Prime THERAPEUTICS™

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Agenda Topics

Prime THERAPEUTICS™

Overview of Disease State

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Anticonvulsants

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ANTICONVULSANTS : SUCCINIMIDES

Disease State Description - Anticonvulsants

Epilepsy/Seizure Disorders

- Epilepsy is one of the most common disorders of the central nervous system (CNS), affecting 3.4 million Americans
  - Defined as 2 unprovoked seizures more than 24 hours apart, or 1 unprovoked seizure with at least a 60% probability of further seizures in the next 10 years
- Isolated seizures may occur during a febrile illness, after head trauma, or as a result of withdrawal from alcohol or sedative/hypnotics

The International League Against Epilepsy (ILAE), 2017

- Revised seizure classifications which are based on 3 key features: seizure origin in the brain, level of awareness during the seizure, and other seizure features
  - Generalized seizures: Involves both sides of the brain at onset and may involve cortical and subcortical structures
  - Focal to bilateral seizures: Seizures that starts on 1 side or area of the brain and spread to both sides and may or may not affect awareness and are further broken down as “aware” and “impaired awareness”
    - In some cases, it may not be possible to determine the patient’s level of awareness, and, therefore, the term of awareness may be considered as “awareness unknown” or not used
  - Unknown onset seizures: Area of onset not evident
  - Non-motor: If other symptoms, such as changes in sensation, emotions, and thinking occur
  - Generalized tonic-clonic seizure: Seizures with stiffening (tonic) and jerking (clonic)
  - Absence seizures: Generalized non-motor seizures involving brief changes in awareness, staring, and repeated movements

Disease State Description - Anticonvulsants

The International League Against Epilepsy (ILAE), 2022

- Developed classifications of epilepsy syndromes
  - Epilepsy syndrome is defined as a characteristic cluster of clinical and electroencephalography (EEG) features, often supported by specific etiological findings (structural, genetic, metabolic, immune, and infectious)
  - ILAE provides definitions and classifications of syndromes according to categories divided by age of onset
    - Syndromes commonly have age-dependent presentations, features, and specific comorbidities
  - Neonates and infants: Focuses on the clinical and laboratory features of epilepsy syndromes with onset from birth to 2 years of age and includes 2 major groups of syndromes (self-limited epilepsy syndrome, and developmental and epileptic encephalopathies)
    - Generally, children with epilepsy developing very early in life experience significant cognitive and behavioral comorbidity and have higher rates of drug resistance
  - Onset between ages 2 and 12 years: Categorized broadly as self-limited focal epilepsies, generalized epilepsy syndromes (theorized to have a genetic cause), and developmental and/or epileptic encephalopathies
    - Childhood syndromes may evolve from syndromes of infancy or may present with a severe, acute encephalopathy following prior normal development
  - Idiopathic generalized epilepsy syndromes and syndromes that occur with a variable age of onset, either in childhood or beyond the age of 18 years are further described and categorized by ILAE

Guidelines - Anticonvulsants

The American Academy of Neurology (AAN), 2024

- Issued a guideline for use of antiseizure medications (ASMs) in patients with epilepsy of childbearing potential (PWECP)
- According to the guideline, healthcare professionals (HCPs) should recommend ASMs and doses that optimize seizure control and fetal outcomes at the earliest possible opportunity prior to conception
- To reduce risk for major congenital malformations, lamotrigine, levetiracetam, or oxcarbazepine should be considered when appropriate and valproic acid should be avoided when possible
- The guideline also recommends supplementation with ≥ 0.4 mg folic acid daily before and during pregnancy for all PWECPs treated with ASMs

diazepam (Libervant)

April 2024 – FDA approved for acute treatment of intermittent, stereotypic episodes of frequent seizure activity (e.g., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 2 to 5 years old

Warnings:

- **BBWs: Risk of concomitant use with opioids; Abuse, misuse, and addiction; Dependence and withdrawal reactions**
- **CI: Acute-narrow angle glaucoma**
- **Central nervous system (CNS) depression, suicidal behavior and ideation, glaucoma**
- **Scheduled IV Controlled Substance**

Recommended Dosage:

- **Dependent on the patient's weight and administered by a caregiver**
- **Second Dose (if needed): May be administered at least 4 hours after the first dose**
- **Do not use more than 2 doses to treat a single episode**
- **Do not use to treat > 1 episode every 5 days or > 5 episodes per month**

Availability:

- **Buccal film: 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg**

Weight	Libervant Dose
6 kg to 10 kg	5 mg
11 kg to 15 kg	7.5 mg
16 kg to 20 kg	10 mg
21 kg to 25 kg	12.5 mg
26 kg to 30 kg	15 mg

lacosamide (Motpoly XR)

June 2024 – FDA approved new indication for adjunctive therapy for treatment of primary generalized tonic-clonic seizures in adults and pediatrics weighing ≥ 50 kg

FDA Indications:

- Treatment of partial-onset seizures in adults and in pediatric patients weighing at least 50 kg
- **Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and in pediatric patients weighing at least 50 kg**

Warnings:

- Schedule V Controlled Substance, suicidal behavior and ideation, dizziness, ataxia, cardiac rhythm and conduction abnormalities, syncope, drug reaction with eosinophilia and systemic symptoms (DRESS)/multi-organ hypersensitivity
- Motpoly XR should be gradually withdrawn to minimize the potential of increased seizure frequency

Recommended Dosage:

Age and Body Weight	Initial Dosage	Titration Regimen	Maintenance Dosage
Adults (17 years and older)	Monotherapy: 200 mg once daily **Adjunctive Therapy: 100 mg once daily**	**Increase by 100 mg once daily every week**	Monotherapy: 300 mg to 400 mg once daily **Adjunctive Therapy: 200 mg to 400 mg once daily**
Pediatric patients ≥ 50 kg	**100 mg once daily**	**Increase by 100 mg once daily every week**	Monotherapy: 300 mg to 400 mg once daily **Adjunctive Therapy: 200 mg to 400 mg once daily**

- **Dose adjustment is recommended for severe renal impairment and mild or moderate hepatic impairment**
- **Use in severe hepatic impairment is not recommended**

Availability:

- Extended-release Capsules:100 mg, 150 mg, 200 mg

Alzheimer's Agents

ANTIDEMENTIA AGENTS :
ANTIDEMENTIA AGENTS : ANTI-AMYLOID ANTIBODIES

Disease State Description - Alzheimer's Agents

Dementia

- Characterized by irreversible loss of or decline in memory and other cognitive abilities
- Approximately 6.7 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 fifth leading cause of death in the United States (US)
- Other types of dementia include cerebrovascular dementia, Lewy body disease, Parkinson’s disease (PD) dementia, frontotemporal lobar degeneration, hippocampal sclerosis, and mixed pathologies
- Some individuals may have reversible dementia due to an underlying cause such as thyroid hormone imbalance, vitamin deficiency, or increased brain pressure

Alzheimer’s Disease (AD)

- 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 Agents

Discontinuation

- **August 2024 – Namenda XR (memantine ER)**
  - Abbvie announced discontinuation of brand-name Namenda XR (memantine ER) capsules
  - Generics remain available

- **November 2024 – Namenda (memantine)**
  - Actavis announced discontinuation of brand-name Namenda 5 mg and 10 mg tablets
  - Generics remain available

Alzheimer's Agents

donanemab-azbt (Kisunla)

July 2024 – FDA approved an amyloid beta-directed antibody for treatment of Alzheimer's disease

- Treatment should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in the clinical trials
- Presence of amyloid beta pathology should be confirmed prior to starting treatment

Warnings:

- BBW: Monoclonal antibodies directed against aggregated forms of beta amyloid, including Kisunla, can cause amyloid related imaging abnormalities (ARIA), as ARIA with edema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H)
  - ARIA is usually asymptomatic, although serious and life-threatening events can rarely occur
  - Serious intracerebral hemorrhages >1 cm have occurred in patients treated with this class of medications
  - ARIA-E can cause focal neurologic deficits that can mimic ischemic stroke
- Infusion-Related Reactions: The infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy initiated as clinically indicated; consider pre-treatment with antihistamines, acetaminophen, or corticosteroids prior to subsequent dosing

Recommended Dosage:

- 700 mg intravenous infusion over 30 minutes every 4 weeks for the first 3 doses, then 1,400 mg every 4 weeks
- Consider stopping dosing based on reduction of amyloid plaques to minimal levels on amyloid positron emission tomography (PET) imaging

Availability:

- Injection: 350 mg/20 mL (17.5 mg/mL) in a single-dose vial

COPD Agents

ASTHMA AND COPD AGENTS : ANTICHOLINERGICS
ASTHMA AND COPD AGENTS : LONG ACTING MUSCARINIC AGENTS
ASTHMA AND COPD AGENTS : PHOSPHODIESTERASE 4 INHIBITORS
ASTHMA AND COPD AGENTS : LONG ACTING MUSCARINIC AGENT/ LONG ACTING BETA AGONIST COMBINATIONS

Disease State Description - COPD Agents

Chronic Obstructive Pulmonary Disease (COPD)

- Heterogenous lung condition characterized by chronic respiratory symptoms (e.g., dyspnea, cough, sputum production, and/or exacerbations) due to abnormalities of the airway and/or alveoli that cause persistent, often progressive, airflow obstruction
- In the United States (US), it is estimated that the number of individuals with a COPD diagnosis is approximately 16 million, and is now one of the top three causes for death worldwide
  - However, the US Preventive Services Task Force (USPSTF) recommends against routine screening for COPD in asymptomatic adults
- The most common COPD types are chronic bronchitis (CB) and pulmonary emphysema
  - Chronic bronchitis is defined by the presence of cough with expectorated sputum on a regular basis over a defined period and is present in 3% to 7% of healthy adults and up to 74% of patients with COPD
  - Pulmonary emphysema is a progressive lung disease that damages the air sacs (alveoli) in the lungs, making it difficult to breath

Guidelines - COPD Agents

The GOLD Global Initiative for Chronic Obstructive Lung Disease guidelines, 2025

- **Diagnosis:** A post-bronchodilator forced expiratory volume in 1 second to forced vital capacity ratio (FEV1/FVC) < 0.7 confirms presence of airflow limitation and a diagnosis of COPD
  - Overdiagnosis of COPD in elderly patients and underdiagnosis in 1% of young adults
  - For adults aged < 50 years with suspected COPD and a repeated (FEV1/FVC) < 0.7 , comparing the ratio with a predicted LLN or with z-scores may aid in managing this group of patients
- **Treatment for Dyspnea:** If the addition of a second long-acting bronchodilator does not improve symptoms, switch to inhaler device or molecules, implement or escalate nonpharmacologic treatment, or consider adding ensifentrine
- **Exacerbations Management:** For patients on Long-acting beta-2 agonists (LABA) + long-acting muscarinic antagonists (LAMA) + inhaled corticosteroids (ICS) with continued exacerbations:
  - Consideration of dupilumab for those with eosinophil levels ≥ 300 cells/μL and symptoms of chronic bronchitis
  - Consideration of azithromycin for not current smokers
  - Roflumilast considered for patients with FEV1 <50%, chronic bronchitis symptoms, and a history of previous severe exacerbations
- **Management of patients currently on LABA+ICS:**
  - Patients with major symptoms are advised to change to LABA/LAMA or LABA/LAMA/ICS depending on prior ICS response
  - Patient who have COPD with no features of asthma on LABA/ICS and are well-controlled for symptoms and exacerbations: continue treatment
  - For patients with further exacerbations:
    - Blood eosinophil count <100 cells/μL: Switch to LABA/LAMA
    - Blood eosinophil count ≥ 100 cells/μL: Escalate to LABA/LAMA/ICS

COPD Agents

Ensifentrine (Ohtuvayre)

June 2024 - FDA approved a first-in-class selective dual inhibitor of phosphodiesterase 3 (PDE3) inhibitor and phosphodiesterase 4 (PDE4), for maintenance treatment of COPD in adults

Warnings:

- Should not use to treat acute symptoms of bronchospasm
- If paradoxical bronchospasm occurs, discontinue and institute alternative therapy
- Increase in psychiatric adverse reactions, including suicidality
- Ensifentrine exposure increases in patients with hepatic impairment; use with caution

Recommended Dosage:

- 3 mg (one ampule) twice daily administered by oral inhalation using a standard jet nebulizer with a mouthpiece

Availability:

- Inhalation suspension: 3 mg/2.5 mL aqueous suspension in unit-dose ampules

Immunomodulators, Asthma

ASTHMA AND COPD AGENTS : MONOCLONAL ANTIBODIES

Disease State Description - Immunomodulators, Asthma

Asthma

- Annually, there approximately 1 million emergency department visits in the United States (US) due to asthma
- An estimated 8.7% of adults and 6.2% of children have asthma in the US
- Asthma is typically characterized by chronic airway inflammation and hyperresponsiveness and is diagnosed based on history of respiratory symptoms (e.g., wheeze, shortness of breath, cough) and evidence of variable expiratory airflow limitation
- Type 2 inflammation is present in most individuals with severe asthma and is characterized by the presence of cytokines and elevation of eosinophils or fractional concentration of exhaled nitric oxide (FeNO)

Guidelines - Immunomodulators, Asthma

The Global Initiative for Asthma (GINA), 2024

- The global strategy for asthma management and prevention states:
  - Although most patients will be able to achieve good asthma control with standard management strategies, a subset of patients remain uncontrolled even when treatments are optimized
  - For patients with Type 2 inflammation:
    - A trial of non-biologic therapies is recommended as the first step in treatment, with consideration of individual patient phenotypes
    - If non-biologic interventions are not effective, targeted biologic treatment can be an option, if available
      - Appropriate candidates have exacerbations and/or poor symptom control despite use of at least high-dose ICS/LABA therapy and should display allergic or eosinophilic biomarkers or need maintenance oral corticosteroids (OCS)
      - There are no head-to-head trials directly comparing biologic agents for patients with severe asthma who are eligible for more than one product
      - After a biologic agent is started, treatment should be given for 3-4 months in order to assess response
        - If response is good, treatment may be continued
        - If response is bad, treatment should be stopped, with consideration of a change to an alternative biologic agent
        - If response is unclear, a continued trial for an additional 6-12 months may be recommended

Guidelines - Immunomodulators, Asthma

Eosinophilic granulomatosis with polyangiitis (EGPA)

- Previously known as Churg-Strauss syndrome, is a systemic vasculitis of small-to-medium vessels, characterized by hypereosinophilia in the blood and tissues, inflammation of small to medium blood vessels, and the development of granulomas, inflammatory nodular lesions
- Many affected individuals have a history of allergy and/or asthma
- EGPA is a rare disease state affecting 1 to 3 out of 100,000 adults per year
- Onset may occur between 15 and 70 years of age, but diagnosis is typically made between 30 and 50 years of age
- While the direct cause of the disease is unknown, autoimmune, environmental, and genetic factors are thought to play a role
- Symptoms in early stages of the disease include coughing, wheezing, shortness of breath, and nasal symptoms
  - As hypereosinophilia and vasculitis progress, patients may experience fever, weight loss, abdominal pain, joint pain, and numbness
  - Ultimately, cardiac and neurologic manifestations can be life-threatening

Immunomodulators, Asthma

benralizumab (Fasenra)

September 2024 – FDA approved new indication for treatment of adults with eosinophilic granulomatosis with polyangiitis (EGPA)

FDA Indication:

- Add-on maintenance treatment of adult and pediatric patients ≥ 6 years old with severe asthma, and with an eosinophilic phenotype
- **Treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA)**

Limitation:

- Not for relief of acute bronchospasm or status asthmaticus

Warnings:

- Hypersensitivity reactions: anaphylaxis, angioedema, urticaria, rash

Recommended Dosage:

- Asthma in patients 6 to 11 years old is based on body weight
  - < 35 kg: 10 mg (one injection) SC every 4 weeks for the first 3 doses, then every 8 weeks thereafter
  - ≥ 35 kg: 30 mg (one injection) SC every 4 weeks for the first 3 doses, then every 8 weeks thereafter
- Asthma in patients ≥ 12 years of age: 30 mg SC every 4 weeks for first 3 doses followed by once every 8 weeks thereafter
- **EGPA: 30 mg SC every 4 weeks**

Availability:

- 10 mg/0.5 mL and 30mg/mL solution in a single-dose prefilled syringe
- 30 mg/mL solution in a single-dose autoinjector pen

Immunomodulators, Atopic Dermatitis

ATOPIC DERMATITIS AGENTS : JANUS KINASE (JAK) INHIBITORS - ORAL
ATOPIC DERMATITIS AGENTS : JANUS KINASE (JAK) INHIBITORS - TOPICAL
ATOPIC DERMATITIS AGENTS : MONOCLONAL ANTIBODIES
ATOPIC DERMATITIS AGENTS : PHOSPHODIESTERASE 4 INHIBITORS – TOPICAL

Disease State Description - Immunomodulators, Atopic Dermatitis

Atopic dermatitis (AD)

- 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
- Often referred to as “eczema,” AD affects up to 13% of children and about 7.3% of adults in the United States (US)
- 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 years
- 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”
- Evidence suggests that patients with asthma or food allergies have an increased severity of AD
- There are also associations between AD and allergic rhinitis, anxiety, depression, heart disease, osteoporosis, and obesity

Guidelines - Immunomodulators, Atopic Dermatitis

The American Academy of Allergy & Immunology/American College of Allergy, Asthma and Immunology (AAAAI/ACAAI) Joint taskforce (JTF), 2024

- Updated Guidelines for Atopic Dermatitis
- Emphasize a patient-centered approach, recommending a combination of topical and systemic treatments, including biologics, and emphasize the importance of education, trigger avoidance, and adherence to treatment plans
- Recommend treatment begin with topical therapies (topical corticosteroids, topical calcineurin inhibitors, crisaborole ointment, ruxolitinib cream) for any severity of AD (mild to severe)
- For moderate to severe disease, all recommend systemic therapy +/- topical therapy
- Most patients require topical treatments with biologics
- Dupilumab and tralokinumab are both strongly favored with high certainty of evidence for moderate to severe AD
- Dupilumab performed slightly better across several outcomes

Immunomodulators, Atopic Dermatitis

tralokinumab-ldrm (Adbry)

June 2024 – New dosage form of 300 mg/2mL single-dose autoinjector was approved for use in adults only

FDA Indications:

- Treatment of moderate-to-severe atopic dermatitis in adults 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; can be used with or without topical corticosteroids

Warnings:

- Hypersensitivity reactions, including anaphylaxis, and angioedema, conjunctivitis and keratitis, parasitic (helminth) infections, and risk of infection with live vaccines

Dosage:

- Adults: 600 mg subcutaneously loading dose, followed by 300 mg subcutaneously every other week
  - 300 mg SC every 4 weeks may be considered for adults < 100 kg who achieve clear or almost clear skin after 16 weeks of treatment
- Pediatrics Patients ≥ 12 years old: 300 mg subcutaneously loading dose, followed by 150 mg subcutaneously every other week

Availability:

- **Injection:**
  - 150 mg/mL solution in a single-dose prefilled syringe with needle guard
  - **300 mg/2 mL solution in a single-dose autoinjector**

Immunomodulators, Atopic Dermatitis

dupilumab (Dupixent)

September 2024 – FDA approved expanded indication for add-on maintenance treatment of inadequately controlled chronic rhinosinusitis with nasal polyps (CRSwNP) (previously chronic rhinosinusitis with nasal polyposis) to include pediatric patients aged 12 years and older; previously this indication was only approved in adults

October 2024 - FDA approved new indication as an add-on maintenance treatment for adults with inadequately controlled COPD and an eosinophilic phenotype

FDA Indications:

- Treatment of adult and pediatric patients ≥ 6 months with moderate-to-severe Atopic Dermatitis (AD) 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
- Add-on maintenance treatment of adult and pediatric patients aged 6 years and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma
  - Limitations of Use: Not for the relief of acute bronchospasm or status asthmaticus
- **Add-on maintenance treatment in adult and pediatric patients aged 12 years and older with inadequately controlled chronic rhinosinusitis with nasal polyps (CRSwNP)**
- Treatment of adult and pediatric patients aged 1 year and older, weighing at least 15 kg, with Eosinophilic Esophagitis (EoE)
- Treatment of adult patients with prurigo nodularis (PN)
- **Add-on maintenance treatment of adult patients with inadequately controlled COPD and an eosinophilic phenotype**
  - **Limitations of Use: Not for the relief of acute bronchospasm**

Immunomodulators, Atopic Dermatitis

dupilumab (Dupixent)

Warnings:

- Hypersensitivy reactions, including anaphylaxis, conjunctivitis and keratitis, eosinophilic conditions, reduction in corticosteroid dosage, arthralgia, parasitic (helminth) infections, avoid use of live vaccines

Recommended Dosage:

- **Stratified by indication, age, and weight (see TCR/PI)**
- **CRSwNP: 300 mg SC every other week**
- **COPD: 300 mg SC every other week**

Availability:

- Injection:
  - Single-Dose Pre-Filled Syringe with Needle Shield : 300 mg/2 mL and 200 mg/1.14 mL
  - Single-Dose Pre-Filled Pen: 300 mg/2 mL and 200 mg/1.14 mL

Immunomodulators, Atopic Dermatitis

lebrikizumab-lbkz (Ebglyss)

September 2024 - FDA approved an interleukin-13 antagonist indicated for the treatment of adult and pediatric patients 12 years of age and older who weigh at least 40 kg with moderate-to-severe atopic dermatitis 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

Warnings:

- **Hypersensitivity reactions, including angioedema and urticaria, conjunctivitis and keratitis, parasitic (helminth) infections, and avoid use of live vaccines during treatment**

Recommended Dosage:

- **Starting dose: 500 mg (two 250 mg injections) SC at Week 0 and Week 2, followed by 250 mg (one injection) SC every 2 weeks until Week 16 or later, when adequate clinical response is achieved**
- **Maintenance dose: 250 mg SC every 4 weeks**

Availability:

- **Injection:**
  - **250 mg/2 mL in a single-dose prefilled pen**
  - **250 mg/2 mL in a single-dose prefilled syringe with needle shield**

Cytokine and CAM Antagonist

CYTOKINE AND CAM ANTAGONISTS :

Disease State Description - Cytokine and CAM Antagonist

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 several proteins that contribute to the inflammatory response
- The actions of the individual cytokines are widely varied and contributes 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

Disease State Description - Cytokine and CAM Antagonist

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:
  - Immunoglobulin (Ig) superfamily
    - Bind to integrins on leukocytes and mediates their flattening onto the blood vessel wall with their subsequent extravasation into surrounding tissue
  - 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
  - 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

Disease State Description - Cytokine and CAM Antagonist

Ulcerative colitis (UC)

- Chronic inflammatory disease primarily affecting the colon and rectum and affects nearly 2 million individuals in the United States
- It has a protracted relapsing-remitting course with up to one-fifth of patients requiring colectomy and one-third requiring hospitalization for management of their disease
- UC only affects the inner lining of the colon and does not reach through other layers of the intestine wall, causing swelling and ulcers all along its path, leaving no healthy tissue
- Symptoms includes stool with blood or mucus, caused by ulcers, stomach cramping with bowel movement, and urgent need to have a bowel movement

Guidelines - Cytokine and CAM Antagonist

The American Gastroenterological Association (AGA), 2024

- Living Clinical Practice Guideline on Pharmacological Management of Moderate-to-Severe Ulcerative Colitis in Outpatient Adults
- Suggest early use of advanced therapies and/or immunomodulator therapy, rather than gradual step up after failure of 5-aminosalicylates
- Recommends the use of infliximab, golimumab, vedolizumab, tofacitinib, upadacitinib, ustekinumab, ozanimod, etrasimod, risankizumab, and guselkumab, and suggests the use of adalimumab, filgotinib, and mirikizumab over no treatment
- Patients who are naïve to advanced therapies (first-line therapy): Suggests higher-efficacy medication or intermediate-efficacy medication rather than a lower-efficacy medication
  - High efficacy medications: infliximab, vedolizumab, ozanimod, etrasimod, upadacitinib, risankizumab, and guselkumab
  - Intermediate efficacy medications: golimumab, ustekinumab, tofacitinib, filgotinib, and mirikizumab
  - Lower efficacy medications: adalimumab
- Patients who have previously been exposed to 1 or more advanced therapies, particularly tumor necrosis factor (TNF)-α antagonists: Suggests using a higher-efficacy medication or an intermediate-efficacy medication rather than a lower-efficacy medication
  - High efficacy medications: tofacitinib, upadacitinib, and ustekinumab
  - Intermediate efficacy medications: filgotinib, mirikizumab, risankizumab, and guselkumab
  - Lower efficacy medications: adalimumab, vedolizumab, ozanimod, and etrasimod
- Suggests the use of infliximab, adalimumab, and golimumab in combination with an immunomodulator over corresponding monotherapy
- No recommendation in favor of, or against, the use of non-TNF antagonist biologics in combination with an immunomodulator over non-TNF biologic alone
- Patients with UC who are in corticosteroid-free clinical remission for ≥ 6 months on combination therapy of TNF antagonists and an immunomodulator: Suggests against withdrawal of TNF antagonists, but makes no recommendation in favor of, or against, withdrawing immunomodulators
- Failed 5-aminosalicylates and have escalated to therapy with immunomodulators or advanced therapies: Suggests stopping 5-aminosalicylates

Disease State Description - Cytokine and CAM Antagonist

Crohn’s Disease

- Chronic inflammatory disease that can affect any part of the digestive tract, from the mouth to the anus
- Crohn's disease can impact a person's quality of life, but most people who have it can still lead active lives with long periods of remission
- CD affect all layers of the intestine walls, moving outward, causing swelling in patches, leaving areas of healthy tissue
- Symptoms include diarrhea that is usually not bloody, malnutrition (when parts of the digestive tract that absorb nutrients become inflamed, and mouth sores (as the entire digestive tract can be affected)

Guidelines - Cytokine and CAM Antagonist

The American Gastroenterological Association (AGA), 2021

- Adult outpatients with moderate to severe CD:
  - Recommends TNF antagonist (moderate evidence) or ustekinumab (moderate evidence) over no treatment for induction and maintenance of remission
  - Suggests the use of vedolizumab over no treatment for induction and maintenance of remission (low/moderate evidence)
- Biologic treatment-naïve adult outpatients with moderate to severe CD:
  - Recommends infliximab, adalimumab, or ustekinumab (moderate evidence) over certolizumab pegol (low evidence)
  - Suggest the use of vedolizumab over certolizumab pegol for the induction of remission
- Adult outpatients with moderate to severe CD who never responded to TNF antagonists:
  - Recommends ustekinumab (moderate evidence)
  - Suggests vedolizumab (low evidence) over no treatment of the induction of remission
- Patients previously responded to infliximab
  - Recommends adalimumab or ustekinumab (moderate evidence for both)
  - Suggests vedolizumab (low evidence) over no treatment for the induction of remission
- Recommends the use of biologic drug monotherapy over thiopurine monotherapy for the induction of remission (moderate evidence)
- Adult outpatients with moderate to severe CD who are treatment-naïve to biologics and immunomodulators:
  - Suggests infliximab plus thiopurines over infliximab monotherapy (moderate evidence) and adalimumab plus thiopurines over adalimumab monotherapy (very low evidence) for induction and maintenance of remission
- Does not make recommendations regarding the use of ustekinumab or vedolizumab as monotherapy or in combination with another agent
- Suggest the early introduction of a biologic over waiting until failure of 5-aminosalicylates and/or corticosteroids (low evidence)
- Patients with active perianal fistula:
  - Recommends infliximab over no treatment for the induction and maintenance of fistula remission (moderate evidence)
  - Suggests adalimumab, ustekinumab, or vedolizumab over no treatment for the induction or maintenance of fistula remission (low evidence)

Disease State Description - Cytokine and CAM Antagonist

Uveitis

- Non-infectious intermediate and posterior uveitis is inflammation of the intermediate and posterior uvea, while panuveitis is inflammation of the anterior chamber, vitreous humor, and choroid or retina simultaneously
  - Together, these represent the most severe and highly recurrent forms of uveitis
- The incidence of all cases of uveitis is approximately 25 to 52 cases per 100,000 patients per year, and anterior uveitis is the most common form of uveitis
- Initial treatment is typically with topical corticosteroids
- Adalimumab is generally reserved for patients with disease non-responsive to initial treatment
- Other treatments include systemic glucocorticoids, immunosuppressives, and intraocular implants

Guidelines - Cytokine and CAM Antagonist

American College of Rheumatology (ACR) and Arthritis Foundation, 2019

- Published guidelines on the treatment of uveitis associated with JIA, one of the most common extraarticular manifestation of JIA
- The group recommends select topical glucocorticoids in patients with JIA and active chronic anterior uveitis for short-term control, but for those who are unable to control symptoms with short-term therapy, they recommend adding systemic therapy in order to taper topical glucocorticoids
  - Changing or escalating systemic therapy is recommended after ≥ 3 months if control is not achieved
- For JIA patients who develop new chronic anterior uveitis despite stable systemic therapy, they recommend topical glucocorticoids prior to changing or escalating systemic therapy right away
- Regarding specific agents, they group recommends SC methotrexate conditionally over oral methotrexate; however, use of a TNF antagonist with methotrexate in severe active disease and sight-threatening complications is conditionally recommended over methotrexate monotherapy
- If starting a TNF antagonist, they conditionally recommend a monoclonal antibody over etanercept
  - Dose or frequency of the TNF antagonist should be escalated for an inadequate response prior to trying another biologic
  - Likewise, if a patient has failed a TNF antagonist following an escalated dose/frequency, changing to a different TNF antagonist is conditionally recommended over another biologic
- Abatacept or tocilizumab as biologics and mycophenolate, leflunomide, or cyclosporine as nonbiologic options are conditionally recommended in patients who have failed methotrexate and 2 monoclonal antibody TNF antagonists
- The disease should be well-controlled for 2 years on a DMARD and/or biologic therapy prior to tapering
- For pediatric patients with spondyloarthritis who develop acute anterior uveitis, the group conditionally recommends topical glucocorticoids prior to a change in systemic therapy

Disease State Description - Cytokine and CAM Antagonist

Psoriasis

- Chronic, inflammatory, immune-mediated, multisystem disease that affects up to 3.2% of the US population
- Psoriasis presents with well-demarcated, red plaques with silvery scale
- Although any area of the skin may be involved the most common areas affected are the scalp, elbows, knees, and presacral region
- Severity of psoriasis is defined by total body surface area (BSA) involved, with involvement of 3% BSA considered mild, involvement of 3%-10% BSA is considered moderate, and involvement of greater than 10% considered severe disease
- A classification of severe also can be made without BSA consideration if there are serious emotional consequences or when it occurs in areas including but not restricted to the hands, feet, scalp, face, or genital area

Psoriatic arthritis (PsA)

- Chronic inflammatory musculoskeletal disease associated with psoriasis, that commonly presents with peripheral arthritis, dactylitis, enthesitis, and spondylitis
- Nail lesions, including pitting and onycholysis occur in approximately 80%-90% of patients with PsA
- The incidence of PsA is approximately 6 per 100,000 per year and the prevalence is 1 to 2 per 1,000 people in the general population and affects men and women equally
- The distribution of the peripheral arthritis varies from asymmetric oligoarthritis (involving ≤ 4 joints) to symmetric polyarthritis (involving ≥ 5 joints)
- Distal interphalangeal joints are commonly affected and sometimes are the only joints affected
- Axial disease, when present normally occurs together with peripheral arthritis

Guidelines - Cytokine and CAM Antagonist

American Academy of Dermatology and National Psoriasis Foundation, 2020

- The group recommends methotrexate for the treatment of moderate to severe psoriasis in adults, although it is less effective than adalimumab and infliximab for cutaneous psoriasis (strength of recommendation A)
  - It is also effective for psoriatic arthritis (peripheral, not axial) but is less effective than TNF antagonists (strength of recommendation B)
- They recommend apremilast for the treatment of moderate to severe psoriasis in adults (strength of recommendation A)
- They recommend adalimumab, etanercept, and infliximab (strength of recommendation A for all) for moderate to severe psoriasis
- Treatment response with TNF antagonists is best ascertained at 12 to 16 weeks following initiation (infliximab at 8 to 10 weeks)
- Brodalumab, guselkumab, ixekizumab, secukinumab, tildrakizumab, and ustekinumab, with a response ascertained after 12 weeks, are also recommended for moderate to severe psoriasis (strength of recommendation A for all).
- The group also stated that risankizumab is recommended for moderate to severe psoriasis (response ascertained after 12 weeks); however, they assigned this a strength of recommendation B as this was not FDA-approved at the time of guideline publication
- They also state that while there is no evidence to support combining risankizumab with adjunct topical or systemic therapies, there is no reason that combination therapy should be considered unsafe
- Based on limited data from a retrospective case series, apremilast may be combined with TNF antagonists (adalimumab, etanercept, infliximab) or ustekinumab to augment efficacy to treat moderate to severe cases (recommendation C for all)

Guidelines - Cytokine and CAM Antagonist

ACR and National Psoriasis Foundation, 2018

- Published a guideline on the treatment of psoriatic arthritis (PsA) and emphasized a treat-to-target approach
- For initial treatment in treatment-naïve patients with active PsA:
  - Recommends treatment with a TNF antagonist over an oral small molecule (e.g., methotrexate, sulfasalazine, cyclosporine, leflunomide, apremilast), an IL-17 inhibitor (brodalumab, ixekizumab, secukinumab), or an IL-12/23 inhibitor (e.g., ustekinumab) (conditional recommendations based on low or very low levels of evidence)
  - In addition, an oral small molecule is recommended over an IL-17 inhibitor or IL-12/23 inhibitor, and methotrexate, specifically, is recommended over an NSAID (conditional recommendations, all very low evidence)
  - Use of an IL-17 antagonist is recommended over an IL-12/23 antagonist (conditional recommendation, very low evidence)
- In patients with active PsA despite treatment with an oral small molecule
  - Recommends switching to a TNF antagonist over a different oral small molecule, IL-17 inhibitor, IL-12/23 inhibitor, abatacept, tofacitinib, or a TNF antagonist in combination with methotrexate (conditional recommendations, low to moderate evidence)
  - Recommend switching to an IL-17 antagonist, over a different oral small molecule, an IL-12/23 inhibitor, abatacept, tofacitinib, or an IL-17 antagonist in combination with methotrexate, and to an IL-12/23 inhibitor over a different oral small molecule, abatacept, tofacitinib, or an IL-12/23 inhibitor in combination with methotrexate (conditional recommendations, very low to moderate evidence)
  - Recommends adding apremilast to an oral small molecule rather than switching to apremilast and recommends switching to another oral small molecule rather than adding another non-apremilast small molecule (conditional recommendations, low evidence)

Guidelines - Cytokine and CAM Antagonist

ACR and National Psoriasis Foundation, 2018 continued

- In adults with active PsA despite treatment with TNF antagonist monotherapy
  - Recommends switching to a different TNF antagonist over switching to an IL-17 or IL-12/23 inhibitor, abatacept, or tofacitinib, or adding methotrexate, although adding methotrexate to a different TNF antagonist is an option (conditional recommendations, very low or low evidence)
  - Recommend switching to an IL-17 inhibitor (without methotrexate) over switching to an IL-12/23 inhibitor (without methotrexate), abatacept, or tofacitinib and switching to an IL-12/23 inhibitor over switching to abatacept or tofacitinib (conditional recommendations, very low or low evidence)
- In adults with active PsA despite treatment with TNF antagonist and methotrexate therapy
  - Recommends switching to a different TNF antagonist plus methotrexate over a different TNF antagonist but recommends switching to IL-17 or -12/23 inhibitor monotherapy (over IL-17 or -12/23 inhibitor in combination with methotrexate) (conditional recommendations, very low evidence)
- Several other conditional recommendations are included in the guidelines based on patients with active disease despite treatment, and, in general, the recommendations prefer alternative treatments in the following order: TNF antagonist, IL-17 inhibitor, IL-12/23 inhibitor, and addition of methotrexate
- A notably strong recommendation in these guidelines is that in adult patients with active PsA and frequent serious infections who are both oral small molecule- and biologic treatment–naïve, an oral small molecule should be started over a TNF antagonist

Disease State Description - Cytokine and CAM Antagonist

Juvenile idiopathic arthritis

- Juvenile idiopathic arthritis, formerly known as juvenile rheumatoid arthritis, is the most common type of arthritis in children under the age of 16
- Juvenile idiopathic arthritis can cause persistent joint pain, swelling and stiffness; some children may experience symptoms for only a few months, while others have symptoms for many years
- Some types of juvenile idiopathic arthritis can cause serious complications, such as growth problems, joint damage and eye inflammation
- Treatment focuses on controlling pain and inflammation, improving function, and preventing damage

Guidelines - Cytokine and CAM Antagonist

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
- 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)

Guidelines - Cytokine and CAM Antagonist

ACR/Arthritis Foundation, 2019 continued

- 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)

Guidelines - Cytokine and CAM Antagonist

American College of Rheumatology (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

Disease State Description - Cytokine and CAM Antagonist

Axial Spondyloarthritis

- Spondyloarthritis (SpA) is a disease with multiple forms differentiated with a phenotypic presentation depending on axial (axSpA) damage, peripheral rheumatological manifestations, extra-musculoskeletal damage, and comorbidities
  - Axial spondyloarthritis (axSpA) is an inflammatory condition primarily affecting the spine and can be subdivided into ankylosing spondylitis (AS), also known as radiographic axSpA, and non-radiographic axial spondyloarthritis (nr-axSpA)
- SpA has both genetic and environmental causes
  - Approximately 30% of the genetic aspect is explained by genetic markers, 75% of which comes from HAL-B27
  - Current data show a roll of microbiota especially intestinal microbiota and dysbiosis as environmental factors for the disease
  - Other environmental factors that contribute to the disease are diet, tobacco use, infections in childhood, as well as stress (mechanical and neuropsychological)

Guidelines - Cytokine and CAM Antagonist

Pan American League of Associations for Rheumatology, 2023

- Recommendations for management of axial spondyloarthritis
  - In patients with active axSpA with inadequate response to NSAID treatment, treatment with biologic DMARDs (bDMARDs), TNF-inhibitor or IL-17 inhibitor is strongly recommended (strongly favor, moderate level of evidence)
  - When TNF-inhibitors and IL-17 inhibitors are contraindicated or unavailable, treatment with JAK inhibitors is strongly recommended (strongly favor, moderate level of evidence)
  - In patients who achieve stable or inactive disease activity state after treatment with bDMARDs and NSAIDs and/or conventional synthetic DMARDs (csDMARDs), discontinuation of NSAIDs and/or csDMARDs is strongly recommended (strongly favor, low quality of evidence)
  - Biosimilars to bDMARDs are strongly recommended as a therapeutic option (strongly favour, moderate level of evidence)
  - In patients with treatment failure with a first bDMARD, treatment with a bDMARD with a different mechanism of action or a JAK inhibitor is strongly recommended (strongly favor, very low level of evidence)
  - In patients with axSpA and recurrent and/or refractory uveitis, treatment with monoclonal antibody TNF inhibitor therapies over other bDmards is conditionally recommended (conditionally favor, very low level of evidence)
  - In patients with axSpA and inflammatory bowel disease (IBD), treatment with monoclonal antibody TNF inhibitor therapies over other bDmards or JAK inhibitors is strongly recommended (strongly favor, very low level of evidence)
  - In patients with sustained remission for at least 12 months and receiving treatment with bDMARDS, reducing the dose or extending the dosing intervals of bDMARDS is conditionally recommended (conditionally favour, low level of evidence)

Disease State Description - Cytokine and CAM Antagonist

Giant cell arteritis (GCA)

- Also known as temporal arteritis
- Systemic inflammatory vasculitis of unknown etiology that is classified as a large-vessel vasculitis, but typically also involves small and medium arteries
- Most commonly, it affects the occipital, ophthalmic, posterior ciliary, proximal vertebral, and vertebral arteries
- While the incidence of GCA ranges from 0.5 to 27 cases per 100,000 people in those at least 50 years old, the incidence is higher in the northern areas of the US
- It occurs in older persons and can result in a wide variety of neurologic, ophthalmologic, and systemic complications
- The primary treatment for GCA is high-dose corticosteroids, although clinical studies on various dosing protocols are limited
  - Steroids are generally continued until the resolution of symptoms and then may be tapered slowly to the lowest dose that adequately suppresses symptoms

Guidelines - Cytokine and CAM Antagonist

ACR/Arthritis Foundation, 2021

- ACR published joint guidelines regarding the treatment of GCA
- For medical management of newly diagnosed GCA, the group generally recommends the use of oral glucocorticoids
  - Once clinical remission is reached, the dose of the oral glucocorticoid may be tapered
- They conditionally recommend the addition of tocilizumab to oral glucocorticoids over oral glucocorticoids alone (low to high level of evidence)
- In patients with active extracranial large vessel involvement, ACR conditionally recommends the addition of a non-glucocorticoid immunosuppressive (e.g., methotrexate, tocilizumab) over glucocorticoids alone (very low to low evidence)
- Agents that can be considered non-glucocorticoid immunosuppressives include abatacept, azathioprine, cyclophosphamide, leflunomide, methotrexate, mycophenolate mofetil, TNF antagonists, and tocilizumab, although the group recognizes that data are limited for several of these in this patient group
- For patients who relapse while receiving moderate to high dose glucocorticoids, ACR conditionally recommends the addition of a non-glucocorticoid immunosuppressive agent (for glucocorticoid sparing)
- For patients with GCA who relapse with symptoms of cranial ischemia, ACR conditionally recommends adding a non-glucocorticoid immunosuppressive agent (e.g., methotrexate, tocilizumab; in addition to increasing the dose of glucocorticoids), further clarifying that ACR conditionally recommends adding tocilizumab over adding methotrexate
- Recommendations for relapse described above are based on limited evidence and expert opinion (no dedicated literature review)

Disease State Description - Cytokine and CAM Antagonist

Hidradenitis Suppurativa (HS)

- HS is a chronic condition that affects the terminal follicular epithelium in apocrine gland-bearing skin, such as the armpits or perianal area
- It typically occurs in adolescents (generally after puberty) and adults, is generally diagnosed clinically, and affects approximately 1% to 2% of the U.S. population
- Select signs and symptoms include erythema, raised bumps or lesions, painful lesions, and local arthritis or arthralgia
- In addition to nonpharmacologic treatments, pharmacologic treatment includes anti-inflammatories, antibiotics, antiandrogens, and biologics
  - Surgery may also be considered in some patients

Guidelines - Cytokine and CAM Antagonist

United States and Canadian Hidradenitis Suppurativa Foundations, 2019

- North American clinical management guidelines for hidradenitis suppurativa
- An algorithm on treatment suggests pain management, mental health care, wound care, avoidance of triggers, tobacco cessation, weight reduction, use of tetracyclines, rifampin, clindamycin for all patients at every HS stage
- As patients progress from HS stage I (mild disease) to HS stages II and III (moderate/severe disease), anti-TNF agents (adalimumab, infliximab) may be added
- Guideline recommendations for use of biologics:
  - Adalimumab at the approved HS dosing is recommended to improve disease severity and quality of life in patients with moderate-to-severe HS
  - Infliximab is recommended for moderate-to-severe disease; however, dose-ranging studies are needed to determine the optimal dosage for management.
  - Anakinra, 100 mg daily, may be effective for HS; however, dose-ranging studies are needed to determine the optimal dosage for management
  - Ustekinumab, 45 to 90 mg administered every 12 weeks, may be effective for HS; however, placebo-controlled dose ranging studies are needed to determine the optimal dosage for management
  - The limited available evidence does not support etanercept for the management of HS

Cytokine and CAM Antagonist

spesolimab-sbzo (Spevigo)

March 2024 - FDA approved expanded indication for the IL-36 receptor antagonist to include pediatric patients 12 years of age and older and weighing at least 40 kg for the treatment of generalized pustular psoriasis (GPP) and can now be administered subcutaneously (SC)

- **Previously only indicated for flares in adults with generalized pustular psoriasis as an intravenous (IV) infusion**

FDA Indications:

- **Treatment of GPP in adults and pediatric patients ≥ 12 years of age and weighing ≥ 40 kg**

Recommended Dosage:

- **Subcutaneous Treatment of GPP When Not Experiencing a Flare**
  - **Administer a subcutaneous loading dose of 600 mg (four 150 mg injections) by a healthcare professional (HCP), followed by 300 mg (two 150 mg injections) subcutaneously 4 weeks later and every 4 weeks thereafter**
  - **For subsequent 300 mg doses, patient may self-inject or caregiver may administer after proper training in SC injection technique**
  - **If initiating SC after treatment of a flare with IV Spevigo, initiate SC Spevigo 300 mg (two 150 mg injections) every 4 weeks, starting 4 weeks after the IV treatment for the flare (no SC loading dose required after treating a flare with IV therapy)**
- **Intravenous Treatment of GPP Flare**
  - **IV administration requires an HCP to administer in a healthcare setting**
  - **Administer as a single 900 mg dose by IV infusion over 90 minutes; if flare symptoms persist, may administer an additional IV 900 mg dose one week after the initial dose**

Availability:

- **Subcutaneous Injection: Injection: 150 mg/mL solution in a single-dose prefilled syringe**
- Intravenous Infusion: Injection: 450 mg/7.5 mL (60 mg/mL) solution in a single-dose vial

Cytokine and CAM Antagonist

adalimumab-adaz (Hyrimoz)

April 2024 - FDA granted Hyrimoz interchangeability status to Humira

FDA Indications:

- **Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Crohn's Disease (CD), Ulcerative Colitis (UC), Plaque Psoriasis (Ps), Hidradenitis Suppurativa (HS), and Uveitis (UV)**

Warnings:

- **BBW: Serious infections**
- **BBW: Malignancy**

Recommended Dosage:

- **Stratified by indication and age (found in TCR/PI)**

Availability:

- **Injection:**
  - **Single-dose prefilled pen (Sensoready Pen): 40 mg/0.8 mL, 40 mg/0.4 mL and 80 mg/0.8 mL**
  - **Single-dose prefilled glass syringe (with BD UltraSafe Passive Needle Guard): 40 mg/0.4 mL and 80 mg/0.8 mL**
  - **Single-dose prefilled glass syringe: 10 mg/0.1 mL and 20 mg/0.2 mL**

Cytokine and CAM Antagonist

upadacitinib (Rinvoq)

May 2024 - Indications for treatment of active psoriatic arthritis (PsA) and active polyarticular JIA (pJIA) in patients who have had an inadequate response or intolerance to one or more TNF blocker have both been expanded to include patients 2 years of age and older and Rinvoq LQ oral solution has been approved for use in pediatric patients

FDA Indications:

- Adult patients: Moderately to severely active RA, UC, CD, or ankylosing spondylitis who have had an inadequate response or intolerance to ≥ 1 TNF blockers, or active non-radiographic axial spondyloarthritis with objective signs of inflammation who have had an inadequate response or intolerance to TNF blocker therapy
- **Treatment of adults and pediatric patients ≥ 2 years old: Active PsA or active polyarticular juvenile idiopathic arthritis who have had an inadequate response or intolerance to ≥ 1 TNF blockers**
- Treatment of adults and pediatric patients ≥ 12 years old 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 are inadvisable

Warnings:

- BBW: Serious infections, mortality, malignancy, major adverse cardiovascular events (MACE), and thrombosis

Dosage:

- **Dosing stratified by indication, age, and weight (Found in TCR or PI)**
- **Rinvoq LQ oral solution should be used for patients < 30 kg and is not substitutable with Rinvoq extended-release tablets**
  - **Changes between these formulations should be made by an HCP**

Availability:

- Rinvoq Extended-release tablets: 15 mg, 30 mg, and 45 mg; **Rinvoq LQ oral solution: 1 mg/mL**

Cytokine and CAM Antagonist

apremilast (Otezla)

May 2024 - FDA approved expanded indication for treatment of pediatric patients 6 to 17 years old weighing at least 20 kg with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy

FDA Indications:

- Treatment of adult patients with active psoriatic arthritis
- Treatment of adult patients with plaque psoriasis who are candidates for phototherapy or systemic therapy
- **Treatment of pediatric patients 6 years of age and older and weighing at least 20 kg with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy**
- Treatment of adult patients with oral ulcers associated with Behçet's Disease

Dosage:

- **Initial titration is recommended to reduce GI symptoms**
- Adults with Plaque Psoriasis, Psoriatic Arthritis, or Behçet's Disease recommended maintenance dose: 30 mg twice daily
- **Pediatric Patients ≥ 6 Years Old with Moderate to Severe Plaque Psoriasis recommended maintenance dose:**
  - **Patients weighing 20 kg to < 50 kg: 20 mg orally twice daily**
  - **Patients weighing ≥ 50 kg: 30 mg orally twice daily**
- **Dosage adjustments are required in patients with severe renal impairment**

Availability:

- Tablets: 10 mg, 20 mg, 30 mg

Cytokine and CAM Antagonist

mirikizumab-mrkz (Omvoh)

May 2024 - FDA approved a 100 mg/mL single-dose prefilled syringe presentation

January 2025 – FDA approved new indication for treatment of moderate to severe active Crohn's disease (CD) in adults

FDA Indication:

- Treatment of moderately to severely active ulcerative colitis in adults
- **Treatment of moderately to severely Crohn's disease in adults**

Warnings:

- Infections: Do not initiate in patients with a clinically important active infection until the infection resolves or is adequately treated
- Hepatotoxicity : Monitor liver enzymes and bilirubin levels at baseline and for at least 24 weeks of treatment and thereafter according to routine patient management

Recommended Dosage:

- Ulcerative Colitis
  - Induction: 300 mg IV infusion administered by a healthcare professional over at least 30 minutes at Weeks 0, 4, and 8
  - Maintenance: 200 mg SC at Week 12, and every 4 weeks thereafter
- **Crohn's disease**
  - **Induction: 900 mg IV infusion administered by a healthcare professional over at least 90 minutes at Weeks 0, 4, and 8**
  - **Maintenance: 300 mg SC at Week 12, and every 4 weeks thereafter**

Availability:

- Intravenous infusion: 300 mg/15 ml (20 mg/mL) solution in a single dose vial
- Subcutaneous injections: 100 mg/mL or 200 mg/2mL solution in a single-dose prefilled pen or prefilled syringe

Cytokine and CAM Antagonist

adalimumab-aacf (Idacio)

June 2024 – FDA approved additional presentations: single-dose prefilled syringe 40 mg/0.8 mL, prefilled pen 40 mg/0.8 mL starter package (4 count and 6 count), and single-dose 40 mg/0.8 mL glass vial kit for institutional use only

- **Previously, the single-dose prefilled pen (40 mg/0.8 mL) were supplied in a 2-count carton only**

FDA Indication:

- Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Crohn's Disease (CD), Ulcerative Colitis (UC), and Plaque Psoriasis (Ps), Hidradenitis Suppurativa (HS), and Uveitis (UV)

Warnings:

- BBW: Serious infections
- BBW: Malignancy

Recommended Dosage:

- Stratified by indication and age (found in TCR/PI)

Availability:

- **Injection:**
  - **Single-dose prefilled pen: 40 mg/0.8 mL**
  - **Single-dose prefilled glass syringe: 40 mg/0.8 mL**
  - **Single-dose glass vial kit for institutional use only: 40 mg/0.8 mL**

Cytokine and CAM Antagonist

sarilumab (Kevzara)

June 2024 – FDA approved new indication for treatment of active polyarticular juvenile idiopathic arthritis (pJIA) in patients weighing 63 kg or greater

FDA Indications:

- Treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to ≥ 1 DMARDs
- Treatment of adult patients with polymyalgia rheumatica (PMR) who have had an inadequate response to corticosteroids or who cannot tolerate corticosteroid taper
- **Treatment of patients who weigh 63 kg or greater with active polyarticular juvenile idiopathic arthritis (pJIA)**

Warnings:

- BBW: Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial, invasive fungal, viral, and infections due to other opportunistic pathogens

Dosage:

- RA: 200 mg subcutaneously once every 2 weeks as monotherapy or in combination with methotrexate or other conventional DMARDs
- PMR: 200 mg subcutaneously once every 2 weeks in combination with a tapering course of corticosteroids or as monotherapy following discontinuation of corticosteroids
- **pJIA: 200 mg subcutaneously once every 2 weeks using the 200 mg/1.14 mL pre-filled syringe**
  - **Can be used as monotherapy or in combination with conventional DMARDs**

Availability:

- Injection: 150 mg/1.14 mL and 200 mg/1.14 mL solution in a single-dose pre-filled syringe
- Injection: 150 mg/1.14 mL and 200 mg/1.14 mL solution in a single-dose pre-filled pen
  - Pre-filled pen is intended for use in pediatric patients

Cytokine and CAM Antagonist

risankizumab-rzaa (Skyrizi)

June 2024 - FDA approved new indication for treatment of moderately to severely active ulcerative colitis in adults

FDA Indication:

- Treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy, active psoriatic arthritis in adults, moderately to severely active CD in adults, and **moderate to severely active UC in adults**

Warnings:

- Infections: If clinically important infection develops, do not administer until the infection resolves
- Hepatotoxicity in Treatment of Inflammatory Bowel Disease: 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

Recommended Dosage:

Indication	Induction	Maintenance
Crohn's Disease (CD)	600 mg IV infusion over a period of at least 1 hour at Week 0, Week 4, Week 8	180 mg or 360 mg SC at Week 12, and every 8 weeks thereafter; use the lowest effective dosage needed to maintain therapeutic response
Ulcerative Colitis (UC)	**1200 mg IV infusion over a period of at least 2 hours at Week 0, Week 4, Week 8**	**180 mg or 360 mg SC at Week 12, and every 8 weeks thereafter; use the lowest effective dosage needed to maintain therapeutic response**

Availability:

- Subcutaneous injections:
  - Single-dose prefilled pen: 150 mg/mL
  - Single-dose prefilled syringe: 90 mg/mL, 150 mg/mL
  - Single-dose prefilled cartridge: 180 mg/1.2 mL (150 mg/mL), 360 mg/2.4 mL (150 mg/mL)
- Intravenous infusion: Single-dose vial: 600 mg/10 ml (60 mg/mL)

Cytokine and CAM Antagonist

tocilizumab-bavi (Tofidence)

July 2024 – FDA approved new indications for adults with giant cell arteritis (GCA) and hospitalized adults with coronavirus disease 2019 (COVID-19) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)

FDA Indications:

- Adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs
- **Adult patients with giant cell arteritis (GCA)**
- Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis (PJIA)
- Patients 2 years of age and older with active systemic juvenile idiopathic arthritis (SJIA)
- **Hospitalized adult patients with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO**

Warnings:

- BBW: Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial, invasive fungal, viral, and infections due to other opportunistic pathogens

Dosage:

- Dosing stratified by indication, age, and weight (Found in TCR or PI)
- **GCA: 6 mg per kg every 4 weeks in combination with a tapering course of glucocorticoids; can be used alone following discontinuation of glucocorticoids**
- **COVID-19: 8 mg per kg administered by a 60-minute intravenous infusion; if signs or symptoms worsen or do not improve, one additional dose may be given at least 8 hours after the initial dose**

Availability:

- Intravenous 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

Cytokine and CAM Antagonist

ustekinumab-ttwe (Pyzchiva)

July 2024 – FDA approved ustekinumab-ttwe as a biosimilar to Stelara

December 2024 – FDA approved new presentation of 45 mg/0.5 mL single-dose vial for subcutaneous injection

- **This presentation was developed to accurately administer drug to pediatric patients weighing < 60 kg**

FDA Indications:

- **Adult patients: Moderate to severe Plaque Psoriasis (PsO) who are candidates for phototherapy or systemic therapy; active Psoriatic Arthritis (PsA), moderately to severely acting Crohn's disease (CD); moderately to severely active ulcerative colitis (UC)**
- **Pediatric patients (6 years of age or older): moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy; active Psoriatic Arthritis (PsA)**

Warnings:

- **Infections: Serious infections have occurred; avoid starting treatment during any clinically important active infection. If a serious infection or clinically significant infection develops, discontinue treatment until the infection resolves**

Dosage:

- **Dosing stratified by indication, age and weight based (See PI or TCR)**

Availability:

- **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 and CAM Antagonist

nemolizumab-ilto (Nemluvio)

August 2024 – FDA approved an interleukin-31 receptor antagonist for treatment of adults with prurigo nodularis

December 2024 – FDA approved new indication for the treatment of adults and pediatric patients 12 years and older with moderate to severe atopic dermatitis in combination with topical corticosteroids and/or calcineurin inhibitors when the disease is not adequately controlled with topical prescription therapies

Warnings:

- **Hypersensitivity: If a clinically significant hypersensitivity reaction occurs, immediately institute appropriate therapy and discontinue**
- **Vaccinations: Avoid use of live vaccines during treatment**

Recommended Dosage:

- **Prurigo Nodularis:**
  - **Adults < 90 kg: Initial dose of 60 mg (two 30 mg injections) SC, followed by 30 mg SC every 4 weeks**
  - **Adults ≥ 90 kg: Initial dose of 60 mg (two 30 mg injections) SC, followed by 60 mg SC every 4 weeks**
- **Atopic Dermatitis:**
  - **Initial dose of 60 mg (two 30 mg injections) SC, followed by 30 mg SC every 4 weeks**
  - **Following 16 weeks of treatment: 30 mg SC every 8 weeks for patients who achieve clear or almost clear skin**
  - **Topical therapies can be discontinued once the disease has sufficiently improved**

Availability:

- **For injection: single-dose pre-filled dual-chamber pen containing 30 mg of nemolizumab-ilto lyophilized powder and diluent, water for injection**

Cytokine and CAM Antagonist

adalimumab-atto (Amjevita)

August 2024 – FDA approved new presentations of the following concentrations: 10mg/0.2 mL, 20 mg/0.4 mL, 40 mg/0.8 mL in a prefilled syringe and 40 mg/0.8 mL in a prefilled autoinjector

FDA Indications:

- Rheumatoid Arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's Disease (CD), Ulcerative Colitis (UC), Plaque Psoriasis (Ps), Hidradenitis Suppurativa (HS), and Uveitis (UV)

Warnings:

- BBW: Serious infections
- BBW: Malignancy

Dosage:

- Dosing stratified by indication, age and weight based (See PI or TCR)

Availability:

- Injection:
  - **Single-dose prefilled SureClick® autoinjector**: 80 mg/0.8 mL, **40 mg/0.8 mL**, 40 mg/0.4 mL
  - **Single-dose prefilled glass syringe**: 80 mg/0.8 mL, **40 mg/0.8 mL**, 40 mg/0.4 mL, **20 mg/0.4 mL**, 20 mg/0.2 mL, **10 mg/0.2 mL**

Cytokine and CAM Antagonist

guselkumab (Tremfya)

September 2024 - FDA approved new indication for treatment of adults with moderately to severely active ulcerative colitis

FDA Indication:

- Treatment of moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy
- Treatment of active psoriatic arthritis (can be used alone or in combination with a conventional DMARD)
- **Treatment of moderately to severely active ulcerative colitis**

Warnings:

- Hypersensitivity reactions including anaphylaxis, increase risk of infections, evaluate tuberculosis (TB) prior to initiating treatment, and avoid use of live vaccine

Recommended Dosage:

- Plaque Psoriasis or Psoriatic Arthritis: 100 mg subcutaneously at Week 0, Week 4, and every 8 weeks thereafter
- **Ulcerative Colitis:**
  - **Induction: 200 mg intravenous infusion over at least one hour at Week 0, Week 4, and Week 8 by health care professional**
  - **Maintenance: 100 mg SC at Week 16, and every 8 weeks thereafter, or 200 mg SC at Week 12, and every 4 weeks thereafter**
  - **Use the lowest effective recommended dosage to maintain therapeutic response**

Availability:

- Intravenous Infusion: 200 mg/20 mL (10 mg/mL) solution in a single-dose vial
- Subcutaneous Injection:
  - 100 mg/mL in a single-dose One-Press patient-controlled injector
  - 200 mg/2 mL in a single-dose prefilled pen
  - 100 mg/mL, 200 mg/2 mL in a single-dose prefilled syringe

Cytokine and CAM Antagonist

certolizumab pegol (Cimzia)

September 2024 – FDA approved a new indication for treatment of active polyarticular Juvenile Idiopathic Arthritis (pJIA) for patients 2 years of age and older

FDA Indications:

- Reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy
- Treatment of adults with moderately to severely active rheumatoid arthritis
- **Treatment of active polyarticular juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older**
- Treatment of adult patients with active psoriatic arthritis
- Treatment of adults with active ankylosing spondylitis
- Treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation
- Treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy

Warnings:

- BBW: Serious infection
- BBW: Malignancy

Recommended Dosage:

- Dosing stratified by indication (See PI or TCR)
- **pJIA**
  - **10 kg to < 20 kg: 100 mg SC initially and at Weeks 2 and 4, followed by 50 mg every other week**
  - **20 kg to < 40 kg: 200 mg SC initially and at Weeks 2 and 4, followed by 100 mg every other week**
  - **≥40 kg: 400 mg initially and at weeks 2 and 4, followed by 200 mg every other week**

Availability:

- Injection: 200 mg lyophilized powder in a single-dose vial
- Injection: 200 mg/mL solution in a single-dose prefilled syringe

Cytokine and CAM Antagonist

bimekizumab-bkzx (Bimzelx)

September 2024 - FDA approved new indications for: (1) adults with active psoriatic arthritis (PsA), (2) adults with active ankylosing spondylitis (AS), and (3) adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation

October 2024 - Two new 2 mL device presentations was approved: 320 mg/2 mL (160 mg/mL) single-dose prefilled autoinjector and 320 mg/2 mL (160 mg/mL) single-dose pre-filled syringe

November 2024 – FDA approved for treatment of adults with moderate to severe hidradenitis suppurativa (HS)

FDA Indications:

- Treatment of adults with moderate to severe plaque psoriasis (PSO) who are candidates for systemic therapy or phototherapy, **active psoriatic arthritis (PsA), active non-radiographic axial spondyloarthritis (nraxSpA) with objective signs of inflammation, active ankylosing spondylitis (AS), moderate to severe hidradenitis suppurativa (HS)**

Recommended Dosage:

- **PsA, Nr-axSpA, AS: 160 mg by subcutaneous injection every 4 weeks**
- **HS: 320 mg by subcutaneous injection at Week 0, 2, 4, 6, 8, 10, 12, 14 and 16, then every 4 weeks thereafter**

Availability:

- Injection: 160 mg/mL in a single-dose prefilled syringe or single-dose prefilled autoinjector
- **Injection: 320 mg/2 mL (160 mg/mL) in a single-dose prefilled syringe or single-dose prefilled autoinjector**

Cytokine and CAM Antagonist

ustekinumab-kfce (Yesintek)

December 2024 – FDA approved Yesintek as a biosimilar to Stelara

FDA Indications:

- **Adult patients: Moderate to severe Plaque Psoriasis (PsO) who are candidates for phototherapy or systemic therapy; active Psoriatic Arthritis (PsA), moderately to severely acting Crohn's disease (CD); moderately to severely active ulcerative colitis (UC)**
- **Pediatric patients (6 years of age or older): moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy; active Psoriatic Arthritis (PsA)**

Warnings:

- **Infections: Serious infections have occurred; avoid starting treatment during any clinically important active infection. If a serious infection or clinically significant infection develops, discontinue treatment until the infection resolves**

Dosage:

- **Dosing stratified by indication, age and weight based (See PI or TCR)**

Availability:

- **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 and CAM Antagonist

ustekinumab-stba (Steqeyma)

December 2024 – FDA approved Steqeyma as a biosimilar to Stelara

FDA Indications:

- **Adult patients: Moderate to severe Plaque Psoriasis (PsO) who are candidates for phototherapy or systemic therapy; active Psoriatic Arthritis (PsA), moderately to severely acting Crohn's disease (CD); moderately to severely active ulcerative colitis (UC)**
- **Pediatric patients (6 years of age or older): moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy; active Psoriatic Arthritis (PsA)**

Warnings:

- **Infections: Serious infections have occurred; avoid starting treatment during any clinically important active infection. If a serious infection or clinically significant infection develops, discontinue treatment until the infection resolves**

Dosage:

- **Dosing stratified by indication, age and weight based (See PI or TCR)**

Availability:

- **Subcutaneous Injection:**
  - **Injection: 45 mg/0.5 mL or 90 mg/mL solution in a single-dose prefilled syringe**
- **Intravenous Infusion:**
  - **Injection: 130 mg/26 mL (5 mg/mL) solution in a single-dose vial**

Cytokine and CAM Antagonist

ustekinumab-auub (Wezlana)

December 2024 – FDA approved new presentation of 45 mg/0.5 mL and 90 mg/mL solution in single-dose prefilled ConfiPen autoinjector presentations; these autoinjector pens are for SC injection and are biosimilar to Stelara 45 mg/0.5 mL and 90 mg/mL single-dose PFS, respectively

FDA Indication:

- Adult patients: 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; moderately to severely active ulcerative colitis
- Pediatric patients (6 years of age or older): moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy; active Psoriatic Arthritis (PsA)

Warnings:

- Serious infections: Do not start during any clinically important active infection; if a serious infection or clinically significant infection develops, consider discontinuing treatment until the infection resolves

Recommended Dosage:

- Dosing stratified by indication, age and weight based (Found in TCR/PI)

Availability:

- 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
  - **Injection: 45 mg/0.5 mL or 90 mg/mL solution in a single-dose prefilled ConfiPen autoinjector**
- Intravenous Infusion:
  - Injection: 130 mg/26 mL (5 mg/mL) solution in a single-dose vial

Cytokine and CAM Antagonist

adalimumab-ayrk (Simlandi)

February 2025 – FDA approved new formulations of 80 mg/0.8 mL single-dose autoinjector

FDA Indications:

- Rheumatoid Arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's Disease (CD), Ulcerative Colitis (UC), Plaque Psoriasis (Ps), Hidradenitis Suppurativa (HS), and Uveitis (UV)

Warnings:

- BBW: Serious infections
- BBW: Malignancy

Dosage:

- Dosing stratified by indication, age and weight based (See PI or TCR)

Availability:

- Injection:
  - **Single-dose autoinjector: 80 mg/0.8 mL**, and 40 mg/0.4 mL
  - Single-dose prefilled glass syringe: 80 mg/0.8 mL, 40 mg/0.4 mL, 20 mg/0.2 mL

Cytokine and CAM Antagonist

Discontinuation

- **December 2024 - adalimumab-adbm**
  - Boehringer Ingelheim discontinued adalimumab-adbm (unbranded version of Cyltezo) 40 mg/0.8 mL prefilled pen starter package for psoriasis/uveitis and adalimumab-adbm 40 mg/0.8 mL prefilled pen starter package for CD/UC/HS
  - All other formulations of both Cyltezo and unbranded adalimumab-adbm remain available

Erythropoiesis Stimulating Proteins

HEMATOPOIETIC AGENTS : ERYTHROID MATURATION AGENTS
HEMATOPOIETIC AGENTS : ERYTHROPOIESIS-STIMULATING AGENTS (ESAS)
HEMATOPOIETIC AGENTS : HYPOXIA-INDUCIBLE FACTOR PROLYL HYDROXYLASE INHIBITORS

Disease State Description - Erythropoiesis Stimulating Agents

Anemia

- A frequent complication, affecting over 3 million Americans
- Associated with serious diseases such as chronic kidney disease (CKD), thyroid disease, liver disease, and cancer, as well as chronic inflammatory conditions like rheumatoid arthritis or inflammatory bowel disease
- Erythropoietin is a glycoprotein produced in the kidneys that stimulates RBC production from bone marrow and acts on the erythroid progenitor cells in the bone marrow to cause late differentiation and maturity of the RBCs
- Endogenous production of erythropoietin by the kidney is normally regulated by the level of tissue oxygenation
- Hypoxia and anemia generally increase the production of erythropoietin, which in turn stimulates erythropoiesis
- In normal individuals, plasma erythropoietin levels range from 0.01 to 0.03 units/mL and may increase 100- to 1,000-fold during hypoxia or anemia
- Patients with CKD have impaired production of erythropoietin, which is the primary cause of their anemia

Erythropoiesis Stimulating Agents

vadadustat (Vafseo)

March 2024 - FDA approved the hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitor for the treatment of anemia due to chronic kidney disease (CKD) in adults who have been receiving dialysis for at least 3 months

Limitation:

- Not been shown to improve quality of life, fatigue, or patient well-being
- Not indicated for use:
  - As a substitute for transfusion in patients requiring immediate correction of anemia
  - In patients with anemia due to CKD not on dialysis

Warnings:

- BBW: Increased risk of death, myocardial infarction, stroke, venous thromboembolism, and thrombosis of vascular access
- CI: Uncontrolled hypertension
- Hepatic Impairment: Not recommended for use in patients with cirrhosis or active, acute liver disease
- Pregnancy: May cause fetal harm

Recommended Dosage:

- Starting dose: 300 mg orally once daily, with or without food
- Adjust dose in increments of 150 mg to achieve or maintain hemoglobin levels of 10 g/dL to 11 g/dL
- Doses may range from 150 mg to a maximum of 600 mg

Availability:

- Tablets: 150 mg, 300 mg and 450 mg

Erythropoiesis Stimulating Agents

methoxy polyethylene glycol-epoetin beta (Mircera)

May 2024 - FDA approved expanded indication for treatment of anemia associated with CKD to include pediatric patients 3 months to 17 years old on dialysis and not on dialysis who are converting from another ESA after their hemoglobin (Hb) level was stabilized with an ESA

FDA Indications:

- Treatment of anemia associated with chronic kidney disease (CKD) in:
  - **Pediatric patients 3 months to 17 years of age on dialysis or not on dialysis who are converting from another ESA after their Hb level was stabilized with an ESA**
  - Adult patients on dialysis and adult patients not on dialysis

Limitation:

- Not been shown to improve quality of life, fatigue, or patient well-being
- Not indicated and is not recommended for use:
  - In the treatment of anemia due to cancer chemotherapy
  - As a substitute for RBC transfusions in patients who require immediate correction of anemia

Warnings:

- BBW: Increased risk of death, myocardial infarction, stroke, VTE, thrombosis of vascular access, and tumor progression or recurrence
- CI: Uncontrolled hypertension, pure red cell aplasia (PRCA) that begins after treatment with Mircera or other erythropoietin protein drug

Recommended Dosage:

- **Pediatric Patients**
  - **Starting dose is calculated based on total weekly ESA dose at time of conversion and should be administered once every 4 weeks as intravenous or subcutaneous injection**
  - **Dose adjustments should be made based on Hb response**
  - **< 6 years of age: Maintain the same route of administration as the previous ESA**

Availability:

- Injection: 30 mcg, 50 mcg, 75 mcg, 100 mcg, 120 mcg, 150 mcg, 200 mcg, or 250 mcg in 0.3 mL solution in single-dose prefilled syringes
- Injection: 360 mcg in 0.6 mL solution in single-dose prefilled syringes

Erythropoiesis Stimulating Agents

Discontinuation

- **November 2024 – daprodustat (Jesduvroq)**
  - GlaxoSmithKline discontinued the manufacture of Jesduvroq 1 mg, 2 mg, 4 mg, 6 mg, and 8 mg tablets due to business reasons

Colony Stimulating Factors

HEMATOPOIETIC AGENTS : GRANULOCYTE COLONY-STIMULATING FACTORS (G-CSF)

Disease State Description - Colony Stimulating Factors

Neutropenia

- Myelosuppressive chemotherapy can induce neutropenia and febrile neutropenia, which are dose-limiting toxicities of chemotherapy
  - Neutropenia: < 500 neutrophils/µL or < 1,000 neutrophils/µL and a predicted decline to ≤ 500/µL during the 48 hours after the dose
  - Febrile Neutropenia: ≥ 38.3°C (101°F) orally or ≥ 38°C (100.4°F) sustained over one hour in a patient with neutropenia
- Febrile neutropenia can cause increased diagnostic and treatment costs, prolonged hospitalizations, and broad-spectrum antibiotic use which may necessitate chemotherapy dose reductions, treatment delays, and may ultimately compromise treatment outcomes
- The risk of febrile neutropenia is dependent on treatment and dose intensity, which is often underreported
- Colony stimulating factors (CSF) are hematopoietic growth factors that have been shown to decrease the likelihood of neutropenic complications resulting from chemotherapy and to improve relative chemotherapy dose intensity
- Prophylactic CSF use can reduce the severity, risk, and duration of febrile neutropenia and decrease rates of infection and hospitalizations

Guidelines - Colony Stimulating Factors

The National Comprehensive Cancer Network (NCCN), 2024

- Updated practice guidelines for Hematopoietic Growth Factors in patients with solid tumors and lymphoid blood cancers
- Safety data appear similar between filgrastim (Neupogen), pegfilgrastim (Neulasta), and their biosimilars, and the subcutaneous (SC) route is preferred for all agents
- To date, there are insufficient head-to-head comparative studies on the clinical benefits of granulocyte colony-stimulating factors (G-CSFs) and granulocyte-macrophage colony stimulating factor (GM-CSFs)
- Subcutaneous filgrastim, tbo-filgrastim, and pegfilgrastim have a category 1 recommendation stating there is high-level evidence from randomized, controlled clinical trials, and there is uniform NCCN consensus that they prophylactically reduce the risk of febrile neutropenia; however, the guidelines advise caution should be used with prophylactic use of G-CSFs administered with chemotherapy and radiation concurrently

Colony Stimulating Factors

filgrastim-txid (Nypozi)

July 2024 - FDA approved biosimilar to filgrastim (Neupogen)

FDA Indication:

- Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever
- Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML)
- Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT)
- Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis
- Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia
- Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)

Warnings:

- Fatal sickle cell crises: Discontinue if sickle cell crisis occurs
- Glomerulonephritis: Evaluate and consider dose-reduction or interruption if causality is likely

Recommended Dosage:

- Dosing stratified by indication and weight

Availability:

- Injection: 300 mcg/0.5 mL,480 mcg/0.8 mL in a single-dose prefilled syringe

Colony Stimulating Factors

filgrastim-sndz (Zarxio)

December 2024 - FDA approved new indication to increase survival in patients acutely exposed to myelosuppressive doses of radiation (hematopoietic subsyndrome of acute radiation syndrome [H-ARS])

FDA Indication:

- Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever
- Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML)
- Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT
- Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis
- Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia
- **Increase survival in patients acutely exposed to myelosuppressive doses of radiation (H-ARS)**

Warnings:

- Fatal sickle cell crises: Discontinue if sickle cell crisis occurs
- Glomerulonephritis: Evaluate and consider dose-reduction or interruption if causality is likely

Recommended Dosage:

- Dosing stratified by indication and weight
- **H-ARS: 10 mcg/kg SC as a single daily injection, administered as soon as possible after the suspected or confirmed exposure to radiation doses > 2 gray (Gy)**
  - **Continue until the ANC remains > 1,000/mm^3 for 3 consecutive CBCs (monitored approximately every third day) or exceeds 10,000/mm^3 after a radiation-induced nadir**

Availability:

- Injection
  - 300 mcg/mL, 480 mcg/1.6 mL (300 mcg/mL) in a single-dose-vial
  - 300 mcg/0.5 mL,480 mcg/0.8 mL in a single-dose prefilled syringe with BD UltraSafe Passive Needle Guard

Duchenne Muscular Dystrophy

NEUROMUSCULAR AGENTS : MUSCULAR DYSTROPHY AGENTS

Disease State Description and Guidelines – Duchenne Muscular Dystrophy

Duchenne Muscular Dystrophy (DMD)

- Rare X-linked genetic disorder that involves progressive muscle weakness from degeneration of muscle tissue leading to loss of ambulation, osteoporosis, cardiac and respiratory failure, and death typically by 30 years of age
- This wasting away of muscle is the result of genetic mutations that lead to the inability to produce dystrophin, a protein which is essential for keeping muscle cells intact
  - The most common mutation responsible for DMD is a deletion over one or more exons (60-70%)
  - Exon duplications account for 10-15%
- The disease affects approximately 1 in 3600 to 6000 male births and has a prevalence of approximately 1 in every 7,250 males aged 5 to 24 years
- Boys typically present with symptoms (e.g., abnormal gait and proximal weakness) between the ages of 3 and 5 years
- Without treatment, ambulation is usually lost by 12 years of age

The American Academy of Neurology (AAN)

- Practice guideline published in 2016 (reaffirmed in 2022) for corticosteroid treatment DMD recommends prednisone and deflazacort as the standard of care treatment for DMD
- Although prednisone and deflazacort are associated with improved motor function, adverse effects include weight gain, slowing of growth, and bone loss
- These guidelines were published prior to the FDA approval of vamorolone

Duchenne Muscular Dystrophy

givinostat (Duvyzat)

March 2024 - FDA approved a histone deacetylase inhibitor indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients 6 years of age and older

Warnings:

- **Hematological Changes: May cause dose-related thrombocytopenia and other signs of myelosuppression, including anemia and neutropenia; monitor platelets; dosage adjustment or discontinuation may be needed**
- **Increased Triglycerides: Dosage modification may be needed; discontinuation may be needed**
- **Gastrointestinal Disturbances: Adjust dosage if moderate or severe diarrhea occurs; antiemetics or antidiarrheal medications may be considered during treatment; discontinue if the symptoms persist**
- **QTc Prolongation: Avoid use in patients who are at an increased risk for ventricular arrhythmias**

Recommended Dosage:

- **Based on patient's body weight administered orally twice daily with food**
- **Baseline platelet levels and triglycerides should be assessed as therapy should not be started in patients with platelet count < 150 x 10^9/L**
- **Dosage modifications may be needed for decreased platelet counts, diarrhea, increased triglycerides, or QTc prolongation**

Availability:

- **Oral suspension: 8.86 mg/mL**

Oncology, Oral – Hematological
Oncology, Oral – Other

ONCOLOGY AGENTS : ISOCITRATE DEHYDROGENASE-1 (IDH1) INHIBITORS - ORAL

Disease State Description – Oncology, Oral

Central Nervous System (CNS) Tumors

- Primary brain tumors include a heterogeneous group of cancers with differing histological features, management, and outcomes
- Regardless of the specific tumor subtype, initial neurosurgical intervention is usually recommended to remove as much tumor as is safely possible, ideally with a goal of gross total resection (GTR)
  - Surgical tumor removal also allows for tissue assessment to provide diagnostic information
- Gliomas, the most common brain tumor seen in adults, are divided into subtypes based on distinct histological and molecular features, including 1p/19q-codeletion (an unbalanced translocation between chromosomes 1 and 19) and isocitrate dehydrogenase 1/2 (IDH1/IDH2) mutational status
  - Oligodendrogliomas: IDH1/IDH2 mutation with a 1p/19q-codeletion
  - Astrocytomas: IDH1/IDH2-mutated gliomas without a 1p/19q-codeletion
- According to the World Health Organization (WHO) classification for central nervous system (CNS) tumors, oligodendrogliomas can be classified as grades 2 or 3 and astrocytomas can be classified as grades 2, 3, or 4
  - These tumor grades are related to expected clinical behaviors for the specific tumor subtype, with higher grades indicating more advanced disease and worse prognosis
  - Grade 2 oligodendrogliomas and astrocytomas exhibit continuous growth and have the potential to develop aggressive features over time

Guidelines – Oncology, Oral

National Comprehensive Cancer Network (NCCN), 2024 – Guidelines on Central Nervous System Cancers

- **Postoperative management for patients with grade 2 gliomas, including IDH1/IDH2-mutated oligodendrogliomas and astrocytomas**
  - Guided by performance status (PS), treatment preferences, and individual patient characteristics (tumor size, presence of neurologic deficits, IDH mutational status)
    - Good PS with no residual disease: Observation alone
    - Good PS with residual disease: Radiation therapy (RT) plus chemotherapy, IDH inhibitor, observation alone, or enrollment in a clinical trial
    - Poor PS: RT plus chemotherapy, IDH inhibitor, or palliative/supportive care
  - Vorasidenib for IDH1 or IDH2 mutations was added as an option
    - Adjuvant Treatment after surgery/biopsy and treatment of RT and chemotherapy is not preferred
      - Good PS: Preferred
      - Poor PS: Useful in certain circumstances
      - Recurrent or Progressive Disease after RT and chemotherapy with good PS: Preferred

vorasidenib (Voranigo)

August 2024 – FDA approved an isocitrate dehydrogenase-1 (IDH1) and isocitrate dehydrogenase-2 (IDH2) inhibitor indicated for the treatment of adult and pediatric patients 12 years and older with Grade 2 astrocytoma or oligodendroglioma with a susceptible IDH1 or IDH2 mutation following surgery including biopsy, sub-total resection, or gross total resection

Warnings:

- **Hepatotoxicity: Monitor liver function tests every 2 weeks during the first 2 months of treatment, then monthly for the first 2 years of treatment, and as clinically indicated; withhold, reduce the dose or discontinue based on severity**
- **Embryo-Fetal Toxicity: Can cause fetal harm; advise patients of the potential risk to a fetus and to use effective nonhormonal contraception**

Recommended Dosage:

- **Recommended dosage in adults: 40 mg orally once daily**
- **Recommended dosage in pediatric patients 12 years of age and older based on body weight:**
  - **<40 kg: 20 mg orally once daily**
  - **≥40 kg: 40 mg orally once daily**

Availability:

- **Tablets: 10 mg and 40 mg**

Oncology, Injectable

ONCOLOGY AGENTS : AUTOLOGOUS CELLULAR IMMUNOTHERAPY (CAR-T)

Disease State Description - Oncology, Injectable

Cutaneous Melanoma Skin Cancer

- The incidence of melanoma skin cancer in the United States is increasing, but the death rate due to melanoma is declining due to advances in treatment
- The median age at diagnosis is 65 years
- Risk factors for the development of melanoma include both genetic factors (skin type, inherited germline mutations) and environmental factors (excess sun exposure, UV-based artificial tanning)
- Despite the relationship to UV exposure, melanoma can also occur in areas of the body without substantial sun exposure and can occur in any ethnic group

Guidelines - Oncology, Injectable

National Comprehensive Cancer Network (NCCN), 2025 – Guideline on Cutaneous Melanoma

- Unresectable or metastatic melanoma
  - First-line preferred regimens:
    - Combination checkpoint blockade (preferred): Nivolumab/ipilimumab, nivolumab/relatlimab
    - Anti-programmed cell death protein 1 (Anti-PD-1) monotherapy: pembrolizumab, nivolumab
  - Second-line/subsequent systemic preferred regimens:
    - Anti-PD-1 monotherapy: pembrolizumab, nivolumab
    - Combination checkpoint blockade: nivolumab/ipilimumab; nivolumab/relatlimab
    - Pembrolizumab/low-dose ipilimumab for progression following anti-PD-1 therapy
    - Combination targeted therapy with BRAF V600 mutation positive: Dabrafenib/trametinib, vemurafenib/cobimetinib, encorafenib/binimetinib
    - Tumor-infiltrating lymphocyte therapy (TIL): Lifileucel
- Nivolumab IV monotherapy may be substituted with Nivolumab and hyaluronidase-nvhy subcutaneous injection
  - Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab
  - Nivolumab and hyaluronidase-nvhy is not approved for concurrent use with IV ipilimumab
- Lifileucel may be considered for patients with good performance status who progress on systemic therapy:
  - Without BRAF V600 Mutation present and previously treated with anti-PD-1 based therapy
  - With BRAF V600 Mutation present and previously treated with anti-PD-1 based therapy and BRAF/MEK inhibitor combination therapy

Oncology, Injectable

lifileucel (Amtagvi)

February 2024 – FDA granted accelerated approval of a tumor-derived autologous T cell immunotherapy based on objective response rate (ORR) for the treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor

- **Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s)**

Warnings:

- **BBW: Treatment-related mortality, prolonged severe cytopenia, severe infection, cardiopulmonary and renal impairment**
  - **Monitor patients for prolonged severe cytopenia and monitor for internal organ hemorrhage**
  - **Treat severe infections**
  - **Monitor cardiopulmonary and renal functions throughout the treatment course**
  - **Administer in an inpatient hospital setting; an intensive care facility and specialists skilled in cardiopulmonary or intensive care medicine must be available**

Recommended Dosage:

- **Dosing range is between 7.5×10^9 and 72×10^9 viable cells**
- **Administer a lymphodepleting regimen before infusion**
- **Premedicate the patient with acetaminophen, or equivalent, and diphenhydramine, or another H1-antihistamine**
- **Administer IL-2 (aldesleukin) after infusion**

Availability:

- **Cell suspension for intravenous infusion**
- **A single dose of Amtagvi contains 7.5×10^9 to 72×10^9 viable cells suspended in 1 to 4 patient-specific infusion bag(s)**

Disease State Description - Oncology, Injectable

Chronic Lymphocytic Leukemia (CLL) / Small Lymphocytic Lymphoma (SLL)

- Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) are chronic lymphoproliferative disorders characterized by the progressive accumulation of non-functional B-lymphocyte
- CLL and SLL are different manifestations of the same disease
  - In CLL, a significant portion of the abnormal lymphocytes are in the blood as well as in the bone marrow
  - In SLL, there is a relative lack of abnormal lymphocytes in the blood; instead, abnormal lymphocytes are found predominantly in the lymph nodes, bone marrow, and other lymphoid tissues
- Chemoimmunotherapy regimens including those containing cyclophosphamide or chlorambucil were previously the standard of care for patients with CLL/SLL
- However, the advent of targeted treatments such as the Bruton kinase (BTK) inhibitors and BCL2 inhibitors have provided this population with safer and more effective treatment options that are advocated by current guidelines

Disease State Description - Oncology, Injectable

National Comprehensive Cancer Network (NCCN), 2025 – Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

- First-line therapy without del(17p)/TP53 mutations:
  - Covalent BTK Inhibitor (cBTKi)-based regimen (continuous treatment):
    - Preferred regimens: Acalabrutinib ± obinutuzumab, or zanubrutinib
  - BCL2 inhibitor (BCL2i)-containing regimen (time-limited treatment)
    - Preferred regimens: Venetoclax + obinutuzumab, or venetoclax + acalabrutinib ± obinutuzumab
  - Chemoimmunotherapy (CIT) or Immunotherapy
- First-line therapy with del(17p)/TP53 mutations:
  - Clinical trial
  - cBTKi-based regimens (Continuous treatment)
  - BCL2i-containing regimens (Time-limited treatment)
- Therapy for relapse or refractory disease after prior BTKi-based and BCL2i-containing regimens:
  - Preferred regimens: Chimeric antigen receptor (CAR) T-cell therapy (lisocabtagene maraleucel, CD19-directed), or ncBTKi-based regimen (pirtobrutinib, if not previously given)

Disease State Description and Guidelines - Oncology, Injectable

Follicular Lymphoma (FL)

- Most common subtype of indolent non-Hodgkin's lymphoma (NHL)
- Excess amounts of abnormal B lymphocytes form clusters (follicles) in the lymph nodes and sometimes other tissues
- Due to the indolent nature of FL, the median survival is approximately 10 years
- Highly treatable and may be curable in certain circumstances

National Comprehensive Cancer Network (NCCN), 2025 – B-Cell Lymphomas

- Classic Follicular Lymphoma Guidelines
  - For patients requiring treatment, enrollment in a clinical trial or the following treatments are recommended:
    - Preferred first-line regimens, low tumor burden: Rituximab monotherapy
    - Preferred first-line regimens, high tumor burden: Bendamustine plus obinutuzumab or rituximab; CHOP (cyclophosphamide, doxorubicin,vincristine, prednisone) plus obinutuzumab or rituximab; CVP (cyclophosphamide, vincristine, prednisone) plus obinutuzumab or rituximab; lenalidomide + rituximab
  - Second-line or subsequent therapy (generally, a first-line regimen is not repeated):
    - Preferred regimens: Bendamustine + obinutuzumab or rituximab; CHOP + obinutuzumab or rituximab; CVP + obinutuzumab or rituximab; lenalidomide+ rituximab; Tafasitamab-cxix + lenalidomide + rituximab (≥1 prior systemic therapy including an anti-CD20 mAb)
  - Third-line and subsequent treatment options include those regimens not already used as first- or second-line treatment as well as:
    - T-cell engager therapy: Bispecific antibody therapy (epcoritamab-bysp, mosunetuzumab-axgb); Chimeric antigen receptor (CAR) T-cell therapy (axicabtagene ciloleucel, lisocabtagene maraleucel, tisagenlecleucel)
    - Small molecule inhibitors: Tazemetostat (irrespective of EZH2 mutational status), zanubrutinib + obinutuzumab

Disease State Description - Oncology, Injectable

Mantle Cell Lymphoma (MCL)

- MCL, while technically classified as an aggressive lymphoma, possesses characteristics of both indolent and aggressive NHLs
- The median overall survival is approximately 4 to 5 years, but there is no evidence of a survival plateau, which is similar to indolent lymphomas
- The chromosomal translocation t(11;14) is usually present in MCL
- MCL is highly resistant to conventional chemotherapy and displays an aggressive disease course

Disease State Description - Oncology, Injectable

National Comprehensive Cancer Network (NCCN), 2025 – B-Cell Lymphomas

- Mantel Cell Lymphoma Guidelines
  - Stage I-II MCL that is nonbulky and noncontiguous: Less-aggressive induction therapy regimen such as bendamustine plus rituximab (BR)
  - Stage I-II disease MCL that is nonbulky and contiguous: Involved-site radiation therapy (ISRT) or a less-aggressive induction therapy regimen with or without ISRT
  - Classical TP53 wild type, stage II bulky noncontiguous and stage III-IV: Aggressive therapy (in patients who are candidates)
  - TP53 mutations: Clinical trial enrollment
  - Advanced-stage disease in younger patients and selected elderly fit patients: Aggressive approach with induction therapy followed by consolidation therapy consisting of high-dose therapy with autologous hematopoietic stem cell transplantation (HSCT) rescue
  - Elderly patients who are not candidates for any of the above regimens: Consider palliative chemotherapy, using milder chemo-immunotherapy regimens (chlorambucil plus rituximab, or BR)
  - Second-line and subsequent therapy preferred regimens:
    - Covalent BTKi (continuous) – acalabrutinib or zanubrutinib
    - Lenalidomide (continuous) + rituximab
  - Progressive disease after prior covalent BTKi
    - Non-covalent BTKi (continuous): Pirtobrutinib
    - CAR T-cell therapy: Brexucabtagene autoleucel or lisocabtagene maraleucel
  - Progressive disease after CAR T-cell therapy and pirtobrutinib or ineligible for CAR T-cell therapy: Glofitamab-gxbm

Oncology, Injectable

FDA Communications

- **B-cell Maturation Antigen (BCMA) – Directed or CD-19 – Directed Autologous Chimeric Antigen Receptor (CAR) T cell Immunotherapies**
  - April 2024 - The FDA has issued a communication on the Boxed Warning requirement related to the risk of T cell malignancies following receipt of B-cell maturation antigen (BCMA)-directed or CD19-directed autologous chimeric antigen receptor (CAR) T-cell immunotherapies
  - June 2024 - REMS for CAR T cell immunotherapies has been modified to remove requirements for educational and training materials
    - The requirement for reporting adverse events (AE) suggestive of cytokine release syndrome (CRS) or neurological toxicities has also been removed from the REMS
    - AE reporting requirements will continue in compliance with federal regulations and have been deemed adequate for routine safety monitoring of these agents

Oncology, Injectable

lisocabtagene maraleucel (Breyanzi)

March 2024 – FDA granted accelerated approval for new indication of adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have received at least 2 prior lines of therapy, including a Bruton tyrosine kinase (BTK) inhibitor and a B-cell lymphoma 2 (BCL-2) inhibitor

May 2024 - FDA granted accelerated approval for new indication of adult patients with relapsed or refractory follicular lymphoma (FL) who have received 2 or more prior lines of systemic therapy

May 2024 - FDA approved new indication for adults with relapsed or refractory mantle cell lymphoma (MCL) who have received at least 2 prior lines of systemic therapy, including a BTK inhibitor

FDA Indications:

- Treatment of adult patients with large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and FL grade 3B, who have: (1) Refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy; or (2) Refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age; or (3) Relapsed or refractory disease after 2 or more lines of systemic therapy
  - Limitations of Use: Not indicated for the treatment of patients with primary central nervous system lymphoma
- **Treatment of adult patients with relapsed or refractory CLL or SLL who have received ≥ 2 prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor ****
- **Treatment of adult patients with relapsed or refractory FL who have received ≥ 2 prior lines of systemic therapy ****
- **Treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) who have received ≥ 2 prior lines of systemic therapy, including a Bruton tyrosine kinase (BTK) inhibitor**

***** These indications are approved under accelerated approval based on response rate and duration of response; continued approval for these indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s)***

lisocabtagene maraleucel (Breyanzi)

Warnings:

- **BBW**: Cytokine release syndrome (CRS), neurologic toxicities, and **secondary hematological malignancies**
  - CRS, including fatal or life-threatening reactions has occurred; do not administer to patients with active infection or inflammatory disorders; treat severe or life-threatening CRS with tocilizumab with or without corticosteroids
  - Neurologic toxicities, including fatal or life-threatening reactions has occurred, including concurrently with CRS, after CRS resolution, or in the absence of CRS; monitor for neurologic events after treatment and provide supportive care and/or corticosteroids as needed
  - **T cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies**
  - Only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS)

Recommended Dosage:

- Administer a lymphodepleting regimen of fludarabine and cyclophosphamide before infusion
- Premedicate with acetaminophen and an H1 antihistamine
- LBCL after one line of therapy: 90 to 110 × 10^6 CAR-positive viable T cells
- LBCL after two or more lines of therapy: 50 to 110 × 10^6 CAR-positive viable T cells
- **CLL/SLL, FL and MCL: 90 to 110 × 10^6 CAR-positive viable T cells**
- Administered in a REMS-certified healthcare facility

Availability:

- Cell suspension for infusion
- A single dose of Breyanzi consists of 1:1 CAR-positive viable T cells of the CD8 and CD4 components, with each componen separately in one to four single-dose 5 mL vials
  - Each mL contains ≥ 1.5 × 10^6 to 70 × 10^6 CAR-positive viable T cells

Disease State Description - Oncology, Injectable

Multiple Myelomas (MM)

- Multiple myeloma is a malignant neoplasm of plasma cells that accumulate in the bone marrow leading to bone destruction and marrow failure
- Multiple myeloma accounts for approximately 1.8% of all malignancies and 18% of all hematologic malignancies in the US
- The median age of diagnosis is 69 years
- The 5-year relative survival rate is 57.9%, and overall survival now is estimated to be 8 to 10 years among patients with standard-risk disease, but it is significantly lower in patients that exhibit high-risk features
- Patients with symptomatic MM must have ≥ 1 myeloma-defining event which may include hypercalcemia, renal insufficiency, anemia, or lytic bone lesions
- This constellation of effects is often referred to by the acronym “CRAB” and is likely an indicator of end organ dysfunction associated with MM
- Multiple myeloma is sensitive to a variety of agents, but the disease is not considered curable with currently available drug therapies
- The clinical course of MM usually involves initial responses to chemotherapy, but these responses may be transient; thus, re-treatment with multiple rounds of therapy with different agents may be required to treat relapse

Guidelines - Oncology, Injectable

National Comprehensive Cancer Network (NCCN), 2025 – Multiple Myeloma

- Systemic therapy should not be delayed for radiation therapy (RT)
  - Data suggest that systemic therapy and palliative RT can be used concurrently without evidence of increased toxicity, but that patients should be carefully monitored for toxicities
- Preferred regimen for primary therapy for transplant candidates: Daratumumab/lenalidomide/bortezomib/dexamethasone
- Preferred regimen for maintenance therapy: lenalidomide
- Preferred regimen for primary non-transplant candidates:
  - Daratumumab/lenalidomide/dexamethasone
  - Isatuximab-irfc/bortezomib/lenalidomide/dexamethasone (for patients <80 years old who are not frail)
  - Lenalidomide/bortezomib/dexamethasone
- Relapse/refractory disease
  - Heavily emphasizes newer immunotherapies like bispecific antibodies and CAR T-cell therapies, often used in combination with traditional drugs like proteasome inhibitors (PI) and immunomodulatory drugs (IMiDs), with regimens tailored based on prior treatment exposure and patient factors
  - CAR T-Cell Therapy
    - After one prior line of therapy including IMiD and a PI, and refractory to lenalidomide: ciltacabtagene autoleucel
    - After two prior lines of therapies including an IMiD, an anti-CD38 monoclonal antibody and a PI: idecabtagene vicleucel

idecabtagene vicleucel (Abecma)

April 2024 – FDA approved expanded indication for the treatment of adult patients with relapsed or refractory multiple myeloma after two or more prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody

- **Previously approved for patients who had failed at least four lines of therapy**

FDA Indication:

- **Treatment of adult patients with relapsed or refractory multiple myeloma after two or more prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody**

Warnings:

- **BBW**: Cytokine release syndrome, neurologic toxicities, hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), prolonged cytopenia, and **secondary hematological malignancies**

Recommended Dosage:

- Administer a lymphodepleting chemotherapy regimen of cyclophosphamide and fludarabine before infusion
- Premedicate with acetaminophen and an H1-antihistamine
- Dosing range is 300 to 510 × 10^6 CAR-positive T cells
- Administer at a REMS-certified healthcare facility

Availability:

- Cell suspension for intravenous infusion
- A single dose of Abecma contains a cell suspension of 300 to 510 x 10^6 CAR-positive T cells in one or more infusion bags

ciltacabtagene autoleucel (Carvykti)

April 2024 - FDA approved expanded indication for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 1 prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent, and are refractory to lenalidomide

- **Previously approved for patients who had failed at least four lines of therapy**

FDA Indication:

- **Treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 1 prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent, and are refractory to lenalidomide**

Warnings:

- **BBW**: Cytokine release syndrome, neurologic toxicities, hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), prolonged cytopenia, and **secondary hematological malignancies**

Recommended Dosage:

- Administer a lymphodepleting regimen of cyclophosphamide and fludarabine before infusion
- Premedicate with acetaminophen and an H1-antihistamine
- Dosing range is $0.5\text{-}1.0\times10^{6}$ CAR-positive viable T cells per kg of body weight
- Maximum dose of 1×10^{8} CAR-positive viable T cells per single-dose infusion
- Administer at a REMS-certified healthcare facility

Availability:

- Cell suspension for intravenous infusion
- A single dose of Carvykti contains a cell suspension of $0.5\text{-}1.0\times10^{6}$ CAR-positive viable T cells per kg body weight in one infusion bag

Disease State Description - Oncology, Injectable

Synovial Sarcoma (SS)

- Rare and aggressive disease that accounts for 5%-10% of all soft tissue sarcomas
- Typically affects younger adults and children, with a peak incidence in the fourth decade of life
- In > 95% of cases, the oncogenic driver is a translocation between chromosomes X and 18 that leads to the formation of the SS18::SSX fusion oncogenes
- Surgery with or without radiotherapy and/or chemotherapy can be effective in localized disease, especially in children
- However, the prognosis in the advanced stages is poor, with treatment strategies that heavily rely on traditional cytotoxic chemotherapies
- Standard first line treatment of advanced unresectable or metastatic synovial sarcoma includes combination anthracycline-based chemotherapy regimens
- There is no consensus on optimal second line therapy

afamitresgene autoleucel (Tecelra)

August 2024 – FDA approved a melanoma-associated antigen A4 (MAGE-A4)-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adults with unresectable or metastatic synovial sarcoma who have received prior chemotherapy, are HLA-A*02:01P, -A*02:02P, -A*02:03P, or -A*02:06P positive and whose tumor expresses the MAGE-A4 antigen as determined by FDA-approved or cleared companion diagnostic devices

- **Approved under accelerated approval based on overall response rate and duration of response; continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial**

Warnings:

- **BBW: Cytokine release syndrome (CRS), which may be severe or life-threatening**
  - **At the first sign of CRS, immediately evaluate patient for hospitalization and institute treatment with supportive care**
  - **Ensure healthcare providers have immediate access to medications and resuscitative equipment to manage CRS**

Recommended Dosage:

- **Administer a lymphodepleting regimen of cyclophosphamide and fludarabine**
- **Premedicate with acetaminophen and an H1-antihistamine**
- **Dosing range is between 2.68 x 10^9 to 10 x 10^9 MAGE-A4 T cell receptor (TCR) positive T cells**

Availability:

- **Cell suspension for intravenous infusion.**
- **Provided in one or more infusion bag(s) containing 2.68 x 10^9 to 10 x 10^9 MAGE-A4 TCR positive T cells**

Disease State Description - Oncology, Injectable

Acute lymphoblastic leukemia (ALL)

- Most common form of childhood leukemia, with 53.5% of patients diagnosed before the age of 20 years
- Approximately 29.6% of cases of ALL are diagnosed at age 45 years or older, with 13.7% of cases diagnosed at 65 years or older
- Overall survival (OS) outcomes for children with ALL have improved dramatically in the last decades, such that 5-year overall survival is estimated to be 89% in children
- Unfortunately, as age of diagnosis increases, the overall survival rates decrease; adolescents and young adults have an estimated 61% overall survival, while adults diagnosed with ALL have only a 20% to 40% overall survival
- Aside from patient age, prognosis is also influenced by cytogenetic markers or genetic abnormalities
- Newly diagnosed pediatric ALL patients are often classified for the purposes of treatment as being low risk, standard risk, high risk, or very high risk
- All treatment regimens for ALL are generally divided into phases
- These phases often include induction, consolidation, and maintenance

Guidelines - Oncology, Injectable

National Comprehensive Cancer Network (NCCN), 2024 – Acute Lymphoblastic Leukemia

- NCCN recommends enrolling patients with ALL in a clinical trial, if possible
- Otherwise, NCCN recommendations for first-line treatment are based on risk stratification and age:
  - Philadelphia chromosome–positive (Ph+) ALL:
    - Adolescent and Young Adults: Chemotherapy and tyrosine kinase inhibitor (TKI), followed by allogeneic stem cell transplantation (SCT) if an appropriate donor is available; if transplantation is not feasible, continue multiagent chemotherapy and a TKI
    - Adults < 65 years: Chemotherapy and TKI; consider allogeneic SCT if an appropriate donor is available and the patient has good performance status and no or limited comorbidities; if transplantation is not feasible, continue multiagent chemotherapy and a TKI
    - Adults ≥ 65 years or with substantial comorbidities: TKI and corticosteroids or TKI and chemotherapy (evaluate end-organ reserve, end-organ dysfunction, and performance status)
  - Philadelphia chromosome–negative (Ph-) ALL:
    - Adolescent and Young Adults: Pediatric-style multiagent chemotherapy
    - Adults < 65 years: Multiagent chemotherapy
    - Adults ≥ 65 years or with substantial comorbidities: Multiagent chemotherapy or corticosteroids (evaluate end-organ reserve, end-organ dysfunction)
  - Relapse/Refractory therapy:
    - Ph+ B-ALL treatment cnd Ph- B-ALL treatment: Obecabtagene autoleucel (following therapy that has included TKIs) added
    - Ph- B-ALL treatment and T-ALL: Revumenib (KMT2A rearranged) added

obecabtagene autoleucel (Aucatzyl)

November 2024 – FDA approved a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)

Warnings:

- **BBW: Cytokine release syndrome (CRS), neurologic toxicities, and secondary hematological malignancies**
  - **CRS: Do not administer to patients with active infection or inflammatory disorders**
  - **Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) including fatal or life-threatening reactions has occurred, including concurrently with CRS or after CRS resolution; monitor for neurologic signs and symptoms after treatment**
  - **T cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies**

Recommended Dosage:

- **Administer a lymphodepleting chemotherapy regimen of fludarabine/cyclophosphamide**
- **Premedicate with acetaminophen**
- **Total recommended dose is 410 × 10^6 CD19 chimeric antigen receptor (CAR)-positive viable T cells**
- **The treatment regimen consists of a split dose infusion to be administered on Day 1 and Day 10 (± 2 days)**
- **Dosage regimen is determined by the tumor burden assessed by bone marrow blast percentage from a sample obtained within 7 days prior to the start of lymphodepletion**

Availability:

- **Cell suspension for infusion**
- **Contains a total recommended dose of 410 x 10^6 CD19 CAR-positive viable T cells supplied in 3 to 5 infusion bags**

No Significant Clinical Updates

❖ **Immunomodulators, Atopic Dermatitis**
- ATOPIC DERMATITIS AGENTS : IMMUNOSUPPRESSIVE AGENTS - TOPICAL

❖ **Glucocorticoid, Oral**
- CORTICOSTEROIDS : GLUCOCORTICOSTEROIDS – ORAL

- **Pompe Disease and Enzyme Replacement, Gaucher Disease**
- HEMATOPOIETIC AGENTS : GAUCHER DISEASE

❖ **Oncology, Oral – Prostate**
- ONCOLOGY AGENTS : ANTINEOPLASTIC ESTROGENS – ORAL

❖ **Oncology, Oral – Breast**
- ONCOLOGY AGENTS : NITROGEN MUSTARDS – ORAL
- ONCOLOGY AGENTS : PHOSPHATIDYLINOSITOL 3-KINASE (PI3K) INHIBITORS - ORAL

❖ **Oncology, Oral – Other**
- ONCOLOGY AGENTS : IMIDAZOTETRAZINES - ORAL
- ONCOLOGY AGENTS : NITROSOUREAS - ORAL

❖ **Oncology, Oral – Hematologic**
- IMMUNE MODULATORS : THALIDOMIDE ANALOGUES
- ONCOLOGY AGENTS : ALKYLATING AGENTS - ORAL
- ONCOLOGY AGENTS : ANTINEOPLASTICS MISC - ORAL
- ONCOLOGY AGENTS : HISTONE DEACETYLASE INHIBITORS - ORAL
- ONCOLOGY AGENTS : ISOCITRATE DEHYDROGENASE-1 (IDH1) INHIBITORS - ORAL
- ONCOLOGY AGENTS : ISOCITRATE DEHYDROGENASE-2 (IDH2) INHIBITORS - ORAL
- ONCOLOGY AGENTS : JANUS ASSOCIATED KINASE (JAK) INHIBITORS – ORAL
- ONCOLOGY AGENTS : NITROGEN MUSTARDS - ORAL
- ONCOLOGY AGENTS : PHOSPHATIDYLINOSITOL 3-KINASE (PI3K) INHIBITORS - ORAL
- ONCOLOGY AGENTS : PROTEASOME INHIBITORS - ORAL
- ONCOLOGY AGENTS : XPO1 INHIBITORS - ORAL
- ONCOLOGY AGENTS : BCL-2 INHIBITORS - ORAL

❖ **Oncology, Injectable**
- ONCOLOGY AGENTS : GENE THERAPIES

Glucocorticoids, Inhaled

ASTHMA AND COPD AGENTS : INHALED CORTICOSTEROID COMBINATIONS
ASTHMA AND COPD AGENTS : INHALED CORTICOSTEROIDS

Glucocorticoids, Inhaled

Discontinuation

- **May 2024 - ArmonAir Digihaler (fluticasone)**
  - Teva discontinued the manufacture of ArmonAir Digihaler 55 mcg, 113 mcg, and 232 mcg metered powder inhaler

- **May 2024 - AirDuo Digihaler (fluticasone/salmeterol)**
  - Teva discontinued the manufacture of AirDuo Digihaler 55 mcg/14 mcg, 113 mcg/14 mcg, and 232 mcg/14 mcg metered powder inhaler

Sickle Cell Anemia Agents

HEMATOPOIETIC AGENTS : SICKLE CELL ANEMIA
HEMATOPOIETIC AGENTS : SICKLE CELL ANEMIA - SELECTIN BLOCKERS

Sickle Cell Anemia Agents

New Generic

- **July 2024 – l-glutamine**
  - FDA approved the first generic to Emmaus Medical's Endari 5 gram/packet oral solution from Novitium

Market Withdrawal and FDA Communication

- **September 2024 – voxelotor (Oxbryta)**
  - Pfizer voluntarily withdrew all lots of Oxbryta from the global market and discontinued all active clinical trials for the drug
    - Decision to withdraw Oxbryta is based on totality of clinical data that suggest an imbalance in vaso-occlusive crises and fatal events, whereby, the overall benefit of use no longer outweigh the risks
  - The FDA also issued an alert regarding the market withdrawal
    - Patients and caregivers should contact their health care professional about changing to another treatment option

Oncology, Oral – Breast

ONCOLOGY AGENTS : ANTIESTROGENS - ORAL

Oncology, Oral

Discontinuation

- **August 2024 - toremefine (Fareston)**
  - Kyowa Kirin announced, effective August 31, 2024, distribution and fulfillment of orders for toremefine (Fareston) 60 mg tablets in the United States will cease

Oncology, Oral – Breast
Oncology, Oral – Hematological

ONCOLOGY AGENTS : ANTIMETABOLITES – ORAL

FDA Communication

- **January 2025 – capecitabine (Xeloda)**
  - FDA provided communication to increase awareness of recent updates to the product labeling of capecitabine and fluorouracil (5-FU) related to risks associated with dihydropyrimidine dehydrogenase (DPD) deficiency
  - Healthcare providers should be aware and inform patients of the risks of DPD prior to treatment
  - Patients with certain homozygous or compound heterozygous variants in the DPYD gene, known to result in complete or near complete absence of DPD activity (complete DPD deficiency), are at increased risk for acute early-onset toxicity and serious, including fatal, adverse reactions (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity)
  - Patients with partial DPD activity (partial DPD deficiency) may also have increased risk of serious, including fatal, adverse reactions