AHCCCS
Arizona Health Care Cost Containment System

AHCCCS Pharmacy and Therapeutics Committee

23 May 2019

Welcome and Introductions

- Sara Salek, MD, Chief Medical Officer, AHCCCS
  - Meeting Minutes 29 April 2019
  - Review
  - Vote

Magellan Class Reviews

Classes for Review: Non-Supplemental Rebate Class Review

- Analgesics, Narcotics Long
- Antibiotics, Inhaled
- Anticoagulants
- Antimigraine Agents, Other (CGRPs)
- Antipsychotics Second Generation Oral
- Antipsychotics Long Acting Injectables
- COPD Agents
- Cytokine and CAM Antagonists
- Epinephrine, Self-Injected

Magellan Class Reviews

Classes for Review: Non-Supplemental Rebate Class Review

- Glucocorticoids, Inhaled
- Growth Hormone
- Hepatitis C Agents (Direct Acting)
- Hypoglycemics, Incretin Mimetics/Enhancers
- Hypoglycemics, Insulin and Related Agents
- Opiate Dependence Treatments
- Pancreatic Enzymes
- Progestational Agents
- Stimulants and Related Agents

Magellan Drug Class Reviews

Hind Douiki, Pharm.D.

Analgesics, Narcotics Long

Analgesics, Narcotics Long

Class Overview: Products

- buprenorphine (buprenorphine transdermal, Butrans)
- buprenorphine HCl (Belbuca)
- fentanyl (Duragesic Matrix, fentanyl transdermal)
- hydrocodone bitartrate (Hysingla ER & Zohydro ER)
- hydromorphone HCl (Exalgo, hydromorphone ER)
- methadone HCl (methadone concentrate, solution, tablet & sol tab)
- morphine sulfate (Arymo ER, Kadian, Morphabond ER, morphine ER capsule (gen. Avinza & Kadian), morphine ER tablet, MS Contin)

Analgesics, Narcotics Long

Class Overview: Products

- morphine sulfate/naltrexone (Embeda)
- oxycodone HCl (oxycodone ER, Oxycontin)
- oxycodone myristate (Xtampza ER)
- oxymorphone HCl (*Opana ER*,* oxymorphone ER)
- tapentadol HCl (Nucynta ER)
- tramadol HCl (Conzip, tramadol ER (gen. Conzip, Ryzolt & Ultram))

**Voluntarily withdrawn from the market in 2017*

Analgesics, Narcotics Long

Abuse -Deterrent Products: continued

- hydrocodone ER (Zohydro ER)**
- hydromorphone ER (Exalgo)**
- oxymorphone ER (*Opana ER****)**
- tapentadol ER (Nucynta ER)**

*** These products have abuse-deterrent properties but have not been approved by the FDA as abuse-deterrent*

****Voluntarily withdrawn from the market in 2017*

Analgesics, Narcotics Long

- Opioid agonists reduce pain through interaction with opioid mu-receptors located in the brain, spinal cord, and smooth muscle
- The primary site of therapeutic action is the central nervous system (CNS)
- Opioid agonists produce respiratory depression by direct action on the brain stem respiratory center
- Buprenorphine is a partial agonist/antagonist of opioid receptors
- Naltrexone, a component of Embeda, is a centrally-acting mu-receptor antagonist that reverses the analgesic effects of mu-receptor agonists by competing for binding sites with opioids

Analgesics, Narcotics Long

- No clinical data exist that distinguish analgesic efficacy of any of these products from the others
- Pain management must be individualized and patients who do not respond to one opioid may respond to another
- Abuse deterrent formulations do not enhance analgesic properties
- All opioids can be abused and are subject to illicit use
- Abuse deterrent formulations are intended to make misuse more difficult, but do not affect diversion

Analgesics, Narcotics Long

Product/Guideline Updates

- The FDA issued a Drug Safety Communication warning of serious harm to patients if opioid pain medications are discontinued or rapidly decreased in patients who were physically dependent on opioids
- This warning comes in response to reports of withdrawal symptoms, uncontrolled pain, psychological distress, and suicide
- The package inserts for opioids will be updated to include additional guidance on safely decreasing doses

Analgesics, Narcotics Long

Product/Guideline Updates

- The CDC provided clarification on their 2016 Guideline for Prescribing Opioids for Chronic Pain
- CDC stated that their guidelines on opioid prescribing were not intended to deny opioid therapy for pain management for any patients with chronic pain, particularly in patients with sickle cell disease, undergoing cancer treatment, or cancer survivors with chronic pain
- The aim of the 2016 guideline was to ensure that clinicians and patients consider all safe and effective treatment options with the goal to reduce inappropriate use

Analgesics, Narcotics Long

Product/Guideline Updates

- The National Comprehensive Cancer Network (NCCN) published guidelines on the treatment of cancer pain in adults in 2018 and do not specify the use of one specific opioid over another for all patients
- They recommend against the use of meperidine (due to CNS toxicity) and mixed agonist-antagonists (limited usefulness) for cancer pain
- They suggest using the same opioid when both a short-acting and long-acting opioid are appropriate, when available
- They also provide extensive dosing, adverse effect management, and assessment guidance

Antibiotics, Inhaled

Antibiotics, Inhaled

Class Overview: Products

- Arikayce (amikacin liposome)
- Bethkis (tobramycin)
- Cayston (aztreonam)
- Kitabis Pak (tobramycin)
- Tobi (tobramycin)
- Tobi Podhaler (tobramycin)
- tobramycin pak (tobramycin)
- tobramycin solution (tobramycin)

Antibiotics, Inhaled

- Inhaled antibiotics are used in the treatment of Cystic Fibrosis
- CF is an autosomal recessive disorder caused by mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene located on chromosome number 7
- The typical manifestation of CF involves progressive obstructive lung disease that has been associated with impaired mucous clearance, difficulty clearing pathogens, and risk of chronic pulmonary infection and inflammation
- As pulmonary infection is the main source of morbidity and mortality, antibiotics play an important role in CF therapy to control the progression of the disease

Antibiotics, Inhaled

- The Cystic Fibrosis Foundation (CFF) recommends inhaled antibiotic therapy for the treatment of initial or new growth of *P. aeruginosa*, with preference for tobramycin for 28 days
- Chronic use of inhaled tobramycin and inhaled aztreonam are recommended in the 2013 CF Pulmonary Guidelines to reduce exacerbation for patients who are ≥ 6 years of age with persistent *P. aeruginosa* cultures in the airways (strength of recommendation A for moderate to severe disease; strength of recommendation B for mild disease)
- In patients with pulmonary exacerbations marked by chronic infection of *P. aeruginosa*, treatment with the combination of aminoglycoside and beta-lactam antibiotic is recommended

Antibiotics, Inhaled

- The CF Foundation also recommends alternate-month administration of both tobramycin and aztreonam in patients persistently infected with *P. aeruginosa (*grade B recommendation)
- In 2016, a clinical guideline for CF in preschool-aged children (ages 2 to 5 years) was developed by the CFF. For this patient population, CFF recommends oral, inhaled, and/or IV antibiotics for treatment of pulmonary exacerbations and every other month administration of inhaled antibiotics in patients with persistent *P. aeruginosa* infection

Antibiotics, Inhaled

New Drug to Class:
Arikayce (amikacin liposome)

Antibiotics Inhaled

New Drug to Class: Arikayce

- The first drug to be approved under the new Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD pathway)
- Was also approved under the Accelerated Approval Pathway
- Indicated for the treatment of *Mycobacterium avium complex* (MAC) lung disease as part of a combination antibacterial drug regimen in patients who do not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regiment therapy

Antibiotics Inhaled

New Drug to Class: Arikayce

- Should be reserved for use in adults with limited or no alternative treatment options due to limited clinical safety and effectiveness data
- Approved as 590 mg/8.4 mL unit-dose vial for oral inhalation via the Lamira Nebulizer System; it is dosed as one inhalation daily

Antibiotics Inhaled

New Drug to Class: Arikayce

- Contraindications include history of hypersensitivity to any aminoglycoside
- Boxed warning regarding the risk of increased respiratory adverse reactions
- Warnings include hypersensitivity pneumonitis, hemoptysis, bronchospasm, exacerbations of underlying pulmonary disease, ototoxicity, nephrotoxicity, neuromuscular blockade, and embryo-fetal toxicity

Antibiotics Inhaled

New Drug to Class: Arikayce

- Common adverse reactions in patients with refractory MAC lung disease observed were dysphonia, cough, bronchospasm, hemoptysis, ototoxicity, upper airway irritation, musculoskeletal pain, fatigue/asthenia, exacerbation of underlying pulmonary disease, diarrhea, and nausea
- Pre-treatment with short-acting selective beta-2 agonists should be considered for patients taking Arikayce if they have a history of hyperreactive airway disease, COPD, asthma, or bronchospasm

Antibiotics Inhaled

New Drug to Class: Arikayce

- The safety and efficacy of Arikayce were demonstrated in a randomized, controlled clinical trial where patients were assigned to one of two treatment groups
- One group of patients received Arikayce plus a background multi-drug antibacterial regimen, while the other treatment group received a background multi-drug antibacterial regimen alone
- By the sixth month of treatment, 29 percent of patients treated with Arikayce had no growth of mycobacteria in their sputum cultures for three consecutive months compared to 9 percent of patients who were not treated with Arikayce

Anticoagulants

Anticoagulants

Drug	Manufacturer	DVT prophylaxis				DVT Treatment
		Hip Replacement	Knee Replacement	Hip Fracture surgery	Abdominal Surgery	
Injectable						
dalteparin (Fragmin®)	Pfizer	X	-	-	X	-
enoxaparin (Lovenox®)	generic, Sanofi-Aventis	X	X	-	X	X (without PE in outpatient setting, with or without PE in inpatient setting)
fondaparinux (Arixtra®)	generic, Mylan	X	X	X	X	X

Anticoagulants

Drug	Manufacturer	DVT prophylaxis				DVT Treatment
		Hip Replacement	Knee Replacement	Hip Fracture surgery	Abdominal Surgery	
Oral						
apixaban (Eliquis®)	Bristol-Myers Squibb	X	X	-	-	X
betrixaban (Bevyxxa®)	Portola	-	-	-	-	-
dabigatran (Pradaxa®)	Boehringer Ingelheim	X	-	-	-	X
edoxaban (Savaysa®)	Daiichi Sankyo	-	-	-	-	X
rivaroxaban (Xarelto®)	Janssen	X	X	-	-	X
warfarin (Coumadin®)	generic, Bristol-Myers Squibb	--	--	--	--	X

Anticoagulants

Class Overview – Other indications:

- dalteparin (Fragmin)
  - Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction (MI) when concurrently administered with aspirin
  - Deep vein thrombosis (DVT) prophylaxis for immobile medical patients who are at risk for thromboembolic complications
  - Extended treatment of symptomatic venous thromboembolism (VTE) (proximal DVT and/or pulmonary embolism [PE]), to reduce the recurrence of VTE in patients with cancer

Anticoagulants

Class Overview – Other indications:

- enoxaparin (Lovenox)
  - For the prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction in conjunction with aspirin
  - DVT prophylaxis to prevent thromboembolic complications in medical patients with severely restricted mobility during acute illness
  - Treatment of acute ST-segment elevation myocardial infarction (STEMI) managed medically or with subsequent percutaneous coronary intervention (PCI)

Anticoagulants

Class Overview – Other indications:

- fondaparinux (Arixtra)
  - Treatment of acute Pulmonary Embolism (PE) when initial therapy is administered in the hospital and with warfarin
- apixaban (Eliquis)
  - To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF)
  - For the treatment of PE
  - To reduce the risk of recurrent DVT and PE following initial therapy

Anticoagulants

Class Overview – Other indications:

- betrixaban (Bevyxxa)
  - For the prophylaxis of VTE in adult patients hospitalized for acute medical illness who are at risk for thromboembolic complications due to moderate or severely restricted mobility and other risk factors for VTE
- dabigatran (Pradaxa)
  - To reduce the risk of stroke and systemic embolism in patients with NVAF
  - To reduce the risk of recurrence of DVT and PE following initial therapy

Anticoagulants

Class Overview – Other indications:

- edoxaban (Savaysa)
  - To reduce the risk of stroke and systemic embolism in patients with NVAF
- warfarin (Coumadin)
  - Prophylaxis and/or treatment of the thromboembolic complications associated with atrial fibrillation (AF) and/or cardiac valve replacement
  - Reduce the risk of death, recurrent myocardial infarction, and thromboembolic events, such as stroke or systemic embolization, after myocardial infarction
  - Prophylaxis and/or treatment of venous thrombosis and its extension, and PE

Anticoagulants

Class Overview – Other indications:

- rivaroxaban (Xarelto)
  - To reduce the risk of stroke and systemic embolism in patients with NVAF
  - For the treatment of PE
  - For the reduction in the risk of recurrence of DVT and of PE for patients at continued risk for recurrent DVT and/or PE following initial 6-months treatment for DVT and/or PE
  - To reduce the risk of major cardiovascular (CV) events (CV death, MI, and stroke) in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD) when used in combination with aspirin

Anticoagulants

Class Summary:

- Low molecular weight heparins (LMWHs) are important treatment options in DVT and PE management with advantages over unfractionated heparin (UFH)
- LMWHs have been shown to reduce mortality rates after acute DVT and provide similar efficacy as UFH
- While subcutaneous (SC) anticoagulants have subtle differences in methods of preparation, pharmacokinetic parameters, and anti-Xa activity, the clinical characteristics are similar
- The newer oral anticoagulants show comparable efficacy and superiority or non-inferiority to warfarin for stroke prevention in NVAF with similar to lower overall rates of major bleeding

Anticoagulants

Class Summary:

- The newer oral agents do not require laboratory monitoring and the associated dose adjustments required with warfarin therapy
- Except for dabigatran, however, none of these new anticoagulants have an antidote currently available
- Dabigatran does has corresponding reversal agent (idarucizumab [Praxbind])
- Meta-analysis found the newer oral anticoagulants to have an approximately 10% reduction in all-cause mortality in patients with avalvular atrial fibrillation
- A network meta-analysis reported statistically similar reductions in the risk of VTE or VTE-related death for all newer oral anticoagulants

Anticoagulants

Product/Guideline Updates:

- The American College of Cardiology (ACC) published guidelines on managing acute bleeding in patients taking direct oral anticoagulants and warfarin
- This includes a decision tree and guidance on the clinical use of anticoagulant reversal agents and when to restart anti-coagulations
- Xarelto is now approved in combination with aspirin to reduce the risk of major CV events (CV death, MI, and stroke) in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD)
- The dosage for this indication is 2.5 mg orally twice daily, with or without food, in combination with aspirin (75-100 mg) once daily

Anticoagulants

Product/Guideline Updates:

- The American Heart Association/American College of Cardiology issued a focused update of the 2014 Guideline on the Management of Patients with Atrial Fibrillation
- The most notable recommendation change is that the novel oral anticoagulants (NOACs) are now recommended over warfarin to prevent stroke in patients with atrial fibrillation, except in those with moderate-to-severe mitral stenosis or a mechanical heart valve

Antimigraine Agents, Other (CGRPs)

Antimigraine Agents, Other (CGRPs)

Class Overview:

Drug	Manufacturer	Indication(s)
erenumab-aooe (Aimovig)	Amgen	Preventive treatment of migraine in adults
fremanezumab-vfrm (Ajovy)	Teva	Preventive treatment of migraine in adults
galcanezumab-gnlm (Emgality)	Eli Lilly	Preventive treatment of migraine in adults

Antimigraine Agents, Other (CGRPs)

- Migraines account for 10% to 20% of all headaches in adults and affect over 39 million men, women, and children in the United States
- Non-opioid analgesia with a nonsteroidal anti-inflammatory drugs (NSAIDs), or combinations such as aspirin or acetaminophen plus caffeine, are recommended as first-line therapy for patients with mild to moderate migraine pain
- Triptans have become the drugs of choice for treating acute migraine attacks with a response rate of about 60%
- Studies suggest that 38% to 50% of migraineurs are candidates for preventive therapy

Antimigraine Agents, Other (CGRPs)

- The 2012 (reaffirmed in 2015) practice guidelines by the American Academy of Neurology (AAN) and the American Headache Society (AHS) advise that antiepileptic drugs (divalproex sodium, sodium valproate, topiramate) and beta-blockers (metoprolol, propranolol, timolol) are established as *effective* in migraine prevention (Level A)
- Antidepressants (amitriptyline, venlafaxine) and beta-blockers (atenolol, nadolol) are *probably effective* in migraine prevention (Level B)
- In 2018, the FDA approved three calcitonin gene-related peptide (CGRP) inhibitors: erenumab-aooe (Aimovig), fremanezumab-vfrm (Ajovy), and galcanezumab-gnlm (Emgality), for preventative treatment of migraines in adults

Antimigraine Agents, Other (CGRPs)

- The AHS recommends initiating CGRP inhibitors for migraine prophylaxis in patients ≥ 18 years of age with the following:
  - Diagnosis of migraine (with or without aura) experiencing 4 to 7 monthly headache days with moderate disability and inability to tolerate or inadequate response to a 6-week trial of at least 2 oral prophylactic agents
  - Diagnosis of migraine (with or without aura) experiencing 8 to 14 monthly headache days and inability to tolerate or inadequate response to a 6-week trial of at least 2 oral prophylactic agents
  - Diagnosis of chronic migraine and either inability to tolerate or inadequate response to a 6-week trial of at least 2 oral prophylactic agents or at least 6 months of onabotulinumtoxinA treatment

Antimigraine Agents, Other (CGRPs)

New Drug to Class: Aimovig (erenumab-aooe)

Antimigraine Agents, Other (CGRPs)

New Drug to Class: Aimovig

- The first monoclonal antibody approved that inhibits CGRP
- It is self-administered at a dose of 70 mg subcutaneously once monthly and the dose may increase to 140 mg, if needed
- The needle cap of the prefilled syringe contains latex-derivative dry natural rubber, which may cause allergic reactions in individuals sensitive to latex
- The most common adverse reactions in Aimovig clinical studies occurring in at least 3% of treated patients and more often than placebo) are injection site reactions and constipation

Antimigraine Agents, Other (CGRPs)

New Drug to Class: Aimovig

- **Study 1** was a randomized, multi-center, 6-month, placebo-controlled, double-blind study evaluating Aimovig for the preventive treatment of episodic migraine
- 955 patients with a history of episodic migraine were randomized to receive either Aimovig 70 mg, Aimovig 140 mg, or placebo by subcutaneous injection once monthly for 6 months
- Participants in the Aimovig 70 mg and 140 mg treatment arms experienced reductions of 3.2 and 3.7 days from baseline in monthly migraine days, respectively, as compared to a 1.8-day reduction in the placebo arm

Antimigraine Agents, Other (CGRPs)

New Drug to Class: Aimovig

- **Study 2** was a randomized, multi-center, 3-month, placebo-controlled, double-blind study evaluating Aimovig for the preventive treatment of episodic migraine
- 577 patients with a history of episodic migraine were randomized to receive either Aimovig 70 mg or placebo by subcutaneous injection once monthly for 3 months
- Subjects receiving Aimovig experienced a statistically significant 2.9-day reduction from baseline in monthly migraine days at month 3, as compared to a 1.8-day reduction in the placebo arm

Antimigraine Agents, Other (CGRPs)

New Drug to Class: Aimovig

- **Study 3** was a randomized, multi-center, 3-month, placebo-controlled, double-blind study evaluating Aimovig as a preventive treatment of chronic migraine
- 667 patients with a history of chronic migraine with or without aura were randomized to receive Aimovig 70 mg, Aimovig 140 mg, or placebo by subcutaneous injections once monthly for 3 months
- Participants experienced a 6.6-day reduction from baseline in monthly migraine days at month 3 in each of the Aimovig treatment arms compared to a 4.2-day reduction in the placebo arm

Antimigraine Agents, Other (CGRPs)

New Drug to Class: Ajovy (fremanezumab-vfrm)

Antimigraine Agents, Other (CGRPs)

New Drug to Class: Ajovy

- It is self-administered at a dose 225 mg subcutaneously once monthly or 675 mg every 3 months.
- The most common adverse reactions (≥5% and greater than placebo) were injection site reactions
- The FDA approval of Ajovy was based on two multicenter, randomized, 3-month, double-blind, placebo-controlled studies in adults with a history of episodic migraine (Study 1) or Chronic Migraine (Study 2)

Antimigraine Agents, Other (CGRPs)

New Drug to Class: Ajovy

- **Study 1** enrolled 875 adults with a history of episodic migraine (patients with <15 headache days per month)
- Patients were randomized (1:1:1) to receive subcutaneous injections of either Ajovy 675 mg quarterly, Ajovy 225 mg monthly, or placebo monthly, over a 3-month treatment period
- The primary efficacy endpoint was the mean change from baseline in the monthly average number of migraine days during the 3-month treatment period
- Both monthly and quarterly dosing regimens of Ajovy demonstrated statistically significant improvements for efficacy endpoints compared to placebo over the 3-month period

Antimigraine Agents, Other (CGRPs)

New Drug to Class: Ajovy

- **Study 2** enrolled 1,130 patients, with <15 headache days per month; they were randomized (1:1:1) to receive subcutaneous injections of either Ajovy 675 mg starting dose followed by 225 mg monthly, 675 mg quarterly, or placebo monthly, over a 3-month treatment period
- Subjects treated with Ajovy experienced statistically-significant reduction in the number of monthly headache days of at least moderate severity versus placebo (-2.5 days) during the 12 week period after first dose, for both monthly (-4.6 days) and quarterly (-4.3 days) dosing regimens
- Patients treated with Ajovy experienced significant improvement compared to placebo on all secondary endpoints for both monthly and quarterly dosing regimens, including: response rate, onset of efficacy, efficacy as monotherapy, and disability

Antimigraine Agents, Other (CGRPs)

New Drug to Class:
Emgality (galcanezumab-gnlm)

Antimigraine Agents, Other (CGRPs)

New Drug to Class: Emgality

- It is self-administered at a dose 120 mg subcutaneously once monthly after an initial loading dose of 240 mg
- The most common adverse reactions (incidence ≥2% and at least 2% greater than placebo) in Emgality clinical studies were injection site reactions
- The FDA approval of Emgality was based on two Phase 3 clinical trials in patients with episodic migraine (EVOLVE-1 and EVOLVE-2) and one Phase 3 clinical trial in patients with chronic migraine (REGAIN)
- EVOLVE-1 and EVOLVE-2 were six-month, double-blind, placebo-controlled studies that enrolled adult patients with episodic migraine (defined as 4-14 migraine headache days [MHDs] per month)

Antimigraine Agents, Other (CGRPs)

New Drug to Class: Emgality

- REGAIN was a three-month, double-blind, placebo-controlled study that enrolled adult patients with chronic migraine (defined as at least 15 headache days per month with at least 8 MHDs per month)
- In all three studies, patients were randomized to receive once-monthly placebo, Emgality 120 mg after an initial loading dose of 240 mg, or Emgality 240 mg
- The primary endpoint was the mean change from baseline in the number of monthly MHDs over the double-blind treatment period in the intent-to-treat study population

Antimigraine Agents, Other (CGRPs)

New Drug to Class: Emgality

- In EVOLVE-1, the mean change from baseline over months 1 to 6 was -4.7 days for Emgality 120 mg compared to -2.8 days for placebo (baseline MHDs were 9.2 for Emgality and 9.1 for placebo)
- In EVOLVE-2, the mean change from baseline over months 1 to 6 was -4.3 days for Emgality 120 mg compared to -2.3 days for placebo (baseline MHDs were 9.1 for Emgality and 9.2 for placebo)
- In REGAIN, the mean change from baseline over Months 1 to 3 was -4.8 days for Emgality 120 mg compared to -2.7 days for placebo (baseline MHDs were 19.4 for Emgality and 19.6 for placebo)

Antipsychotics

AHCCCS
Arizona Health Care Cost Containment System

Antipsychotics

Class Overview - Product indications include*:

- Schizophrenia, bipolar disorder, major depressive order, schizoaffective disorder, irritability associated with autism, Tourette's disorder, Parkinson's disease psychosis

Not inclusive of all product indications, all products differ in indication

Antipsychotics

Class Summary:

- Inconclusive evidence remains regarding the overall effectiveness of second generation antipsychotics compared to first generation agents in terms of primary outcomes as seen in changes in rating scale scores, particularly when considering the length of many clinical studies
- However, second generation antipsychotics are associated with less extrapyramidal symptoms (EPS) than first generation antipsychotics
- The question of long-term adverse events with second generation antipsychotic use remains unresolved, particularly related to metabolic disorders
- Second generation antipsychotics have largely replaced first generation antipsychotics in the treatment of psychotic disorders, but the long-term effectiveness and adverse event profiles of these products have not been shown to be definitively better

Antipsychotics

Class Summary:

- Inconclusive data exists to indicate which second generation antipsychotic agent to use first
- Clozapine is used for patients with treatment-resistant schizophrenia and in patients with recurrent suicidal behavior at high risk of suicide
- Clozapine is reserved for refractory patients due to reports of severe neutropenia and seizures occurring, patients taking it must have regular white blood cell and absolute neutrophil counts closely monitored
- Various guidelines exist to help in choosing the best individualized treatment for schizophrenia, bipolar disorder, or major depressive disorder
- Relative occurrences of adverse events may also be considered in product selection

Antipsychotics
Second Generation
Oral

AHCCCS
Arizona Health Care Cost Containment System

Antipsychotics, Second Generation Oral

Drug	Manufacturer	Other Indications	Schizophrenia	Bipolar Disorder			
				Acute Manic Episodes	Depressive Episodes	Acute Mixed Episodes	Maintenance
Second Generation Antipsychotics – Oral							
aripiprazole (Abilify®)	Generic, Otsuka	Major depressive disorder (adjunct); Irritability associated with autistic disorder (ages 6 to 17 years); Tourette's disorder (ages 6 to 18 years)	X (ages ≥ 13 years)	X (ages ≥ 10 years for acute treatment as monotherapy and in combination with lithium or valproate)	--	X (ages ≥ 10 years for acute treatment as monotherapy and in combination with lithium or valproate)	X (monotherapy and in combination with lithium or valproate for ages ≥ 10 years)
aripiprazole (with sensor) (Abilify Mycite®)	Otsuka	Major depressive disorder (adjunct)	X	X (acute treatment as monotherapy and in combination with lithium or valproate)	--	X (acute treatment as monotherapy and in combination with lithium or valproate)	X (monotherapy and in combination with lithium or valproate)
asenapine (Saphris®)	Forest/Allergan	--	X	X (ages ≥ 10 years for acute treatment as monotherapy; adults in combination with lithium or valproate)	--	X (ages ≥ 10 years for acute treatment as monotherapy; adults in combination with lithium or valproate)	X (monotherapy; adults only)

Antipsychotics, Second Generation Oral

Drug	Manufacturer	Other Indications	Schizophrenia	Bipolar Disorder			
				Acute Manic Episodes	Depressive Episodes	Acute Mixed Episodes	Maintenance
Second Generation Antipsychotics – Oral							
brexpiprazole (Rexulti®)	Otsuka	Major depressive disorder (adjunct)	X	--	--	--	--
cariprazine (Vraylar™)	Allergan	--	X	X (acute treatment)	--	X (acute treatment)	--
clozapine (Clozaril®)	Generic Novartis/HLS	--	X (treatment-resistant schizophrenia; reducing suicidal behavior in schizophrenia or schizoaffective disorder	--	--	--	--
clozapine (Fazaclo®)	Generic, Jazz						
clozapine (Versacloz®)	Jazz /Trupharma						

Antipsychotics, Second Generation Oral

Drug	Manufacturer	Other Indications	Schizophrenia	Bipolar Disorder			
				Acute Manic Episodes	Depressive Episodes	Acute Mixed Episodes	Maintenance
Second Generation Antipsychotics – Oral							
iloperidone (Fanapt®)	Vanda	--	X	--	--	--	--
lurasidone (Latuda®)	Sunovion	--	X (ages ≥ 13 years)	--	X (ages ≥ 10 years as monotherapy and in combination with lithium or valproate)	--	--
olanzapine (Zyprexa®)	Generic, Eli Lilly	Treatment-resistant depression (in combination with fluoxetine);	X (ages ≥ 13 years; second-line in adolescents due to metabolic effects)	X (ages ≥ 13 years as monotherapy and in combination with lithium or valproate; second-line in adolescents due to metabolic effects)	X (ages ≥ 10 years; in combination with fluoxetine)	X (ages ≥ 13 years as monotherapy and in combination with lithium or valproate; second-line in adolescents due to metabolic effects)	X (ages ≥ 13 years)

Antipsychotics, Second Generation Oral

Drug	Manufacturer	Other Indications	Schizophrenia	Bipolar Disorder			
				Acute Manic Episodes	Depressive Episodes	Acute Mixed Episodes	Maintenance
Second Generation Antipsychotics – Oral							
olanzapine/ fluoxetine (Symbyax®)	Generic, Eli Lilly	Treatment-resistant depression	--	--	X (ages ≥ 10 years for acute episodes)	--	--
paliperidone ER (Invega®)	Generic, Janssen	Schizoaffective disorder (monotherapy or adjunct with mood stabilizers and/or antidepressants)	X (ages ≥ 12 years)	--	--	--	--
pimavanserin (Nuplazid™)	Acadia	Hallucinations and delusions associated with Parkinson's disease (PD) psychosis	--	--	--	--	--

Antipsychotics, Second Generation Oral

Drug	Manufacturer	Other Indications	Schizophrenia	Bipolar Disorder			
				Acute Manic Episodes		Depressive Episodes	Acute Mixed Episodes	Maintenance
Second Generation Antipsychotics – Oral								
quetiapine (Seroquel®)	Generic, AstraZeneca	--	X (ages ≥ 13 years)	X (ages ≥ 10 years as monotherapy; adults in combination with lithium or valproate)		X	--	X (in combination with lithium or divalproex)
quetiapine ER (Seroquel XR®)	generic., AstraZeneca	Major depressive disorder (adjunct)	X (ages ≥ 13 years)	X (ages ≥ 10 years as monotherapy; adults in combination with lithium or valproate)		X	X (ages ≥ 10 years as monotherapy; adults in combination with lithium or valproate)	X (in combination with lithium or divalproex)

Antipsychotics, Second Generation Oral

Drug	Manufacturer	Other Indications	Schizophrenia	Bipolar Disorder			
				Acute Manic Episodes	Depressive Episodes	Acute Mixed Episodes	Maintenance
Second Generation Antipsychotics – Oral							
risperidone (Risperdal®)	Generic, Janssen	Irritability associated with autistic disorder (ages 5-17 years)	X (ages ≥ 13years)	X (ages ≥ 10 years as monotherapy; adults in combination with lithium or valproate)	--	X (ages ≥ 10 years as monotherapy; adults in combination with lithium or valproate)	--
ziprasidone (Geodon®)	generic., Pfizer	--	X	X (acute episodes)	--	X (acute episodes)	X (in combination with lithium or divalproex)

Antipsychotics, Second Generation Oral

Product/Guideline Updates:

- The FDA issued a statement regarding safety concerns with Nuplazid which analyzed post marketing reports related to serious adverse events and deaths
- The statement indicated they found no new or unexpected safety risks with its use and the benefit continues to outweigh risks
- An evidence-based review published in 2019 on behalf of the Movement Disorders Society found Nuplazid to be efficacious and to have an acceptable risk without requiring specialized monitoring

Antipsychotics, Second Generation Oral

Product/Guideline Updates:

- The researchers concluded that its use for psychosis in PD is clinically useful, but they also state that there is a lack of safety data regarding durability beyond 6 weeks
- Notably, they also weigh in on other agents in this class that are not indicated for PD psychosis
- They state that olanzapine is not clinically useful (not efficacious), quetiapine is possibly useful (limited evidence), and clozapine is also useful but requires specialized monitoring
- They also emphasize that all antipsychotics should be used with great caution in patients with psychosis-associated dementia due to the risk of adverse effects (e.g., falls, impaired cognition, pneumonia, cardiovascular effects, stroke, and death)

Antipsychotics

Product/Guideline Updates:

- The American Geriatrics Society (AGS) removed aripiprazole from the preferred medications for treating psychosis in patients with Parkinson's disease and replaced it with Nuplazid
- In 2018, the labeling for brexpiprazole (Rexulti) was updated to include a warning regarding pathological gambling and other compulsive behaviors based on post-marketing case reports with Rexulti

Antipsychotics
Atypical Long-Acting Injectable

Antipsychotics, Atypical Long-Acting Injectable

Drug	Manufacturer	Other Indications	Schizophrenia	Bipolar Disorder
Second Generation Antipsychotics – Long Acting Injectable				
aripiprazole ER (Abilify Maintena®)	Otsuka	--	X	X (maintenance treatment as monotherapy)
aripiprazole lauroxil ER (Aristada™)	Alkermes	--	X	--
aripiprazole lauroxil ER (Aristada Initio™)	Alkermes	--	X (for initial dose or select missed doses only)	--
olanzapine (Zyprexa® Relprevv)	Eli Lilly	--	X	--

Antipsychotics, Atypical Long-Acting Injectable

Drug	Manufacturer	Other Indications	Schizophrenia	Bipolar Disorder
Second Generation Antipsychotics – Long Acting Injectable				
paliperidone palmitate (Invega Sustenna®)	Janssen	Schizoaffective disorder (monotherapy and as an adjunct to mood stabilizers or antidepressants)	X	--
paliperidone palmitate (Invega Trinza®)	Janssen	--	X (treatment in patients after they have been adequately treated with Invega Sustenna for ≥ 4 months)	--
risperidone microspheres (Risperdal Consta®)	Janssen	--	X	X (maintenance treatment as monotherapy or in combination with lithium or valproate)
risperidone ER suspension§ (Perseris™)	Indivior	--	X	--

Antipsychotics, Atypical Long-Acting Injectable

Class Summary:

- There are not enough comparative data to support distinctions among the injectable second generation antipsychotics
- A meta-analysis evaluated the impact of long-acting injectable antipsychotic frequency on efficacy and other outcomes
- No differences were found in psychotic symptoms or quality of life between injectables dosed every 2 or 4 weeks
- Safety analyses were also very similar, with the exception of injection-site pain, which was lower with every 2 week formulations compared to every 4 week formulations
- Overall, data is very limited

Antipsychotics, Atypical Long-Acting Injectable

New Drug to Class:
Perseris (risperidone)

Antipsychotics, Atypical Long-Acting Injectable

New Drug to Class: Perseris

- Indicated for the treatment of schizophrenia in adults
- Is approved as 90 and 120 mg injectable suspensions; the recommended dose is 90 mg or 120 mg SC once monthly
- Supplementation with oral risperidone or a loading dose is not necessary but patients should have established tolerability with oral risperidone
- Was approved via 505(b)(2) pathway
- Contraindications, warnings, drug interactions, and adverse reactions are similar to other injectable risperidone products
- No comparative trials are available

COPD Agents

COPD Agents

Class Overview: Antimuscarinics – Short-Acting

- ipratropium inhalation aerosol - (Atrovent HFA)
- ipratropium inhalation solution - (ipratropium inhalation solution)

Class Overview: Antimuscarinics – Long-Acting

- aclidinium bromide - (Tudorza Pressair)
- glycopyrrolate - (Seebri Neohaler)
- tiotropium bromide inhalation spray - (Spiriva Respimat)
- tiotropium inhalation powder - (Spiriva HandiHaler)
- umeclidinium - (Incruse Ellipta)
- revefenacin - (Yupelri)

COPD Agents

Class Overview: Beta Agonist/Antimuscarinic Combination – Short-Acting

- albuterol/ipratropium MDI CFC-Free - (Combivent Respimat)
- albuterol/ipratropium inhalation solution - (albuterol/ipratropium inhalation solution)

Class Overview: Beta Agonist/Antimuscarinic Combination – Long-Acting

- formoterol/glycopyrrolate - (Bevespi Aerosphere)
- indacaterol/glycopyrrolate - (Utibron Neohaler)
- tiotropium/olodaterol - (Stiolto Respimat)
- umeclidinium/vilanterol - (Anoro Ellipta)

COPD Agents

Class Overview: Phosphodiesterate 4 (PDE-4) Inhibitor

- roflumilast - (Daliresp)

COPD Agents

- Chronic obstructive pulmonary disease (COPD) is a disease state characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema
- Airflow obstruction is generally progressive, may be accompanied by airway hyperreactivity, and may be partially reversible
- Progressive persistent obstruction or limitation of airflow is associated with an enhanced chronic inflammatory response in both the airways and the lung to noxious particles or gases
- Exacerbations and comorbidities contribute to the overall severity in individual patients
- COPD continues to be a leading cause of chronic morbidity and mortality worldwide

COPD Agents

- Both chronic bronchitis and emphysema predispose patients to a common collection of symptoms and impairments in respiratory function
- These include reductions in forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC ratio, and forced expiratory flow
- A COPD exacerbation is defined as an acute event characterized by worsening of the patient's respiratory symptoms that varies from the normal daily variations and requires a change in medication
- Prior to 2017, patient groups were categorized into an alphabetic (ABCD) classification system based on exacerbation risk and symptoms in combination with airway limitation
- Patients are now classified separately by *both their GOLD severity and exacerbation/symptom assessment*

COPD Agents

2019 GOLD Guidelines	
Assessment of Airflow Limitation	
Gold 1	Mild, FEV1 ≥ 80% predicted
Gold 2	Moderate, FEV1 50% to 79% predicted
Gold 3	Severe, FEV1 30% to 49% predicted
Gold 4	Very severe, FEV1 < 30% predicted

COPD Agents

2019 GOLD Guidelines	
Assessment of Exacerbation Risk and Symptoms	
Patient Group A	Low Risk, Less Symptoms: 0 to 1 exacerbations per year (not leading to hospitalization); and CAT score < 10 or mMRC grade 0 to 1
Patient Group B	Low Risk, Less Symptoms: 0 to 1 exacerbations per year (not leading to hospitalization); and CAT score ≥ 10 or mMRC grade ≥ 2
Patient Group C	High Risk, Less Symptoms: ≥ 2 exacerbations per year or ≥ 1 exacerbation leading to hospitalization; and CAT score < 10 or mMRC grade 0 to 1
Patient Group D	High Risk, Less Symptoms: ≥ 2 exacerbations per year or ≥ 1 exacerbation leading to hospitalization; and CAT score ≥ 10 or mMRC grade ≥ 2

mMRC - Modified British Medical Research Council questionnaire used only to assesses breathlessness

COPD Agents

GOLD Guidelines Group A:

- Short-acting inhaled bronchodilator used on an as-needed basis is recommended as first choice while a long-acting beta$_2$-agonist or anticholinergic and the combination of short-acting inhaled beta$_2$-agonist and short-acting anticholinergic are considered as alternatives

GOLD Guidelines Group B:

- Regular use of a long-acting beta2 agonist (LABA) or long-acting antimuscarinic (LAMA) is recommended, while the combination of a LABA plus a LAMA is an alternative treatment

COPD Agents

GOLD Guideline Group C:

- Monotherapy with a long-acting bronchodilator, with preference given to LAMAs. If exacerbations persist, fixed combinations of LABA/LAMA or LABA/inhaled corticosteroids (ICS) may be tried; due to increased risk of pneumonia with ICS agents, a LABA/LAMA combination is preferred

GOLD Guideline Group D:

- The same initial therapeutic plan may be utilized as those in Group C with a goal of reducing exacerbations. There is some evidence for use of triple therapy for Group D patients (ICS plus LABA/LAMA). If exacerbations persist with triple therapy, Daliresp may be added in patients with FEV1 < 50% predicted and chronic bronchitis

COPD Agents

- Bronchodilator medications are central to the symptomatic management of COPD
- Act to improve emptying of the lungs, reduce dynamic hyperinflation at rest and during exercise, and improve exercise performance
- Are given either on an as-needed basis for relief of persistent or worsening symptoms or on a regular basis to prevent or reduce symptoms
- Regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting agents
- Combining bronchodilators of different pharmacological classes may improve efficacy and decrease the risk of side effects
- There is insufficient evidence to recommend one long-acting agent over another

COPD

New Drug to Class: Yupelri (revefenacin)

COPD Agents

New Drug to Class: Yupelri

- An anticholinergic inhalation solution indicated for the maintenance treatment of patients with COPD
- approved as 175 mcg/3 mL unit-dose vials of inhalation solution and dosed as a 175 mcg vial inhaled once daily via a standard jet nebulizer with a mouthpiece connected to an air compressor
- It should not be initiated in patients with acutely deteriorating COPD or used to treat acute symptoms
- Additional warnings include paradoxical bronchospasm, worsening of narrow-angle glaucoma and urinary retention, as well as immediate hypersensitivity reactions

COPD Agents

New Drug to Class: Yupelri

- Most common adverse reactions (incidence greater than or equal to 2% and more common than placebo) include cough, nasopharyngitis, upper respiratory tract infection, headache, and back pain
- The FDA approval of Yupelri was based on two replicate, randomized, double-blind, placebo-controlled, parallel-group phase III trials designed to provide pivotal efficacy data for once-daily revefenacin over a dosing period of twelve weeks
- The studies enrolled a combined total over 1,250 patients with moderate to very severe COPD and assessed two doses (88 mcg and 175 mcg) of Yupelri inhalation solution or matched placebo administered once daily via a standard jet nebulizer

COPD Agents

New Drug to Class: Yupelri

- Both trials met their primary efficacy endpoint, demonstrating statistically significant improvements over placebo in trough FEV1 after 12 weeks of dosing for each of the Yupelri doses studied
- The improvements in trough FEV1 compared to placebo for the intent-to-treat population across both studies were 118 mL and 145 mL for 88 mcg and 175 mcg, respectively
- In pre-specified pooled analyses, Yupelri produced increases in trough FEV1 in the subgroup (38%) of patients using background LABA containing therapies and in the subgroup of patients who were not using concomitant LABA therapy

COPD Agents

New Drug to Class: Yupelri

- The improvements in FEV1 for the LABA subgroup were 92 mL and 135 mL for 88 mcg and 175 mcg, respectively; for the non-LABA subgroup were 131 mL and 150 mL for 88 mcg and 175 mcg, respectively

COPD Agents

Product/Guideline Updates

- In 2017, the European Respiratory Society and American Thoracic Society (ERS/ATS) produced joint guidelines on the prevention and management of COPD exacerbations
- They recommend LAMA use over LABA monotherapy to prevent exacerbations in patients with at least 1 exacerbation during the previous year
- They suggest treatment with Daliresp to prevent future exacerbations in patients who have COPD with severe or very severe airflow obstruction and symptoms of chronic bronchitis and exacerbations, despite optimal inhaled therapy
- The 2019 GOLD guidelines place a great focus on the assessment of inhaler technique and adherence to improve therapeutic outcomes

Cytokine and CAM Antagonists

Cytokine and CAM Antagonists

Drug	Rheumatoid Arthritis	Juvenile Idiopathic Arthritis	Ankylosing Spondylitis	Plaque Psoriasis	Psoriatic Arthritis	Crohn's Disease	Ulcerative Colitis
TNF Agents							
adalimumab (Humira®)	X	X (≥ 2 years)	X	X	X	X (≥ 6 years)	X
certolizumab pegol (Cimzia®)	X	--	X	--	X	X	--
etanercept (Enbrel®)	X	X (≥ 2 years)	X	X (≥ 4 years)	X	--	--
golimumab SC (Simponi®)	X	--	X	--	X	--	X
golimumab IV (Simponi® Aria®)	X	--	--	--	--	--	--
infliximab (Remicade®)	X	--	X	X	X	X (≥ 6 years)	X (≥ 6 years)

Cytokine and CAM Antagonists

Drug	Rheumatoid Arthritis	Juvenile Idiopathic Arthritis	Ankylosing Spondylitis	Plaque Psoriasis	Psoriatic Arthritis	Crohn's Disease	Ulcerative Colitis
Other Biologic Agents							
abatacept (Orencia®)	X	X (≥ 6 years: IV) (≥ 2 years: SC)	--	--	X	--	--
anakinra (Kineret®)	X	--	--	--	--	--	--
brodalumab (Siliq™)	--	--	--	X	--	--	--
canakinumab (Ilaris®)	--	X (≥ 2 years)	--	--	--	--	--
guselkumab (Tremfya™)	--	--	--	X	--	--	--
ixekizumab (Taltz®)	--	--	--	X	--	--	--

Cytokine and CAM Antagonists

Drug	Rheumatoid Arthritis	Juvenile Idiopathic Arthritis	Ankylosing Spondylitis	Plaque Psoriasis	Psoriatic Arthritis	Crohn's Disease	Ulcerative Colitis
Other Biologic Agents							
rilonacept (Arcalyst®)	--	--	--	--	--	--	--
sarilumab (Kevzara®)	X	--	--	--	--	--	--
secukinumab (Cosentyx®)	--	--	X	X	X	--	--
tildrakizumab-asmn (Ilumya™)	--	--	--	X	--	--	--
tocilizumab (Actemra®)	X	X (≥ 2 years) (IV only)	--	--	--	--	--
ustekinumab (Stelara®)	--	--	--	X	X	X	--
vedolizumab (Entyvio®)	--	--	--	--	--	X	X

Cytokine and CAM Antagonists

Drug	Rheumatoid Arthritis	Juvenile Idiopathic Arthritis	Ankylosing Spondylitis	Plaque Psoriasis	Psoriatic Arthritis	Crohn's Disease	Ulcerative Colitis
Non-Biologic Agents							
apremilast (Otezla®)	--	--	--	x	x	--	--
baricitinib[r] (Olumiant®)	x	--	--	--	--	--	--
tofacitinib (Xeljanz®, Xeljanz XR®)	x	--	--	--	--	--	--

Cytokine and CAM Antagonists

- Cytokines and cell adhesion molecules (CAMs) have indications for use in rheumatoid arthritis (RA), plaque psoriasis, psoriatic arthritis, Crohn's disease, ankylosing spondylitis (AS) as well as other disease states
- For many disease states, including rheumatoid arthritis there is no evidence that any one tumor necrosis factor (TNF) antagonist should be used before another
- There is no evidence that any one TNF antagonist is more effective than any other for the treatment of RA or AS
- In the absence of specific head-to-head trials, there is no indication of a specific 'first choice' for treatment in many of the targeted diseases so secondary indicators such as adverse reactions and cost may be considered
- Many of the guideline documents do not include some of the newer agents

Cytokine and CAM Antagonists

New Drug to Class: Ilumya (tildrakizumab-asmn)

Cytokine and CAM Antagonists

New Drug to Class: Ilumya

- An interleukin-23 antagonist indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy
- The recommended dose is 100 mg administered subcutaneously at weeks 0, 4, and every 12 weeks thereafter; it should only be administered by a healthcare professional
- Warnings include hypersensitivity reactions, infections, and tuberculosis
- Most common (≥1%) adverse reactions associated with Ilumya treatment are upper respiratory infections, injection site reactions, and diarrhea

Cytokine and CAM Antagonists

New Drug to Class: Ilumya

- The FDA approval of Ilumya for the treatment of adults with moderate-to-severe plaque psoriasis was based on data from the Phase III reSURFACE clinical development program
- In the two multicenter, randomized, double-blind, placebo-controlled trials (reSURFACE 1 and reSURFACE 2), 926 adult patients were treated with Ilumya (N=616) or placebo (N=310)
- Both studies met the primary efficacy endpoints, demonstrating significant clinical improvement with Ilumya 100 mg compared to placebo when measured by at least 75 percent of skin clearance (Psoriasis Area Sensitivity Index or PASI 75) and Physician's Global Assessment (PGA) score of "clear" or "minimal" at week 12 after two doses

Cytokine and CAM Antagonists

New Drug to Class: Ilumya

- Of the patients in the reSURFACE 1 study, 74% achieved 75% skin clearance at week 28 after three doses, and 84% of patients who continued receiving Ilumya 100 mg maintained PASI 75 at week 64 compared to 22% of patients who were re-randomized to placebo
- Also, 69% of the patients receiving Ilumya 100 mg who had a PGA score of "clear" or "minimal" at week 28 maintained this response at week 64 compared to 14% of patients who were re-randomized to placebo

Cytokine and CAM Antagonists

New Drug to Class: Olumiant (baricitinib)

Cytokine and CAM Antagonists

New Drug to Class: Olumiant

- A Janus kinase (JAK) inhibitor indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies
- Use of Olumiant in combination with other JAK inhibitors, biologic Disease-modifying antirheumatic drugs (DMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended
- Approved as 2 mg tablets and the recommended dose is 2 mg once daily
- May be used as monotherapy or in combination with methotrexate or other DMARDs

Cytokine and CAM Antagonists

New Drug to Class: Olumiant

- Initiation should be avoided (and therapy interrupted) in patients with hemoglobin less than 8 g/dL, an Absolute Lymphocyte Count less than 500 cells/mm3, or an Absolute Neutrophil Count less than 1000 cells/mm3
- Boxed Warnings include serious infections, tuberculosis, lymphoma and other malignancies, as well as thrombosis
- Additional warnings include gastrointestinal perforations and vaccinations
- Adverse reactions (greater than or equal to 1%) include: upper respiratory tract infections, nausea, herpes simplex, and herpes zoster

Cytokine and CAM Antagonists

New Drug to Class: Olumiant

- The FDA approval of Olumiant was based on two dose-ranging trials and two confirmatory phase 3 trials
- The dose-ranging studies I and II included a 12-week randomized comparison of Olumiant 1, 2, 4, and 8 mg versus placebo in 301 and 145 patients, respectively
- In study I, the observed ACR response was similar for Olumiant 1 and 2 mg daily and for Olumiant 4 and 8 mg daily, with the highest response for Olumiant 8 mg daily
- In study II, there was not a clear trend of dose response, with similar response rates for 1 mg and 4 mg and 2 mg and 8 mg

Cytokine and CAM Antagonists

New Drug to Class: Olumiant

- The efficacy and safety of Olumiant 2 mg once daily was assessed in two confirmatory phase 3 trials
- Both were randomized, double-blind, multicenter trials in patients with active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR)/European League Against Rheumatism 2010 criteria
- Patients over 18 years of age were eligible if at least 6 tender and 6 swollen joints were present at baseline
- The two studies (Studies III and IV) evaluated Olumiant 2 mg and 4 mg

Cytokine and CAM Antagonists

New Drug to Class: Olumiant

- Study III was a 24-week trial in 684 patients with moderately to severely active rheumatoid arthritis who had an inadequate response or intolerance to conventional DMARDs (cDMARDs)
- Patients received Olumiant 2 mg or 4 mg once daily or placebo added to existing background cDMARD treatment
- From Week 16, non-responding patients could be rescued to receive Olumian 4 mg once daily
- The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 12
- ACR20 was reached by 39% in the placebo arm and 66% in the Olumiant 2 mg/day arm at Week 12

Cytokine and CAM Antagonists

New Drug to Class: Olumiant

- Study IV was a 24-week trial in 527 patients with moderately to severely active rheumatoid arthritis who had an inadequate response or intolerance to 1 or more TNF inhibitor therapies with or without other biologic DMARDs (TNFi-IR)
- Patients received Olumiant 2 mg or 4 mg once daily or placebo added to background cDMARD treatment
- From Week 16, non-responding patients could be rescued to receive Olumiant 4 mg once daily
- The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 12
- ACR20 was reached by 27% in the placebo arm and 49% in the Olumiant 2 mg/day arm at Week 12

Cytokine and CAM Antagonists

Product/Guideline Updates:

- Cyltezo (adalimumab-adbm), the 2nd biosimilar for Humira, is indicated for RA, , juvenile idiopathic arthritis (JIA), psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis and plaque psoriasis
- Subcutaneous dosing varies based on indication. It is approved as single-use prefilled syringes containing 40 mg/0.8 mL
- Warnings include serious infections, invasive fungal infections, malignancies, anaphylaxis and Hepatitis B virus reactivation
- Most common adverse reactions include infections, injection site reactions, headache and rash

Cytokine and CAM Antagonists

Product/Guideline Updates:

- An international multidisciplinary task force issued consensus-based recommendations on the use of biosimilars for rheumatologic diseases
- Biosimilars are not considered superior or inferior to the originator product
- Biosimiliars should be considered safe and effective for all the originator product's approved indications
- The decision to substitute a biosimilar product for a reference drug should be made by the prescriber

Cytokine and CAM Antagonists

Product/Guideline Updates:

- Ixifi, a biosimilar for Remicade, is approved for the following conditions in adults: Crohn's disease, ulcerative colitis, rheumatoid arthritis with methotrexate, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis
- It is also approved for pediatric Crohn's disease. Dosing varies depending on indication
- Kevzara (sarilumab) is now approved as 150 mg/1.14 mL and 200 mg/1.14 mL solution in single-dose prefilled pens
- Xeljanz is now approved for the treatment of patients with moderately to severely active ulcerative colitis; it was already approved for the treatment of rheumatoid arthritis and psoriatic arthritis

Cytokine and CAM Antagonists

Product/Guideline Updates:

- Actemra (tocilizumab) is now approved for subcutaneous dosing in pediatric patients 2 years of age and older with systemic juvenile idiopathic arthritis
- For patients transitioning from intravenous therapy to subcutaneous administration, the subcutaneous dose should be administered when the next IV dose is due
- Hyrimoz (adalimumab-adaz), a biosimilar to Humira, has been approved; it is not interchangeable with the reference product but it has the same indications as the reference product

Cytokine and CAM Antagonists

Product/Guideline Updates:

- Actemra is now available in a 162 mg/0.9mL single-dose prefilled autoinjector (ACTPen) for subcutaneous administration
- ACR and National Psoriasis Foundation (NPF) issued joint guidelines for psoriatic arthritis (PsA)
- ACR/NPF recommend a treat-to-target approach and TNFα inhibitors as first-line in patients with active PsA

Cytokine and CAM Antagonists

Product/Guideline Updates:

- Strong recommendations (based on moderate-quality evidence) include:
  - Preference of a TNFα inhibitor monoclonal antibody biologic over a TNFα inhibitor biologic soluble receptor biologic (e.g., etanercept) or an interleukin (IL)-17 inhibitor
  - Preference of an IL 12/23 inhibitor over an IL-17 inhibitor
  - Start an oral small molecule (OSM) drug over a TNFα inhibitor biologic in patients with active PsA and frequent serious infections who are both OSM and biologic treatment-naïve
  - Recommend against smoking

Cytokine and CAM Antagonists

Product/Guideline Updates:

- Tremfya (guselkumab) is now available in a single-dose prefilled autoinjector (One-Press) for subcutaneous injection
- The American Academy of Dermatology (AAD) and the National Psoriasis Foundation (NPF) issued guidelines for the management and treatment of psoriasis, particularly in relation to comorbidities
- The guidelines encourage dermatologists treating patients with psoriasis to be proactive in educating and screening patients for psoriatic arthritis
- In patients with comorbid inflammatory bowel disease, the group recommends involvement from a gastroenterologist

Cytokine and CAM Antagonists

Product/Guideline Updates:

- Discontinuation of a TNF inhibitor may be needed to resolve skin issues that arise following TNF inhibitor initiation; IL-17 inhibitor therapy should be avoided in inflammatory bowel disease (IBD)
- Other notable comorbidities addressed include CV disease, metabolic syndrome, mental health
- The FDA issued a safety announcement regarding an increased risk of pulmonary embolism and death found in an ongoing clinical trial with the use of doses higher than the FDA approved dosing for RA for Xeljanz and Xeljanz XR
- The clinical trial is expected to be completed by the end of 2019 with investigators switching patients to a lower dose

Cytokine and CAM Antagonists

Product/Guideline Updates:

- Cimzia is now approved for use in adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy
- It is now also approved for the treatment of non-radiographic axial spondyloarthritis (nr-asXpA) in adults with objective signs of inflammation
- The dose for this indication is 400 mg (2 x 200 mg) subcutaneously initially and at weeks 2 and 4, followed by 200 mg every 2 weeks or 400 mg every 4 weeks
- Cimzia was already approved for the treatment of AS, RA, PsA, plaque psoriasis, and Crohn's disease

Epinephrine, Self-injected

Epinephrine, Self-Injected

Class Overview: Products

- epinephrine 0.3 mg* (Auvi-Q**, EpiPen, Symjepi)
- epinephrine 0.15 mg* (Auvi-Q**, Epipen Jr.)
- epinephrine 0.1 mg (Auvi-Q**)

*** The generic epinephrine by Impax/Lineage is an authorized generic of Amedra's/Impax's Adrenaclick*

**Manufacturer withdrew from the CMS rebate program in 2017*

Epinephrine, Self-Injected

- Self-injected epinephrines are indicated for the emergency treatment of Type I allergic reactions including anaphylaxis to stinging insects, biting insects, allergen immunotherapy, foods, drugs, diagnostic testing substances, and other allergens
- These products are also indicated for the emergency treatment of idiopathic anaphylaxis and exercise-induced anaphylaxis
- Patients should carry two doses of epinephrine; more than two sequential doses of epinephrine should only be administered under direct medical supervision
- Practice guidelines do not distinguish preference of one self-injectable epinephrine product over another

Epinephrine, Self-Injected

Product/Guideline Updates:

- The FDA issued a warning letter to a facility which manufacturers EpiPen, identifying significant violations of current good manufacturing practice requirements and instructs Mylan to take corrective action
- FDA is not aware of defective EpiPens currently on the market and recommends that patients continue to use their prescribed epinephrine auto-injector
- The FDA approved a generic version of EpiPen and EpiPen Jr manufactured by Teva. A launch date has not been established

Epinephrine, Self-Injected

Product/Guideline Updates:

- Symjepi is now approved in a new 0.15 mg strength for emergency treatment of allergic reactions, including anaphylaxis
- It is intended for patients weighing 33-66 pounds

Glucocorticoids, Inhaled

Glucocorticoids, Inhaled

Class Overview: Single Agent Glucocorticoid Products

- beclomethasone HFA - (QVAR, QVAR RediHaler)
- budesonide powder - (Pulmicort FlexHaler)
- budesonide solution - (Pulmicort Respules)
- ciclesonide aerosol - (Alvesco)
- flunisolide HFA - (Aerospan)
- fluticasone furoate powder – (Arnuity Ellipta)
- fluticasone propionate aerosol – (Flovent HFA)
- fluticasone propionate powder – (ArmonAir Respiclick, Flovent Diskus)
- mometasone furoate aerosol – (Asmanex HFA)
- mometasone furoate powder – (Asmanex Twisthaler)

Glucocorticoids, Inhaled

Class Overview: Glucocorticoid/Long-Acting Beta$_2$ (LABA) Combination Products

- budesonide/formoterol aerosol - (Symbicort)
- fluticasone furoate/vilanterol powder - (Breo Ellipta)
- fluticasone propionate/salmeterol aerosol - (Advair HFA)
- fluticasone propionate/salmeterol powder - (Advair Diskus, AirDuo RespiClick, Wixela inhub)
- mometasone/formoterol aerosol - (Dulera)

Class Overview: Glucocorticoid/Long-Acting Anticholinergic/Long-Acting Beta$_2$ (LABA) Combination Products

- fluticasone furoate/umeclidinium/vilanterol powder - (Trelegy Ellipta)

Glucocorticoids, Inhaled

- Prevalence and incidence of asthma in the U.S. continues to rise, affecting approximately 8.4% of the population
- Clinical studies have demonstrated the efficacy of inhaled corticosteroids (ICS) in improving lung function, reducing symptoms, reducing frequency and severity of exacerbations, plus improving the quality of life of patients with asthma
- The 2007 National Heart, Lung, and Blood Institute, (NHLBI), and the 2018 Global Initiative for Asthma (GINA) guidelines denote inhaled glucocorticoids as currently the most effective anti-inflammatory medications for the treatment of persistent asthma
- The 2018 GINA guidelines offer a control-based management plan which adjusts treatment through a continuous cycle of assessment and review of the patient's response to therapy as it relates to symptom control, future risk of exacerbations, and side effects

Glucocorticoids, Inhaled

- The products listed in the class overview are not indicated for the relief of acute bronchospasm. Patients with asthma should be prescribed a rescue/reliever agent for instances of bronchospasm
- One of the newer agents in this class, fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta) is not approved for use in asthma
- For asthma therapy, the combination products should only be prescribed for patients not adequately controlled on a single-agent asthma control medication, such as an ICS, or for patients whose severity of asthma symptoms warrants initiation of treatment with both an ICS and a LABA
- At the initial diagnosis and periodically (and during exacerbations); patient's FEV_1 should be evaluated for treatment progress/success

Glucocorticoids, Inhaled

- In asthma therapy, corticosteroids suppress cytokine generation, recruitment of airway eosinophils, and release of inflammatory mediators, reducing airway hyper-responsiveness
- LABAs lead to bronchial relaxation and a decrease in the release of mediators of immediate hypersensitivity from mast cells
- LAMAs antagonizes the action of released acetylcholine causing bronchodilation
- Delivery system selection as well as the patients' ability to properly use the device are important factors in the clinical success of ICS therapy
- Metered dose inhalers (MDIs) are pressurized spray inhalers, available in suspension and solution

Glucocorticoids, Inhaled

- MDIs deliver approximately 15% to 35% of the administered dose to the lungs
- Spacer chambers may be used with most MDIs to make them easier to use and help deliver a greater drug amount to the airway
- Products in this review with MDI devices include Advair HFA, Aerospan, Alvesco, Asmanex HFA, Dulera, Flovent HFA, QVAR, QVAR Redihaler, and Symbicort. QVAR Redihaler differs from conventional MDIs as it is breath activated, and should not be used with a spacer or volume holding chamber
- Dry-powder inhalers (DPIs) are breath-actuated devices that release the drug in the form of a dry powder upon inhalation

Glucocorticoids, Inhaled

- While DPIs minimize some of the difficulties in coordinating MDI usage, they have a tendency to result in more dosage variation at low inspiratory flow rates (< 20 L/min)
- Products in this review with DPI devices include Advair Diskus, AirDuo RespiClick, ArmonAir RespiClick, Arnuity Ellipta, Asmanex Twisthaler, Breo Ellipta, Flovent Diskus, Pulmicort Flexhaler, and Trelegy Ellipta
- Products in this review that are nebulized include budesonide and Pulmicort respules
- Several of the products listed also carry indications in the treatment of COPD

Glucocorticoids, Inhaled

Single Agents	Indication	Age Indication
Aerospan	asthma maintenance therapy	patients 6 years and older
Alvesco	asthma maintenance therapy	patients 12 years and older
ArmonAir RespiClick	asthma maintenance therapy	patients 12 years and older
Arnuity Ellipta	asthma maintenance therapy	patients 5 years and older
Asmanex HFA	asthma maintenance therapy	patients 12 years and older
Asmanex Twisthaler	asthma maintenance therapy	patients 4 years and older
Flovent Diskus	asthma maintenance therapy	patients 4 years and older
Flovent HFA	asthma maintenance therapy	patients 4 years and older

Glucocorticoids, Inhaled

Single Agents	Indication	Age Indication
Pulmicort Flexhaler	asthma maintenance therapy	patients 6 years and older
Pulmicort Respules	asthma maintenance therapy	patients 12 months to 8 years
QVAR	asthma maintenance therapy	patients 5 years and older
QVAR Redihaler	asthma maintenance therapy	patients 4 years and older

Glucocorticoids, Inhaled

Combination Agents	Indication	Age Indication
AirDuo RespiClick	asthma maintenance therapy	patients 12 years and older
Advair Diskus	asthma maintenance therapy	patients 4 years and older
Advair HFA	asthma maintenance therapy	patients 12 years and older
Breo Ellipta	asthma maintenance therapy	patients 18 years and older
Dulera	asthma maintenance therapy	patients 12 years and older
Symbicort	asthma maintenance therapy	patients 6 years and older

Glucocorticoids, Inhaled

- When used in equivalent dosages, efficacy among all ICS is similar
- There are differences among the agents in dosage frequency and the number of inhalations needed for each dose. Most are recommended for twice daily use
- Arnuity Ellipta, Breo Ellipta and Asmanex Twisthaler can be dosed once daily
- Alvesco, QVAR and QVAR Redihaler are either converted during absorption (beclomethasone) or in the lung (ciclesonide)
- FDA cautions on the use of LABA products in asthma, also apply to the combination ICS/LABA products but no longer is a boxed warning
- The FDA recommends against the use of LABA without the use of an ICS, and for the shortest duration possible to maintain asthma control

Glucocorticoids, Inhaled

2018 GINA Guidelines Step Approach	
Adults and Pediatrics 6 Years and Older	
Step 1	As-needed reliever medication • Recommended: SABA • Alternative Controller: consider addition of low dose ICS (controller option)
Step 2	One controller AND an as-needed reliever medication • Preferred controller: low-dose ICS + SABA • Alternative controllers: leukotriene modifier or low dose theophylline* (if over 12 years)
Step 3	One or 2 controllers and an as-needed reliever medication • Preferred for adolescents and adults: low-dose ICS AND a LABA as maintenance plus as-needed • SABA OR ICS/formoterol maintenance and reliever therapy† • Preferred for children 6 to 11 years of age: medium dose ICS + as-needed SABA • Alternative controllers: medium- or high-dose ICS, OR low-dose ICS + leukotriene modifier, OR low-dose ICS + sustained-release theophylline* • Sublingual immunotherapy (SLIT) may be considered in adults with allergic rhinitis or house dust mite sensitivity and exacerbations despite ICS use

Glucocorticoids, Inhaled

2018 GINA Guidelines Step Approach	
Adults and Pediatrics 6 Years and Older	
Step 4	Two or more controllers AND an as-needed reliever medication • Preferred for adolescents and adults: medium/high-dose ICS + LABA plus as-needed SABA OR ICS/ formoterol maintenance and reliever therapy • Preferred for children 6 to 11 years of age: referral to expert for assessment and advice • Alternative controllers: For adults and adolescents: medium-or high dose ICS + leukotriene modifier, OR medium-or high-dose ICS + sustained release theophylline*, OR adding tiotropium • Sublingual immunotherapy (SLIT) may be considered in adults with allergic rhinitis or house dust mite sensitivity and exacerbations despite ICS use
Step 5	Higher level of care and/or add-on treatment • In addition to Step 4 treatment, refer for add-on treatment: Tiotropium, monoclonal antibody treatment (omalizumab [anti-IgE therapy], mepolizumab or reslizumab [anti-IL-5 therapy]), low dose oral corticosteroids, or sputum guided therapy

Glucocorticoids, Inhaled

Product/Guideline Updates:

- Trelegy Ellipta is now approved for the maintenance treatment of airflow obstruction in patients with COPD and to reduce exacerbations of COPD in patients with a history of exacerbations
- The new indication no longer specifies current use of fluticasone furoate/vilanterol (Breo Ellipta) in patients who require additional bronchodilation or the current use of umeclidinium (Incruse Ellipta) and Breo Ellipta
- Meda/Mylan announced that they plan to discontinue sales of Aerospan as of January 26, 2018

Glucocorticoids, Inhaled

Product/Guideline Updates:

- Arnuity Ellipta (fluticasone furoate) is now approved for the maintenance treatment of asthma in patients 5 years of age and older; it was previously approved for patients 12 years of age and older
- A 50 mcg strength was also approved and the recommended dose for patients 5 to 11 years of age is 50 mcg
- Fluticasone/Salmeterol (Advair) (AG) and Wixela Inhub are new generics for Advair Diskus; additional labelers are expected in 2020

Growth Hormone

Growth Hormone

Class Overview: Products

- Genotropin cartridge & syringe (somatropin)
- Humatrope cartridge & vial (somatropin)
- Norditropin pens (somatropin)
- Nutropin AQ NuSpin cartridge (somatropin)
- Omnitrope cartridge & vial (somatropin)
- Saizen cartridge & vials (somatropin)
- Serostim vials (somatropin)
- Zomacton vials (somatropin)
- Zorbtive vials (somatropin)

Growth Hormone

- The primary indication for these products is growth hormone deficiency (GHD): Genotropin; Humatrope; Norditropin; Nutropin AQ; Omnitrope; Saizen; Zomacton
- Several products carry an indication for Turner Syndrome: Genotropin; Humatrope; Norditropin; Nutropin AQ; Omnitrope; Zomacton
- Six products are indicated for Idiopathic Short Stature: Genotropin; Humatrope; Nutropin AQ; Omnitrope; Norditropin; Zomacton
- The following products are indicated for Small for Gestational Age: Genotropin; Humatrope; Norditropin; Omnitrope; Zomacton

Growth Hormone

- Genotropin, Omnitrope, and Norditropin are indicated for Prader-Willi Syndrome
- Humatrope is also indicated for Short Stature Homeobox Gene
- Serostim is only indicated for HIV wasting or cachexia to increase lean body mass and weight, and improve physical endurance
- Zorbtive is indicated for Short Bowel Syndrome only

Growth Hormone

- Growth hormone replacement products are, by definition, similar in their clinical effects
- No head-to-head data are available
- No pharmacologic difference among the agents exists in terms of safety and efficacy
- The 2009 American Association of Clinical Endocrinologists Clinical Practice Guidelines indicated no evidence to support any specific product over another

Growth Hormone

Product/Guideline Updates:

- In February 2018, Zomacton (somatropin) received a new indication for replacement of endogenous growth hormone (GH) in adults with GH deficiency
- In July 2018, Zomacton (somatropin) received additional new indications to treat pediatric patients with:
  - Growth failure due to idiopathic short stature (ISS)
  - Short stature homeobox-containing gene (SHOX)
  - Turner syndrome (TS)
  - Small for gestational age (SGA) with no catch-up growth by 2 to 4 years of age

Growth Hormone

Product/Guideline Updates:

- Norditropin Flexpro and Nordiflex (somatropin) received new pediatric indications for idiopathic short stature and growth failure due to Prader-Willi syndrome

Hepatitis C Agents
Direct Acting

Hepatitis C Agents (*Direct Acting)*

Class Overview: Products – Direct Acting Agents

- ***Oral Combination Products***
  - elbasvir/grazoprevir – (Zepatier)
  - glecaprevir/pirbrentasvir – (Mavyret)
  - ledipasvir/sofosbuvir – (Harvoni)
  - ombitasvir/paritaprevir/ritonavir/dasabuvir – (Viekira Pak & Viekira XR)*
  - ombitasvir/paritaprevir/ritonavir – (Technivie)*
  - sofosbuvir/velpatasvir – (Epclusa)
  - sofosbuvir/velpatasvir/voxilaprevir – (Vosevi)

**Have been discontinued by the manufacturer*

Hepatitis C Agents (*Direct Acting)*

Class Overview: Products – Direct Acting Agents

- ***Oral NS5A Inhibitors***
  - daclatasvir – (Daklinza)

- ***Oral NS5B Polymerase Inhibitors***
  - sofosbuvir – (Sovaldi)

Hepatitis C Agents (*Direct Acting*)

- Approximately 2.7 million people in the US are chronically infected
- The American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) Recommendations for Testing, Managing, and Treating Hepatitis C recommend the use of different antiviral therapies based on the genotype identified and co-morbidities
- The guidelines also provide treatment recommendations for patients who have failed previous therapy (partial or null responders), patients co-infected with HIV, patients with renal impairment, patients with hepatic impairment, and patients who develop recurrent HCV post liver transplant

Hepatitis C Agents (*Direct Acting*)

- All of these clinical parameters help determine appropriate agent selection, likelihood of response, and treatment duration
- The guidelines define recommended regimens (favored for most patients) and alternative regimens (optimal in a particular subset of patients)

Hepatitis C Agents (*Direct Acting*)

Product/Guideline Updates:

- AASLD/IDSA updated the HCV guidelines; key revisions include:
  - The additions of the fixed-dose pangenotypic DAAs Vosevi and Mavyret
  - The role of testing for resistance to some HCV medications that may exist in patients prior to starting therapy
  - Significant changes to the following sections have been made:
    - Treatment of HCV Infection
    - Retreatment of Persons in Whom Prior Treatment Has Failed
    - Unique Populations sections (HIV-co-infection, kidney disease, severe liver disease, and post liver transplant)

Hepatitis C Agents (*Direct Acting*)

Product/Guideline Updates:

- New sections have been added:
  - HCV Resistance Primer
  - Kidney Transplant Patients
  - HCV in Pregnancy
  - HCV in Children

- Janssen announced the discontinuation of Olysio (simeprevir) due to a significant decline in utilization and the availability of more effective therapies; product supply became no longer available as of May 2018

Hepatitis C Agents (*Direct Acting)*

Product/Guideline Updates:

- Abbvie has announced that it is voluntarily discontinuing sales of Viekira XR and Technivie in the US due to changes in HCV treatment practices; effective 1/1/2019 they became no longer be available in the U.S.
- Bristol Myers Squibb has made a business decision to discontinue Daklinza
- The 90 mg tablets were discontinued in December 2018; the 30 mg and 60 mg tablets will no longer be available in June 2019

Hepatitis C Agents (*Direct Acting*)

Product/Guideline Updates:

- Gilead has launched authorized generic versions of Epclusa and Harvoni in the US through a newly created subsidiary, Asegua Therapeutics
- Mayvret is now approved to treat pediatric patients 12 years of age and older or weighing at least 45 kg who have chronic HCV genotype 1,2,3,4,5 or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A)
- The indication for the treatment of genotype 1 infection in patients who have previously been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both, has also been expanded to include pediatric patients 12 years of age and older or weighing at least 45 kg
- Dosing for adult and pediatric patients is 3 tablets once daily with food

Hypoglycemics, Incretin Mimetics/Enhancers

Hypoglycemics, Incretin Mimetics/Enhancers

Class Overview: Amylin Analogues

- pramlintide - (Symlin)

Class Overview: Dipeptidyl Peptidase-4 Enzyme Inhibitors (DPP-4)

- alogliptin - (Nesina)
- alogliptin/metformin - (Kazano)
- alogliptin/pioglitazone - (Oseni)
- linagliptin - (Tradjenta)
- linagliptin/empagliflozin - (Glyxambi)
- linagliptin/metformin - (Jentadueto)

Hypoglycemics, Incretin Mimetics/Enhancers

Class Overview: Dipeptidyl Peptidase-4 Enzyme Inhibitors (DPP-4)

- linagliptin/metformin extended-release - (Jentadueto XR)
- saxagliptin - (Onglyza)
- saxagliptin/dapagliflozin - (Qtern)
- saxagliptin/metformin extended-release - (Kombiglyze XR)
- sitagliptin - (Januvia)
- itagliptin/ertugliflozin – (Steglujan)
- sitagliptin/metformin - (Janumet)
- sitagliptin/metformin extended-release - (Janumet XR)

Hypoglycemics, Incretin Mimetics/Enhancers

Class Overview: Glucagon-Like Peptide-1 Receptor Agonists (GLP-1)

- albiglutide - (Tanzeum)*
- dulaglutide - (Trulicity)
- exenatide - (Byetta)
- exenatide extended-release - (Bydureon; Bydureon Bcise)
- liraglutide - (Victoza)
- liraglutide/insulin degludec - (Xultophy)
- lixisenatide - (Adlyxin)
- lixisenatide/insulin glargine - (Soliqua)
- semaglutide - (Ozempic)

**discontinued*

Hypoglycemics, Incretin Mimetics/Enhancers

- It is estimated that over 30.3 million people in the US have diabetes; type 2 diabetes (T2DM) accounts for about 90% to 95% of all diagnosed cases of diabetes in adults
- Per the latest American Diabetes Association (ADA), American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE), American College of Physicians (ACP), and meta-analyses, metformin is recommended as first line therapy for the treatment of T2DM, along with lifestyle interventions, unless metformin is contraindicated
- Per the 2019 ADA Standards of Medical Care in Diabetes, if metformin fails to produce the target HbA1c after 3 months of therapy, a thiazolidinedione (TZD), sulfonylurea (SU), dipeptidyl peptidase-4 (DPP-4) inhibitor, SGLT2 inhibitor, glucagon-like peptide-1 (GLP-1) receptor agonist, or basal insulin should be added in patients *without* atherosclerotic cardiovascular disease (ASCVD) or CKD

Hypoglycemics, Incretin Mimetics/Enhancers

- In patients *with* ASCVD or CKD, the addition of an agent with known CV or renal benefit (select GLP-1 agonist or select SLGT2 inhibitor) is preferred
- The selection of medications should be patient-centric and prescribers should consider potential issues such as HbA1c target, impact on weight and hypoglycemia, side effects, the frequency and mode of administration, patient adherence, patient preference, and cost
- TZDs and SUs are generally considered less safe than GLP-1 receptor agonists, SGLT2 inhibitors, DPP-4 inhibitors, or alpha-glucosidase inhibitors

Hypoglycemics, Incretin Mimetics/Enhancers

- Per the 2018 AACE/ACE guidelines, agents for monotherapy are recommended in the following order (highest to lowest recommendation): metformin, GLP-1 receptor agonists, SGLT2 inhibitors, DPP-4 inhibitors, or alpha-glucosidase inhibitor
- AACE/ACE indicates that Victoza and Jardiance may offer renal and CV benefit. They also suggest that Onglyza and Nesina may be associated with possible CV risk; there may be increased risk of bone fractures with Invokana; and increased congestive heart failure (HF) risk with sulfonylureas, glinides, and insulin

Hypoglycemics, Incretin Mimetics/Enhancers

- In 2017, the ACP updated their recommendations for T2DM and advised that metformin can be safely used in patients with mild renal impairment and in select patients with moderate impairment
- The ACP's revised guidelines for T2DM suggest a sulfonylurea, TZD, SGLT-2 inhibitor, or a DPP-4 inhibitor as preferred second-line treatments
- The 2018 World Health Organization (WHO) guidelines for treatment intensification in patients with T2DM recommend addition of a DPP-4 inhibitor, a SGLT2 inhibitor, or a TZD if insulin is unsuitable in patients with T2DM who do not achieve glycemic control with metformin and/or a sulfonylurea

Hypoglycemics, Incretin Mimetics/Enhancers

- Amylin Analogues slow gastric emptying, suppresses glucagon secretion, and centrally modulates appetite. They may also be used for type 1 diabetes
- DPP-4 Enzyme Inhibitors increase insulin secretion and reduce glucagon secretion by preventing inactivation of GLP-1
- GLP-1 Receptor Agonists enhance glucose-dependent insulin secretion, suppress elevated glucagon secretion, and slow gastric emptying

Hypoglycemics, Incretin Mimetics/Enhancers

- HbA1c improvements for Amylin Analogues average 0.3% to 0.6% with a potential weight reduction of 0.5 kg to 1.5 kg
- HbA1c improvements for DPP-4s average 0.5% to 1%. These agents are weight-neutral and have a low hypoglycemia risk when used as monotherapy or in conjunction with metformin
- For GLP-1 receptor agonists, Tanzeum averages HbA1c reductions of 0.7% to 0.9%; Trulicity averages 0.7% to 1.6%; Byetta/Bydureon and Victoza average reductions in HbA1c of 0.5% to 1.6%; Adlyxin reductions average 0.3% to 0.65%; and Ozempic reductions of 1.4% to 1.5%
- No data are available for use of these agents in pediatric populations

Hypoglycemics, Incretin Mimetics/Enhancers

Product/Guideline Updates:

- The ADA and the European Association for the Study of Diabetes (EASD) updated their 2015 position statement on the management of T2DM
- They include a decision cycle for patient-centered glycemic management of T2DM to prevent complications & optimize QOL Additional focus is placed on lifestyle management and diabetes self-management education and support
- Efforts targeting weight loss, including lifestyle, medication, and surgical interventions, are recommended for those with obesity

Hypoglycemics, Incretin Mimetics/Enhancers

Product/Guideline Updates:

- An SGLT2 inhibitor or GLP-1 receptor agonist with proven CV benefit is recommended for patients with CVD
- An SGLT2 inhibitor with proven benefit is recommended for patients with chronic kidney disease or clinical heart failure and atherosclerotic cardiovascular disease
- If an SGLT2 is contraindicated, a GLP-1 receptor agonist shown to reduce CKD progression should be used
- The first injectable medication recommended is a GLP-1 receptor agonist

Hypoglycemics, Incretin Mimetics/Enhancers

Product/Guideline Updates:

- In August 2018, the FDA issued another safety communication regarding the risk of Fournier's gangrene with the use of the SGLT2 inhibitors
- Xultophy (insulin degludec/liraglutide) is now indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM
- The indication was previously limited to use in patients who were inadequately controlled on basal insulin (< 50 units daily) or Victoza (≤ 1.8 mg daily)
- Dosing sections were updated to provide additional guidance for dosing in treatment-naïve patients and patients currently on basal insulin or GLP-1 receptor agonists

Hypoglycemics, Incretin Mimetics/Enhancers

Product/Guideline Updates:

- Soliqua (insulin glargine/lixisenatide) is now approved as an adjunct to diet and exercise to improve glycemic control in adults with T2DM
- The indication was previously limited to use in patients who were inadequately controlled on basal insulin (< 60 units daily) or Adlyxin
- The recommended starting dose has been updated to include this expanded patient population

Hypoglycemics, Incretin Mimetics/Enhancers

Product/Guideline Updates:

- The American College of Cardiology (ACC) and American Heart Association (AHA) released a new guideline on the primary prevention of cardiovascular disease (CVD)
- According to ACC/AHA, the majority of CVD is related to smoking, poor diet, sedentary lifestyle, elevated body mass index and hypercholesterolemia, hypertension and diabetes (major risk factors)
- ACC/AHA provide recommendations for the type of diet and amount of exercise for patients, particularly for patients with T2DM
- SGLT2 inhibitors and GLP-1 agonists are recommended in patients with T2DM with additional CV risk factors

Hypoglycemics, Incretin Mimetics/Enhancers

Product/Guideline Updates:

- Prophylactic aspirin in middle-aged adults is now considered a Class IIb recommendation due to the lack of net benefit
- ACC/AHA recommends against the use of aspirin among patients > 70 years of age who are at risk for bleeding
- Qtern (dapagliflozin/saxagliptin) is now approved as an adjunct to diet and exercise to improve glycemic control in adults with T2DM
- The indication no longer contains the language limiting use to patients who have had inadequate control on Farxiga with or without Onglyza

Hypoglycemics, Incretin Mimetics/Enhancers

Product/Guideline Updates:

- The ADA published a consensus report on medical nutrition therapy (MNT), which now includes use in prediabetic patients
- Research shows that MNT can lower HbA1c at least as well as antidiabetic agents for T2DM
- Key recommendations include:
  - patients with prediabetes who are overweight or obese should be referred to an intensive lifestyle intervention with personalized goals
  - adults with T1DM or T2DM should be referred for individualized MNT
  - macronutrient distribution should be based on individualized assessment of current eating patterns, preferences, and metabolic goals

Hypoglycemics, Insulin and Related Agents

Hypoglycemics, Insulin and Related Agents

Class Overview: Rapid-Acting Insulins

- human insulin inhalation powder - (Afrezza)
- insulin aspart - (Fiasp; Novolog)
- insulin glulisine - (Apidra)
- insulin lispro - (Admelog; Humalog; Humalog Junior)

Class Overview: Regular Insulins

- human insulin - (Humulin R; Novolin R)

Class Overview: Intermediate Insulins

- human insulin NPH - (Humulin N; Novolin N)

Hypoglycemics, Insulin and Related Agents

Class Overview: Long-Acting Insulins

- insulin degludec - (Tresiba)
- insulin detemir - (Levemir)
- insulin glargine U-100 - (Basaglar; Lantus)
- insulin glargine U-300 - (Toujeo)

Class Overview: Rapid/Intermediate-Acting Combination Insulins

- insulin aspart 70/30 - (Novolog Mix 70/30)
- insulin lispro 50/50; 75/25 - (Humalog Mix 50/50, 75/25)

Class Overview: Regular/Intermediate-Acting Combination Insulins

- human insulin 70/30 - (Humulin 70/30; Novolin 70/30)

Hypoglycemics, Insulin and Related Agents

- Exogenous insulin supplements deficient levels and temporarily restores the body's ability to properly utilize carbohydrates, fats, and proteins
- Multiple insulin products are available and used in the management of both T1DM and T2DM
- Insulin therapy is the treatment of choice for T1DM and T2DM in pregnancy as it does not cross the placenta to a measurable degree
- Regarding T1DM in pediatrics, the ADA advises that most children and adolescents be treated with intensive insulin regimens via multiple daily injections or continuous subcutaneous infusion
- Basal insulin is appropriate as initial therapy if the patients cannot take metformin, or as add-on to initial metformin titration if HbA1c is ≥ 8.5% and the patient is symptomatic, or as add-on if metformin monotherapy is no longer adequate to meet HbA1c goals

Hypoglycemics, Insulin and Related Agents

- In newly diagnosed T2DM patients with markedly symptomatic and/or elevated blood glucose levels (≥ 300 mg/dL) or HbA1c (≥ 10%), basal insulin therapy, typically plus metformin with or without additional noninsulin agents, should be considered from the beginning
- If target HbA1c is not achieved after 3 months, then the addition of a rapid-acting mealtime insulin or a GLP-1 agonist, or change to premixed insulin should be considered
- According to AACE/ACE guidelines, insulin is required in all patients with T1DM
- For T2DM, they state that patients with a HbA1c > 9% with symptoms should begin insulin therapy with or without other agents

Hypoglycemics, Insulin and Related Agents

- AACE/ACE also advises that insulin therapy can be considered for patients with T2DM when HbA1c > 8%, or therapy with 2 or more oral antidiabetic agents or GLP-1 therapy fails to achieve target glycemic control, or in patients with long-standing T2DM who are unlikely to achieve their HbA1c goals
- All of the rapid-acting insulins except Fiasp are approved for use in pediatric patients as well as for use in external insulin pumps
- Insulin therapy is contraindicated during episodes of hypoglycemia
- Basaglar (insulin glargine 100 U/ml), and Admelog (insulin lispro 100 U/ml), were approved as 'follow-on' products to Lantus and Humalog respectively

Hypoglycemics, Insulin and Related Agents

- In 2013, the American Academy of Pediatrics (AAP) issued new guidance for the management of newly diagnosed T2DM in children and adolescents.
- They advise clinicians to initiate insulin therapy in:
  - Children and adolescents with T2DM who are ketotic or in diabetic ketoacidosis
  - Patients whom the distinction between types 1 and 2 diabetes mellitus is unclear
  - Any patient with a blood glucose level at least 250 mg/dL or HbA1c > 9%

Hypoglycemics, Insulin and Related Agents

Product/Guideline Updates:

- The FDA issued a Safety Communication regarding the use of pen needles when injecting medicine
- The FDA has received reports of patients using standard pen needles to administer insulin without removing the inner needle cover, resulting in the insulin not being injected and the risk for hyperglycemia
- This included 1 case that resulted in hospitalization and death
- The FDA advised healthcare providers to instruct patients on the proper use of pen needles for medication delivery and ensure that the patient can demonstrate proper technique
- At time of dispensing, HCPs should remind patients of the type of pen needle and how to use it

Hypoglycemics, Insulin and Related Agents

Product/Guideline Updates:

- The Endocrine Society issued guidelines for the Treatment of Diabetes in Older Adults with particular focus on screening and treating patients aged 65 years and older with potential co-morbities including:
  - Renal impairment, cognitive dysfunction, increased risks for poor medication adherence, hypoglycemia, falls, and loss of independence in daily living activities
- Outpatient diabetes regimens should minimize the risk of hypoglycemia and first line treatment should be metformin
- Oral agents with higher risks of hypoglycemia, such as sulfonylureas and meglitinides, should be avoided and insulin should be used sparingly

Opiate Dependence Treatments

Opiate Dependence Treatments

Class Overview: Buprenorphine Products

- buprenorphine extended-release injection - (Sublocade)
- buprenorphine implant - (Probuphine)
- buprenorphine sublingual - (buprenorphine sublingual tablets)

Class Overview: Buprenorphine/Naloxone Combination Products

- buprenorphine/naloxone buccal film - (Bunavail)
- buprenorphine/naloxone sublingual film - (Suboxone)
- buprenorphine/naloxone sublingual tablets - (buprenorphine/naloxone sublingual tablets; Zubsolv)

Opiate Dependence Treatments

Class Overview: Naloxone Products

- naloxone HCl nasal spray - (Narcan)
- naloxone HCl injection - (naloxone syringe, vial, Evzio)

Class Overview: Naltrexone Products

- naltrexone HCl tablets - (naltrexone HCl tablets)
- naltrexone extended-release injectable suspension - (Vivitrol)

Class Overview: Alpha Agonist Product

- lofexidine (Lucemyra)

Opiate Dependence Treatments

- Prescription opioids continue to become increasingly abused
- The 2016 National Survey on Drug Use and Health (NSDUH) reported there was an estimated 28.6 million Americans aged 12 years and older who were current illicit drug users
- There were approximately 11.8 million people aged 12 or older in the U.S. who misused opioids in the past year
- Approximately 20.1 million people aged 12 or older in 2016 were considered to have a substance use disorder (SUD)
- This includes 15.1 million people with an alcohol use disorder, 7.4 million people with an illicit drug use disorder, and 2.1 million had an opioid use disorder
- Despite the availability of multiple guidelines and resources for the initiation and management of medications for opioid dependency, there is no consensus on the ideal duration of maintenance therapy

Opiate Dependence Treatments

- Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor
- Naloxone is an antagonist at the mu-opioid receptor. Buprenorphine/naloxone was co-formulated in order to prevent patients from abusing buprenorphine in combination with other opioids
- Naltrexone is an opioid antagonist with highest affinity for the mu opioid receptor. Naltrexone blocks the effects of opioids by competitive binding at opioid receptors
- There is a risk for opioid withdrawal symptoms during the transition of patients from full opioid agonists to a partial opioid agonist like buprenorphine

Opiate Dependence Treatments

- In clinical trials, few differences in the adverse event profile were noted among Suboxone sublingual film, Zubsolv sublingual tablets, Bunavail buccal film and buprenorphine sublingual tablets. Comparative data between formulations for induction or maintenance treatment are limited
- There is no maximum duration of maintenance treatment for buprenorphine extended-release injection (Sublocade) or buprenorphine/naloxone sublingual tablet and sublingual and buccal film (Bunavail, Suboxone, Zubsolv, generic)
- For some patients, treatment may continue indefinitely
- Bunavail, Suboxone, Zubsolv and the generic should be prescribed based consideration of visit frequency; provision for multiple refills are not recommended early in treatment or without appropriate follow-up

Opiate Dependence Treatments

- Medication-assisted treatment (MAT) for opioid addiction using a buprenorphine-containing product or naltrexone formulation should be accompanied by counseling and psychosocial support
- Narcan offers a method for emergency treatment for opioid overdose until medical treatment is obtained; however it is not a substitute for emergency medical care
- Alpha2 adrenergic agonists are often used in combination with other agents to target multiple withdrawal symptoms
- In 2016, a meta-analysis was completed to review clinical trials for the effectiveness of alpha2-adrenergic agonists (i.e. clonidine, Lucemyra, guanfacine) in the management of the acute phase of opioid withdrawal; there was insufficient data to provide a comparison of the alpha2 adrenergic agonists for effectiveness

Opiate Dependence Treatments

Sublocade Clinical Trial

- 504 treatment-seeking adults with moderate or severe OUD were randomized to monthly Sublocade 300/300 mg (6×300 mg injections), Sublocade 300/100 mg (2×300 mg injections + 4×100 mg injections) or placebo (6× placebo injections) for 24 weeks and received weekly individual drug counselling
- Sublocade met the primary efficacy endpoint, with both dosage regimens, demonstrating mean percentage abstinence rates significantly higher than those of the placebo group (300/300 mg: 41.3% and 300/100 mg: 42.7% compared with 5.0% for placebo)
- Both Sublocade dosage regimens also met the key secondary endpoint for treatment success, as defined by participants with ≥80% opioid abstinence during weeks 5-24, (300/300 mg: 29.1%; 300/100 mg: 28.4%; placebo: 2.0%)

Opiate Dependence Treatments

Sublocade Clinical Trial

- Mean withdrawal and craving scores in both Sublocade groups remained relatively constant and were consistently lower than those observed in the placebo group
- Retention was nearly twice as high with Sublocade compared to placebo
- No compensatory non-opioid drug use (e.g., amphetamine and methamphetamine, barbiturates, benzodiazepines, cocaine, cannabinoids and phencyclidine) was observed during Sublocade treatment

Opiate Dependence Treatments

Probuphine Clinical Trial

- 177 adults who had opioid dependence as their primary diagnosis and who were clinically stable on a sublingual buprenorphine dosage of no more than 8 mg per day as a Suboxone tablet participated in a randomized, double-blind, double-dummy study
- The patients were randomly assigned to receive four buprenorphine implants and placebo sublingual tablets or sublingual buprenorphine/naloxone tablets and placebo implants
- In the group treated with buprenorphine implants, 63% showed no evidence of illicit opioid use throughout the six-month study period compared with 64% of the patients given sublingual buprenorphine
- 13% receiving buprenorphine implants required supplemental sublingual buprenorphine but had no evidence of opioid use

Opiate Dependence Treatments

New Drug to Class: Lucemyra (lofexidine)

Opiate Dependence Treatments

New Drug to Class: Lucemyra

- A central alpha-2 adrenergic agonist indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults
- Dosage is three 0.18 mg tablets taken orally 4 times daily at 5- to 6-hour intervals
- Treatment may be continued for up to 14 days with dosing guided by symptoms
- Should be discontinued with a gradual dose reduction over 2 to 4 days

Opiate Dependence Treatments

New Drug to Class: Lucemyra

- Warnings include:
  - Risk of Hypotension, Bradycardia, and Syncope
  - Risk of QT Prolongation
  - Increased Risk of CNS Depression with Concomitant use of CNS Depressant Drugs
  - Increased Risk of Opioid Overdose after Opioid Discontinuation
  - Risk of Discontinuation Symptoms
- Most common adverse reactions (incidence ≥ 10% and notably more frequent than placebo) are orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth

Opiate Dependence Treatments

New Drug to Class: Lucemyra

- Was studied in the acute, in-patient setting and will not be used as an outpatient treatment
- Is not a treatment for OUD, but can be used as part of a broader, long-term treatment plan for managing OUD
- The FDA approval of Lucemyra was based on two randomized, double-blind, placebo-controlled trials
- Both studies were carried out in patients meeting DSM-IV criteria for opioid dependence who were physically dependent on short-acting opioids (e.g., heroin, hydrocodone, oxycodone)
- In both trials, patients also had access to a variety of support medications for withdrawal symptoms

Opiate Dependence Treatments

New Drug to Class: Lucemyra

- Study 1 was a 2-part efficacy, safety, and dose-response study
- The first part of the study was an inpatient, randomized, double-blind, placebo-controlled design consisting of 7 days of inpatient treatment (Days 1-7) with Lucemyra 2.16 mg total daily dose (0.54 mg 4 times daily) (n=229), Lucemyra 2.88 mg total daily dose (0.72 mg 4 times daily) (n=222), or matching placebo (n=151)
- The second part of the study was an open-label design where all patients who successfully completed Days 1-7 were eligible to receive open-label treatment with variable-dose Lucemyra treatment (as determined by the investigator, but not to exceed 2.88 mg total daily dose) for up to an additional 7 days (Days 8-14) in either an inpatient or outpatient setting as determined by the investigator and the patient

Opiate Dependence Treatments

New Drug to Class: Lucemyra

- No patient received Lucemyra for more than 14 days
- The two endpoints to support efficacy were the mean Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop) total score on Days 1 – 7 of treatment and the proportion of patients that completed 7 days of treatment
- Of the randomized and treated patients, 28% of placebo patients, 41% of Lucemyra 2.16 mg, and 40% of Lucemyra 2.88 mg patients completed 7 days of treatment
- The mean SOWS-Gossop scores for Days 1–7 were 8.8, 6.5, and 6.1 for placebo, Lucemyra 2.16 mg and Lucemyra 2.88 mg, respectively

Opiate Dependence Treatments

New Drug to Class: Lucemyra

- Study 2 was an inpatient, randomized, multicenter, double-blind, placebo-controlled trial
- 264 patients were treated with Lucemyra tablets (2.88 mg/day [0.72 mg four times daily]) or matching placebo for 5 days (Days 1-5)
- All patients then received placebo on Days 6 and 7 and were discharged on Day 8
- The two endpoints to support efficacy were the mean SOWS-Gossop total score on Days 1 – 5 of treatment and the proportion of patients that completed 5 days of treatment

Opiate Dependence Treatments

New Drug to Class: Lucemyra

- The SOWS-Gossop was administered at baseline and once daily 3.5 hours after the first morning dose on Days 1 – 5
- Of the randomized and treated patients, 33% of placebo patients and 49% of Lucemyra patients completed 5 days of treatment
- The mean SOWS-Gossop scores for Days 1 – 5 were 8.9 and 7.0 for placebo and Lucemyra 2.88 mg, respectively

Opiate Dependence Treatments

Product/Guideline Updates

- The U.S. Surgeon General is recommending that more individuals, including family, friends and those who are personally at risk for an opioid overdose keep naloxone on hand, as part of the ongoing effort to respond to the sharp increase among drug overdose deaths
- In December 2018, the Department of Health and Human Services (DHHS) also released a statement recommending clinicians to co-prescribe naloxone to patients prescribed an opioid who are at risk of opioid overdose

Opiate Dependence Treatments

Product/Guideline Updates

- This includes patients:
  - At high risk of experiencing or responding to an opioid overdose
  - Receiving ≥ 50 morphine milligram equivalents (MME) per day
  - With respiratory comorbidities (e.g. sleep apnea, COPD)
  - Take other medications which enhance opioid complications (e.g., benzodiazepines)
  - With a non-opioid substance use disorder (e.g., alcohol)
  - Who have decreased opioid tolerance (e.g., after release from incarceration or other controlled setting)

Opiate Dependence Treatments

Product/Guideline Updates

- Naloxone should also be prescribed to individuals at high risk of responding to an opioid overdose, such as a family member or friend of a person with an opioid use disorder
- The generic for Suboxone film is now available.
- The generic for Narcan 4mg/spray nasal spray was approved by the FDA

Pancreatic Enzymes

Pancreatic Enzymes

Class Overview: Products

- Creon
- Pancreaze
- Pertzye
- Viokace
- Zenpep

Pancreatic Enzymes

Class Overview: Product Indications

- Pancreaze, Pertzye, and Zenpep are indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions in both adults and children
- Creon is indicated for these conditions, as well as exocrine pancreatic insufficiency due to chronic pancreatitis and pancreatectomy
- Other conditions that may result in exocrine pancreatic insufficiency include ductal obstruction from a neoplasm and gastrointestinal bypass surgery

Pancreatic Enzymes

Class Overview: Product Indications

- Viokace is indicated for the treatment of exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy in combination with a proton pump inhibitor in adults only

Pancreatic Enzymes

Product	Manufacturer	Formulation	Amylase (Units)	Lipase (Units)	Protease (Units)	Notes
Creon® 3,000	AbbVie	Capsule (EC, DR)	15,000	3,000	9,500	For infants, capsule contents may be administered directly to the mouth or with a small amount of applesauce Capsule can be opened for patients unable to swallow
Creon 6,000			30,000	6,000	19,000	
Creon 12,000			60,000	12,000	38,000	
Creon 24,000			120,000	24,000	76,000	
Creon 36,000			180,000	36,000	114,000	

Pancreatic Enzymes

Product	Manufacturer	Formulation	Amylase (Units)	Lipase (Units)	Protease (Units)	Notes
Pancreaze®	Janssen	Capsule (DR)	10,850	2,600	6,200	Capsule can be opened for patients unable to swallow For infants, capsule contents may be administered directly to the mouth or with a small amount of acidic food such as applesauce. Contents should be followed by breast milk or formula but may not be administered directly into breast milk or formula.
			24,600	4,200	14,200	
			61,500	10,500	35,500	
			98,400	,16,800	56,800	
			83,900	21,000	54,700	

Pancreatic Enzymes

Product	Manufacturer	Formulation	Amylase (Units)	Lipase (Units)	Protease (Units)	Notes
Pertzye™ 4,000	Digestive Care	Capsule (DR)	15,125	4,000	14,375	Only pancreatic enzyme containing bicarbonate-buffered enteric-coated microspheres Capsule can be opened for patients unable to swallow Pertzye 400 (infants up to 12 months): For infants, capsule contents may be administered directly to the mouth or with a small amount of acidic food with a pH ≤ 4.5, such as applesauce. Contents should be followed by breast milk or formula but may not be administered directly into breast milk or formula.
Pertzye™ 8,000			30,250	8,000	28,750	
Pertzye 16,000			60,500	16,000	57,500	
Pertzye 24,000						

Pancreatic Enzymes

Product	Manufacturer	Formulation	Amylase (Units)	Lipase (Units)	Protease (Units)	Notes
Viokace™ 10,440	Aptalis	Tablet	39,150	10,440	39,150	Tablets should be swallowed whole and not crushed
Viokace 20,880			78,300	20,880	78,300	Should not be used in pediatric patients; may result in tablet degradation in the gastric environment which may result in suboptimal growth

Pancreatic Enzymes

Product	Manufacturer	Formulation	Amylase (Units)	Lipase (Units)	Protease (Units)	Notes
Zenpep 3,000	Aptalis	Capsule (EC,DR)	14,000	3,000	10,000	For infants, capsule contents may be administered directly to the mouth or with a small amount of acidic food with a PH greater than 4.5 such as applesauce Capsule can be opened for patients unable to swallow
Zenpep 5,000			24,000	5,000	17,000	
Zenpep 10,000			42,000	10,000	32,000	
Zenpep 15,000			63,000	15,000	47,000	
Zenpep 20,000			84,000	20,000	63,000	
Zenpep 25,000			105,000	25,000	79,000	
Zenpep 40,000			168,000	40,000	126,000	

Pancreatic Enzymes

Class Summary:

- Pancreatic enzyme supplements differ in enzyme content and bioavailability
- These products have demonstrated favorable risk-benefit profiles in the treatment of exocrine pancreatic insufficiency due to cystic fibrosis and other conditions
- Dosing of these products should be individualized in accordance with the individual products prescribing information and the CFF Consensus Guidelines

Pancreatic Enzymes

Product/Guideline Updates:

- There is no recent information of significance in this class

Progestational Agents *(Makena)*

Progestational Agents (Makena)

Agents in Class

- Makena MDV (hydroxyprogesterone caproate)
- Makena SDV (hydroxyprogesterone caproate)

Progestational Agents (Makena)

- Indicated to reduce the risk of preterm birth, defined as birth of an infant prior to 37 week of gestation, in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth
- Preterm birth affects nearly 1 of every 10 infants born in the U.S. each year
- Preterm-related causes of death accounted for 17% in 2015 of all infant deaths
- Preterm birth is also a leading cause of long-term neurological disabilities in children

Progestational Agents (Makena)

- Not intended for use in women with multiple gestations or other risk factors for preterm birth
- Various hydroxprogesterone caproate formulations are not therapeutically equivalent
- Makena is available as multidose vial: 5 mL (250 mg/mL); preservative free single-dose vial: 1 mL (250 mg/mL); auto-injector (275 mg/1.1 mL)

Progestational Agents (Makena)

Product/Guideline Updates:

- Makena is now available as a single-use auto-injector, which contains a shorter, thinner non-visible needle compared to the intramuscular Makena injection

Stimulants and Related Agents

Stimulants and Related Agents

Class Overview: Product Indications

- ADHD (attention deficit hyperactivity disorder), Narcolepsy
- Other: exogenous obesity, binge eating disorder

Stimulants and Related Agents

Drug	Manufacturer	ADHD			Narcolepsy (Age ≥6 years)	Other Indications
		Age 3–5 years	Age ≥ 6 years	Adults		
Stimulants: Immediate-Release						
amphetamine sulfate (Evekeo™)	generic, Arbor	X	X	--	X	Exogenous obesity age ≥12 years
armodafinil (Nuvigil®)	generic, Cephalon	--	--	--	--	Excessive sleepiness associated with narcolepsy, OSA, and SWD for age ≥ 17 years
dexmethylphenidate IR (Focalin™)	generic, Novartis	--	X	--	--	--
dextroamphetamine IR (Zenzedi™)	generic, Arbor	X	X (≤ 16 years)	--	X	--
dextroamphetamine solution (Procentra™)	Generic, Independence	X	X (≤ 16 years)	--	X	--

Stimulants and Related Agents

Drug	Manufacturer	ADHD			Narcolepsy (Age ≥6 years)	Other Indications
		Age 3–5 years	Age ≥ 6 years	Adults		
Stimulants: Immediate-Release						
methamphetamine (Desoxyn®)	Generic, Recordati	--	X	--	--	Exogenous obesity in adults and adolescents ≥ 12 years of age
methylphenidate IR (Methylin, Ritalin®)	generic, Shionogi	--	X	--	X	--
mixed amphetamine salts IR (Adderall®)	generic., Teva	X	X	--	X	--
modafinil (Provigil®)	generic, Cephalon	--	--	--	--	Excessive sleepiness associated with narcolepsy, OSA, and SWD for age ≥ 17 years

Stimulants and Related Agents

Drug	Manufacturer	ADHD			Narcolepsy (Age ≥6 years)	Other Indications
		Age 3–5 years	Age ≥ 6 years	Adults		
Stimulants: Extended-Release						
amphetamine ER (Adzenys ER, XR-ODT™)	Neos	--	X	X	--	--
amphetamine ER (Dyanavel® XR)	Tris	--	X	X	--	--
dexmethylphenidate ER (Focalin XR®)	Generic, Novartis	--	X	X	--	--
dextroamphetamine ER (Dexedrine®)	generic., Amedra	--	X (≤ 16 years)	--	X	--
lisdexamfetamine dimesylate (Vyvanse®)	Shire	--	X	X	--	Moderate to severe binge eating disorder in adults

Stimulants and Related Agents

Drug	Manufacturer	ADHD			Narcolepsy (Age ≥6 years)	Other Indications
		Age 3–5 years	Age ≥ 6 years	Adults		
Stimulants: Extended-Release						
methylphenidate ER OROS (Concerta®)	generic, Janssen	--	X	X	--	--
methylphenidate ER	generic	--	X	--	--	--
methylphenidate ER (Metadate ER®, Ritalin SR®),	generic, Upstate	--	X	X	X	--
methylphenidate ER (Aptensio XR®)	Rhodes	--	X	X	--	--
methylphenidate ER† (Cotempla XR-ODT®)	Neos	--	X	--	--	--
methylphenidate ER (QuilliChew™ ER)	Pfizer	--	X	X	--	--

Stimulants and Related Agents

Drug	Manufacturer	ADHD			Narcolepsy (Age ≥6 years)	Other Indications
		Age 3–5 years	Age ≥ 6 years	Adults		
Stimulants: Extended-Release						
methylphenidate ER (Quillivant XR®)	Pfizer	--	X	X	--	
methylphenidate ER (Ritalin LA®)	generic, Novartis	--	X	--	--	--
methylphenidate transdermal (Daytrana™)	Noven	--	X	--	--	--
mixed amphetamine salts ER (Adderall XR®)	generic, Shire	--	X	X	--	--
mixed amphetamine salts ER (Mydayis®)	Shire	--	--	-- (≥ 13 years)	--	--

Stimulants and Related Agents

Drug	Manufacturer	ADHD			Narcolepsy (Age ≥6 years)	Other Indications
		Age 3–5 years	Age ≥ 6 years	Adults		
Non-Stimulants						
atomoxetine (Strattera®)	generic, Eli Lilly	--	X	X	--	--
clonidine ER (Kapvay™)	generic, Concordia	--	X	--	--	Treatment of ADHD as adjunct to stimulants
guanfacine ER (Intuniv™)	generic, Shire	--	X	--	--	Treatment of ADHD as adjunct to stimulants

Stimulants and Related Agents

Class Summary:

- ADHD has been diagnosed in approximately 15% of children 4 to 17 years of age and about 4% of adults
- Meta-analyses and reviews confirm the short-term efficacy of stimulant medications in reducing the core symptoms of ADHD: *inattention, hyperactivity, and impulsivity*
- Studies have not shown clear advantages of any one stimulant medication over another or between dosage forms of a given agent
- The AAP states that stimulants are equally effective for ADHD
- The AAP recommends that, if a trial with 1 drug compound group is ineffective or poorly tolerated, a trial of a medication from a different drug group should be used

Stimulants and Related Agents

Class Summary:

- The individual agents used for the treatment of ADHD are associated with different contraindications and precautions for use
- This may influence the selection of appropriate therapy in patients with comorbidities (e.g., coexistent tic disorders or Tourette's syndrome)
- The 2011 AAP Clinical Practice Guideline for the School Aged Child with ADHD recommends stimulant medication and/or behavioral therapy for the treatment of ADHD in children
- The guideline states that, in many cases, the stimulants improve the child's ability to follow rules and decrease emotional overactivity, leading to improved relationships and performance

Stimulants and Related Agents

Class Summary:

- Studies have shown that 70% to 75% of patients respond to the first stimulant medication on which they are started; response increases to 90% to 95% when a second stimulant is tried
- Except for atomoxetine (Strattera), clonidine ER (Kapvay), and guanfacine ER (Intuniv), all of the drugs approved for treatment of ADHD by the FDA are stimulants and are classified as controlled substances
- Dextroamphetamine has a greater potential for diversion and misuse than the other drugs used for ADHD
- Vyvanse is the first and only FDA-approved treatment for moderate to severe binge eating disorder in adults

Stimulants and Related Agents

Product/Guideline Updates:

- Evekeo is now available as a generic
- Evekeo is now available as an orally disintegrating tablet that may be substituted (1mg:1mg basis) with the already approved tablet formulation

New Drug Reviews

Non-Supplemental Rebate Classes

Hind Douiki, Pharm.D.

New Products

- Apadaz (benzhydrocodone/acetaminophen)
- Delstrigo (doravirine/lamivudine/tenofovir disoproxil fumarate)
- Epidiolex (cannabidiol)
- Motegrity (prucalopride)
- Pifeltro (doravirine)
- Xofluza (baloxavir marboxil)

Apadaz (benzhydrocodone/acetaminophen)

- Indicated for the short-term (no more than 14 days) management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate
- Benzhydrocodone is a pro-drug of hydrocodone, it is chemically inert on its own and requires gastrointestinal enzymes to exert its therapeutic effect
- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, Apadaz should be reserved for use in patients for whom alternative treatment options (e.g., non-opioid analgesics):
  - Have not been tolerated or are not expected to be tolerated
  - Have not provided adequate analgesia or are not expected to provide adequate analgesia

Apadaz (benzhydrocodone/acetaminophen)

- Treatment is initiated at one (6.12 mg benzhydrocodone/325 acetaminophen) or two tablets every four to six hours as needed for pain; dosage should not exceed 12 tablets in a 24-hour period
- The lowest effective dose is to be used for the shortest duration consistent with individual patient treatment goals
- Dosing should be individualized based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse
- Should not be stopped abruptly in a physically-dependent patient

Apadaz (benzhydrocodone/acetaminophen)

- Contraindications include:
  - Significant respiratory depression
  - Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment
  - Known or suspected gastrointestinal obstruction, including paralytic ileus
  - Hypersensitivity to hydrocodone or acetaminophen
- Boxed warnings:
  - Risks of addiction, abuse, and misuse, which can lead to overdose and death
  - Serious, life-threatening, or fatal respiratory depression

Apadaz (benzhydrocodone/acetaminophen)

- Boxed warnings (continued):
  - Accidental ingestion, especially by children
  - Neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, with prolonged use of Apadaz during pregnancy
  - Fatal overdose risk with concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers)
  - Risk of acute liver failure with acetaminophen use
  - Risk of profound sedation, respiratory depression, coma, and death when opioids are used concurrently with benzodiazepines or other CNS depressants, including alcohol

Apadaz (benzhydrocodone/acetaminophen)

- Other warnings:
  - Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients
  - Adrenal Insufficiency
  - Severe Hypotension
  - Serious Skin Reactions
  - Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

Apadaz (benzhydrocodone/acetaminophen)

- Most common adverse reactions (>5%) are nausea, somnolence, vomiting, constipation, pruritus, dizziness, and headache
- No comparative data is available
- Only Pharmacokinetic and Human Abuse Potential Clinical Trials have been conducted

Delstrigo (doravirine/lamivudine/tenofovir disoproxil fumarate)

- A three-drug combination of doravirine (a nonnucleoside reverse transcriptase inhibitor [NNRTI]), lamivudine, and tenofovir disoproxil fumarate (both nucleoside analogue reverse transcriptase inhibitors)
- Indicated as a complete regimen for the treatment of HIV-1 infection in adult patients with no antiretroviral treatment history
- Dosage is 1 tablet (100 mg of doravirine, 300 mg of lamivudine, and 300 mg of tenofovir disoproxil fumarate) once daily
- Safety and efficacy of Delstrigo have not been established in pediatric patients less than 18 years of age

Delstrigo (doravirine/lamivudine/tenofovir disoproxil fumarate)

- At initiation and during treatment, on a clinically appropriate schedule, the following should be assessed:
  - Serum creatinine
  - Estimated creatinine clearance
  - Urine glucose and urine protein
  - Serum phosphorus in patients with chronic kidney disease
- Not recommended in patients with estimated creatinine clearance below 50 mL per minute
- Contraindicated when co-administered with drugs that are strong cytochrome P450 CYP3A enzyme inducers
- Boxed warning is severe acute exacerbations of hepatitis B

Delstrigo (doravirine/lamivudine/tenofovir disoproxil fumarate)

- Additional warnings:
  - New onset or worsening renal impairment
  - Bone loss and mineralization defects
  - Immune Reconstitution Syndrome
- Most common adverse reactions (incidence greater than or equal to 5%, all grades) are dizziness, nausea, and abnormal dreams
- The FDA approval was based on 48-week data from a randomized, multicenter, double-blind, active controlled Phase III trial, DRIVE-AHEAD
- Subjects were HIV-1 infected with no antiretroviral treatment history
- 728 participants were randomized and received at least 1 dose of either Delstrigo or efavirenz (EFV) 600 mg/ emtricitabine (FTC) 200 mg/ tenofovir disoproxil fumarate (TDF) 300 mg once daily

Delstrigo (doravirine/lamivudine/tenofovir disoproxil fumarate)

- Delstrigo demonstrated sustained viral suppression through 48 weeks, meeting its primary endpoint of non-inferior efficacy compared to EFV/FTC/TDF
- 84% of subjects in the Delstrigo group achieved viral suppression of HIV-1 RNA <50 copies/mL versus 81% in the EFV/FTC/TDF group
- Of the 21% of study participants with a high viral load at baseline (HIV-1 RNA >100,000 copies/mL), 77% in the Delstrigo group and 72% in the EFV/FTC/TDF group achieved HIV-1 RNA <50 copies/mL at Week 48
- Mean CD4+ T-cell counts in the Delstrigo and EFV/FTC/TDF groups increased from baseline by 198 and 188 cells/mm3, respectively

Epidiolex (cannabidiol)

- The first purified marijuana derived drug
- Indicated for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients 2 years of age and older
- It is approved as a 100 mg/mL oral solution and dosed 2.5 to 10 mg/kg twice daily
- Warning include:
  - Hepatocellular Injury
  - Somnolence and Sedation
  - Suicidal Behavior and Ideation
  - Hypersensitivity Reactions
  - Withdrawal syndrome

Epidiolex (cannabidiol)

- The most common adverse reactions for Epidiolex (10% or more and greater than placebo) include somnolence; decreased appetite; diarrhea; transaminase elevations; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder, poor quality sleep; and infections
- A schedule V controlled substance
- No comparative data are available
- The effectiveness of Epidiolex for the treatment of seizures associated with LGS was established in two randomized, double-blind, placebo-controlled trials in patients aged 2 to 55 years
- Study 1 (N=171) compared a dose of Epidiolex 20 mg/kg/day with placebo, while Study 2 (N=225) compared a 10 mg/kg/day dose and a 20 mg/kg/day dose of Epidiolex with placebo

Epidiolex (cannabidiol)

- In both studies, patients had a diagnosis of LGS and were inadequately controlled on at least one Anti Epileptic Treatment (AED)
- In Study 1 the median percentage reduction in monthly drop seizure frequency from baseline was 43.9% (IQR -69·6 to -1·9) in the Epidiolex group and 21.8% (IQR -45·7 to 1·7) in the placebo group
- The mean Subject/Caregiver Global Impression of Change (S/CGIC) score at last visit was 3 in the Epidiolex group ("slightly improved") compared with 3.7 (closely associated with "no change") in the placebo group
- In study 2 a median reduction in drop-seizure frequency during treatment was 37.2% for Epidiolex 10 mg/kg/day, 41.9% for Epidiolex 20 mg/kg/day, and 17.2% for placebo

Epidiolex (cannabidiol)

- The mean S/CGIC score at last visit was 3 for the 10 mg/kg/day dosage and 3.2 for the 20 mg/kg/day dose indicating "slightly improved" compared with 3.6 in the placebo group indicating "no change"
- The effectiveness of Epidiolex for the treatment of seizures associated with DS was demonstrated in a randomized, double-blind, placebo-controlled trial
- 120 patients aged 2 to 18 years were randomly assigned to receive Epidiolex 20 mg/kg/day, or placebo
- Patients had a diagnosis of treatment-resistant DS and were inadequately controlled with at least one concomitant AED
- This study resulted in a median change of -38.9% in the Epidiolex group versus -13.3% in the placebo group

Motegrity (prucalopride)

- A serotonin-4 (5-HT4) receptor agonist indicated for the treatment of chronic idiopathic constipation (CIC) in adults
- It is approved as a 1 mg and 2 mg tablet and the recommended dosage is 2 mg once daily for adults
- In patients with severe renal impairment (creatinine clearance (CrCL) less than 30 mL/min), the dose is 1 mg once daily
- Contraindicated in patients with intestinal perforation or obstruction due to:
  - Structural or functional disorder of the gut wall
  - Obstructive ileus
  - Severe inflammatory conditions of the intestinal tract such as Crohn's disease, ulcerative colitis, and toxic gacolon/megarectum

Motegrity (prucalopride)

- Warning: Suicidal Ideation and Behavior
- Most common adverse reactions (≥2%) are headache, abdominal pain, nausea, diarrhea, abdominal distension, dizziness, vomiting, flatulence, and fatigue
- No comparative data is available
- The FDA approval of Motegrity was based on six double-blind, placebo-controlled, randomized, multicenter clinical studies lasting 12 weeks (studies 1-5) or 24 weeks (study 6) conducted in 2,484 adults

Motegrity (prucalopride)

- During studies, significantly more patients taking Motegrity achieved the primary endpoint (an average of ≥3 complete spontaneous bowel movements [CSBMs] per week over 12 weeks, considered normalization of BM frequency) than those in the placebo group (19-38% Motegrity ≤2 mg vs. 10-20% placebo) across five of six trials
- Rapid response was seen with Motegrity as early as week 1, with improvements maintained throughout 12 weeks of treatment

Pifeltro (doravirine)

- A non-nucleoside reverse transcriptase inhibitor (NNRTI), is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adult patients with no prior antiretroviral treatment history
- Approved as a 100-mg tablet and dosed as 1 tablet orally once daily in adult patients
- If taken concurrently with rifabutin, the dose is 1 tablet taken twice daily
- Contraindicated when co-administered with drugs that are strong cytochrome P450 (CYP)3A enzyme inducers
- Warning: Immune Reconstitution Syndrome

Pifeltro (doravirine)

- Most common adverse reactions (incidence greater than or equal to 5%, all grades) are nausea, dizziness, headache, fatigue, diarrhea, abdominal pain, and abnormal dreams
- The FDA approval was based on 48-week data from a randomized, multicenter, double-blind, active controlled Phase III trial, DRIVE-FORWARD
- Subjects were HIV-1 infected with no antiretroviral treatment history
- 766 subjects were randomized and received at least 1 dose of either Pifeltro (doravirine [DOR]) once daily or darunavir 800 mg + ritonavir 100 mg (DRV+r) once daily each in combination with emtricitabine/tenofovir DF (FTC/TDF) or abacavir/lamivudine (ABC/3TC)

Pifeltro (doravirine)

- After 96 weeks of treatment, the proportion of subjects achieving HIV-1 RNA less than 50 copies/mL was 73.1% in the DOR group and 66% in the DRV+r group
- Results for subjects with high baseline viral load (HIV-1 RNA greater than 100,000 copies/mL) were 65.4% for DOR and 65.2% for DRV+r
- The mean change from baseline in CD4+ T-cell count at 96 weeks was 224 cells/mm3 and 207 cells/mm3 for DOR and DRV+r, respectively

Xofluza (baloxavir marboxil)

- A polymerase acidic (PA) endonuclease inhibitor indicated for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours
- Available information on drug susceptibility patterns for circulating influenza virus strains should be considered when deciding whether to use Xofluza
- Approved as 20 mg and 40 mg tablets administered as a single dose of 40 mg in patients weighing 40 kg to < 80 kg; 80 mg for patients ≥80 kg
- Carries a warning regarding the risk of bacterial infection that may co-exist or present with influenza-like symptoms that would not be susceptible to treatment with this antiviral

Xofluza (baloxavir marboxil)

- Co-administration of Xofluza should be avoided with:
  - Dairy products
  - Calcium-fortified beverages
  - Polyvalent cation-containing laxatives, antacids, or oral supplements (e.g., calcium, iron, magnesium, selenium, or zinc)
- Adverse events reported in at least 1% of adult and adolescent subjects treated with Xofluza included diarrhea (3%), bronchitis (2%), nasopharyngitis (1%), headache (1%) and nausea (1%)
- Safety and efficacy in patients less than 12 years of age or weighing less than 40 kg have not been established

Xofluza (baloxavir marboxil)

- The FDA approval of Xofluza was based on two randomized controlled clinical trials
- 1,832 patients were assigned to receive either Xofluza, a placebo, or oseltamivir within 48 hours of experiencing flu symptoms
- The primary endpoint of both trials was time to alleviation of symptoms
- This was defined as the time when all seven symptoms (cough, sore throat, nasal congestion, headache, feverishness, myalgia, and fatigue) had been assessed by the subject as none or mild for a duration of at least 21.5 hours

Xofluza (baloxavir marboxil)

- In both trials, Xofluza treatment at the recommended dose resulted in a statistically significant shorter time to alleviation of symptoms compared with placebo in the primary efficacy population
- In Trial 2, there was no difference in the time to alleviation of symptoms between subjects who received Xofluza (54 hours) and those who received oseltamivir (54 hours)
- For adolescent subjects (12 to 17 years of age) in Trial 2, the median time to alleviation of symptoms for subjects who received Xofluza was 54 hours compared to 93 hours in the placebo arm

Executive Session

Public Therapeutic Class Votes

Biosimilar Update

Suzi Berman, RPh

BIOSIMILAR UPDATE

- There is no Biosimilar update for this P&T meeting.

- *As a reminder – per AHCCCS Policy 310-V: AHCCCS Contractors shall not transition to a biosimilar drug until AHCCCS has determined that the biosimilar drug is overall more cost-effective to the state than the continued use of the brand name drug.*

P&T Meeting Dates

- **2019 Meeting Dates:**
  - October 16, 2019

- **2020 Meeting Dates:**
  - January 22, 2020
  - May 19 & 20, 2020