs did not separate out as robustly from the FGAs with respect to overall efficacy and times to treatment discontinuation.
    - Due to relatively high discontinuation rates across all treatment arms, potential biases regarding optimal dosing of individual drugs, and clear differences in treatment-emergent side effect profiles, the implications of CATIE are subject to interpretation which may preclude definitive guidance in developing pharmacotherapy guidelines for patients with schizophrenia as a whole.
- The role of the SGAs has been clearly established in the treatment of bipolar disorder and schizophrenia (and, in the case of aripiprazole, quetiapine extended-release and olanzapine/fluoxetine combination therapy, as adjunctive treatment of major depressive disorder).
- Meta-analyses evaluating the roles of available atypical antipsychotics in the treatment of schizophrenia suggest that all agents are significantly more effective than placebo.[51-63,75-79] The trends for respective efficacy suggest that clozapine is the most effective agent in the class, followed by olanzapine and risperidone. Aripiprazole tended to exhibit lower efficacy than the other agents.[51-63,75-79]

- A meta-analysis in adult patients with bipolar disorder found risperidone to be the most effective treatment option (taking into account both efficacy and tolerability).[75] The next best treatment options, in order of decreased efficacy, were olanzapine, haloperidol, quetiapine, carbamazepine, aripiprazole, valproate, lithium, and ziprasidone. Lamotrigine, topiramate and gabapentin were found to be less effective than placebo.
- In the management of major depressive disorder, aripiprazole, quetiapine, and risperidone augmentation therapies were associated with improved outcomes.[84]
- The efficacy and safety of brexpiprazole in the treatment of schizophrenia was demonstrated by two pivotal multicenter, randomized, double-blind, placebo controlled six week trials, VECTOR and BEACON.[29,30] Positive and Negative Syndrome Scale (PANSS) scores were significantly improved with brexpiprazole when compared to placebo. Treatment differences were -8.72 (P<0.0001), -7.64 (P=0.0006) and -6.47 (P=0.0022) for brexpiprazole 2 mg, 4 mg, and 4 mg respectively.[29,30]
- The efficacy of cariprazine for the treatment of schizophrenia was established in three, 6-week, randomized, double-blind, placebo-controlled trials in patients with a diagnosis of schizophrenia. In each study, the primary endpoint was change from baseline in PANSS total score at the end of week six.[4,35,36] There was a significant improvement in PANSS when each fixed-dose or flexable-dose range cariprazine group was compared to placebo (P value varies; all significant when reported).[4,35,36]
- The efficacy of cariprazine in the acute treatment of bipolar mania was established in three, three-week placebo-controlled trials in patients with a diagnosis of bipolar I disorder with manic or mixed episodes with or without psychotic features. In each study, the primary endpoint was decrease from baseline in Young Mania Rating Scale (YMRS) total score at the end of week three.[4,69,70] In the first study, there was a demonstrated improvement with cariprazine dose groups (3 to 6 mg/day or 6 to 12 mg/day) compared to placebo on the YMRS total score (-P<0.05 for both comparisons). However, the 6 to 12 mg/day dose group showed no additional advantage.[4,69] In the second study, there was a demonstrated improvement with cariprazine (3 to 12 mg/day) compared to placebo on the YMRS total score (15.0 vs. -8.9, respectively; P<0.05).[4] In the third study, cariprazine (3 to 12 mg/day) was superior to placebo on the YMRS total score (19.6 vs. -15.3, respectively; P<0.05).[4,70]
- The efficacy of asenapine in the treatment of schizophrenia in adults has been evaluated in four, published, randomized, double-blind, placebo-controlled, and active-controlled (haloperidol, risperidone, and olanzapine) trials, ranging in duration from six weeks to one year[31-34]. The efficacy and safety of asenapine in the treatment of manic or mixed bipolar I disorder were evaluated in five placebo-controlled, and active-controlled (olanzapine) studies in adult patients, with or without psychotic features.[64-68]
    - In a direct-comparison study, asenapine was less effective than olanzapine in terms of changes from baseline in PANSS and Clinical Global Impression-Severity of Illness (CGI-S) scores.[34] Study discontinuation due to inadequate efficacy was noted in 14% of patients receiving olanzapine compared to 25% of patients in the asenapine group. Mean weight gain was 0.9 kg with asenapine and 4.2 kg with olanzapine.[34] In another study, clinically significant weight gain was noted in 17% of patients receiving risperidone and 9% of patients in the asenapine group.[31]
    - In a pooled analysis of patients experiencing bipolar mania, asenapine and olanzapine were comparable in terms of reduction from baseline in Young Mania Rating Scale (YMRS) scores at week-52 of therapy.[68]
    - A meta-analysis of various antimanic therapy options, found that asenapine was associated with a statistically significant improvement in YMRS scores from baseline compared to placebo (mean difference, -0.30; -0.53 to -0.07), though it was less effective compared to olanzapine (0.22; 0.08 to 0.37).[75]
- Iloperidone has been studied as monotherapy for the treatment of adult patients with an acute or subacute exacerbation of schizophrenia.
    - Three six-week, randomized, double-blind, placebo- and active comparator (risperidone and haloperidol)-controlled studies found iloperidone to be significantly more effective than placebo.[39]

  - One four-week, placebo- and active- comparator (ziprasidone)-controlled study found a significant improvement in PANSS scores with iloperidone therapy compared to placebo.[38]
- Lurasidone has been investigated for the treatment of adult patients with acute and chronic symptoms of schizophrenia in two six-week, placebo-controlled studies and two 21-day studies directly comparing the safety and efficacy of lurasidone 120 mg once daily with ziprasidone 80 mg twice daily.[44-47]
  - Lurasidone and ziprasidone were comparable in terms of reduction in total PANSS, PANSS positive symptom, PANSS general symptom, CGI-S scores and several cognition scales.[41-42] In addition, both drugs were comparable in terms of rates of discontinuation for any reason rate and discontinuation due to adverse events.[45,46] Both therapies were associated with a small weight loss from baseline and neither therapy was associated with a clinically significant ECG abnormality.
  - Of note, lurasidone was more effective in improving negative symptom PANSS scores compared to ziprasidone (*P*=0.046).[46]
- The safety and efficacy of pimavanserin for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis was established in a single, six-week, double-blind, placebo-controlled trial in 185 patients. Patients in the pimavanserin group experienced a greater decrease in Parkinson's Disease-Adapted Scale for Assessment of Positive Symptoms Scores compared to placebo (-5.79 and -2.73, respectively, 95% CI, -4.91 to -1.20; P=0.001). Pimavanserin was well tolerated, with no worsening of motor function or significant safety concerns.[12,291]
- Available evidence suggests that, except for clozapine, olanzapine is associated with greater weight gain compared to all other atypical antipsychotic agents. In contrast, ziprasidone is associated with a low incidence of weight gain.[221]
- Data from the Food and Drug Administration Adverse Reporting System (AERS) indicates that the risk of experiencing a diabetes-related adverse event is greatest with olanzapine, followed by risperidone, and least with ziprasidone and aripiprazole, across all age groups.[250]
- Risperidone is associated with the greatest risk of prolactin elevation-related adverse events.[51-63,75-79,267]
- Risperidone, aripiprazole and ziprasidone are associated with a high incidence of extrapyramidal adverse events.[229] Quetiapine is associated with the least risk of extrapyramidal adverse events.[229]
- The incidence of sexual dysfunction was noted to be higher with the use of olanzapine, risperidone, and clozapine than with quetiapine, ziprasidone or aripiprazole.[233]
- The Agency of Healthcare Research and Quality (AHRQ) is the lead federal agency for research on healthcare quality, costs, outcomes and patient safety. In 2011, AHRQ had issued an update to a prior 2007 review of scientific evidence on the safety and effectiveness of atypical antipsychotics for off-labeled use.[85,196]
  - Indications associated with moderate/high strength of evidence for the use of atypical antipsychotics included general anxiety disorder (quetiapine), dementia (aripiprazole, olanzapine, risperidone), depression (aripiprazole, quetiapine, risperidone), augmentation of selective serotonin reuptake inhibitors for obsessive compulsive disorder [OCD] (risperidone), and post-traumatic stress disorder [PTSD] (risperidone).[96] Refer to Appendices IIa and IIb for additional details.
- The AHRQ had conducted a systematic review of literature on the safety and efficacy of antipsychotics in children and adolescents.[102,103] For details, refer to Appendices IIIa and IIIB.
  - Indications associated with moderate strength evidence for the use of atypical antipsychotics included disruptive behavior disorder, bipolar disorder, schizophrenia, and Tourette's syndrome.
  - No significant differences between the different atypical antipsychotics were noted in the identified head-to-head comparisons.
  - The risks of weight gain (weight gain: 4.6 kg) and dyslipidemia were highest with olanzapine. Weight gain with ziprasidone was not significantly different from placebo. The other atypical antipsychotics were associated with intermediate weight gain.

  - Risperidone was associated with the greatest incidence of prolactin-related adverse events (consistent with adult data).
  - Extrapyramidal adverse events were significantly more common with risperidone and aripiprazole compared to placebo.
- According to a systematic review by Safer et al, weight gain secondary to atypical antipsychotics is greater in children and adolescents than in adults.[264]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Antipsychotics are a mainstay in therapy for schizophrenia.[314-316]
  - Lithium, valproate and/or antipsychotics are recommended as initial therapy of bipolar disorder.[301-304]
  - The American Psychiatric Association guideline recommends the use of antipsychotics for the management of psychosis or agitation in patients with dementia.[305]
  - For the treatment of anxiety disorders, sertraline is recommended as a first-line pharmacotherapeutic agent.[299,300] Second-line treatment options include serotonin norepinephrine reuptake inhibitors (SNRIs) or switching to alternative selective serotonin reuptake inhibitors (SSRIs). Augmentation therapy with antipsychotics is an option in treatment-refractory patients but the guidelines recommend that initiation of combination therapy be limited to specialists.
  - In major depressive disorder, first-line treatment options include SSRIs, SNRIs, bupropion or mirtazapine.[308-310] Antipsychotic augmentation therapy is an option for patients who have failed antidepressant monotherapy.
  - In obsessive compulsive disorder, SSRIs and cognitive behavioral therapy are recommended as first-line treatment options.[311] Patients who have failed an SSRI trial may be offered augmentation therapy with an antipsychotic or cognitive behavioral therapy. Similarly, SSRIs and SNRIs are considered to be first-line treatment options for the treatment of post-traumatic stress disorder (PTSD).[312,313]
  - Atypical antipsychotics may be used as adjunctive therapy for the management of treatment-refractory PTSD.[312]
  - For the treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP), guidelines recommend the use of atypical antipsychotics, specifically clozapine or quetiapine, which have the most clinical data to support use. Both clinical guidelines recommend against the use of olanzapine for PDP due limited efficacy.[317-318]
  - The European Society for the Study of Tourette Syndrome guideline recommends risperidone as a first-line agent for the treatment of tics.[329] Aripiprazole has a role in treatment-refractory patients.
  - The American Academy of Child and Adolescent Psychiatry (AACAP) guideline acknowledges that atypical antipsychotics are the most commonly prescribed class of drugs for the treatment of maladaptive aggression, regardless of diagnosis; yet emphasize that pharmacotherapy should not be used as the only intervention in children with oppositional defiant disorder.[325]
  - Although the antipsychotics are not addressed in national and international insomnia treatment guidelines, the National Institute of Health (NIH) Consensus and State-of-the-Science Statement on Manifestations and Management of Chronic Insomnia in Adults state that due to the lack of evidence supporting the short and long term efficacy of antipsychotics, in addition to their significant risks, their use in the treatment of chronic insomnia cannot be recommended.[331]
  - In a practice guideline on the use of atypical antipsychotics in children and adolescents, issued by the AACAP in 2011, the panel recommends that prior to initiation of antipsychotic therapy patients should undergo a thorough diagnostic assessment, evaluation for comorbid medical conditions and concomitant medications.[329] Furthermore, a multidisciplinary plan that includes education and psychotherapy should be established. The prescriber should also have a thorough discussion of the risks and benefits of psychotropic medication.

- Of the atypical antipsychotics, risperidone is recognized as an agent with the most substantial amount of methodologically stringent evidence for use in pediatric patients.[329]
- There is almost no data to support the use of atypical antipsychotics in pre-school aged children.[329] The guideline recommends a marked amount of caution before using these agents in pre-schoolers.
- Given the risk of metabolic side-effects, pediatric patients receiving atypical antipsychotic therapy should be closely monitored for changes in weight, blood pressure, fasting plasma glucose and lipid profile.[329]

Table 2. Evidence for the Use of Atypical Antipsychotics in Pediatrics (2011 AACAP guideline)[318]

	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasi-done	Aripiprazole
Schizophrenia/ Psychosis	+++	+++*	++++*	++++*	+	++++*
Bipolar Disorder	++	+++*	+++*	++++*	+++	+++*
Disruptive behavior disorders/ Aggression	++	+++	+++	++	+	+
Autism/ PDD irritability	+	++++*	+++	+	+	++++*
Tourette's/tics		++++	+		+++	
PTSD	+					
Eating Disorder			+			
Long-term safety studies		+		+		

PDD=pervasive developmental disorder; PTSD=post-traumatic stress disorder
++++ Multiple randomized controlled studies
+++ One randomized controlled study
++ Uncontrolled study
+ Case studies
* FDA approved in children and/or adolescents

- Other Key Facts:
  - Paliperidone is an active metabolite of risperidone and therefore carries some similarity in chemical structure and pharmacologic effects with the parent drug.
  - The use of clozapine is limited due to a risk of agranulocytosis.
  - Aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone are available generically.
  - Pimavanserin has a unique indication among atypical antipsychotics, the treatment of hallucinations and delusions associated with PDP.[12]

Appendix I: Summary of the Strength of Evidence for Off-Label Efficacy Outcomes (adopted from 2011 AHRQ systematic review)[196]

Indication	Strength of Evidence	Findings	Conclusions
Dementia	**High**	The 2011 meta-analysis of PCTs, aripiprazole, olanzapine, and risperidone were superior to placebo as treatment of behavioral symptoms as measured by total scores on BEHAVE-AD, BPRS, and NPI. Effect sizes were generally considered to be "small"	Aripiprazole, olanzapine, and risperidone **have efficacy** as treatment for behavioral symptoms of dementia.

Indication	Strength of Evidence	Findings	Conclusions
		in magnitude. Psychosis –risperidone was superior to placebo, as measured by thepsychosis subscales of the BEHAVE-AD, BPRS, and NPI. Results for aripiprazole did not meet conventional levels of statistical significance. Agitation – Aripiprazole, olanzapine and risperidone were superior to placebo, as measured by the agitation subscales of the BEHAVE-AD, BPRS, NPI, and CMAI. Three head to head trials compared atypicals; none was found superior.	
Depression			
Augmentation of SSRI/SNRI	**Moderate** (risperidone, aripiprazole, quetiapine) **Low** (olanzapine, ziprasidone)	The meta-analysis used "response" to treatment and remission as outcome. Pooling trials that reported the HAM-D as outcome, the relative risk of responding for participants taking quetiapine or risperidone was significantly higher than for placebo. Other trials reported MADRS scores; the relative risk of responding for participants taking aripiprazole was significantly higher than those taking placebo. Risperidone was included in two trials. These reported the drug superior to placebo. The relative risk of responding for participants taking aripiprazole was significantly higher than those taking placebo. Olanzapine had only two trials, so pooling was not performed; the trials reported olanzapine superior to placebo. In one available ziprasidone trial, the drug was superior to placebo in terms of MADRS scores. One trial compared ziprasidone at differing levels augmenting	Aripiprazole, quetiapine, and risperidone **have efficacy** as augmentation to SSRIs/SNRIs for major depressive disorder. Olanzapine and ziprasidone **may also have efficacy.**

Indication	Strength of Evidence	Findings	Conclusions
		sertraline to sertraline alone. This trial found a greater improvement in CGI-S and MADRS scores augmenting with ziprasidone at 160mg than either augmentation with ziprasidone at 80mg or sertraline alone. However, there was no significant difference in HAMD-17, CGI-I or HAM-A scores.	
Monotherapy	**Moderate**	Olanzapine alone was no better than placebo in improving symptoms at six or 12 weeks in three trials. Outcomes were too heterogeneous to allow pooling. In five PCTs, quetiapine was superior according to relative risk of both responding and remitted as measured by MADRS.	Olanzapine **does not have efficacy** as monotherapy for major depressive disorder. Quetiapine **has efficacy** as monotherapy for major depressive disorder er
Obsessive Compulsive Disorder (OCD)			
Augmentation of SSRIs	**Moderate** (risperidone) **Low** (olanzapine)	The 2006 meta-analysis pooled results of nine trials of risperidone, olanzapine, or quetiapine as augmentation therapy in patients who were resistant to treatment with SSRI. Atypical antipsychotics had a clinically important benefit, (measured by the Yale-Brown Obsessive-Compulsive Scale (YBOCS), when used as augmentation therapy. Relative risk of "responding" significant for augmentation with quetiapine and risperidone. The updated 2011 meta-analysis found risperidone superior to placebo, as measured by changes in the Y-BOCS. There were too few studies (two) of olanzapine augmentation to permit separate pooling of this drug. Both trials reported olanzapine superior to placebo. One new head to head trial found no difference in effect between olanzapine and risperidone as SSRI augmentation. One new head to head trial found	Risperidone **has efficacy** in improving OCD symptoms when used as an adjunct to SSRI in treatment refractory patients. Olanzapine **may have efficacy.** Quetiapine is more **efficacious** than ziprasidone and clomipramine. e.

Indication	Strength of Evidence	Findings	Conclusions
		quetiapine more effective than ziprasidone as SSRI augmentation. In one new trial, quetiapine produced a significant reduction in Y-BOCS score, while clomipramine did not.	
Augmentation of citalopram	**Low** (quetiapine) **Very low** (risperidone)	One trial of risperidone reported no differences between groups in achieving a response to therapy, but patients maintained on risperidone had a significantly longer period of time to relapse compared to placebo (102 vs 85 days). Two trials found quetiapine superior to placebo as augmentation for citalopram, according to Y-BOCS and CGI-I scores.	Quetiapine and risperidone **may be efficacious** as augmentation to citalopram in OCD patients.
Post-Traumatic Stress Disorder	**Moderate** (risperidone) **Low** (Olanzapine) **Very Low** (Quetiapine)	Three trials enrolled men with combat-related PTSD; these showed a benefit in sleep quality, depression, anxiety, and overall symptoms when risperidone or olanzapine was used to augment therapy with antidepressants or other psychotropic medication. Three trials of olanzapine or risperidone as monotherapy for abused women with PTSD were inconclusive regarding efficacy. One trial found a three-fold decline in PTSD Scale (CAPS) scores in patients treated with quetiapine monotherapy compared to placebo. There were too few olanzapine studies (two) to pool; one reported olanzapine superior to placebo, while one did not. A meta-analysis of risperidone, using CAPS scores as outcome, found risperidone to be superior to placebo. In a meta-analysis by condition, atypical antipsychotics were	Risperidone is **efficacious** in reducing combat-related PTSD symptoms when used as an adjunct to primary medication.

Indication	Strength of Evidence	Findings	Conclusions
		efficacious for combat-related PTSD but not PTSD in abused women.	
Personality Disorders			
Borderline	**Low** (aripiprazole) **Very low** (quetiapine, olanzapine)	Four trials provide evidence that olanzapine is superior to placebo and may be superior to fluoxetine. The benefit of adding olanzapine to dialectical therapy in one trial was small. Two trials of olanzapine found no difference from placebo in any outcomes compared to placebo. Aripiprazole was superior to placebo in one small trial. Another trial found aripiprazole superior to placebo in improving SCL-90, HAM-D, and HAM-A scores at 8 months and less self-injury at 18 months. A trial of ziprasidone found no significant difference in CGI-BPD, depressive, anxiety, psychotic or impulsive symptoms compared to placebo at 12 weeks. One trial found quetiapine to be superior to placebo on BPRS and PANSS scales. Due to heterogeneity of outcomes, a meta-analysis could not be performed.	Olanzapine had **mixed results** in seven trials, aripiprazole was found **efficacious** in two trials, quetiapine was found **efficacious** in one trial, and ziprasidone was found **not efficacious** in one trial.
Schizotypal	**Low**	Risperidone was superior to placebo in one small trial. In another trial risperidone was found to be no different from placebo on a cognitive assessment battery.	Risperidone had **mixed results** when used to treat schizotypal personality disorder in two small trials.
Tourette's Syndrome	**Low**	Risperidone was superior to placebo in one small trial, and it was at least as effective as pimozide or clonidine for eight to 12 weeks of therapy in the three other trials. One trial of ziprasidone showed variable efficacy compared to placebo.	Risperidone **is at least as efficacious as pimozide or clonidine** for Tourette's syndrome.
Anxiety	**Moderate**	Three placebo-controlled trials of quetiapine as monotherapy for Generalized Anxiety Disorder (GAD) could be pooled; relative	Quetiapine **has efficacy** as treatment for Generalized Anxiety Disorder.

Indication	Strength of Evidence	Findings	Conclusions
		risk of responding on HAM-A favored the quetiapine group. One head to head trial showed no difference between risperidone and paroxetine on HAM-A score improvement. One trial each found quetiapine equally effective as paroxetine and escitalopram.	
Attention Deficit/Hyperactivity Disorder			
No comorbidity	**Low**	One trial showed risperidone superior to placebo in reducing scores on the Children's Aggression Scale–Parent version (CAS-P).	Risperidone **may be efficacious** in treating children with ADHD with no serious co-occurring disorders.
Mental retardation	**Low**	One trial showed risperidone led to greater reduction in SNAP-IV (Swanson, Nolan, and Pelham teacher & parent rating scale) scores than methylphenidate.	Risperidone **may be superior to methylphenidate** in treating ADHD symptoms in mentally retarded children.
Bipolar	**Low**	Two trials of aripiprazole showed no effect on SNAP-IV (Swanson, Nolan, and Pelham teacher & parent rating scale) scores than placebo.	Aripiprazole is **inefficacious** in reducing ADHD symptoms in children with bipolar disorder.
Eating Disorders	**Moderate** (olanzapine) **Low** (quetiapine)	In a pooled analysis of three trials, there was no difference in change in BMI at either one or three months with olanzapine compared to placebo. One trial of quetiapine reported no statistical difference from placebo in BMI increase at three months.	Olanzapine and quetiapine **have no efficacy** in increasing body mass in eating disorder patients.
Insomnia	**Very Low**	In one small trial (N=13) of quetiapine, sleep outcomes were not statistically different from placebo.	Quetiapine may be **inefficacious** in treating insomnia.
Substance Abuse			
Alcohol	**Moderate** (aripiprazole) **Low** (quetiapine)	Two trials of aripiprazole and one of quetiapine reported percentage of patients completely abstinent during follow-up. In a pooled analysis, the effect vs placebo was insignificant.	Aripiprazole is **inefficacious** in treating alcohol abuse/ dependence. Quetiapine may also be **inefficacious.**
Cocaine	**Low**	Two trials of olanzapine and one of risperidone reported there was no difference in efficacy vs placebo as measured by the Addiction Severity Index (ASI).	Olanzapine is **inefficacious** in treating cocaine abuse /dependence. Risperidone may also be

Indication	Strength of Evidence	Findings	Conclusions
			inefficacious.
Meth-amphetamine	**Low**	One trial found aripiprazole inefficacious in reducing use of intravenous amphetamine, as measured by urinalysis. Another trial found aripiprazole inefficacious in reducing craving for methamphetamine.	Aripiprazole is **inefficacious** in treating methamphetamine abuse/ dependence.
Methadone	**Low**	One trial of methadone-treated patients found no difference between risperidone and placebo in reduction of cocaine or heroin use.	Risperidone is an **inefficacious** adjunct to methadone maintenance

ADHD=attention-deficit hyperactivity disorder; BEHAVE-AD=Behavioral Pathology in Alzheimer's Disease Scale; BPRS=Brief Psychiatric Rating Scale; CGI-BPD=Clinical Global Impression Scale for Borderline Personality Disorder; CGI-I=Clinical Global Impression Improvement; CGI-S=Clinical Global Impression-Severity; CMAI =Cohen-Mansfield Agitation Inventory; HAM-A = Hamilton Anxiety Scale; HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale; MDD=major depressive disorder; NPI=Neuropsychiatric Inventory; OCD=obsessive-compulsive disorder; PANSS=Positive and Negative Syndrome Scale; PCT=placebo-controlled trial; PTSD=post-traumatic stress disorder; SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin-norepinephrine reuptake inhibitors; ZAN-BPD=Zanarini Rating Scale for Borderline Personality Disorder

Appendix II: Summary of Adverse Events of Atypical Antipsychotics for Off-Label Use (adopted from 2011 AHRQ systematic review)[196]

Adverse Event	Head-to-Head Studies	Active Comparator Studies	Placebo-Controlled Studies
Weight Gain			
Elderly	In one large trial (CATIE-AD) patients who were treated with olanzapine, quetiapine, or risperidone averaged a monthly gain of 1.0, 0.7, and 0.4 lbs respectively, compared to a monthly weight loss of 0.9 lbs for placebo patients.	More common in patients taking olanzapine than risperidone or conventional antipsychotics, particularly if their BMI was less than 25 at baseline, according to a large cohort study.	According to the meta-analysis, more common in patients taking olanzapine and risperidone than placebo.
Adults	More common in olanzapine patients than ziprasidone patients in one trial.	More common among patients taking olanzapine than patients taking conventional antipsychotics in three trials. More common in patients taking aripiprazole than patients taking conventional antipsychotics in one	According to the meta-analysis, more common in patients taking aripiprazole, olanzapine, quetiapine, and risperidone than placebo.

Adverse Event	Head-to-Head Studies	Active Comparator Studies	Placebo-Controlled Studies
		trial. More common among patients taking olanzapine than patients taking mood stabilizers in two trials.	
Children/Adolescents	No head to head studies	No difference between clonidine and risperidone in one trial.	More common in patients taking risperidone in two PCTs. No difference in one small PCT of ziprasidone.
Mortality-in the elderly	No difference between olanzapine and risperidone according to a meta-analysis of six trials of olanzapine published in 2006.	Six large cohort studies compared mortality in elderly patients taking atypical and conventional antipsychotics. Four of these studies found a significantly higher rate of death with conventional antipsychotics, while two found no statistical difference in mortality between the drug classes.	The difference in risk for death was small but statistically significant for atypicals, according to a 2006 meta-analysis which remains the best available estimate. Sensitivity analyses found no difference between drugs in the class. Patients taking atypicals had higher odds of mortality than those taking no antipsychotics in the two cohort studies that made that comparison. There are no trials or large observational studies of ziprasidone in this population.
Endocrine			
Elderly	No evidence reported	No evidence reported	No difference in endocrine events in risperidone patients in one PCT. Regarding diabetes, risk was elevated but not statistically significant in one industry-sponsored cohort study of olanzapine patients.
Adults	Diabetes more common in patients taking olanzapine than patients taking risperidone in one trial.	No evidence reported	Endocrine events more common in patients taking quetiapine, risperidone, and ziprasidone in one PCT each. More common in olanzapine in two pooled PCTs.

Adverse Event	Head-to-Head Studies	Active Comparator Studies	Placebo-Controlled Studies
			Diabetes more common in patients taking quetiapine in six pooled PCTs; however, the pooled odds ratio was elevated at 1.47 but not statistically significant. More common in olanzapine patients in one PCT; the odds ratio of 5.14 was not statistically significant, with very wide confidence intervals (0.6 to 244). Lower odds of diabetes in risperidone patients in one large observational study.
Cerebrovascular Accident (CVA)	No evidence reported	Hospitalization for CVA was increased in the first week after initiation of typical antipsychotics, but not for initiation of atypicals in a large cohort study.	More common in risperidone patients than placebo according to four PCTs pooled by the manufacturer. In a meta-analysis of PCTs, risperidone was the only drug associated with an increase. More common in olanzapine than placebo according to five PCTs pooled by the manufacturer.
Extrapyramidal Symptoms (EPS)			
Elderly	More common in patients taking aripiprazole and risperidone patients than patients taking quetiapine in one large trial (CATIE-AD).	No evidence reported	More common in patients taking risperidone, according to the meta-analysis. Quetiapine and aripiprazole were not associated with an increase. More common in olanzapine in one PCT.
Adults	No evidence reported	Less likely in patients taking quetiapine than mood stabilizers in one small trial. Less likely in patients taking olanzapine or aripiprazole than patients taking conventional	More common in patients taking aripiprazole, quetiapine, and ziprasidone than placebo according to the meta-analysis.

Adverse Event	Head-to-Head Studies	Active Comparator Studies	Placebo-Controlled Studies
		antipsychotics in one trial each.	
Sedation			
Elderly	More common in elderly patients taking olanzapine or quetiapine than risperidone according to the meta-analysis, but not statistically significant.	No difference in one trial of olanzapine vs benzodiazepines. No difference in three trials of olanzapine and three of risperidone vs conventional antipsychotics.	More common in patients taking aripiprazole, olanzapine, quetiapine, and risperidone than placebo according to the meta-analysis.
Adults	More common in patients taking quetiapine than risperidone in two trials. No difference in one trial of risperidone vs olanzapine.	Olanzapine patients had higher odds than mood stabilizer patients in two trials. More common in olanzapine and quetiapine patients than SSRIs patients in three and two trials respectively. Olanzapine patients had lower odds than patients taking conventional antipsychotics in the pooled analysis of three trials.	More common in patients taking aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone than placebo in the meta-analysis.
Children/Adolescents	No head-to-head trials	No difference in one small trial of clonidine vs risperidone. More patients on haloperidol than risperidone reported sleep problems in one trial.	Less common in aripiprazole patients than placebo patients in one PCT. No difference from placebo in one small PCT of ziprasidone.

BMI=body mass index; CATIE-AD=Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease; CVA=cerebrovascular accident; EPS=extrapyramidal symptoms; PCT=placebo-controlled trial; SSRI=serotonin selective reuptake inhibitor

Appendix III: Summary of the Strength of Evidence for Efficacy Outcomes in Children and Adolescents (adopted from the 2012 AHRQ systematic review)[103]

Outcome	Comparison (# of studies)	Strength of Evidence	Summary
Pervasive developmental disorder			
Autistic symptoms	FGA vs SGA (2 RCTs)	Low	No significant difference
	SGA vs placebo (7	Low	Significant effect in favor of SGA on ABC (MD, 218.3; 95% CI, 227.1 to 29.5; I2, 79.6%);

Outcome	Comparison (# of studies)	Strength of Evidence	Summary
	RCTs)		CARS (MD, 24.9; 95% CI, 28.5 to 21.4; I2, 64%).
CGI	SGA vs placebo (3 RCTs)	Low	No significant difference
OC symptoms	SGA vs placebo (3 RCTs)	Low	Significant effect in favor of SGA (MD, 21.7; 95% CI, 23.2 to 20.3; I2, 49%).
Medication adherence	SGA vs placebo (2 RCTs)	Low	No significant difference
Disruptive behavior disorder			
Aggression	SGA vs placebo (5 RCTs)	Low	No significant difference
Anxiety	SGA vs placebo (4 RCTs)	Low	No significant difference
Behavior symptoms	SGA vs placebo (7 RCTs)	Moderate	Significant effect in favor of SGA for ABC (MD, 221.0; 95% CI, 231.1 to 210.8; I2, 62%); BPI (MD, 23.8; 95% CI, 26.2 to 21.4; I2, 0%); NCBRF (MD, 26.9; 95% CI, 210.4 to 23.5; I2, 62%).
CGI	SGA vs placebo (7 RCTs)	Moderate	Significant effect in favor of SGA for CGI–I (MD, 21.0; 95% CI, 21.7 to 20.3; I2, 45%); CGI–S (MD, 21.3; 95% CI, 22.2 to 20.5; I2, 78%).
Medication adherence	SGA vs placebo (5 RCTs)	Low	No significant difference
Bipolar Disorder			
CGI	SGA vs placebo (7 RCTs)	Moderate	Significant effect in favor of SGA (MD, 20.7; 95% CI, 20.8 to 20.5; I2, 36%).
Depression	SGA vs placebo (7 RCTs)	Low	No significant difference
Manic Symptoms	SGA vs placebo (7 RCTs)	Low	All except one study significantly favored SGA (studies not pooled due to high heterogeneity).
Medication adherence	SGA vs placebo (7 RCTs)	Low	Significant effect in favor of placebo (RR, 2.0; 95% CI, 1.0 to 4.0; I2, 0%).
Suicide-related behavior	SGA vs placebo (7 RCTs)	Moderate	No significant difference for suicide-related deaths, attempts, or ideation.
Schizophrenia			
CGI	FGA vs SGA (3 RCTs)	Low	Significant effect in favor of SGA (MD, 20.8; 95% CI, 21.3 to 20.3; I2, 0%).

Outcome	Comparison (# of studies)	Strength of Evidence	Summary
	Clozapine vs olanzapine (2 RCTs)	Low	No significant difference
	Olanzapine vs risperidone (3 RCTs)	Low	No significant difference
	SGA vs placebo (6 RCTs)	Moderate	Significant effect in favor of SGA (MD, 20.5; 95% CI, 20.7 to 20.3; I2, 28%).
Positive and negative symptoms	FGA vs SGA (3 RCTs)	Low	No significant difference
	Clozapine vs olanzapine (2 RCTs, 1 PCS)	Low	No significant difference
	Olanzapine vs risperidone (3 RCTs, 1 PCS)	Low	No significant difference
	SGA vs placebo (6 RCTs)	Moderate	Significant effect in favor of SGA (MD, 28.7; 95% CI, 211.8 to 25.6; I2, 38%).
Medication adherence	FGA vs SGA (2 RCTs, 1 PCS)	Low	No significant difference
	Clozapine vs quetiapine (2 RCTs)	Low	No significant difference
	Olanzapine vs risperidone (4 RCTs, 1 PCS)	Low	No significant difference
	SGA vs placebo (2 RCTs)	Low	No significant difference
Suicide-related behaviors	SGA vs placebo (5 RCTs)	Low	No significant difference
Tourette syndrome			
Tics	SGA vs placebo (2 RCTs)	Moderate	Significant effect in favor of SGA (MD, 27.0; 95% CI, 210.3 to 23.6; I2, 0%)
Behavioral symptoms			
Autistic symptoms	Risperidone vs placebo (2RCTs)	Low	Significant effect in favor of risperidone in one study; NR in second study.

ABC=Aberrant Behavior Checklist, BPI=Behavior Problem Inventory, CARS=Childhood Autism Rating Scale, CGI–I=Clinical Global Impressions–Improvement, CGI–S=Clinical Global Impressions–Severity, NCBRF=Nisonger Child Behavior Rating Scale, NR=not reported, OC=obsessive-compulsive, PCS=prospective cohort study, RR=relative risk

Appendix IIIb: Summary of Evidence for Adverse Events in Children and Adolescents (adopted from 2012 AHRQ systematic review)[103]

Outcome	Strength of Evidence	SGA vs SGA	Placebo-Controlled Studies
Dyslipidemia	Low	Aripiprazole was significantly favored over olanzapine (RR, 0.25; 95% CI, 0.08 to 0.8)[a] and 95% CI, 271.3 to 27.4).[a] No significant differences were observed for clozapine vs olanzapine, olanzapine vs quetiapine and quetiapine vs risperidone.	Significant effect in favor of placebo over aripiprazole (RR, 2.5; 95% CI, 1.4, 4.4)[a], olanzapine (RR, 2.4; 95% CI, 1.2 to 4.9; I^2, 45%), and quetiapine (RR, 2.4; 95% CI, 1.1 to 5.4; I2, 0%).
	Moderate	Significant effect in favor of risperidone compared with olanzapine for cholesterol (MD, 10.2 mg/dL; 95% CI, 3.1 to 17.2; I^2, 0%) and triglycerides (MD, 17.3 mg/dL; 95% CI, 3.5 to 31.1; I2, 0%).	NA
EPS	Low	No significant difference for clozapine vs olanzapine, clozapine vs risperidone, olanzapine vs quetiapine, olanzapine vs risperidone, quetiapine vs risperidone.	No significant differences for placebo compared to olanzapine or quetiapine.
	Moderate	NA	Significant effect in favor of placebo over aripiprazole (RR, 4.2; 95% CI, 2.4 to 7.2; I^2, 0%) and risperidone (RR, 2.7; 95% CI, 1.4 to 4.9; I^2, 0%).
Insulin Resistance	Low	No significant difference for olanzapine vs quetiapine, olanzapine vs risperidone or quetiapine vs risperidone.	No significant difference between aripiprazole and placebo or olanzapine and placebo.
Prolactin-related sexual side effects	Low	Significant effect in favor of clozapine over olanzapine (MD, 210.8 ng/dL; 95% CI, 216.7 to 24.8; I^2, 21%). No significant difference for quetiapine vs risperidone.	Significant effect in favor of placebo over risperidone in seven or eight studies (not pooled due to heterogeneity). No significant difference for quetiapine compared to placebo.
	Moderate	Significant effect in favor of olanzapine over risperidone (RR, 0.4; 95% CI, 0.2 to 0.6; I^2, 0%).	Significant effect in favor of aripiprazole over placebo (MD, 24.1 ng/mL; 95% CI, 26.3 to

Outcome	Strength of Evidence	SGA vs SGA	Placebo-Controlled Studies
			21.8; I2, 0%). Significant effect in favor of placebo over olanzapine (MD, 11.5 ng/mL; 95% CI, 8.8 to 14.1; I2, 0%).
Sedation	Low	No significant differences for clozapine vs olanzapine, olanzapine vs quetiapine, olanzapine vs risperidone, quetiapine vs risperidone.	Significant effect in favor of placebo over aripiprazole (RR, 2.7; 95% CI, 1.1 to 6.5; I2, 76%). No significant difference in placebo comparisons with olanzapine and quetiapine.
	Moderate	NA	Significant effect in favor of placebo over risperidone (RR, 2.9; 95% CI, 1.5 to 5.5; I^2, 32%) and ziprasidone (RR, 3.0; 95% CI, 1.7 to 5.2; I^2, 0%).
Weight gain	Low	Significant effect in favor of aripiprazole over olanzapine (MD, 24.1 kg; 95% CI, 25.5 to 22.7),a quetiapine (MD, 21.6 kg; 95% CI, 23.0 to 20.3)[a] and risperidone (MD, 22.3 kg; 95% CI, 23.9 to 20.7).a No significant difference for clozapine vs olanzapine, clozapine vs risperidone, and quetiapine vs risperidone.	No significant difference for ziprasidone compared to placebo.
	Moderate	Significant effect in favor of quetiapine over olanzapine (RR, 1.5; 95% CI, 1.1 to 2.0; I^2, 0%) and risperidone over olanzapine (MD, 2.4 kg; 95% CI, 1.5 to 3.3; I^2, 72%).	Significant effect in favor of placebo over aripiprazole (MD, 0.8 kg; 95% CI, 0.4 to 1.2; I^2, 13%), olanzapine (MD, 4.6 kg; 95% CI, 3.1 to 6.1; I2, 70%), quetiapine (MD, 1.8 kg; 95% CI, 1.1 to 2.5; I^2, 49%), and risperidone (MD, 1.8 kg; 95% CI, 1.5 to 2.1; I^2, 0%).

AE=adverse event; EPS=extrapyramidal symptom; RR=relative risk.
a=Only 1 study contributed to this estimate; therefore, an I^2 value could not be calculated.

References

Please refer to the full therapeutic class review on atypical antipsychotics for a list of references.

Therapeutic Class Overview
Inhaled Anticholinergics

Therapeutic Class Overview/Summary:
The inhaled 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), glycopyrrolate (Seebri Neohaler®), ipratropium (Atrovent®, Atrovent® HFA), tiotropium (Spiriva®, Spiriva Respimat®) and umeclidinium (Incruse Ellipta®) with the combination products including glycopyrrolate/indacaterol (Utibron Neohaler®), umeclidinium/vilanterol (Anoro Ellipta®), tiotropium/olodaterol (Stiolto Respimat®) and ipratropium/albuterol, formulated as either an inhaler (Combivent Respimat®) or nebulizer solution (DuoNeb).[4-15] Ipratropium, a short-acting bronchodilator, has a duration of action of six to eight hours and requires administration four times daily. Aclidinium, glycopyrrolate, tiotropium and umeclidinium are considered long-acting bronchodilators. Aclidinium is dosed twice daily, while glycopyrrolate, 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. Aclidinium, glycopyrrolate, tiotropium and umeclidinium are available as dry powder inhalers for oral inhalation, with tiotropium also formulated as an inhalation aerosol.[4-15]

Aclidinium, glycopyrrolate, ipratropium and tiotropium, 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. Additionally, tiotropium soft mist inhaler (Spiriva Respimat®) has been approved for the chronic management of asthma and updated guidelines recommend its use as add-on thereapy.[9,16] Ipratropium/albuterol is indicated for the treatment of bronchospasms associated with COPD in patients who require more than one bronchodilator. Glycopyrrolate/indacaterol, umeclidinium, umeclidinium/vilanterol and tiotropium/olodaterol are FDA-approved for the maintenance treatment of airflow obstruction in patients with COPD.[4-15]

Table 1. Current Medications Available in the Therapeutic Class[4-15,17]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agents			
Aclidinium (Tudorza® Pressair)	Bronchospasm associated with COPD, maintenance treatment†	Powder for inhalation: 400 µg	-
Glycopyrrolate (Seebri Neohaler®)	Airflow obstruction in patients with COPD, maintenance treatment†	Powder for inhalation: 15.6 µg	-
Ipratropium* (Atrovent HFA®)	Bronchospasm associated with COPD, maintenance treatment	Aerosol for oral inhalation (Atrovent HFA®): 17 µg Solution for nebulization: 500 µg (0.02%)	✔
Tiotropium (Spiriva®, Spiriva	Asthma, maintenance	Aerosol for inhalation	-

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Respimat®)	treatment (aerosol for inhalation); Bronchospasm associated with COPD, maintenance treatment†, reduce exacerbations in patients with COPD	(Spiriva Respimat®): 1.25 µg/actuation 2.5 µg/actuation Powder for inhalation (Spiriva HandiHaler®): 18 µg	
Umeclidinium (Incruse Ellipta®)	Airflow obstruction in patients with COPD, maintenance treatment*	Powder for inhalation: 62.5 µg	-
Combination Products			
Glycopyrrolate/indacaterol (Utibron Neohaler®)	Airflow obstruction in patients with COPD, maintenance treatment†	Powder for inhalation: 15.6 µg/27.5 µg	-
Ipratropium/albuterol* (Combivent Respimat®)	Bronchospasm associated with COPD in patients requiring more than one bronchodilator	Inhalation spray (Combivent Respimat®): 20/100 µg‡ Solution for nebulization (DuoNeb®): 0.5/3.0 mg	✔
Tiotropium/olodaterol (Stiolto Respimat®)	Airflow obstruction in patients with COPD, maintenance treatment†	Inhalation Spray 5/5 µg	-
Umeclidinium/vilanterol (Anoro Ellipta®)	Airflow obstruction in patients with COPD, maintenance treatment†	Powder for inhalation: 62.5/25 µg	-

*Generic available in at least one dosage form or strength.
†Long-term maintenance treatment.
‡Delivering 18 µg of ipratropium and 103 µg of albuterol (90 µg albuterol base).

Evidence-based Medicine

- In general, the inhaled anticholinergics have demonstrated to improve lung function and/or exercise tolerance in patients with chronic obstructive pulmonary disease (COPD).[18-80] Few head-to-head trials have noted significant differences in improvements in lung function favoring tiotropium over ipratropium.[20,43,44] A meta-analysis evaluating tiotropium added to combination inhaled corticosteroid (ICS)/long acting β-agonist (LABA) therapy compared to ICS/LABA alone for the treatment of asthma did not demonstrate a significant difference between the groups in the primary endpoints of exacerbations requiring oral corticosteroids, quality of life or serious adverse events.[81]
- The efficacy of glycopyrrolate is based primarily on the dose-ranging trials in 471 subjects with COPD and two placebo-controlled confirmatory trials in 867 subjects with COPD. The primary efficacy endpoint from the two placebo-controlled confirmatory trials, GEM1 and GEM2, was the change from baseline in FEV_1 $AUC_{0 \text{ to } 12 \text{ h}}$ following the morning dose at day 85 compared with placebo. In both trials, the glycopyrrolate group demonstrated a larger increase in mean change from baseline in FEV_1 $AUC_{0 \text{ to } 12 \text{ h}}$ compared to placebo.
    - In GEM1, the change from baseline least squares (LS) mean was 0.125 L in the glycopyrrolate group compared to -0.014 L in the placebo group (Treatment difference LS Mean, 0.139 L; 95% CI, 0.095 to 0.184; P values not reported).

    - For GEM2, the change from baseline LS mean was 0.115 L in the glycopyrrolate group compared to -0.008 L in the placebo group (Treatment difference LS Mean, 0.123 L; 95% CI, 0.081 to 0.165; P values not reported).[5,77,78]
- The efficacy of indacaterol/glycopyrrolate was based primarily on the results of two 12-week efficacy studies (FLIGHT1 & 2).[12,79] Both were identical, multicenter, randomized, double-blinded, placebo- and active-controlled, and parallel-group trials in subjects with COPD. A total of 2,038 individuals were randomized to indacaterol/glycopyrrolate 27.5 µg/15.6 µg twice-daily (BID), indacaterol 27.5 µg BID, glycopyrrolate 15.6 mcg BID, or placebo BID. The primary endpoint was the change from baseline in FEV_1 AUC_{0-12h} following the morning dose at Day 85 compared with placebo, glycopyrrolate 15.6 µg BID, and indacaterol 27.5 µg BID.
    - In both trials, Utibron Neohaler® (indacaterol/glycopyrrolate) demonstrated a larger increase in mean change from baseline in FEV_1 AUC_{0-12h} compared to placebo, indacaterol 27.5 µg BID, and glycopyrrolate 15.6 µg BID (treatment difference: 103 mL and 88 mL vs indacaterol and glycopyrrolate, respectively, P<0.001). In addition, both indacaterol and glycopyrrolate monotherapies had a statistically greater response than placebo at week 12 in terms of FEV_1 AUC_{0-12h} (treatment difference: 143 mL and 158 mL, respectively, P<0.001).[79]

Key Points within the Medication Class

- According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines:[1]
    - Inhaled bronchodilators are preferred for the management of COPD. Regular use of long-acting β2-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 GOLD guidelines emphasize that the use of long-acting bronchodilators is more effective and convenient than the use of short-acting bronchodilators.
- According to the National Institute for Clinical Excellence (NICE):[2]
    - 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 anticholinergics 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 agent.
- According to the Global Initiative for Asthma (GINA), tiotropium (Spiriva Respimat®) is an option for add-on therapy in patients 12 years and older in uncontrolled asthma at both steps 4 and 5 in the treatment algorithm.[16] Other Asthma guidelines have not been updated since tiotropium has received this expanded indication.[82]
- Other Key Facts:
    - Ipratropium and ipratropium/albuterol solutions for nebulization are the only inhaled anticholinergic products that are currently available generically.

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