Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Washington Pharmacy Advisory Committee Meeting

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Agenda Topics

- Overview of Disease State
- Indications
- Dosage & Formulations
- Guideline Updates

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Analgesics, Narcotics – Long-Acting

ANALGESICS : OPIOID AGONISTS - LONG ACTING

Disease State Description - Opioid, Long-Acting

- While definitions vary, chronic pain is generally defined as pain lasting > 3 months or past the time required for normal tissue healing
  - It has various etiologies, including injury, inflammation, and underlying medical conditions
- Approximately 11.2% of adults report daily pain, which is greatly misunderstood
  - Historically, data have suggested that pain may be undertreated, but newer estimates imply that opioid treatment for pain may be overutilized
  - An estimated 20% of patients presenting to outpatient providers with noncancer pain or pain-related diagnoses, whether acute or chronic, receive an opioid prescription
- Unfortunately, approximately 49,860 people have died from overdoses related to opioid pain medications in the United States (U.S.) in 2019
  - Likewise, drug related deaths have tripled from 1999 to 2017
  - Opioid related overdose deaths in 2017 was higher among males (20.4%) in comparison to females (9.4%)
  - Despite this, persistent pain that is uncontrolled may have clinical, psychological, and social consequences; thus, it is critical to weigh the risks and benefits of opioid use and reevaluate patients routinely for appropriate dose, duration, and treatment choice, including both pharmacologic and non-pharmacologic modalities

Analgesics - Opioid, Long-Acting

- **Recall**
  - **July 2022**
    - **Bryant Ranch Prepack has voluntarily recalled 1 lot of morphine sulfate 30 mg ER tablets and 1 lot of morphine sulfate 60 mg ER tablets to the consumer level**
    - **This recall is due to products carrying incorrect labeling (30 mg product labeled as 60 mg product and vice versa)**

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Antiemetic/Antivertigo Agents

ANTIEMETICS / ANTIVERTIGO AGENTS : 5-HT3 RECEPTOR ANTAGONISTS
ANTIEMETICS / ANTIVERTIGO AGENTS : SUBSTANCE P/NEUROKININ 1 (NK1) RECEPTOR ANTAGONISTS
ANTIEMETICS / ANTIVERTIGO AGENTS : SUBSTANCE P/NEUROKININ 1 RECEPTOR ANTAGONIST COMBINATIONS

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Angiotensin Modulators

ANTIHYPERTENSIVES : DIRECT RENIN INHIBITOR COMBINATIONS
ANTIHYPERTENSIVES : DIRECT RENIN INHIBITORS
ANTIHYPERTENSIVES : NEPRILYSIN INHIB (ARNI)-ANGIOTENSIN II RECEPT ANTAG COMBINATIONS

Disease State Description - Angiotensin Modulators

- **Hypertension**
  - Approximately 108 million (45%) adults in the United States have high blood pressure along with 1 of 3 American adults having prehypertension
  - The highest prevalence is among African American men and women
    - Approximately 56% of African American men and women have high blood pressure compared to about 48% of white men and women and 46% of non-Hispanic Asians and 39% of Hispanics
  - It is estimated that hypertension is controlled in only 24% of patients with the condition

Center for Disease Control, 2020

Guidelines - Angiotensin Modulators

- American College of Cardiology (ACC), American Heart Association (AHA), and Heart Failure Society of America (HFSA) guidelines on the management of heart failure (HF), 2022
  - Patients at risk for HF (stage A) who have hypertension should obtain optimal control of BP using guideline-directed medical therapy (GDMT) (class 1, level A)
  - Patients with pre-HF (stage B) and with left ventricular ejection fraction (LVEF) ≤ 40% should be placed on an ACE inhibitor to prevent symptoms and to reduce mortality (class 1, level A)
  - If a patient is intolerant to an ACE inhibitor and has a history of recent MI, an ARB should be used instead (class 1, level B-R).
  - **Patients with heart failure with reduced ejection fraction (HFrEF) and New York Heart Association (NYHA) class II to III symptoms are recommended to be placed on the angiotensin receptor/neprilysin inhibitor (ARNI) sacubitril/valsartan (Entresto) to reduce morbidity and mortality (class 1, level A); however, if treatment with an ARNI is not feasible, then an ACE inhibitor may be prescribed, or an ARB can be used if a patient is intolerant to an ACE inhibitor (class 1, level A for both).**

Treatment Guidelines - Angiotensin Modulators

- The Kidney Disease: Improving Global Outcomes (KDIGO), 2021
  - Recommend the use of ARBs or other renin-angiotensin-system inhibitors for patients with CKD, diabetes, hypertension, and moderately to severely increased albuminuria, but they recommend avoiding the combination of an ACE inhibitor, ARB, or direct renin inhibitor in patients with CKD, regardless of diabetes diagnosis

- US Preventative Task Force (USPSTF), 2021
  - USPSTF published a Final Recommendation Statement for screening for hypertension in adults
  - The panel recommend office blood pressure measurement (OBPM)
  - The USPSTF recommends obtaining blood pressure measurements outside of the clinical setting for diagnostic confirmation before starting treatment
  - They concluded with high certainty that screening for hypertension in adults has substantial net benefit

Angiotensin Modulators

- **Recalls**
  - valsartan; losartan; irbesartan- May 2021
    - The FDA has updated the searchable list of recalled angiotensin II receptor blockers (ARBs)
  - Irbesartan- October 2021
    - Lupin issued a voluntary recalling of irbesartan tablets and irbesartan/hctz tablets to the consumer level because selected tested batches of the active pharmaceutical ingredient were above the specification limit for the impurity, N-nitrosoirbesartan
    - All batches of Irbesartan Tablets USP 75 mg, 150 mg and 300 mg and Irbesartan and Hydrochlorothiazide Tablets USP, 150 mg/12.5 mg and 300 mg/12.5 mg in the US are being recalled
    - Lupin discontinued the marketing of these agents in Jan 2021
  - quinapril/HCTZ (Accuretic)- March 2022
    - Pfizer has announced a voluntary recall of certain lots of Accuretic tablets and authorized generics by Greenstone to the patient level
    - The recall is due to a nitrosamine impurity, N-nitroso-quinapril, higher than the acceptable daily intake limit
  - quinapril (Accupril)- April 2022
    - Pfizer is voluntarily recalling 5 lots of Accupril (quinapril HCl) tablets to the patient level due to the presence of N-nitroso-quinapril above the acceptable daily intake level
    - The lots were distributed in the US from December 2019 to April 2022

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Hepatitis C Agents

ANTIVIRALS : HEPATITIS C AGENTS- DIRECT ACTING ANTIVIRALS

Disease State Description – Hepatitis C Agents

- Hepatitis C virus (HCV) infection is the most common chronic blood-borne infection in the United States (US)
  - In approximately 15% to 25% of patients who become infected with hepatitis C, the virus is eliminated during the acute phase of the infection by T cell-mediated antiviral mechanisms; however, in the other 75% to 85% of patients, the HCV persists for decades
  - An estimated 23,000 to 46,000 children in the US have HCV
  - Approximately 2.7 million people in the US are chronically infected, although it is estimated that nearly 75% of these people may be unaware of their infection due to the insidious progression of the disease
  - HCV accounts for 40% of chronic liver disease in the US. In patients with chronic HCV infection followed for 20 years, disease progression to cirrhosis occurs in about 20% to 25%
  - Of those who develop cirrhosis, approximately 30% will develop end-stage liver disease over the next 10 years and 1% to 2% per year will develop hepatocellular carcinoma
  - HCV infection is the most common reason for liver transplantation and results in an estimated 8,000 to 10,000 deaths per year in the US
- The most important risk for HCV infection is injection-drug use, which accounts for at least 60% of acute HCV infections in the US
  - Other modes of transmission include mother-to-infant, receiving a blood or organ donation prior to 1992, occupational exposures, chronic hemodialysis, and contaminated devices shared for non-injection drug use, such as intranasal illicit drug use
  - Sexual transmission also occurs but generally seems to be inefficient except among human immunodeficiency virus (HIV)-infected men who have unprotected sex with men
  - Other risk factors include incarceration and receiving a tattoo in an unregulated setting
    - It is estimated that 29% of incarcerated persons in the North America are anti-HCV positive

Centers for Disease Control and Prevention, 2018

Disease State Description – Hepatitis C Agents

- Hepatitis C viral genotype is an important factor in selecting the optimal treatment planning, dictating drug selection, dose, and duration of treatment

- There are 6 HCV genotypes and more than 50 subtypes, and the distribution of HCV genotypes varies across the world
  - Genotype 1 is the most common worldwide and accounts for about 70% to 75% of US infections
    - Among African Americans, the frequency of genotype 1 is even higher at an estimated 90%
    - In the US, genotype 1a and 1b represent about 75% and 25% of genotype 1 cases, respectively
  - Genotypes 2 and 3 account for the majority of the other approximate 25% to 30% HCV infections in the US
  - Genotype 4 predominates in Egypt
  - Genotype 5 is localized to South Africa
  - Genotype 6 to Hong Kong and Southeast Asia

American Association of for the Study of Liver Diseases, 2017

Hepatitis C Agents

- **elbasvir/grazoprevir (Zepatier)**
  - **December 2021: FDA approved expanded indication to include pediatric patients ≥ 12 years old or weighing ≥ 30 kg for the treatment of chronic HCV genotype 1 or 4 infection**
  - **Indications:**
    - **Treatment of chronic HCV genotype 1 or 4 infection in adult and pediatric patients 12 years of age and older or weighing at least 30 kg**
    - Zepatier is indicated for use with ribavirin in certain patient populations
  - **Precautions/Contraindications:**
    - BBW: Risk of Hepatitis B Virus Reactivation- Test all patients for evidence of current or prior HBV infection before initiation of HCV treatment
    - Contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C)
  - **Dosage:**
    - Dosing and treatment length is stratified by treatment history and genotype (Found in PI or TCR)
  - **Formulations:**
    - Tablets: 50 mg elbasvir and 100 mg grazoprevir

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Anticonvulsants

ANTICONVULSANTS : AMPA GLUTAMATE RECEPTOR ANTAGONISTS
ANTICONVULSANTS : BENZODIAZEPINES - RESCUE AGENTS
ANTICONVULSANTS : MISC
ANTICONVULSANTS : SUCCUNIMIDES

Disease State Description- Anticonvulsants

- Epilepsy is one of the most common disorders of the central nervous system (CNS)
  - Defined when a person has 2 or more seizures
  - It affects 2.2 million Americans, with 150,000 new cases diagnosed each year
  - The risk is estimated to be 1% from birth to age 20 years and 3% at age 75 years
- Isolated seizures may also occur during a febrile illness, after head trauma, or as a result of withdrawal from alcohol or sedative/hypnotics
- A seizure is traceable to an unstable cell membrane or cluster of cells. Excessive excitability spreads either locally (partial seizure) or more widely (generalized seizure)
- Partial seizures begin in 1 hemisphere of the brain and, unless they become secondarily generalized, they can cause alterations in motor functioning, sensory symptoms, or automatisms
- If there is no loss of consciousness, they are called simple partial. If there is loss or impairment of consciousness, they are called complex partial
- About 70% of patients with epilepsy can be maintained on 1 drug
  - Noncompliance and evolving refractory epilepsy are common reasons for treatment failure
  - If control is not achieved with 1 drug, an alternative medication should be attempted before others are added to current therapy

Epilepsy Foundation, 2017

Disease State Description- Anticonvulsants

- **Lennox-Gastaut syndrome**
  - One of the most severe forms of childhood epilepsy and is one of the hardest forms to treat
  - Characterized by mental retardation and multiple seizure types
  - Patients have seizures daily, sometimes experiencing several seizures within a day
  - Patients may also experience “drop attacks”, which is defined as a loss of muscle control causing the patient to fall abruptly to the floor
- **Infantile spasm**
  - Primarily consist of a sudden bending forward of the body with stiffening of the arms and legs
  - West Syndrome is characterized by infantile spasms, developmental regression, and a specific pattern on electroencephalography (EEG) testing called hypsarrhythmia (chaotic brain waves)
  - The onset is usually in the first year of life, typically between 4 and 8 months and usually stop by age 5, but may be replaced by other seizure types
- **Dravet syndrome**
  - A rare, catastrophic form of epilepsy that presents in the first year of life and is characterized by frequent, prolonged seizures
  - Patients may experience multiple seizures types during their lifetime
  - Infants with Dravet syndrome often experience multiple comorbidities over their lifetime related to the persistent seizure activity, including behavioral and developmental delay
  - Dravet syndrome is also associated with a 15% to 20% mortality rate due to Sudden Unexpected Death in Epilepsy (SUDEP)
- Goals of treating epilepsy are to reduce the frequency of seizure occurrence along with providing the best possible quality of life for the patient
  - Treatment will depend on the type of seizure
  - Many different classes of drugs are available to treat the different forms of seizures
  - Some patients will require more than 1 drug to control their seizures

National Institute of Neurological Disorders and Stroke, 2018
Dravet Foundation, 2019

Anticonvulsants

- **brivaracetam (Briviact)**
  - **September 2021: FDA approved expanded indication for the treatment of partial onset seizures to include pediatric patients ages 1 month to < 4 years for brivaracetam tablets and oral solution, and expanded the patient population to include pediatric patients ages 1 month to < 16 years for brivaracetam injection for when oral administration is temporarily not feasible**
  - **Indication**
    - **Treatment of partial-onset seizures in patients 1 month of age and older**
  - **Warnings**
    - Pregnancy: Based on animal data, may cause fetal harm
  - **Dosage**
    - Adults (16 Years and Older): The recommended starting dosage for monotherapy or adjunctive therapy is 50 mg twice daily (100 mg per day). Based on individual patient tolerability and therapeutic response, the dosage may be adjusted down to 25 mg twice daily (50 mg per day) or up to 100 mg twice daily (200 mg per day)
    - **Pediatric Patients (1 Month to less than 16 Years): The recommended dosage is based on body weight and is administered orally twice daily**
    - **Injection: for intravenous use only when oral administration is temporarily not feasible; dosing is the same as oral regimen**
  - **Availability**
    - Tablets: 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg
    - Oral solution: 10 mg/mL
    - Injection: 50 mg/5 mL single-dose vial

Anticonvulsants

- **lacosamide (Vimpat)**
  - **October 2021: FDA approved expanded indication for oral and IV monotherapy and adjunctive therapy for the treatment of partial-onset seizures to include patients ≥ 1 month of age to < 4 years of age; previously indicated for partial-onset seizures in patients ≥ 4 years of age**
  - **Indication**
    - Treatment of partial-onset seizures in patients 1 month of age and older
    - **Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in patients 4 years of age and older**
  - **Warnings**
    - Monitor patients for suicidal behavior and ideation
    - Cardiac Rhythm and Conduction Abnormalities: Obtaining ECG before beginning and after titration to steady-state maintenance is recommended in patients with underlying proarrhythmic conditions or on concomitant medications that affect cardiac conduction; closely monitor these patients
  - **Dosage**
    - Adults (17 years and older):
      - Monotherapy for the treatment of partial-onset seizures is 100 mg twice daily
      - Adjunctive therapy for the treatment of partial-onset seizures or primary generalized tonic-clonic seizures is 50 mg twice daily
      - Maximum recommended dosage for monotherapy and adjunctive therapy is 200 mg twice daily
    - **Pediatric Patients 1 month to < 17 years: The recommended dosage is based on body weight and administered orally twice daily**
  - **Availability**
    - 50 mg, 100 mg, 150 mg, 200 mg tablets
    - 200 mg/20 mL single-dose vial for intravenous use
    - 10 mg/mL oral solution

Anticonvulsants

- **topiramate (Eprontia)**
  - **November 2021: FDA has approved a new oral solution formulation of topiramate (Eprontia) indicated 1) as initial monotherapy for treatment of partial-onset or primary generalized tonic-clonic seizures in patients ≥ 2 years old; 2) an adjunctive therapy for treatment of partial-onset seizures, primary generalized tonic-clonic seizures or seizures associated with Lennox-Gastaut syndrome in patients ≥ 2 years of age, and 3) as a preventive treatment for migraine in patients ≥ 12 years of age**
  - **Indication**
    - **Epilepsy:**
      - **Initial monotherapy for the treatment of partial-onset or primary generalized tonic-clonic seizures in patients 2 years of age and older**
      - **Adjunctive therapy for the treatment of partial-onset seizures, primary generalized tonic-clonic seizures, or seizures associated with LennoxGastaut syndrome in patients 2 years of age and older**
    - **Preventive treatment of migraine in patients 12 years of age and older**
  - **Warnings**
    - **Fetal Toxicity: use during pregnancy can cause cleft lip and/or palate and being small for gestational age**
    - **Suicidal behavior and ideation: antiepileptic drugs increase the risk of suicidal behavior or ideation**
    - **Oligohidrosis and hyperthermia: monitor decreased sweating and increased body temperature, especially in pediatric patients**
  - **Dosage**
    - **Stratified by indication and age (See TCR/PI)**
  - **Availability**
    - **Oral solution: 25 mg/mL**

Anticonvulsants

- **ganaxolone (Ztalmy)**
  - **March 2022: The FDA has approved a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator, ganaxolone (Ztalmy). It is indicated for the treatment of seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients ≥ 2 years of age**
  - **Indication**
    - **Treatment of seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients 2 years of age and older**
  - **Warnings**
    - **Pregnancy: Based on animal data, may cause fetal harm**
    - **Suicidal Behavior and Ideation: Monitor patients for suicidal behavior and thoughts**
  - **Dosage**
    - **Administer orally three times daily with food**
    - **Dosage for patients weighing 28 kg or less:**
      - **Starting dosage is 6 mg/kg three times daily (18 mg/kg/day)**
      - **Maximum dosage is 21 mg/kg three times daily (63 mg/kg/daily)**
    - **Dosage for patients weighing over 28 kg:**
      - **Starting dosage is 150 mg three times daily (450 mg daily)**
      - **Maximum dosage is 600 mg three times daily (1800 mg daily)**
  - **Availability**
    - **Oral suspension 50 mg/mL**

Anticonvulsants

- **fenfluramine HCl (Fintepla)**
  - **April 2022: The FDA has approved fenfluramine (Fintepla) for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients who are ≥ 2 years of age; fenfluramine was already FDA-approved for the treatment of seizures associated with Dravet syndrome in patients ≥ 2 years of age**
  - **Indication**
    - **The treatment of seizures associated with** Dravet syndrome and **Lennox-Gastaut syndrome in patients 2 years of age and older**
  - **Warnings**
    - Pregnancy: Based on animal data, may cause fetal harm
    - Suicidal Behavior and Ideation: Monitor patients for suicidal behavior and thoughts
    - Contraindications: Within 14 days of the administration of monoamine oxidase inhibitors due to an increased risk of serotonin syndrome
  - **Dosage**
    - **Lennox-Gastaut Syndrome:**
      - **The initial starting dosage is 0.1 mg/kg twice daily, which should be increased weekly based on tolerability**
      - **Patients not on concomitant stiripentol: The recommended maintenance dosage is 0.35 mg/kg twice daily (maximum daily dosage of 26 mg)**
      - **Patients taking concomitant stiripentol plus clobazam: the recommended maintenance dosage is 0.2 mg/kg twice daily (maximum daily dosage of 17 mg)**
    - Dosing for Dravet Syndrome can be found in TCR/PI
  - **Availability**
    - Oral solution: 2.2 mg/mL fenfluramine

Anticonvulsants

- **stiripentol (Diacomit)**
  - **July 2022: The indication for the treatment of seizures associated with Dravet syndrome in patients taking clobazam has been expanded from patients ≥ 2 years of age to include patients ≥ 6 months old and weighing ≥ 7 kg. Stiripentol is not approved for use as monotherapy**
  - **Indication**
    - **Treatment of seizures associated with Dravet syndrome in patients taking clobazam who are 6 months of age and older and weighing 7 kg or more.** There are no clinical data to support the use as monotherapy in Dravet syndrome
  - **Warnings**
    - Pregnancy: Based on animal data, may cause fetal harm
    - Suicidal Behavior and Ideation: Monitor patients for suicidal behavior and thoughts
    - Neutropenia and Thrombocytopenia: Blood counts should be obtained prior to starting treatment and then every 6 months
  - **Dosage**
    - **The dosage is 50 mg/kg/day, administered by mouth in 2 or 3 divided doses, depending on age and weight**
  - **Availability**
    - Capsule: 250 mg or 500 mg
    - For Oral Suspension: 250 mg or 500 mg

Anticonvulsants

- **zonisamide (Zonisade)**
  - **July 2022: The FDA has approved a new formulation of zonisamide (Zonisade), an oral suspension indicated as adjunctive therapy for the treatment of partial-onset seizures (POS) in adults and pediatric patients ≥ 16 years of age**
  - **Indication**
    - As adjunctive therapy for the treatment of partial onset seizures in adults and pediatric patients 16 years of age and older
  - **Warnings**
    - Serious Hematologic Events: Aplastic anemia and agranulocytosis has been reported with zonisamide treatment
    - Suicidal Behavior and Ideation: Monitor patients for suicidal behavior and thoughts
    - Teratogenicity: Based on animal data, may cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use an effective method of contraception during treatment and for one month after discontinuation
  - **Dosage**
    - The recommended initial dosage is 100 mg daily
    - The dosage may be increased by 100 mg daily every two weeks, based on clinical response and tolerability, to 400 mg daily
    - Patients who are tolerating Zonisade at 400 mg daily and require further reduction of seizures may be increased up to a maximum dosage of 600 mg daily
  - **Availability**
    - **Solution: 100 mg/5 mL**

Anticonvulsants

- **midazolam**
  - **August 2022: The FDA approved midazolam as a 10 mg/0.7 mL autoinjector for the treatment of status epilepticus in adults; approved as a single 10 mg dose given IM in the mid-outer thigh using the prefilled injector**
  - **Indication**
    - **Treatment of status epilepticus in adults**
  - **Warnings**
    - **BBW: Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Monitor patients for respiratory depression and sedation**
    - **BBW: The use of benzodiazepines, including midazolam, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Before prescribing Midazolam Injection and throughout treatment, assess each patient's risk for abuse, misuse, and addiction**
    - **BBW: Abrupt discontinuation or rapid dosage reduction of Midazolam Injection may precipitate acute withdrawal reactions, which can be life-threatening.**
    - **Neonatal Sedation and Withdrawal Syndrome: Midazolam Injection use during pregnancy can result in neonatal sedation and/or neonatal withdrawal**
  - **Dosage**
    - **The recommended dose is a single 10 mg dose, administered by intramuscular injection using the prefilled autoinjector**
  - **Availability**
    - **Injection: 10 mg/0.7 mL in a single-dose pre-filled autoinjector**

Anticonvulsants

- **FDA Communication**
  - **lamotrigine (Lamictal; Lamictal CD; Lamictal ODT; Lamictal XR) – 4/2/2021**
    - **FDA issued Drug Safety Communication for lamotrigine (Lamictal) regarding a potential increased risk of arrhythmias in patients with heart disease as a result of reports of abnormal ECGs**
    - **FDA will continue to evaluate and inform the public and healthcare professionals of their findings as more required in vitro studies are available**
    - **Healthcare Practitioners should assess whether the potential benefits of lamotrigine outweigh the potential risk of arrhythmias for each patient**

Anticonvulsants

- **New Generics**
  - **lacosamide**
    - **March 2022: The FDA has approved generic versions of UCB's Vimpat tablets; it is a multisource generic**
    - **May 2022: First FDA-approved generic for UCB's Vimpat oral solution from Alkem**

- **Discontinuations**
  - **carbamazepine oral suspension- June 2022:**
    - **The FDA has reported Wockhardt Bio has made a business decision to permanently discontinue carbamazepine oral suspension**
  - **diazepam (Diastat) - June 2022:**
    - **The FDA announced that the authorized generic NDCs of the diazepam rectal gel 10 mg and 2.5 mg syringe 2-packs are currently unavailable**
    - **Availability of the generic 10 mg syringe is anticipated in September 2022 and of the 2.5 mg syringe is TBD**
    - **A shortage of 20 mg rectal gel has not been reported**
    - **Bausch Health has no plans to manufacture brand Diastat Rectal Gel (2.5 mg) and Diastat Acudial (10 mg and 20 mg)**

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Androgenic Agents, Injectables/Oral

ENDOCRINE AND METABOLIC AGENTS : ANDROGENS – TESTOSTERONE

Disease State Description – Androgenic Agents, Injectables/Oral

- Male Hypogonadism
  - Male hypogonadism is caused by insufficient production of testosterone and is characterized by low serum concentrations. Hypogonadism may present as testosterone deficiency, infertility, or both
  - Symptoms at presentation will primarily depend on the patient's age at the time of disease onset and can include impotence, decreased libido, fatigue, loss of energy, mood, depression, and regression of secondary sex characteristics
  - Potential risks due to male hypogonadism include osteoporosis, sexual dysfunction, depression, and cardiovascular disease
    - After 30 years of age, testosterone levels in men decrease at rates up to 2% annually
  - Causes of hypogonadism are classified as primary, due to failure of the testes, or secondary, due to failure of the hypothalamus or pituitary gland
    - Either type of hypogonadism may be caused by an inherited (congenital) or acquired factor
  - Conditions resulting in primary hypogonadism include cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchidectomy, chemotherapy, radiation therapy, toxic damage from alcohol or heavy metals, testicular infections (such as mumps) and chromosomal abnormalities such as Klinefelter's Syndrome
  - Patients usually present with low testosterone levels and elevated follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels
  - Secondary (hypogonadotropic) hypogonadism includes idiopathic gonadotropin or luteinizing hormone releasing hormone (LHRH) deficiency and pituitary hypothalamic injury from tumors, trauma, or radiation
    - Testosterone levels are low in patients with secondary hypogonadism, and FSH and LH levels are low or in the normal range.

Androgenic Agents, Injectables/Oral

- **testosterone undecanoate (Tlando)**
  - **April 2022: The FDA has approved a new formulation of testosterone undecanoate (Tlando), an androgen, indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone**
  - **Indications:**
    - **For testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone**
    - **Limitations of Use: Safety and efficacy of TLANDO in males less than 18 years old have not been established**
  - **Precautions/Contraindications:**
    - **BBW: Can cause blood pressure increases that can increase the risk of major adverse cardiovascular events**
    - **Polycythemia: Monitor hematocrit approximately every 3 months during the first year after beginning Tlando and then every 6 months thereafter during treatment. Discontinue treatment if necessary**
    - **Potential for Adverse Effects on Spermatogenesis: May cause azoospermia**
    - **Lipid Changes: Testosterone may affect serum lipid profile. Monitor patient lipid concentrations; if necessary, adjust dosage of lipid lowering drug(s) or discontinue Tlando**
  - **Dosage:**
    - **Recommended dosage is 225 mg orally twice daily with food**
    - **Monitor serum testosterone after initiating TLANDO to determine if treatment should be continued or discontinued**
  - **Formulations:**
    - **Capsules: 112.5 mg**

Androgenic Agents, Injectables/Oral

- **testosterone cypionate**
  - **June 2022: The FDA has approved testosterone cypionate, an androgen, for testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone**
  - **Indications:**
    - **Testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.**
  - **Precautions/Contraindications:**
    - **BBW: Can cause blood pressure increases that can increase the risk of major adverse cardiovascular events**
    - **Schedule III Controlled Substance**
    - **Polycythemia: Monitor hematocrit approximately every 3 months during the first year after beginning treatment and then every 6 months thereafter during treatment. Discontinue treatment if necessary**
  - **Dosage:**
    - **50 mg to 400 mg administered every 2 to 4 weeks as a deep IM injection in the gluteal muscle**
    - **The dose and schedule should be individualized based on the patient's age, diagnosis, response, and side effects**
  - **Formulations:**
    - **200 mg/mL in an SDV**

Androgenic Agents, Injectables/Oral

- **testosterone undecanoate (Kyzatrex)**
  - **July 2022: The FDA approved testosterone undecanoate 100 mg, 150 mg, and 200 mg capsules for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. Kyzatrex is not substitutable with other oral testosterone undecanoate products**
  - **Indications:**
    - **Testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone**
    - **Limitations of Use: Safety and efficacy in males less than 18 years old have not been established**
  - **Precautions/Contraindications:**
    - **BBW: Can cause blood pressure increases that can increase the risk of major adverse cardiovascular events**
    - **Polycythemia: Monitor hematocrit approximately every 3 months during the first year after beginning Kyzatrex and then every 6 months thereafter during treatment. Discontinue treatment if necessary**
    - **Potential for Adverse Effects on Spermatogenesis: May cause azoospermia**
    - **Lipid Changes: Testosterone may affect serum lipid profile. Monitor patient lipid concentrations; if necessary, adjust dosage of lipid lowering drug(s) or discontinue treatment**
  - **Dosage:**
    - **Starting dosage: 200 mg orally once in the morning and once in the evening**
    - **Adjust the dosage to a minimum of 100 mg once in the morning and a maximum of 400 mg twice daily based on serum testosterone drawn 3 to 5 hours after the morning dose at least 7 days after starting treatment or following dose adjustment and periodically thereafter**
  - **Formulations:**
    - **Capsules: 100 mg, 150 mg, 200 mg**

Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Antimigraine Agents

MIGRAINE AGENTS : CALCITONIN GENE-RELATED PEPTIDE (CGRP) RECEPTOR ANTAGONISTS

MIGRAINE AGENTS : SELECTIVE SEROTONIN AGONISTS 5-HT(1)

Disease State Description - Antimigraine Agents

- **Migraine Headache**
  - Accounts for 10% to 20% of all headaches in adults and affects over 37 million men, women, and children in the United States (U.S.)
  - Headache is one of the most common complaints by patients when presenting to a physician
    - 64% of physician-diagnosed patients who experience migraines and 41% of undiagnosed migraine sufferers reported severe impairment or the need for bed rest due to their migraine symptoms
    - In addition, 20.7% of women and 9.7% of men experience migraine, an epidemiologic profile that has remained stable over many years
  - Approximately 85% of patients with migraine headaches suffer less than 3 to 4 attacks per month
    - The median frequency of migraine attacks among migraine sufferers is 1.5 per month
  - Migraine headache must be differentiated from tension-type headache
    - Key criteria for the diagnosis of migraine headache includes an episodic headache lasting from 4 to 72 hours with at least 2 of the following symptoms: unilateral pain, throbbing, aggravated by routine physical activity, pain of moderate to severe intensity
    - During the headache at least 1 of the following are present: nausea and/or vomiting, or photophobia and phonophobia

Migraine Research Foundation, 2022

- **Cluster Headache (CH)**
  - A severe, primary headache disorder characterized by extreme pain on one side of the head and autonomic symptoms (e.g., nasal congestion, lacrimation)
  - CH periods can persist for weeks to months with daily or more frequent attacks of 15 to 180 minutes in duration
  - The estimated lifetime prevalence of CH is more than one in 1,000. CH can be either episodic or chronic in nature with episodic CH being the predominant form
  - Individuals with episodic CH experience periods of attack followed by periods of remission, whereas individuals with chronic CH have minimal to no periods of remission between headache attacks

American Headache Society, 2016

Antimigraine Agents

- **Discontinuation**
  - **dihydroergotamine mesylate (Amerge)**
    - **GSK reported to the FDA intent to discontinue Amerge 1 mg and 2.5 mg blister packs as a business-related decision**
    - **GSK ceased distribution in May 2022**
    - **Generics remain available**

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Pulmonary Arterial Hypertension Agents

PULMONARY HYPERTENSION AGENTS : ENDOTHELIN RECEPTOR ANTAGONISTS
PULMONARY HYPERTENSION AGENTS : PROSTACYCLIN RECEPTOR AGONISTS
PULMONARY HYPERTENSION AGENTS : PROSTAGLANDIN VASODILATORS
PULMONARY HYPERTENSION AGENTS : SGC STIMULATOR
PULMONARY HYPERTENSION AGENTS- PHOSPHODIESTERASE INHIBITORS (PDEI)

Disease State Description - Pulmonary Arterial Hypertension

- The prevalence varies substantially depending on the type, etiology, and underlying condition; estimated to be ~15 per million people
- Pulmonary hypertension (PH) is characterized by an increase in pulmonary arterial pressure and secondary right ventricular failure. This is defined as a resting mean pulmonary arterial pressure (mPAP) ≥ 25 mm Hg
- Symptoms include dyspnea, dizziness, syncope, fatigue, edema (peripheral), angina, palpitations, and other symptoms, all of which are exacerbated by exertion
- PH does not have a cure and, if left untreated, PH is a life-threatening disease with poor prognosis
- Management of PH should be limited to specialized centers where clinicians are experienced in the evaluation and treatment of patients with PH
- Although the number of approved therapies for PAH has grown in the past years, the prognosis is still poor, with approximately 50% mortality within the first 5 years after diagnosis

World Health Organization, 2013

Disease State Description - Pulmonary Arterial Hypertension

- There are many causes of PAH including idiopathic or underlying disease and hereditary causes
  - Cellular changes in the walls of pulmonary arteries, and it appears that mutations in the bone morphogenetic protein receptor type 2 (BMPR2) gene plays a key role in the pathogenesis of heritable PAH
  - Other etiologies in PAH include drugs and toxins, collagen vascular resistance, human immunodeficiency virus (HIV), portal hypertension, chronic thromboembolism, and congenital heart disease
- The World Health Organization (WHO) classifies PH patients into 5 groups based on etiology
  - Group I now refers to pulmonary arterial hypertension (PAH)
  - Group II refers to PH due to left heart disease
  - Group III refers to PH due to lung disease
  - Group IV refers to PH due to blood clots in the lungs
  - Group V refers to refers to PH due to blood and other rare disorders
- In 2013, clinical classifications were updated to provide the same PH classifications for adult and pediatric patients. In addition, the individual categorization of the persistent PH of neonates (PPHN) was included

American College of Cardiology, 2013

Pulmonary Arterial Hypertension Agents

- **treprostinil (Tyvaso DPI)**
  - **May 2022: FDA approved Tyvaso DPI for the treatment of**
    - **(1) PAH (WHO Group 1) to improve exercise ability (studies establishing effectiveness predominately included patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH [56%] or PAH associated with connective tissue diseases [33%]);**
    - **(2) Pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability (study establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia [45%] inclusive of idiopathic pulmonary fibrosis, combined pulmonary fibrosis and emphysema [25%], and WHO Group 3 connective tissue disease [22%])**
  - **Warnings**
    - **Tyvaso DPI may cause symptomatic hypotension**
    - **Tyvaso DPI inhibits platelet aggregation and increases the risk of bleeding**
  - **Dosage**
    - **Administer in 4 separate treatment sessions each day approximately 4 hours apart, during waking hours**
    - **Initial dosage: one 16 mcg cartridge per treatment session**
    - **Dosage should be increased by an additional 16 mcg per treatment session at approximately 1- to 2-week intervals, if tolerated**
    - **Titrate to target maintenance doses of 48 mcg to 64 mcg per treatment session, 4 times daily**
  - **Availability**
    - **Inhalation powder: Single-dose plastic cartridges containing 16, 32, 48, or 64 mcg of treprostinil as a dry powder formulation**

Updated Information

- **Discontinuation**
  - **epoprostenol injection – July 2022**
    - Teva has reported to the FDA discontinuation of epoprostenol sodium for injection and the corresponding sterile diluent
    - No future production is expected for an extended period. GSK's brand name epoprostenol sodium (Flolan) remains available

- **FDA Communication**
  - **bosentan (Tracleer) – May 2022**
    - FDA changed requirements for bosentan REMS, effective June 27, 2022, after which prescriber may delegate a designee for certain administrative activities, and certified pharmacies can to enter testing and counseling information through REMS website
    - Changes were made to the outpatient pharmacy operations to verify safe use conditions for the REMS Pre-Dispense Authorization (PDA)

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Alzheimer's Agents

ANTIDEMENTIA AGENTS

Alzheimer's Agents - Disease State Description

- **Dementia**
  - Characterized by irreversible loss of or decline in memory and other cognitive abilities
  - Approximately 5.8 million Americans aged 65 years and older suffer from Alzheimer's disease (AD)
  - AD is the most common type of dementia, accounting for 60% to 80% of dementia disorders in the elderly and is the sixth leading cause of death in the United States (US)
  - Other types of dementia include vascular dementia, dementia with Lewy bodies, mixed dementia, and frontotemporal dementia
  - Dementia may also be associated with human immunodeficiency virus (HIV), normal pressure hydrocephalus, Huntington's disease, Korsakoff's syndrome, multiple sclerosis (MS), Parkinson's disease (PD), and Creutzfeldt-Jakob disease
  - Many other conditions can cause delirium symptoms, such as thyroid disorder and vitamin deficiencies, but are reversible once the underlying condition is addressed

- **Alzheimer's Disease**
  - AD is characterized by progressive cognitive decline associated with impairment of activities of daily living (ADL) and behavioral disturbances
  - Patients with AD eventually lose all cognitive, analytical, and physical functioning
  - Ten warning signs of AD include memory loss that disrupts daily life, challenges in planning or solving problems, difficulty completing familiar tasks, confusion with time or place, trouble understanding visual images and spatial relationships, new difficulties with speaking or writing, misplacement of items or losing the ability to retrace steps, decreased or poor judgment, withdrawal from work or social activities, and mood or personality changes
  - In addition, there are 3 stages of AD over the course of the disease characterized by symptom severity, rate of disease progression, and level of necessary supportive care for activities of daily living

Alzheimer's Association, 2020

Alzheimer's Agents

- **aducanumab-avwa (Aduhelm)**
  - June 2021: FDA approved Aduhelm, an amyloid beta-directed antibody, indicated for the treatment of Alzheimer's disease
  - Indication
    - Treatment of Alzheimer's disease
    - Treatment with Aduhelm should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with Aduhelm. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s)
  - Limitation
    - Amyloid Related Imaging Abnormalities (ARIA): Enhanced clinical vigilance for ARIA is recommended during the first 8 doses of treatment with Aduhelm, particularly during titration. If a patient experiences symptoms which could be suggestive of ARIA, clinical evaluation should be performed, including MRI testing if indicated
  - Dosage
    - The recommended maintenance dosage is 10 mg/kg administered as an intravenous infusion over approximately one hour every four weeks
    - Obtain a recent (within one year) brain MRI prior to initiating treatment
    - Obtain MRIs prior to the 7th and 12th infusions. If radiographic severe ARIA-H is observed, treatment may be continued with caution only after a clinical evaluation and a follow-up MRI demonstrates radiographic stabilization (i.e., no increase in size or number of ARIA-H
  - Availability
    - Injection: 170 mg/1.7 mL (100 mg/mL) solution in a single-dose vial; 300 mg/3 mL (100 mg/mL) solution in a single-dose vial

Alzheimer's Agents

- **donepezil (Adlarity)**
  - **March 2022: FDA approved Adlarity, an acetylcholinesterase inhibitor indicated for the treatment of mild, moderate, and severe dementia of the Alzheimer's type**
  - **Indication**
    - **The treatment of mild, moderate, and severe dementia of the Alzheimer's type**
  - **Limitation**
    - **Pregnancy: Based on animal data, may cause fetal harm**
    - **Application-site reactions have occurred with Adlarity. Allergic contact dermatitis should be suspected if application-site reactions spread beyond the size of the transdermal system, if there is evidence of a more intense local reaction (e.g., increasing erythema, edema, papules, vesicles), and/or if symptoms do not significantly improve within 48 hours after transdermal system removal**
  - **Dosage**
    - **The recommended starting dosage is 5 mg/day. After 4 to 6 weeks, the dosage may be increased to the maximum recommended dosage of 10 mg/day**
    - **If a patient has been on 5 mg/day oral donepezil for at least 4-6 weeks or on 10 mg/day of oral donepezil, the recommended starting dosage is 10 mg/day**
  - **Availability**
    - **Transdermal System: 5 mg/day and 10 mg/day**

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Magellan Medicaid Administration

Immunomodulators, Atopic Dermatitis

ATOPIC DERMATITIS AGENTS : IMMUNOSUPPRESSIVE AGENTS - TOPICAL
ATOPIC DERMATITIS AGENTS : MONOCLONAL ANTIBODIES
ATOPIC DERMATITIS AGENTS : PHOSPHODIESTERASE 4 INHIBITORS - TOPICAL

Immunomodulators, Atopic Dermatitis - Disease State Description

- Atopic dermatitis (AD) is a chronic, non-contagious, inflammatory disease of the skin resulting from a combination of genetic and environmental factors
- Approximately 70% of patients diagnosed with AD have a positive family history of atopic diseases
  - The odds of developing AD are 2 to 3 times higher in children with one atopic parent and increase to 3 to 5 times higher if both parents are atopic
- Often referred to as “eczema,” AD affects about 17.8 million Americans and accounts for 10% to 20% of all visits to the dermatologist
- Although symptoms of AD can develop at any age, it has been estimated that 60% of patients develop symptoms in the first year of life, while 90% develop symptoms before the age of 5.5 years
- AD is characterized by extremely dry, itchy skin on the insides of the elbows, behind the knees, and on the face, hands, and feet
- In response to the intense itching, patients may scratch or rub the affected area, which leads to further irritation and inflammation
  - As the skin loses moisture from the epidermal layer, it becomes increasingly dry and may begin to crack, weep, crust, and scale
  - This damage to the integrity of the skin renders it less protective and more prone to infection
  - Despite the chronic nature of this dermatologic condition, there may be periods of the disease when the skin improves and periods when the skin worsens
  - Irritants, such as detergents, fumes, tobacco smoke, and alcohol-containing skin products, and allergens like dust mites, pollen, and animal dander can exacerbate AD or cause “flare ups”

American Academy of Dermatology, 2014

Immunomodulators, Atopic Dermatitis

- dupilumab (Dupixent)
  - **June 2021: FDA approved 200 mg/1.14 mL single-dose auto-injector (pre-filled pen) for use in patients ≥ 12 years old; was already approved as 200 mg/1.14 mL pre-filled syringe and auto-injector and 300 mg/2 mL auto-injector & pre-filled syringe**
  - **October 2021: FDA has expanded the indication of add-on maintenance treatment with moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma to patients ≥ 6 years old (previously indicated for those ≥ 12 years of age)**
  - **September 2022: FDA granted approval under Priority Review for the treatment of adults with prurigo nodularis at a recommended dose of 600 mg (two 300 mg injections) followed by 300 mg every other week by SC injection**
  - **November 2022: FDA authorized use of single-dose, pre-filled pens in patients 6 months to < 12 years of age when administered by a caregiver (previously only the prefilled syringe was for use in this age range). The pens deliver 100 mg, 200 mg, and 300 mg; pediatric indications impacted are severe atopic dermatitis and severe asthma, which are approved for patients as young as 6 months and 6 years, respectively.**
  - **Dosage**
    - **Stratified by indication, age, and weight (Specific dosage instructions available in TCR/PI)**
  - **Availability**
    - **Injection: 300 mg/2 mL solution in a single-dose pre-filled pen and syringe with needle shield**
    - **Injection: 200 mg/1.14 mL solution in a single-dose pre-filled pen and syringe with needle shield**
    - **Injection: 100 mg/0.67 mL solution in a single-dose pre0filled syringe with needle shield**

Immunomodulators, Atopic Dermatitis

- tralokinumab-ldrm (Adbry)
  - **December 2021: The FDA has approved tralokinumab-ldrm (Adbry), an interleukin-13 antagonist indicated for the treatment of moderate-to-severe atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable; therapy can be used with or without topical corticosteroids**
  - **Indications**
    - **Treatment of moderate-to-severe atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable**
    - **Can be used with or without topical corticosteroids**
  - **Warning/Precautions**
    - **Conjunctivitis and Keratitis: Patients should report new onset or worsening eye symptoms to their healthcare provider**
    - **Parasitic (Helminth) Infections: Treat patients with pre-existing helminth infections before initiating treatment with Adbry. If patients become infected while receiving treatment and do not respond to anti-helminth treatment, discontinue treatment with Adbry until the infection resolves**
    - **Risk of Infection with Live Vaccines: Avoid use of live vaccines**
  - **Dosage**
    - **The recommended dosage of ADBRY is an initial dose of 600 mg (four 150 mg injections), followed by 300 mg (two 150 mg injections) administered every other week**
    - **A dosage of 300 mg every 4 weeks may be considered for patients below 100 kg who achieve clear or almost clear skin after 16 weeks of treatment**
  - **Availability**
    - **Injection: 150 mg/mL solution in a single-dose prefilled syringe with needle guard**

Immunomodulators, Atopic Dermatitis

- tralokinumab-ldrm (Opzelura)
  - **July 2022: The FDA approved a new indication for ruxolitinib cream (Opzelura), the topical treatment of nonsegmental vitiligo in adult and pediatric patients ≥ 12 years of age**
  - **Indications**
    - The topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adult and pediatric patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable
    - **The topical treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older**
    - Limitations of Use: Use in combination with therapeutic biologics, other JAK inhibitors or potent immunosuppressants such as azathioprine or cyclosporine is not recommended
  - **Warning/Precautions**
    - BBW: Serious infection leading to hospitalization or death
    - BBW: Higher rate of all-cause mortality, including sudden CV death have been observed in patients treated with JAK Inhibitors
    - BBW: Thrombosis, including DVT, PE, and arterial thrombosis, some fatal, have occurred in patients treated with JAK Inhibitors
  - **Dosage**
    - The topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adult and pediatric patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable
    - **The topical treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older**
  - **Availability**
    - Cream: 1.5% ruxolitinib

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Cytokine and CAM Antagonists

Cytokine & CAM Antagonists - Disease State Description

- Cytokines and cell-adhesion molecules (CAMs) are chemical mediators involved in inflammatory processes throughout the body

Cytokines

- Small proteins secreted in response to an immune stimulus for the purpose of mediating and regulating immunity, inflammation, and hematopoiesis
- Derived from monocytes and macrophages and induce gene expression of a number of proteins that contribute to the inflammatory response
- The actions of the individual cytokines are widely varied and they contribute to fibrosis and tissue degeneration associated with chronic inflammation, primarily by inducing the proliferation of fibroblasts and collagenase
- The pro-inflammatory cytokines, tumor necrosis factor (TNF), and interleukin (IL)-1, are involved in tissue destruction in many chronic inflammatory diseases affecting various organs
  - TNFα also has a role in Crohn's disease in stimulation of inflammation

European Respiratory Journal, 2003

Cytokine & CAM Antagonists - Disease State Description

Cell Adhesion Molecules (CAM)

- Cell surface proteins involved in the binding of cells, usually leukocytes, to each other, endothelial cells, or the extracellular matrix
- Specific signals produced in response to wounds and infection control the expression and activation of these molecules
- Most of the CAMs characterized fall into 3 general families of proteins:
  - The immunoglobulin (Ig) superfamily
    - The adhesion molecules that bind to integrins on leukocytes and mediate their flattening onto the blood vessel wall
  - The integrin family
    - Consists of an α chain and a ß chain that mediate cell-to-cell interactions, such as leukocyte adherence to the vascular endothelium
  - The selectin family
    - Involved in the adhesion of leukocytes to activated endothelium followed by extravasation through the blood vessel walls into lymphoid tissues and sites of inflammation
  - Other proteins that are functionally classified as CAMs are involved in strengthening the association of T cells with antigen-presenting cells or target cells, in T cell activation, and in recirculating lymphocytes back to the circulation via the lymphatic system
- Different CAMs have been implicated in inflammatory, fibrotic, and autoimmune diseases

European Respiratory Journal, 2003

Juvenile Idiopathic Arthritis - Treatment Guidelines

ACR/Arthritis Foundation, 2019

- The organization recommends nonsteroidal anti-inflammatory drugs (NSAIDs) conditionally as adjunctive therapy (very low level of evidence)
- Regarding traditional DMARDs for polyarthritis
  - **Methotrexate is conditionally recommended over leflunomide or sulfasalazine** (moderate and very low evidence, respectively)
  - **Subcutaneous (SC) methotrexate is conditionally recommended over oral methotrexate** (very low evidence)
- For biologic DMARDs in patients with polyarthritis
  - **Combination therapy with a DMARD is conditionally recommended over biologic monotherapy when initiating treatment with a biologic** (etanercept [very low evidence], adalimumab [moderate evidence], golimumab [very low evidence], abatacept [low evidence], or tocilizumab [low evidence])
- Combination therapy with a DMARD is strongly recommended for infliximab (low evidence)
- Intraarticular glucocorticoids are conditionally recommended as adjunct therapy (very low evidence), and oral corticosteroids as a bridge therapy are conditionally recommended in patients with moderate or high disease activity (very low evidence); however, bridge therapy is not recommended in patients with low disease activity (very low evidence)
- In addition, the group strongly recommends against adding chronic low-dose glucocorticoids, regardless of disease activity (very low evidence) in polyarthritis patients

Juvenile Idiopathic Arthritis - Treatment Guidelines

ACR/Arthritis Foundation, 2019

- For initial therapy in polyarthritis patients
  - The group strongly recommends **all patients have initial therapy with DMARD over NSAID monotherapy** (moderate evidence), with methotrexate monotherapy conditionally recommended over triple DMARD therapy (low evidence)
- In patients without risk factors (e.g., positive anti-cyclic citrullinated peptide antibodies, positive rheumatoid factor, or presence of joint damage)
  - The group recommends **initial therapy with a DMARD conditionally over a biologic** (low evidence); however, in those with risk factors, the group recognizes that there are situations in which a biologic may be preferred (low evidence; e.g., involvement of high risk joints [cervical spine, wrist, or hip], high disease activity, and or those judged to be high risk of disabling joint damage)
- For subsequent therapy in low disease activity patients, defined as clinical Juvenile Disease Activity Score based on 10 joints (cJADAS-10) ≤ 2.5 and ≥ 1 active joint
  - **Escalation of therapy** (e.g., intraarticular glucocorticoid injection, DMARD dose optimization, methotrexate trial, and adding or changing biologic) is recommended over no escalation (very low evidence)
  - For **subsequent therapy in moderate or high disease activity** (cJADAS-10 > 2.5) **patients receiving DMARD monotherapy**, the group conditionally recommends **adding a biologic to the original DMARD over changing to a second DMARD** (low evidence) or **triple DMARD therapy** (low evidence)
  - For **subsequent therapy in moderate or high disease activity polyarthritis patients receiving a TNF antagonist with or without a DMARD**, the group conditionally recommends **switching to a non-TNF antagonist** (e.g., tocilizumab, abatacept) over switching to a second TNF antagonist (very low evidence); **however, a second TNF antagonist may be appropriate in patients with good initial response to a TNF antagonist who have experienced secondary failure**
  - If the patient is receiving their second biologic, **use of a TNF antagonist, abatacept, or tocilizumab is conditionally recommended over rituximab** (very low evidence)

Juvenile Idiopathic Arthritis - Treatment Guidelines

ACR, 2021

- First-line treatment for oligoarthritis (JIA involving ≤ 4 joints without systemic manifestations) includes intra-articular glucocorticoids and/or NSAIDs (very low evidence)
- If there is an inadequate response, then non-biologic DMARDS (methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, calcineurin inhibitors) are strongly recommended, with methotrexate conditionally recommended as the preferred agent
- If an adequate response is not achieved with a non-biologic DMARD, then ACR strongly recommends a biologic DMARD (TNF inhibitor, abatacept, tocilizumab, anakinra, canakinumab) with no preference of one agent over another (very low evidence). For treatment of systemic JIA (sJIA), a brief trial of NSAIDs is conditionally recommended as initial monotherapy in patients without macrophage activation syndrome (very low evidence)
- Biologic DMARDs (IL-1 and IL-6 inhibitors) are recommended as initial monotherapy in patients with macrophage activation syndrome (very low evidence), with no preference of one agent over another

Ankylosing Spondylitis – Background and Guidelines

Background:

- Axial spondyloarthritis (axSpA) is an inflammatory condition generally affecting the spine and can be furthered subdivided into ankylosing spondylitis (AS; radiographic axSpA) and nonradiographic axSpA (nr-axSpA

American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network

- Published a 2019 update on the treatment of ankylosing spondylitis (AS) and nonradiographic axial spondyloarthritis (SpA)
- In general, recommendations for AS and nonradiographic axial SpA are similar
- TNF antagonists (but not a specific one) are recommended as first biologic (over Cosentyx or Tremfya, which are then recommended over a second TNF antagonist if first does not produce a response)
- All the prior mentioned agents are recommended over Xeljanz
- Concurrent low-dose methotrexate with TNF antagonist is not recommended
- Recommend against a strict treat-to-target strategy
- If a patient's disease is stable, guidelines recommend against discontinuing or tapering of biologics
- Sulfasalazine provides a viable option for select patients who cannot take a TNF antagonist

Recurrent Pericarditis - Background and Guidelines

Background:

- Acute pericarditis is inflammation of the pericardium and symptoms can include chest pain, electrocardiogram (ECG) changes, pericardial effusion, and pericardial friction rub
  - It typically lasts up to 6 weeks, although symptoms may recur, and recurrence may be as high as 15% to 30% in select patients with idiopathic pericarditis
- In recurrent pericarditis, these symptoms return after a symptom-free period of at least 4 to 6 weeks
- Symptoms of recurrent pericarditis include pleuritic chest pain with fever, pericardial rub, ECG changes, new or worsening pericardial effusion, and/or elevation of markers of inflammation; patients may feel well in between attacks and others may have a more persistent disease course
- Studies have suggested that many cases of recurrent pericarditis are caused by an autoimmune disorder, although other causes are possible (e.g., infection)
  - There are no well-established predictors of recurrence

Treatment:

- The pharmacologic treatment of recurrent pericarditis is similar to treatment of acute pericarditis, and includes NSAIDs or aspirin, plus colchicine as typical first-line agents
  - Steroids or combination therapy may also be considered
  - Other agents that may be used for treatment in late-line therapy include rilonacept and the off-label use of anakinra, azathioprine, or immune globulins
- Pericardiectomy may also be considered in select patients

Disease State Description - Ulcerative Colitis

- Ulcerative colitis (UC) is a chronic inflammatory disease primarily affecting the colon and rectum
- UC affects approximately 1,000,000 people in the United States (US) and the incidence continues to increase worldwide. The Center for Disease Control and Prevention (CDC) estimates the current prevalence of UC at 249 per 100,000 adults
  - UC may present at any age, but onset typically peaks between 15 and 30 years of age
- The disease is characterized by superficial infiltration of the bowel wall by inflammatory white cells, resulting in multiple mucosal ulcerations and crypt abscesses
- The predominant symptom of UC is diarrhea, which is usually associated with blood in the stool
  - Additional symptoms may include pain in the lower quadrant or rectum along with systemic features, including fever, malaise, and weight loss (which are more common if a greater portion of the colon is affected)
  - The initial attack of UC may be fulminant with bloody diarrhea, but the disease more commonly begins indolently, with non-bloody diarrhea progressing to bloody diarrhea
  - UC can present initially with any extent of anatomic involvement ranging from disease confined to the rectum to the entire large intestine (pancolitis)
  - Most commonly, UC follows a chronic intermittent course with long periods of quiescence interspersed with acute attacks lasting weeks to months. However, a significant percentage of patients suffer a chronic continuous course

Centers for Disease Control and Prevention, 2015

Disease State Description

- Alopecia Areata
  - Alopecia areata is an autoimmune condition that attacks hair follicles causing hair loss
  - Patchy baldness can develop anywhere on the scalp, face, and body
  - Onset can occur at any age, but most patients develop it during childhood, adolescence, or during their 20s or 30s
  - Approximately half of individuals experience hair regrowth within a few months without treatment
  - Alopecia may reoccur with unpredictable cycles
  - Baricitinib is the only medication FDA-approved for the treatment of alopecia areata in adults
    - Other medications have been used including corticosteroids, immunosuppressants, and agents that stimulate hair regrowth

Cytokine & CAM Antagonists

- adalimumab-adbm (Cyltezo)
  - **October 2021: The FDA has approved the first interchangeable biosimilar to Humira, Cyltezo (adalimumab-adbm). Cyltezo was first approved in August 2017 as a biosimilar to Humira, but was not deemed interchangeable**
  - **October 2021: The juvenile idiopathic arthritis (JIA) indications was expanded to include reducing signs and symptoms of moderate to severely active polyarticular JIA in patients ≥ 2 years of age (previously indicated for patients ≥ 4 years of age)**
  - **Indications**
    - Rhematoid Arthritis (RA), **Juvenile Idiopathic Arthritis (JIA)**, Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Crohn's Disease (CD), Ulcerative Colitis (UC), Plaque Psoriasis (Ps)
  - **Precautions**
    - BBW: Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens
    - BBW: Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including adalimumab products Embryo-Fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception
    - Cardiac adverse reactions: Discontinue infusions in case of serious or life-threatening events
    - Renal toxicity: Discontinue in patients with rising serum creatinine or oliguria
  - **Dosage**
    - Dosing is stratified by indication and age (Found in TCR or PI)
  - **Availability**
    - Injection: 40 mg/0.8 mL and 20 mg/0.4 mL in single-dose prefilled glass syringe

Cytokine & CAM Antagonists

- rituximab-pvvr (Ruxience)
  - **November 2021: FDA approved for the treatment of rheumatoid arthritis (RA) in combination with methotrexate in adult patients with moderately-to severely-active RA who have inadequate response to one or more TNF antagonist therapies**
  - **Indications**
    - Non-Hodgkin's Lymphoma, Chronic Lymphocytic Leukemia, **Rheumatoid Arthritis**, Granulomatosis with Polyangiitis and Microscopic Polyangiitis
  - **Precautions**
    - BBW: Fatal infusion-related reactions within 24 hours of rituximab infusion; approximately 80% of fatal reactions occurred with first infusion. Monitor patients and discontinue infusion for severe reactions
    - BBW: Severe mucocutaneous reactions, some with fatal outcomes
    - Embryo-Fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception
    - Cardiac adverse reactions: Discontinue infusions in case of serious or life-threatening events
    - Renal toxicity: Discontinue in patients with rising serum creatinine or oliguria
  - **Dosage**
    - Dosing is stratified by indications (Found in TCR or PI)
  - **Availability**
    - Injection: 100 mg/10 mL (10 mg/mL) and 500 mg/50 mL (10 mg/mL) solution in single-dose vials

Cytokine & CAM Antagonists

- **adalimumab-aqvh (Yusimry)**
  - **December 2021: The FDA has approved adalimumab-aqvh (Yusimry), a biosimilar to adalimumab (Humira), indicated for certain patients with the following conditions: adults with moderately to severely active RA, moderately to severely active JIA in patients ≥ 2 years old, adults with active PsA, adults with active ankylosing spondylitis, moderately to severely active Crohn's disease in patients ≥ 6 years old, adults with moderately to severely active UC (effectiveness has not been established in pts who have lost response/were intolerant to TNF blockers), and adults with moderate to severe chronic plaque psoriasis**
  - **Dosing**
    - **Dosing is indication, age and weight based. Can be found in TCRs or PIs**
  - **Precautions/Contraindications**
    - BBW: Serious infections
      - Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens
    - BBW: Malignancy
      - Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including adalimumab products
      - Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have occurred in adolescent and young adults with inflammatory bowel disease treated with TNF blockers including adalimumab products
  - **Formulations**
    - Injection: 40 mg/0.8 mL in a single-dose prefilled glass syringe

Cytokine & CAM Antagonists

- **abatacept (Orencia)**
  - **December 2021: FDA approved a new indication for prophylaxis of acute graft versus host disease (aGVHD) in combination with a calcineurin inhibitor and methotrexate, in adults and peds ≥2 years of age undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated-donor; already approved for adult rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, and adult psoriatic arthritis**
  - **Indications**
    - Rheumatoid Arthritis (RA), polyarticular juvenile idiopathic arthritis, psoriatic arthritis (PsA), **acute graft versus host disease**
  - **Dosing**
    - **Acute Graft versus Host Disease:**
      - **For patients 6 years and older, administer at a 10 mg/kg dose (maximum dose 1,000 mg) as a 60-minute infusion on the day before transplantation, followed by a dose on Day 5, 14, and 28 after transplant**
      - **For patients 2 to less than 6 years old, administer a 15 mg/kg dose as a 60 minute infusion on the day before transplantation, followed by a 12 mg/kg dose as a 60-minute infusion on Day 5, 14, and 28 after transplant**
    - **Dosing is indication, age and weight based. Can be found in TCRs or Pis**
  - **Precautions/Contraindications**
    - Serious infections reported. Patients with a history of recurrent infections or underlying conditions predisposing to infections may experience more infections. Discontinue if a serious infection develops
  - **Formulations**
    - Intravenous Infusion:
      - For injection: 250 mg lyophilized powder in a single-dose vial (may use less than full contents of vial or use more than one vial)
    - Subcutaneous Use:
      - Injection: 50 mg/0.4 mL, 87.5 mg/0.7 mL, 125 mg/mL solution in single-dose prefilled syringes
      - Injection: 125 mg/mL solution in a single-dose prefilled ClickJect autoinjectors

Cytokine & CAM Antagonists

- **tofacitinib (Xeljanz/Xeljanz XR)**
  - **December 2021: FDA approved for treatment of adults with active ankylosing spondylitis (AS) who have had an inadequate response or intolerance to ≥ 1 TNF blocker; not recommended for use in combination with biologic DMARDS or potent immunosuppressants (e.g., azathioprine, cyclosporine); already approved for rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, and polyarticular course juvenile idiopathic arthritis**
  - **Indications**
    - Rheumatoid Arthritis (RA), **ankylosing spondylitis (AS)**, ulcerative colitis (UC), polyarticular course juvenile idiopathic arthritis,
  - **Precautions/Contraindications**
    - BBW: Malignancy
    - BBW: Thrombosis
    - BBW: Higher rate of all-cause mortality, including sudden CV death
  - **Dosing**
    - **Ankylosing Spondylitis (AS):**
      - **5 mg twice daily or Xeljanz XR 11 mg once daily**
      - **Recommended dosage in patients with moderate and severe renal impairment or moderate hepatic impairment is 5 mg once daily**
    - **Dosing is indication and age based. Can be found in TCRs or PIs**
  - **Formulations**
    - Tablets: 5 mg, 10 mg tofacitinib
    - XR Tablets: 11 mg, 22 mg tofacitinib
    - Oral Solution: 1 mg/mL tofacitinib

Cytokine & CAM Antagonists

- **apremilast (Otezla)**
  - **December 2021: FDA approved an expanded psoriasis indication for adults with plaque psoriasis who are candidates for phototherapy or systemic therapy; previously, it was only indicated for adults with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy**
  - **Indications**
    - Adult patients with active psoriatic arthritis
    - **Adult patients with plaque psoriasis who are candidates for phototherapy or systemic therapy**
    - Adult patients with oral ulcers associated with Behçet's Disease
  - **Precautions/Contraindications**
    - Diarrhea, Nausea, and Vomiting: Consider dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting
  - **Dosing**
    - To reduce risk of gastrointestinal symptoms, titrate to recommended dosage of 30 mg twice daily according to the following schedule
      - Day 1: 10 mg in morning
      - Day 2: 10 mg in morning and 10 mg in evening
      - Day 3: 10 mg in morning and 20 mg in evening
      - Day 4: 20 mg in morning and 20 mg in evening
      - Day 5: 20 mg in morning and 30 mg in evening
      - Day 6 and thereafter: 30 mg twice daily
    - Dosage in Severe Renal Impairment: Recommended dosage is 30 mg once daily
  - **Formulations**
    - Tablets: 10 mg, 20 mg, 30 mg

Cytokine & CAM Antagonists

- **secukinumab (Cosentyx)**
  - **December 2021: The FDA has expanded the indication for secukinumab to include active juvenile PsA in patients ≥ 2 years of age (previously only indicated for adults with active PsA) and a new indication for active enthesitis-related arthritis in patients ≥ 4 years of age.**
  - **Indications**
    - Moderate to severe plaque psoriasis in patients 6 years and older who are candidates for systemic therapy or phototherapy
    - **Active psoriatic arthritis (PsA) in patients 2 years of age and older**
    - Adults with active ankylosing spondylitis (AS)
    - Adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation
    - **Active enthesitis-related arthritis (ERA) in patients 4 years of age and older**
  - **Precautions/Contraindications**
    - Infections: Serious infections have occurred. Caution should be exercised when considering the use in patients with a chronic infection or a history of recurrent infection. If a serious infection develops, discontinue treatment until the infection resolves
    - Tuberculosis (TB): Prior to initiating treatment with COSENTYX, evaluate for TB
  - **Dosing**
    - **Pediatric Patients 2 years and older: Recommended dosage is administered by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter.**
    - **Other dosing stratified by indication, age, and weight (can be found in TCR/PI)**
  - **Formulations**
    - Injection: 150 mg/mL solution in a single-dose Sensoready pen and in a single-dose prefilled syringe
    - Injection: 75 mg/0.5 mL solution in a single-dose prefilled syringe (for pediatric patients)
    - For Injection: 150 mg, lyophilized powder in a single-dose vial for reconstitution (for healthcare professional use only)

Cytokine & CAM Antagonists

- **adalimumab-bwwd (Hadlima)**
  - **December 2021: The FDA has expanded the indications for** polyarticular juvenile idiopathic arthritis (pJIA) to ≥ 2 years old **as well as the indication for Crohn's disease to ≥ 6 years old**
  - **August 2022: FDA approved a citrate-free, high concentration 100 mg/mL formulation in prefilled syringe (PFS) and prefilled auto-injector presentations with shelf-life of 24 months. For use in patients with RA, JIA, PSO, PsA, AS, CD, and UC. Previously approved in lower concentration (50 mg/mL)**
  - **Indications**
    - Rheumatoid Arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), **Crohn's Disease (CD), Ulcerative Colitis (UC)**, plaque psoriasis (Ps)
  - **Dosing**
    - **Dosing is indication, age and weight based. Can be found in TCRs or PIs**
  - **Precautions/Contraindications**
    - BBW: Serious infections
    - BBW: Malignancy
  - **Formulations**
    - Single-dose prefilled autoinjector (Hadlima PushTouch): 40 mg/ 0.8 mL
    - Single-dose prefilled glass syringe: 40 mg/0.8 mL
    - Single-dose glass vial for institutional use only: 40 mg/0.8 mL
    - Single-dose prefilled autoinjector (Hadlima PushTouch): 40 mg/ 0.4 mL
    - Single-dose prefilled glass syringe: 40 mg/0.4 mL

Cytokine & CAM Antagonists

- **upadacitinib (Rinvoq)**
  - **December 2021: FDA approved a new indication for the treatment of adults with active psoriatic arthritis (PsA) who had inadequate response or intolerance to ≥ 1 TNF blocker; use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants, such as azathioprine and cyclosporine, is not recommended**
  - **March 2022: FDA approved Rinvoq for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response or intolerance to 1 or more TNF blockers**
  - **May 2022: FDA approved for use in adults with active ankylosing spondylitis (AS) who have had an inadequate response or intolerance to one or more TNF blockers**
  - **October 2022: FDA approved a new indication for the treatment of adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation who have had an inadequate response or intolerance to TNF blocker therapy. Rinvoq is not recommended for use in combination with other JAK inhibitors, biologic DMARDs, or potent immunosuppressants (e.g., azathioprine, cyclosporine)**
  - **Indications**
    - Rheumatoid Arthritis (RA), psoriatic arthritis (PsA), atopic dermatitis (AD), ulcerative colitis (UC), ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis
  - **Dosing**
    - **Dosing is indication and age based. Can be found in TCRs or PIs**
  - **Precautions/Contraindications**
    - BBW: Malignancy
    - BBW: Thrombosis
  - **Formulations**
    - Extended-release tablets: 15 mg, 30 mg, and 45 mg

Cytokine & CAM Antagonists

- **abrocitinib (Cibinqo)**
  - **January 2022: The FDA has approved abrocitinib (Cibinqo), a JAK inhibitor, indicated for the treatment of adults with refractory, moderate-to-severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable; it is not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, or with other immunosuppressants**
  - **Indications**
    - **The treatment of adults with refractory, moderate-to-severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable**
    - **Limitation of Use: Not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, or with other immunosuppressants**
  - **Precautions/Contraindications**
    - **BBW: Malignancy**
    - **BBW: Increased risk of serious bacterial, fungal, viral and opportunistic infections**
    - **BBW: Thrombosis**
    - **Renal Impairment: Avoid use in patients with severe renal impairment or end-stage renal disease**
    - **Hepatic Impairment: Avoid use in patients with severe hepatic impairment**
  - **Dosing**
    - **Recommended dosage is 100 mg orally once daily**
    - **200 mg orally once daily is recommended for those patients who are not responding to 100 mg once daily**
  - **Formulations**
    - **Tablets: 50 mg, 100 mg, and 200 mg**

Cytokine & CAM Antagonists

- **risankizumab-rzaa (Skyrizi)**
  - **January 2022: FDA approved for treatment of active psoriatic arthritis (PsA) in adults; previously approved for plaque psoriasis in adults**
  - **June 2022: FDA approved Skyrizi for the treatment of moderately to severely active Crohn's disease in adults**
  - **Indications**
    - Moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy
    - **Active psoriatic arthritis in adults**
    - **Moderately to severely active Crohn's disease in adults**
  - **Precautions/Contraindications**
    - Hepatotoxicity in Treatment of Crohn’s Disease: Drug-induced liver injury during induction has been reported. Monitor liver enzymes and bilirubin levels at baseline and, during induction, up to at least 12 weeks of treatment. Monitor thereafter according to routine patient management
  - **Dosing**
    - **Stratified by indication (found in TCR/PI)**
  - **Formulations**
    - Subcutaneous injection:
      - 150 mg/mL in each single-dose prefilled pen
      - 75 mg/0.83 mL in each single-dose prefilled syringe
      - 150 mg/mL in each single-dose prefilled syringe
      - 180 mg/1.2 mL (150 mg/mL) in each single-dose prefilled cartridge
      - 360 mg/2.4 mL (150 mg/mL) in each single-dose prefilled cartridge
    - Intravenous infusion (3) • Injection: 600 mg/10 mL (60 mg/mL) in each single-dose vial

Cytokine & CAM Antagonists

- **tocilizumab (Actemra)**
  - **March 2022: FDA approved Actemra IV formulation for the treatment of giant cell arteritis with a dosage of 6 mg/kg every 4 weeks administered IV over 60 minutes, prescribed in combination with a tapering course of glucocorticoids The previously approved SC formulation can be self-administered as 162 mg once every weeks in combination with a tapering course of glucocorticosteroids. The IV and SC regimens may be used alone after stopping glucocorticoids. IV formulation is also indication for RA, JIA, and cytokine release syndrome, but not for systemic sclerosis-associated interstitial lung disease (which is only treated with SC formulation). When switching from IV to SC dosage, administer the first SC dose instead of the next scheduled IV dose**
  - **Indications**
    - Rheumatoid Arthritis (RA), Giant Cell Arteritis (GCA), Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD), Polyarticular Juvenile Idiopathic Arthritis (PJIA), Systemic Juvenile Idiopathic Arthritis (SJIA), Cytokine Release Syndrome (CRS)
  - **Precautions/Contraindications**
    - BBW: Serious infections
    - BBW: Tuberculosis
  - **Dosing**
    - Stratified by indication (found in TCR/PI)
  - **Formulations**
    - **IV Infusion:**
      - **Injection: 80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), 400 mg/20 mL (20 mg/mL) in single-dose vials for further dilution prior to intravenous infusion**
    - Subcutaneous Injection
      - Injection: 162 mg/0.9 mL in a single-dose prefilled syringe or single-dose prefilled ACTPen autoinjector

Cytokine & CAM Antagonists

- **baricitinib (Olumiant)**
  - **June 2022: FDA approved a new indication for the treatment of adults with severe alopecia areata**
  - **Indications**
    - The treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF blockers
    - The treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO
    - **The treatment of adult patients with severe alopecia areata**
  - **Precautions/Contraindications**
    - BBW: Increased risk of serious bacterial fungal, viral and opportunistic infections
    - BBW: Higher rate of all-cause mortality including sudden CV death
    - BBW: Malignancies
    - BBW: Thrombosis
  - **Dosing**
    - **Alopecia Areata:**
      - **2 mg once daily. Increase to 4 mg once daily, if the response to treatment is not adequate**
      - **For patients with nearly complete or complete scalp hair loss, with or without substantial eyelash or eyebrow hair loss, consider treating with 4 mg once daily**
      - **Reduce the dose to 2 mg once daily when an adequate response has been achieved**
    - **Stratified by indication (found in TCR/PI)**
  - **Formulations**
    - Tablets: 4 mg, 2 mg, 1 mg

Cytokine & CAM Antagonists

- **adalimumab-adaz (Hyrimoz)**
  - **July 2022: The indication for polyarticular JIA has been expanded to include patients ≥ 2 years old; previously, Hyrimoz was only indicated certain JIA patients ≥ 4 years old. Additionally, the indication of Crohn's disease has also been expanded to include patients ≥ 6 years old; previously, Hyrimoz was only indicated for adults with Crohn's disease**
  - **Indications**
    - Rheumatoid Arthritis (RA), **Juvenile Idiopathic Arthritis (JIA)**, Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), **Crohn's Disease (CD)**, Ulcerative Colitis (UC), and Plaque Psoriasis (Ps)
  - **Precautions/Contraindications**
    - BBW: Increased risk of serious bacterial fungal, viral and opportunistic infections
    - BBW: Malignancies
  - **Dosing**
    - **Stratified by indication and age (found in TCR/PI)**
  - **Formulations**
    - Injection: 40 mg/0.8 mL in a single-dose prefilled glass syringe (with BD UltraSafe Passive Needle Guard)
    - Injection: 40 mg/0.8 mL in a single-dose prefilled pen (Sensoready Pen)
    - Injection: 10 mg/0.2 mL in a single-dose prefilled glass syringe

Cytokine & CAM Antagonists

- **adalimumab-fkjp (Hulio)**
  - **July 2022: The indication for polyarticular juvenile idiopathic arthritis (JIA) has been expanded to include patients ≥ 2 years old; previously, Hulio was only indicated for certain JIA patients ≥ 4 years old. Additionally, the indication of Crohn's disease has also been expanded to include patients ≥ 6 years old; previously, Hulio was only indicated for adults with Crohn's disease**
  - **Indications**
    - Rheumatoid Arthritis (RA), **Juvenile Idiopathic Arthritis (JIA)**, Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), **Crohn's Disease (CD)**, Ulcerative Colitis (UC), and Plaque Psoriasis (Ps)
  - **Precautions/Contraindications**
    - BBW: Increased risk of serious bacterial fungal, viral and opportunistic infections
    - BBW: Malignancies
  - **Dosing**
    - **Stratified by indication and age (found in TCR/PI)**
  - **Formulations**
    - Injection: 40 mg/0.8 mL in a single-dose prefilled glass syringe (with BD UltraSafe Passive Needle Guard)
    - Injection: 40 mg/0.8 mL in a single-dose prefilled pen (Sensoready Pen)
    - Injection: 10 mg/0.2 mL in a single-dose prefilled glass syringe

Cytokine & CAM Antagonists

- **ustekinumab (Stelara)**
  - **August 2022: The FDA approved for the treatment of pediatric patients ≥ 6 years of age with active PsA; previously, only approved in adults with active PsA**
  - **Indications**
    - Adult patients with:
      - Moderate to severe plaque psoriasis (Ps) who are candidates for phototherapy or systemic therapy
      - Active psoriatic arthritis (PsA)
      - Moderately to severely active Crohn's disease (CD)
      - Moderately to severely active ulcerative colitis
    - **Pediatric patients 6 years and older with:**
      - Moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy
      - **Active psoriatic arthritis (PsA)**
  - **Precautions/Contraindications**
    - Tuberculosis (TB): Evaluate patients for TB prior to initiating treatment. Initiate treatment of latent TB before administering Stelara
  - **Dosing**
    - **Stratified by indication and age (found in TCR/PI)**
  - **Formulations**
    - Subcutaneous Injection:
      - Injection: 45 mg/0.5 mL or 90 mg/mL solution in a single-dose prefilled syringe
      - Injection: 45 mg/0.5 mL solution in a single-dose vial
    - Intravenous Infusion
      - Injection: 130 mg/26 mL (5 mg/mL) solution in a single-dose vial

Cytokine & CAM Antagonists

- **adalimumab-afzb; adalimumab-atto (Abrilada; Amjevita)**
  - **August 2022: The FDA approved for use in patients as young as 2 years of age for polyarticular JIA (previously in those ≥ 4 years of age) and in those as young as 6 years of age for CD (previously only in adults)**
  - **Indications**
    - Rheumatoid Arthritis (RA), **Juvenile Idiopathic Arthritis (JIA)**, Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), **Crohn's Disease (CD)**, Ulcerative Colitis (UC), and Plaque Psoriasis (Ps)
  - **Precautions/Contraindications**
    - BBW: Serious infections
    - BBW: Malignancy
  - **Dosing**
    - **Stratified by indication and age (found in TCR/PI)**
  - **Formulations**
    - Injection:
      - Single-dose prefilled pen (ABRILADA Pen): 40 mg/0.8 mL (3)
      - Single-dose prefilled glass syringe: 40 mg/0.8 mL, 20 mg/0.4 mL, 10 mg/0.2 mL
      - Single-dose glass vial for institutional use only: 40 mg/0.8 mL

Cytokine & CAM Antagonists

- **deucravacitinib (Sotyktu)**
  - **September 2022: FDA approved deucravacitinib, an allosteric selective tyrosine kinase 2 inhibitor, for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy**
  - **Indications**
    - **The treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy**
    - **Limitations of Use: Not recommended for use in combination with other potent immunosuppressants**
  - **Precautions/Contraindications**
    - **Tuberculosis: Evaluate for TB prior to initiating treatment**
    - **Malignancy: Malignancies including lymphomas were observed in clinical trials**
    - **Rhabdomyolysis and elevated CPK**
    - **Laboratory Abnormalities: Periodically evaluate serum triglycerides. Evaluate liver enzymes at baseline and thereafter in patients with known or suspected liver disease**
    - **Not recommended in patients with severe hepatic impairment (Child-Pugh C)**
  - **Dosing**
    - **Recommended dosage is 6 mg orally once daily, with or without food**
  - **Formulations**
    - **Tablets: 6 mg**

Cytokine & CAM Antagonists

- **spesolimab-sbzo (Spevigo)**
  - **September 2022: FDA approved the interleukin-36 receptor antagonist, spesolimab-sbzo, for the treatment of generalized pustular psoriasis flares in adults**
  - **Indications**
    - **The treatment of generalized pustular psoriasis flares in adults**
  - **Precautions/Contraindications**
    - **Tuberculosis: Evaluate for TB prior to initiating treatment**
    - **Infections: May increase the risk of infections. Do not initiate treatment during any clinically important active infection. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur after treatment**
  - **Dosing**
    - **Administer as a single 900 mg dose by intravenous infusion over 90 minutes. If flare symptoms persist, may administer an additional intravenous 900 mg dose one week after the initial dose**
  - **Formulations**
    - **Injection: 450 mg/7.5 mL (60 mg/mL) solution in a single-dose vial**

Cytokine & CAM Antagonists

- **FDA Communications**
  - **Xeljanz, Xeljanz XR- February 2021**
    - **FDA is alerting the public that preliminary results from a safety clinical trial show an increased risk of serious heart-related problems and cancer with tofacitinib compared to TNF inhibitors**
    - **FDA advises patients should not stop taking prescribed tofacitinib without consulting their physician**
    - **FDA will communicate final conclusions and recommendations once their review is complete**
  - **Xeljanz, Xeljanz XR; Olumiant, Rinvoq- September 2021**
    - **FDA is requiring revisions to the Boxed Warning of the labels for tofacitinib (Xeljanz/Xeljanz XR), baricitinib (Olumiant), and upadacitinib (Rinvoq) to include information about increased risks of serious heart-related events, cancer, blood clots, and death**
    - **While this change is based on data from clinical trials of tofacitinib (Xeljanz/Xeljanz XR) in treating rheumatoid arthritis and ulcerative colitis, Olumiant and Rinvoq are included in the action based on their shared mechanisms of action with Xeljanz and FDA considers that these medicines may have similar risks as Xeljanz**
    - **This action by the FDA does not apply to other JAK inhibitors (ruxolitinib [Jakafi] and fedratinib [Inrebic], which are used in the oncology setting; FDA is also limiting all approved uses of Xeljanz/Xeljanz XR, Olumiant, and Rinvoq to certain patients who have not responded or cannot tolerate at least 1 TNF blocker**

Cytokine & CAM Antagonists

- **Drug Shortage**
  - **Actemra (tocilizumab)- August 2021**
    - **On 8/20/21, FDA reported that Actemra 200 mg/mL, 400 mg/mL, 80 m/4 mL vials are unavailable**
    - **ASHP also reports shortage of the 162 mg/0.9 mL prefilled syringe and 162 mg/0.9 mL Actipen is available on allocation**
    - **Shortage is due to increased demand**

Appendices

Guidelines - Opioid, Long-Acting

- **American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP), 2020**
  - Published a new clinical practice guideline on the managing acute pain associated from non–low back, musculoskeletal injuries in adults who are outpatient
  - Recommendations are provided for nonpharmacologic and pharmacologic treatment modalities
  - Clinicians are recommended to treat patients with topical NSAIDs with or without menthol gel as first-line therapy to decrease or relieve symptoms and to improve physical functioning and the patient's treatment satisfaction
  - It is suggested that clinicians treat patients with oral NSAIDs (to reduce/relieve symptoms and to improve physical function) or with oral acetaminophen to reduce pain
  - Additionally, it is suggested that clinicians treat patients with specific acupressure for reduction of pain and improvement of physical functioning or with transcutaneous electrical nerve stimulation to reduce pain
  - Lastly, it is suggested against clinicians treating patients with opioids, including tramadol

Opioid, Long-Acting – Guidelines

- FDA, 2019
  - FDA announced changes to the Transmucosal Immediate-Release Fentanyl (TIRF) REMS program
  - Changes include requiring prescribers to document a patient's opioid tolerance concurrently with each prescription of a TIRF medicine for outpatient use
  - Requiring inpatient pharmacies to develop internal policy and procedures to verify opioid tolerance in hospitalized patients requiring TIRF medicines
  - TIRF meds for outpatient use must have evidence or other documentation of safe use conditions, including concurrent documentation of opioid tolerance; and requiring the development of a new patient registry to monitor for serious adverse events including overdose (both fatal and non-fatal)

- CDC, 2019
  - CDC clarified that their guidelines on opioid prescribing are not intended to deny opioid therapy for pain management for any patients with chronic pain, particularly in pts with sickle cell disease, undergoing cancer treatment, and cancer survivors with chronic pain
  - It aims to ensure that clinicians and patients consider all safe and effective treatment options

Opioid, Long-Acting – Guidelines

- **Department of Health and Human Services, 2019**
  - In October 2019, the HHS published a new guideline for clinicians on dosage reduction or discontinuation of long-term opioid analgesics
  - This guidance discusses the risks of opioid taper and advises that opioids should not be quickly tapered or discontinued abruptly due to the potential for opioid withdrawal which can result in acute withdrawal symptoms, pain exacerbation, psychological distress, and suicidal ideation in patients who are physiologically dependent
  - Except for life-threatening circumstances (e.g., impending overdose), it is not recommended to abruptly reduce an opioid dose or discontinue an opioid
  - Guidance details situations when it may be appropriate to taper to a reduced dosage (e.g., pain improvement, patient request, no clinically meaningful improvement in pain or function with opioids, increasing doses without improvements in pain, signs of opioid misuse, side effects impacting function or quality of life, risks for an impending overdose/serious event, concurrent medications or comorbidities increasing the risk for adverse events, extended treatment period without clear benefits versus harms)
  - Other key recommendations include: referring patients with serious mental illness, high suicide risk, or suicidal ideation to a behavioral health provider prior to taper; assessing patients for opioid use disorder if they show signs of opioid misuse and offering medication-assisted treatment if appropriate; advising patients of risks for overdose if they abruptly return to their higher dose; tapering by 5% to 20% every 4 weeks is common, but longer tapering schedules may be required; and considering transition to buprenorphine for patients on high doses and unable to taper

Treatment Guidelines - Angiotensin Modulators

- The American Heart Association (AHA), 2020
  - Issued a Scientific Statement regarding the accurate measurement of blood pressure (BP).
  - Ambulatory BP monitoring is considered the standard for out-of-office BP assessment
  - Automated oscillometric devices have been validated to provide accurate BP measurements while reducing human errors, even without an observer being present
  - For high-risk adults with stage 1 hypertension who have preexisting CVD or an estimated 10-year ASCVD risk of at least 10%, the guideline recommends initiating drug treatment for those with an average BP of 130/80 mm Hg or higher (class I recommendation, high-quality evidence)
  - For lower-risk adults without preexisting CVD and an estimated 10-year ASCVD risk less than 10%, the BP threshold for drug treatment is 140/90 mm Hg or higher (class I recommendation, low-quality evidence)
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Guidelines – Hepatitis C Agents

- The US Preventative Services Task Force, 2020
  - In 2020, the United States Preventive Services Task Force (USPSTF) expanded the population for a 1-time screening to asymptomatic adults 18 to 79 years of age
  - Similarly, joint guidelines from the American Association for Liver Diseases (AASLD) and the Infectious Disease Society of America (IDSA) recommend a 1-time, routine, opt-out HCV testing for anyone 18 years and older

- Centers for Disease Control and Prevention (CDC), 2020
  - Recommends that in areas where the HCV infection rate is ≥ 0.1%, all adults be screened at least once for hepatitis C virus (HCV) infection, and that all pregnant women be screened during each pregnancy

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Guidelines - Antimigraine Agents

- American Headache Society (AHS), 2019
  - Published its position statement on integrating new migraine treatments into clinical practice
  - There were no changes in recommended usage or place in therapy for agents in this class from previous guidelines
  - Included recommendations regarding use non-triptan, injectable agents, including Botox and monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) (Ajovy, Emgality or the CGRP receptor Aimovig) for migraine prevention in patients who experience episodic (CGRP agents only) or chronic (both classes) migraine

- American Academy of Neurology (AAN) & American Headache Society (AHS), 2019
  - In their 2012 practice guidelines (reaffirmed 2015), pharmacologic treatment for episodic migraine prevention in adults, the AAN and the AHS advise that antiepileptic drugs (divalproex sodium, sodium valproate, topiramate) and beta-blockers (metoprolol, propranolol, timolol) are established as effective in migraine prevention, with the exception of frovatriptan which is established for short-term menstrually associated migraine (MAM) prevention
  - Naratriptan, zolmitriptan, antidepressants (amitriptyline, venlafaxine), and beta-blockers (atenolol, nadolol) are probably effective in migraine prevention; but no triptan is approved for the prevention of migraines
  - **In 2019, AAN and AHS updated the guidelines for acute treatment of migraine in children and adolescents**
  - **They endorse the use of sumatriptan/naproxen and almotriptan oral tablets, rizatriptan ODT, and nasal zolmitriptan in adolescents to reduce headache pain**
  - **Triptans have more supportive evidence in adolescents than in children, where NSAIDs and acetaminophen are recommended options**

Treatment Guidelines, European Society of Cardiology (ESC) and the European Respiratory Society (ERS), February 2016

- **At the time of diagnosis of PAH**, the **suggested initial approach is the adoption of general measures** (exercise training, psychosocial support, rehabilitation) **and the initiation of supportive therapy** (oral anticoagulation, diuretics, digoxin, and long-term oxygen therapy, if needed
- **Patients who are at low or intermediate risk for 1-year mortality can be treated with either initial monotherapy or initial oral combination therapy**
- **If initial monotherapy** is chosen, **no evidence-based first-line monotherapy can be proposed** because there are no head-to-head comparisons
- If **initial combination therapy** is chosen, **ambrisentan plus tadalafil has been given a higher grade recommendation** because the combination has proven to be superior to initial ambrisentan or tadalafil monotherapy in delaying clinical failure

Treatment Guidelines, European Society of Cardiology (ESC) and the European Respiratory Society (ERS), February 2016

Therapy	Recommendation	Strength of Recommendation
Initial monotherapy	WHO-FC II: ambrisentan (Letairis), bosentan (Tracleer), macitentan (Opsumit), sildenafil (Revatio), tadalafil (Adcirca), riociguat (Adempas), and selexipag (Uptravi) WHO-FC III: ambrisentan, bosentan, macitentan, sildenafil, tadalafil, riociguat, selexipag, IV epoprostenol (Flolan®/Veletri®), inhaled iloprost (Ventavis), SC or inhaled treprostinil (Remodulin®, Tyvaso) and oral or IV treprostinil (Orenitram, Remodulin) WHO-FC IV: IV epoprostenol (Level I, Grade A), ambrisentan, bosentan, macitentan, sildenafil, tadalafil, riociguat, inhaled iloprost, SC, IV or inhaled treprostinil	Level I, Grade A or B for all Level I, Grade A or B Level IIa or IIb, Grade B or C for treprostinil Level IIb, Grade C
Initial combination therapy	WHO-FC II: • Ambrisentan + tadalafil • Other endothelin receptor antagonist (ERA) + phosphodiesterase type 5 inhibitor (PDE-5i) WHO-FC III: • Ambrisentan + tadalafil • Other ERA + PDE-5i, bosentan + sildenafil + IV epoprostenol, bosentan + IV epoprostenol, other ERA or PDE-5i + SC treprostinil, other ERA or PDE-5i + other IV prostacyclin analogues WHO-FC IV: • Ambrisentan + tadalafil • Other ERA + PDE-5i, bosentan + sildenafil + IV epoprostenol, bosentan + IV epoprostenol, other ERA or PDE-5i + SC treprostinil, other ERA or PDE-5i + other IV prostacyclin analogues	Grade I, Level B Grades IIa, Grade C Grade I, Level B Grades IIa, or IIb Grade C Grades IIa, or IIb Grade C

Magellan Rx MANAGEMENT℠

American College of Chest Physicians (CHEST), 2014 (Updated 2018)

- At the time of diagnosis of PAH
  - The suggested **initial approach** is
    - **Treatment of contributing causes of PAH** (e.g., sleep apnea, systemic hypertension)
    - The **adoption of general measures** (supervised exercise activity, influenza and pneumonia vaccinations, and avoidance of pregnancy, high altitudes, and non-essential surgery)
    - The **initiation of supportive therapy** (oxygen therapy if needed to maintain oxygen saturations > 91%)
    - Palliative care

- Unless there is a contraindication, acute vasoreactivity testing should be performed at a facility with experience in performing and interpreting the test (UCBS)
  - **A trial of high dose oral calcium channel blockers (CCB), such as amlodipine, diltiazem, or nifedipine, is recommended in patients with a positive acute vasoreactive test**
  - Furthermore, **CCBs should not be used empirically to treat PAH** in the absence of demonstrated acute vasoreactivity (UCBS)
  - Patients should be followed closely for response and side effects of therapy. Alternative or additional PAH therapy should be initiated if improvement to WHO FC I or II are not seen after the trial of a CCB

American College of Chest Physicians (CHEST), 2014 (Updated 2018)

- In treatment-naive patients who are not candidates for, or who have failed CCB therapy, treatment is based on WHO functional class (UCBS)
  - In treatment-naïve patients with WHO FC I
    - Continued monitoring for disease progression is advised (UCBS)
  - **In treatment-naïve patients with WHO FC II**
    - **Initial combination therapy with ambrisentan and tadalafil to improve 6-minute walk distance (6MWD) is suggested (weak recommendation, moderate quality evidence)**
    - **In patients who are unwilling to take or cannot tolerate combination therapy, then monotherapy with ambrisentan, sildenafil (strong recommendations, low quality evidence for both), bosentan, macitentan, tadalafil, or riociguat (UCBS for all 4 products) is recommended**
  - **In treatment-naïve patients with WHO FC III without rapid disease progression or poor prognosis**
    - **Initial combination therapy with ambrisentan and tadalafil to improve 6MWD is suggested (weak recommendation, moderate quality evidence)**
    - **In patients who are unwilling to take or cannot tolerate combination therapy, then monotherapy with ambrisentan, bosentan, sildenafil (strong recommendations, low or moderate quality to improve 6MWD for all 3 products), macitentan, tadalafil, or riociguat (UCBS for all 3 products) is recommended**
  - For treatment-naïve patients with WHO FC IV
    - Initial therapy with a parenteral prostanoid agent is recommended (UCBS)
    - In patients who cannot comply with parenteral administration, inhaled prostanoid in combination with an oral endothelin receptor antagonist or an oral PDE-5 inhibitor are alternatives (UCBS)