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# Washington Pharmacy Advisory Committee Meeting

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# Agenda Topics

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

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# COPD Agents:

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

# COPD Agents – Disease State Description

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

- COPD continues to be a leading cause of chronic morbidity and mortality worldwide carrying with it significant economic and social burden
  - COPD is projected by the World Health Organization (WHO) to become the third leading cause by 2030
  - In their 2017 National Health Interview Survey, the CDC reported that the percent of adults who were diagnosed with chronic bronchitis in the past year was 3.5% and those that have ever been diagnosed with emphysema was 1.4%
  - However, the United States Preventive Services Task Force (USPSTF) recommends against routine screening in asymptomatic adults

*Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2018*
*World Health Organization, 2008*
*Centers for Disease Control and Prevention (CDC), 2016*

# COPD Agents – Disease State Description

- Although the precise distinctions between chronic bronchitis and emphysema are a subject of debate, common belief holds that chronic bronchitis is responsible for 85% of COPD
  - Patients with chronic bronchitis experience intermittent airway inflammation and excessive mucus production that leads to frequent, prolonged episodes of productive cough
  - In contrast, 15% of patients with COPD suffer primarily from emphysema, in which destruction of the infrastructure of alveoli and distal airspaces that provide gas exchange and elastic recoil occurs
- Both chronic bronchitis and emphysema predispose patients to a common collection of symptoms and impairments in respiratory function, such as reductions in forced expiratory volume in 1 second ($FEV_1$), forced vital capacity (FVC), $FEV_1$/FVC ratio, and forced expiratory flow ($FEF_{25-75\%}$)

*Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2018*
*World Health Organization, 2008*
*Centers for Disease Control and Prevention (CDC), 2016*

# COPD Agents – Guidelines

- Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2020
  - Recommend treatment plans for COPD based on the aforementioned patient group categories, identified by disease severity (airflow limitation), symptoms, comorbidities and exacerbation/hospitalization risk, although all treatment should be individualized
  - Bronchodilator medications continue to be central to symptom management of COPD across all groups
  - For patients in:
    - **Group A, a short-acting inhaled bronchodilator (beta$_2$-agonist or antimuscarinics) used on an as-needed basis or a long-acting bronchodilator (beta$_2$-agonist or antimuscarinics) is recommended as first choice**
    - **Group B**, regular use of a long-acting beta$_2$ agonist (LABA) or long-acting antimuscarinic (LAMA) is recommended, while the combination of a LABA plus a LAMA is an alternative treatment
      - There is insufficient evidence to recommend one long-acting agent over another
    - **Group C**, focus on monotherapy with a long-acting bronchodilator, with preference given to LAMAs
      - If exacerbations persist, then fixed combinations of LABA/LAMA or LABA/inhaled corticosteroids (ICS) may be tried; due to increased risk of pneumonia with ICS agents, a LABA/LAMA combination is preferred
    - **Group D, initial therapy with a LAMA is recommended as it has effects on both breathlessness and exacerbations**
      - **Patients with more severe symptoms (CAT ≥ 20) can be initiated on LABA/LAMA**
      - **Prescribers may consider a LABA/inhaled corticosteroid (ICS) combination for patients with blood eosinophil counts ≥ 300 cells/µL as this combination has the greatest likelihood of reducing exacerbations or may be preferred in patients with a history of asthma**
      - **Some evidence for use of triple therapy – ICS/LABA/LAMA – in patients with persistent breathlessness or exercise limitation**
      - **If exacerbations still occur with triple therapy, then the oral phosphodiesterase 4 (PDE4) inhibitor roflumilast (Daliresp), which is indicated to decrease the frequency of exacerbations or worsening of symptoms of severe COPD, may be added in patients with an FEV$_1$ < 50% of predicted and chronic bronchitis**
      - **Long-term monotherapy with an ICS at any stage has been shown to be less effective than its use in combination with LABAs**
      - **Following initial therapy, patients should be reassessed for attainment of treatment goals and therapy adjusted as needed**

# COPD Agents – Guidelines

- American Thoracic Society (ATS), 2020
  - In 2020, the American Thoracic Society (ATS) released additional guidelines for the pharmacologic management of COPD
  - These guidelines focus on addressing specific questions developed by an ATS panel regarding significant COPD management issues, including when to use dual and triple therapy and ICS use in COPD patients with blood eosinophilia
  - The panel strongly recommends the use of dual LABA/LAMA therapy over LABA or LAMA monotherapy in COPD patients who complain of exercise intolerance or dyspnea based on pooled evidence demonstrating decreased hospital admissions and exacerbations and improvements in patient quality of life and dyspnea
  - Additionally, the ATS suggests triple therapy (ICS/LABA/LAMA) in COPD patients with a history of ≥ 1 exacerbations requiring hospitalization, oral steroids, or antibiotics in the past year who, despite LABA/LAMA dual therapy, complain of exercise intolerance or dyspnea
  - Further, for patients receiving triple combination therapy who experience no exacerbations over the course of 1 year, they suggest that ICS therapy may be discontinued
  - The ATS also suggests the addition of ICS therapy in COPD patients with blood eosinophilia (≥ 2% blood eosinophils or ≥ 150 cells/µL) who have experienced ≥ 1 exacerbations requiring hospitalization, oral steroids, or antibiotics in the past year
  - Additional management recommendations regarding treatment approaches outside of this therapeutic class review are detailed in the guidelines

# COPD Agents – Guidelines

- American Board of Internal Medicine (ABIM), 2020
  - American Board of Internal Medicine (ABIM) Foundation initiative, called Choosing Wisely, released guidance based on American Academy of Pediatrics (AAP) information
  - Five key evidence-based recommendations regarding therapies and practices used to treat asthma and sleep disorders in pediatric patients were highlighted:
    - (1) Assess adherence to asthma medication before stepping up therapy
    - (2) Do not use a LABA/steroid combination as initial therapy for intermittent or mild persistent asthma
    - (3) Avoid nebulized medication by "blow by" or placing the mask or nebulizer tubing near the child's nose and mouth, rather secure the mask to the child's face or use a t-piece
    - (4) Do not interpret pediatric sleep studies using adult standards
    - (5) Do not routinely use airway clearance therapy when asthma, bronchiolitis, or pneumonia are present

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# Glucocorticoids, Inhaled

## ASTHMA AND COPD AGENTS : INHALED CORTICOSTEROID COMBINATIONS

## ASTHMA AND COPD AGENTS : INHALED CORTICOSTEROID

# Glucocorticoids, Inhaled – Disease State Description

- In 2018, total asthma prevalence was estimated to be 7.5% of the population, or approximately 26.7 million Americans
- Further, the National Health Statistics Report shows that asthma appears to disproportionately affect minority groups, females, children, and individuals of low socioeconomic status which can place significant pressure on public health systems
- The National Asthma Education and Prevention Program (NAEPP) has defined asthma as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role
  - In susceptible individuals, inflammation may cause recurrent episodes of wheezing, breathlessness, chest tightness, and coughing
  - These episodes are usually associated with airflow obstruction that is often reversible, either spontaneously or with treatment
  - The inflammation also causes an increase in bronchial hyper-responsiveness to a variety of stimuli
- Studies have demonstrated the efficacy of inhaled corticosteroids (ICS) in improving lung function, reducing symptoms, reducing frequency and severity of exacerbations, and improving the quality of life (QoL) of patients with asthma
  - The 2007 National Heart, Lung, and Blood Institute (NHLBI) states that inhaled glucocorticoids are currently the most effective anti-inflammatory medications for the treatment of persistent asthma
  - The 2019 GINA full report advises that all patients with asthma should receive ICS-containing controller treatment to reduce risk of serious exacerbations and to control symptoms

*Centers for Disease Control and Prevention (CDC), 2020*

# Glucocorticoids, Inhaled – Guidelines

- Global Initiative for Asthma (GINA), 2020
  - Offer a control-based management plan to adjust treatment in a continuous cycle of assessment, treatment, and review of the patient's response as it relates to symptom control, future risk of exacerbations, and side effects
  - Equally important in this process is identifying the patient's own goals regarding their asthma management to ensure improved outcomes
  - During this continuous cycle, a stepwise treatment approach is offered to achieve control using the patient's current level of control as the baseline
  - If the patient is not controlled on the current regimen, treatment should be stepped up until control is achieved
  - If control is maintained for at least 3 months on the current regimen, treatment can be stepped down to the lowest step and dosage that maintains control
  - A combination ICS/long-acting beta$_2$-agonist (LABA) product is the preferred step-up treatment for adults and adolescents ≥ 12 years currently on a low dose ICS who continue to have persistent symptoms and/or exacerbations
  - The risk of exacerbations can be reduced in adolescents and adults who are using other alternative therapies with treatment of a low dose ICS/formoterol (with beclomethasone or budesonide). For children (6 to 11 years of age) with persistent symptoms, an increased ICS dose is preferred over use of an ICS/LABA agent
  - Notably, as of 2019, GINA guidelines no longer recommend SABA-only treatment for Step 1 patients; rather, all adults and adolescents should receive symptom-driven or regular low dose ICS-containing controlled treatment
  - GINA also emphasizes the impact of inhaler technique and adherence. Management of exacerbations in primary care using reliever medications is also discussed

# Glucocorticoids, Inhaled – Guidelines

- National Asthma Education and Prevention Program (NAEPP), 2020 Update

| Severity of Asthma | Adults and Children ≥ 12 Years | Children 5 to 11 Years of Age | Children from Birth to 4 Years of Age |
|---|---|---|---|
| **Step 1 Intermittent Asthma** | SABA as needed (no daily medications needed) | SABA as needed (no daily medications needed) | SABA as needed (no daily medications needed)<br>**Add short course of ICS at start of RTI** |
| **Step 2 Persistent Asthma** | Low-dose ICS<br>Alternative: cromolyn, LTRA, nedocromil, **zileuton (Zyflo),** or theophylline | Low-dose ICS<br>Alternative: cromolyn, LTRA, nedocromil, or theophylline | Low-dose ICS<br>Alternative: cromolyn or montelukast |
| **Step 3 Persistent Asthma** | Low-dose ICS **+ formoterol**<br>Alternative: **medium-dose ICS, low-dose ICS + LABA, low-dose ICS + LAMA,** low-dose ICS + LTRA, low-dose ICS + theophylline, or low-dose ICS + zileuton | **Low-dose ICS + formoterol**<br>Alternative: **low-dose ICS + LABA,** low-dose ICS + LTRA, or low-dose ICS + theophylline | Medium-dose ICS |
| **Step 4 Persistent Asthma** | Medium-dose ICS **+ formoterol**<br>Alternative: **medium-dose ICS + LABA, medium-dose ICS + LAMA**, medium-dose ICS and 1 of the following: LTRA, theophylline, or zileuton | **Medium-dose ICS + formoterol**<br>Alternative: **medium-dose ICS + LABA,** medium-dose ICS + LTRA, or medium-dose ICS + theophylline | Medium-dose ICS + LABA<br>**Alternative: medium-dose ICS + montelukast** |
| **Step 5 Persistent Asthma** | **Medium-dose ICS + LABA + LAMA**<br>**Alternative: Medium-high-dose ICS + LABA, high-dose ICS + LTRA** | High-dose ICS + LABA<br>Alternative: high-dose ICS + LTRA, or high-dose ICS + theophylline | High-dose ICS + LABA<br>**Alternative: high-dose ICS + montelukast** |
| **Step 6 Persistent Asthma** | High-dose ICS + LABA + oral corticosteroid | High-dose ICS + LABA + oral corticosteroid<br>Alternative: high-dose ICS + LTRA + oral corticosteroid, high-dose ICS + theophylline + oral corticosteroid | High-dose ICS + LABA + oral corticosteroid<br>**Alternative: high-dose ICS + montelukast + oral corticosteroid** |

# Glucocorticoids, Inhaled

- budesonide/formoterol fumarate/glycopyrrolate (Breztri Aerosphere)
  - **July 2020: FDA approved Breztri Aerosphere, a combination of budesonide (an ICS), glycopyrrolate (an anticholinergic), and formoterol fumarate (a LABA), indicated for the maintenance treatment of patients with COPD (limitations of use: not indicated for the relief of acute bronchospasm or for the treatment of asthma)**
  - **Indications**
    - **A combination of budesonide, an inhaled corticosteroid (ICS); glycopyrrolate, an anticholinergic; and formoterol fumarate, a long-acting beta2-adrenergic agonist (LABA), indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD)**
  - **Precautions**
    - **LABA monotherapy increases the risk of serious asthma-related events**
    - **Deterioration of disease and acute episodes: Do not initiate in acutely deteriorating asthma or to treat acute symptoms**
  - **Dosage**
    - **Maintenance treatment of COPD: 2 inhalations twice daily administered by oral inhalation**
  - **Availability**
    - **Inhalation aerosol: Pressurized metered dose inhaler containing a combination of budesonide (160 mcg), glycopyrrolate (9 mcg), and formoterol fumarate (4.8 mcg) per inhalation**

# Glucocorticoids, Inhaled

- fluticasone furoate, umeclidinium, and vilanterol (Trelegy Ellipta)
  - **September 2020: FDA approved expanded indication for Trelegy Ellipta, which is now indicated for the maintenance treatment of asthma in patients ≥ 18 years. Previously indicated only for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD). It is not indicated for relief of acute bronchospasm**
  - **Indications**
    - Indicated for:
      - The maintenance treatment of patients with chronic obstructive pulmonary disease (COPD)
      - **The maintenance treatment of asthma in patients aged 18 years and older**
    - Limitations of use: Not indicated for relief of acute bronchospasm
  - **Precautions**
    - LABA monotherapy increases the risk of serious asthma-related events
    - Deterioration of disease and acute episodes: Do not initiate in acutely deteriorating asthma or to treat acute symptoms
  - **Dosage**
    - Maintenance treatment of COPD: 1 actuation of 100/62.5/25 mcg once daily administered by oral inhalation
    - **Maintenance treatment of asthma: 1 actuation of 100/62.5/25 mcg or 200/62.5/25 mcg once daily administered by oral inhalation**
  - **Availability**
    - Inhalation powder: 2 foil blister strips of powder formulation for oral inhalation. One strip contains fluticasone furoate 100 or 200 mcg per blister and the other contains umeclidinium/vilanterol 62.5/25 mcg per blister

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# Immunomodulators, Asthma

## ASTHMA AND COPD AGENTS : MONOCLONAL ANTIBODIES

# Immunomodulators, Asthma - Overview of Disease State

- Eosinophilic granulomatosis with polyangiitis (EGPA) (previously known as Churg-Strauss syndrome)
  - A systemic vasculitis of small-to-medium vessels, characterized by allergic rhinitis, asthma, and hypereosinophilia
  - EGPA is a rare disease state affecting 1 to 3 out of 100,000 patients, with a higher incidence of about 1 per 15,000 in patients with asthma
  - Onset may occur between 15 and 70 years of age, but diagnosis is typically made between 35 and 50 years of age
  - While the direct cause of the disease is unknown, HLA-DRB4 positivity may be a genetic risk factor
  - Symptoms can vary from mild to life-threatening
- Diagnosis
  - A diagnosis may be confirmed if in addition to vasculitis, patients also have at least 4 of the following features: asthma, eosinophilia, neuropathy, pulmonary infiltrates, paranasal sinus abnormalities, and eosinophilic vasculitis
  - Scoring systems to assess the severity of vasculitis and guide initial therapy in patients with EGPA include the 5-factor score (FFS) and the Birmingham Vasculitis Activity Score (BVAS)
    - FFS ranges from 0 to 2, and attributes a point for one of the following and 2 points if 2 or more of the following are met: age > 65 years, cardiac insufficiency, gastrointestinal involvement, renal insufficiency, and ear/nose/throat manifestations
    - BVAS has historically been used to a greater extent in research than clinical practice and includes general symptoms in addition to organ involvement It can range from 0 to 68 with 1 point being allotted for persistent symptoms and 2 points for new or worsening symptoms
- Guidelines
  - No US guidelines are currently available for the treatment of EGPA
  - As a consensus, EGPA that is not severe in nature is often treated with oral corticosteroids alone, and more than 90% of patients achieve remission
  - Initial therapy may also include cyclophosphamide for patients with severe, multi-organ disease
  - Patients with severe EGPA may be transitioned to maintenance therapy with azathioprine, methotrexate, or leflunomide; evidence supporting their use is limited
  - Other treatments include anti-IL-5 antibodies such as Nucala, immunoglobulins, interferon-alpha, rituximab, or inhaled glucocorticoids
  - Notably, Nucala is the only FDA-approved medication for this disease state

# Immunomodulators, Asthma

- mepolizumab (Nucala)
  - **October 2020: FDA approved new indication for Nucala for the treatment of adult and pediatric patients aged ≥ 12 years with hypereosinophilic syndrome (HES) for ≥ 6 months without an identifiable non-hematologic secondary cause**
  - **Indications**
    - An interleukin-5 (IL-5) antagonist monoclonal antibody (IgG1 kappa) indicated for:
      - Add-on maintenance treatment of patients with severe asthma aged 6 years and older, and with an eosinophilic phenotype
      - The treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA)
      - **The treatment of adult and pediatric patients aged 12 years and older with hypereosinophilic syndrome (HES) for ≥6 months without an identifiable non-hematologic secondary cause**
    - Limitations of use: Not for relief of acute bronchospasm or status asthmaticus
  - **Precautions**
    - Do not use to treat acute bronchospasm or status asthmaticus
    - Herpes zoster infections have occurred in patients receiving Nucala. Consider vaccination if medically appropriate
    - Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with NUCALA. Decrease corticosteroids gradually, if appropriate
  - **Dosage**
    - **HES: 300 mg as 3 separate 100-mg injections administered subcutaneously once every 4 weeks**
  - **Availability**
    - For injection: 100 mg of lyophilized powder in a single-dose vial for reconstitution
    - Injection: 100 mg/mL, single-dose, prefilled autoinjector or single-dose prefilled syringe

# Immunomodulators, Asthma

- omalizumab (Xolair)
  - **December 2020: FDA approved new indication for add-on maintenance treatment of nasal polyps in adults with inadequate response to nasal corticosteroids**
  - **Indications**
    - An anti-IgE antibody indicated for:
      - Moderate to severe persistent asthma in adults and pediatric patients 6 years of age and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids
      - **Nasal polyps in adult patients 18 years of age and older with inadequate response to nasal corticosteroids, as add-on maintenance treatment**
      - Chronic idiopathic urticaria in adults and adolescents 12 years of age and older who remain symptomatic despite H1 antihistamine treatment
    - Limitations of Use: Not indicated for acute bronchospasm or status asthmaticus; Not indicated for other allergic conditions or other forms of urticaria
  - **Precautions**
    - Anaphylaxis: Initiate therapy in a healthcare setting prepared to manage anaphylaxis which can be life-threatening and observe patients for an appropriate period of time after administration
    - Malignancy: Malignancies have been observed in clinical studies
  - **Dosage**
    - **Nasal Polyps: XOLAIR 75 to 600 mg SC every 2 or 4 weeks. Determine dose (mg) and dosing frequency by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). See the dose determination chart in TCR/PI**
  - **Availability**
    - Injection: 75 mg/0.5 mL and 150 mg/mL solution in a single-dose prefilled syringe
    - For Injection: 150 mg lyophilized powder in a single-dose vial for reconstitution

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# Gaucher Disease

## HEMATOPOIETIC AGENTS: GAUCHER DISEASE

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# Sickle Cell Anemia

## HEMATOPOIETIC AGENTS: SICKLE CELL ANEMIA

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# Colony Stimulating Factors

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

# Colony Stimulating Factors - Disease State Description

- Myelosuppressive chemotherapy can induce neutropenia (< 500 neutrophils/µL or < 1,000 neutrophils/µL and a predicted decline to ≤ 500/µL during the 48 hours after the dose) and febrile neutropenia (≥ 38.3°C orally or ≥ 38°C sustained over 1 hour) which is a dose-limiting toxicity of chemotherapy
- 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
  - Colony stimulating factors act on hematopoietic cells and stimulate proliferation, differentiation commitment, and some end-cell functional activation
- Prophylactic CSF use can reduce the severity, risk, and duration of febrile neutropenia and decrease rates of infection and hospitalizations
  - Neupogen, Nivestym, Zarxio, Neulasta, Nyvepria, Udenyca, Fulphila, Ziextenzo, and Granix are granulocyte colony-stimulating factors (G-CSF)
  - Leukine is a granulocyte-macrophage colony stimulating factor (GM-CSF)

*National Comprehensive Cancer Network, 2020*

# Colony Stimulating Factors - Guidelines

- **The National Comprehensive Cancer Network (NCCN) v1.2020 Practice Guidelines for Myeloid Growth Factors**
  - Due to the recent approval, pegfilgrastim-apgf (Nyvepria) is not currently addressed by NCCN
  - Since the approval of chimeric antigen receptor-modified T cell (CAR-T) therapies in recent years, NCCN advises against use of G-CSFs within 14 days after receipt of CAR-T therapy, due to concern for exacerbation of cytokine release syndrome (CRS). Use after this time period is considered for treatment of neutropenia
  - NCCN states limited data suggest that patients can alternate between the originator product and the biosimilar without any clinically meaningful differences regarding efficacy or safety

*National Comprehensive Cancer Network, 2020*

# Colony Stimulating Factors

- **pegfilgrastim-apgf (Nyvepria)**
  - June 2020: FDA approved pegfilgrastim-apgf (Nyvepria), a biosimilar to Neulasta
  - Indications
    - A leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia
    - Limitations of Use: Not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation
  - Precautions
    - Fatal splenic rupture: Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture
    - Acute respiratory distress syndrome (ARDS): Evaluate patients who develop fever, lung infiltrates, or respiratory distress. Discontinue in patients with ARDS
  - Dosage
    - Patients with cancer receiving myelosuppressive chemotherapy
      - 6 mg administered subcutaneously once per chemotherapy cycle
      - Do not administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy
      - Use weight-based dosing for pediatric patients weighing less than 45 kg; refer to Table 1
  - Availability
    - Injection: 6 mg/0.6 mL solution in a single-dose prefilled syringe for manual use only

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# Erythropoiesis Stimulating Proteins

## HEMATOPOIETIC AGENTS: ERYTHROPOIESIS STIMULATING AGENTS (ESAS)

# Erythropoiesis Stimulating Proteins - Disease State Description

- **Anemia**
  - A frequent complication, affecting over 3 million Americans
  - Associated with a number of serious diseases, such as chronic kidney disease (CKD), diabetes, heart disease, and cancer, as well as chronic inflammatory conditions like rheumatoid arthritis or inflammatory bowel disease
  - These conditions can cause anemia by interfering with the production of oxygen-carrying red blood cells (RBCs)
  - Sometimes, as in the case of cancer chemotherapy, anemia can be caused by the treatment itself

- **Erythropoietin**
  - A glycoprotein produced in the kidneys that stimulates RBC production from bone marrow
  - 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 subjects, plasma erythropoietin levels range from 0.01 to 0.03 units/mL and may increase 100- to 1,000-fold during hypoxia or anemia
  - In contrast, patients with CKD have impaired production of erythropoietin, which is the primary cause of their anemia
  - Anemia in cancer patients may be related to the disease itself or the effect of concomitantly administered chemotherapeutic agents

# Erythropoiesis Stimulating Proteins - Disease State Description

- **Beta thalassemia**
  - A rare inherited blood disorder marked by the reduction of functional hemoglobin levels, has an incidence of approximately 1 in 100,000 individuals in the general population
  - There are 3 subtypes of beta thalassemia, which are characterized by the severity of symptoms – minor, intermedia, and major
  - Individuals with beta thalassemia major require regular blood transfusions, as often as once every 2 to 4 weeks and are dependent on medical care for survival
  - Treatment for beta thalassemia is highly dependent on type of thalassemia, progression and severity of disease, and the presence or absence of certain symptoms
  - Treatment options may include regular blood transfusions, chelation therapy, folic acid treatment, removal of the spleen and/or gallbladder, and bone marrow transplantation
  - **Luspatercept-aamt (Reblozyl)** is the first FDA-approved erythroid maturation agent, which reduces patient transfusion burden by regulating late-stage RBC maturation
  - It is approved for the treatment of anemia in adult patients with beta thalassemia who require regular red blood cell transfusions

# Erythropoiesis Stimulating Proteins - Guidelines

- **National Comprehensive Cancer Network (NCCN) Guidelines, 2020**
  - State that erythropoiesis stimulating agents (ESAs) are associated with an increased risk of thrombosis, decreased survival, and shortened time to tumor
  - Physicians are advised to use the lowest ESA dose possible to maintain hemoglobin (Hb) levels sufficient to avoid blood transfusions, to prescribe according to Food and Drug Administration (FDA) guidelines, and to obtain patient consent
  - ESAs should be discontinued once the course of chemotherapy has been completed and anemia resolves
  - There is not enough evidence to support the use of ESAs for the treatment of anemia related to myelosuppressive chemotherapy with curative intent, patients receiving non-myelosuppressive therapy, or patients with cancer not receiving therapy

*National Comprehensive Cancer Network, 2020*

- **American Society of Clinical Oncology (ASCO) and American Society of Hematology (ASH)**
  - Updated their 2010 recommendations for use of erythropoiesis-stimulating agents (ESAs) in patients with cancer
  - Guidelines emphasize the intent of treatment be considered when weighing the benefits and risks of these agents (including thromboembolism)
  - ESAs may be offered to patients with chemotherapy-associated anemia whose cancer treatment is not curative in intent and whose hemoglobin level is < 10 g/dL
    - Another option for these patients is a red blood cell transfusion, depending on the severity of the anemia or other clinical circumstances
    - Hemoglobin may be increased to the lowest concentration needed to avoid or reduce the need for red blood cell transfusions, which may vary by patient and condition
    - They can also be used for low-risk myelodysplastic syndrome
  - Regarding biosimilars, they state clinicians should expect similar results among the various formulations (and biosimilars)
  - The goal hemoglobin should be the lowest value that prevents need for transfusion; ESAs should be discontinued if there is a lack of hemoglobin increase by 1 to 2 g/dL by 6 to 8 weeks

*ASCO/ASH, 2010*

# Erythropoiesis Stimulating Proteins

- **luspatercept-aamt (Reblozyl)**
  - **April 2020: FDA approved a new indication for luspatercept-aamt for the treatment of anemia failing an erythropoiesis stimulating agent (ESA) and requiring ≥ 2 red blood cell (RBC) units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)**
  - **Indications:**
    - Anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions
    - **Anemia failing an erythropoiesis stimulating agent and requiring 2 or more RBC units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)**
    - Limitations of Use: Not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia
  - **Warning & Precautions**
    - Thrombosis/Thromboembolism: Increased risk in patients with beta thalassemia. Monitor patients for signs and symptoms of thromboembolic events and institute treatment promptly
    - Hypertension: Monitor blood pressure (BP) during treatment. Initiate anti-hypertensive treatment if necessary
    - Embryo-Fetal Toxicity: May cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception
  - **Dosage:**
    - **The recommended starting dose is 1 mg/kg once every 3 weeks by subcutaneous injection**
  - **Formulations:**
    - For injection: 25 mg lyophilized powder in a single-dose vial for reconstitution
    - For injection: 75 mg lyophilized powder in a single-dose vial for reconstitution

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# Oncology, Oral - Hematologic

# Oncology, Oral- Hematological – Overview of Disease State

- **Marginal Zone Lymphooma (MZL)**
  - MZLs account for approximately 10% of all NHLs and are generally divided into 3 subtypes, nodal MZL, splenic MZL, and the most common subtype, mucosa-associated lymphoid tissue (MALT lymphoma)
  - Lenalidomide plus rituximab is an NCCN category 2B recommendation for first-line therapy of MZLs
  - For elderly or infirm patients, chlorambucil with or without rituximab may also be utilized in the first-line setting
  - Both lenalidomide with or without rituximab and ibrutinib as a single agent are NCCN V4.2020 category 2A, preferred recommendations for second- and subsequent-line therapy of MZL
  - Idelalisib or duvelisib may be used in the second- and subsequent-line of marginal zone lymphoma in patients who are relapsed/refractory after 2 prior therapies
- **Acute Myeloid Leukemia (AML)**
  - Most common form of acute leukemia among adults estimated 5,930 cases diagnosed and 1,500 deaths in the US in 2019
  - In patients who obtain a CR, 3 year survival is 45%, remission rates are inversely proportional to age
  - Cytogenetics plays a large role in determining prognosis and treatment options
  - Acute Promyelocytic Leukemia (APL) is a subtype of AML with distinct features and treatment
- **Diffuse Large B cell lymphoma (DLBCL)**
  - DLBCLs are the most common type of lymphoma and account for 30% of all NHL
  - There are several subtypes of DLBCL, including DLBCL arising from follicular lymphoma (FL)
  - Some patients with FL may undergo conversion to more aggressive lymphomas, such as DLBCL, and this risk increases over time; about 30% of FL patients convert to a more aggressive lymphoma at 10 years post-FL diagnosis
  - The B-cell lymphoma NCCN guidelines V4.2020 list selinexor (Xpovio) as an option for DLBCL not otherwise specified, including DLBCL arising from FL after at least 2 prior systemic therapies

# Oncology, Oral- Hematological – Overview of Disease State

- **Kaposi Sarcoma**
  - Kaposi sarcoma (KS) is a malignancy of the endothelial cells and is characterized by cutaneous red or brown papules, often seen on the lower extremities
  - There are 4 types of KS. Classic KS presents with cutaneous lesions but follows an indolent course
  - It is most common in elderly patients of Mediterranean, Eastern European, Middle Eastern, and/or Jewish descent
  - Endemic KS tends to be more aggressive than classic KS and occurs in younger patients (< 40 years old), as well as in children in equatorial Africa
  - The third type of KS is iatrogenic and occurs in the setting of patients taking immunosuppressive therapy (e.g., organ transplant recipients)
  - The fourth type of KS is seen in patients infected with the human immunodeficiency virus (HIV). In these patients, KS is considered to be an acquired immune deficiency syndrome (AIDS)-defining cancer
  - The risk for developing KS is estimated to be approximately 498-fold higher in HIV-positive patients compared to the general United Stated (US) population
  - Due to the improved treatment options available to AIDS patients, the incidence of this cancer has been declining.
  - The NCCN V3.2020 guidelines for AIDS-related KS list pomalidomide (Pomalyst) as a preferred systemic therapy option for patients with relapsed/refractory disease and note that pomalidomide has been FDA approved for the treatment of adult patients with AIDS-related KS after failure of highly active antiretroviral therapy

# Oncology, Oral- Hematological – Guidelines

- **American Society of Hematology, 2020**
  - Published guidelines for the treatment of newly diagnosed AML in older adults
  - This guideline examined questions around the role of treatment for older adults with AML and the intensity and length of treatment in this patient population
  - The general conclusion of the panel of experts was that for older adults, treatment is recommended over best supportive care, and more-intensive therapy is recommended over less-intensive therapy when it is tolerable to the patient
  - Specific recommendations pertaining to patients who are not appropriate for intensive antileukemic therapy but who are able to receive treatment include a recommendation of monotherapy (e.g., glasdegib, venetoclax) over combination therapy (conditional recommendation based on low certainty)
  - The guidelines further note that when these patients choose combination therapy, there is evidence to support the use LDAC in combination with venetoclax

# Oncology, Oral- Hematological - Overview of Disease State

- IMMUNE MODULATORS : THALIDOMIDE ANALOGUES
  - Lenalidomide
  - Pomalidomide
  - Thalidomide
  - **Pomalyst**
  - Revlimid
- ONCOLOGY AGENTS : ALKYLATING AGENTS - ORAL
  - Myleran
- ONCOLOGY AGENTS : ANTINEOPLASTICS MISC – ORAL
  - Hydrea
  - Hydroxyurea
  - Matulane
- ONCOLOGY AGENTS : BCL-2 INHIBITORS – ORAL
  - Venclexta
- ONCOLOGY AGENTS : HISTONE DEACETYLASE INHIBITORS – ORAL
  - Farydak
  - Zolinza
- ONCOLOGY AGENTS : ISOCITRATE DEHYDROGENASE-1 (IDH1) INHIBITORS – ORAL
  - Tibsovo
- ONCOLOGY AGENTS : ISOCITRATE DEHYDROGENASE-2 (IDH2) INHIBITORS – ORAL
  - Idhifa
- ONCOLOGY AGENTS : JANUS ASSOCIATED KINASE (JAK) INHIBITORS – ORAL
  - Inrebic
  - Jakafi
- ONCOLOGY AGENTS : PROTEASOME INHIBITORS – ORAL
  - Ninlaro
- ONCOLOGY AGENTS : XPO1 INHIBITORS – ORAL
  - **Xpovio**
- ONCOLOGY AGENTS : ANTIMETABOLITES – ORAL
  - Onureg
  - Mercaptopurine
  - Purixan
  - Tabloid
- ONCOLOGY AGENTS : PHOSPHATIDYLINOSITOL 3-KINASE (PI3K) INHIBITORS – ORAL
  - Copiktra
  - Zydelig

# Oncology, Oral- Hematological

- umbralisib (Ukoniq)
  - **February 2021: The FDA has granted Accelerated Approval to umbralisib (Ukoniq), a kinase inhibitor, for the treatment of adults with relapsed or refractory marginal zone lymphoma (MZL) who have received ≥ 1 prior anti-CD20-based regimen OR relapsed or refractory follicular lymphoma (FL) who have received ≥ 3 prior lines of systemic therapy**
  - **Indication**
    - **The treatment of adult patients with:**
      - **Relapsed or refractory marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen**
      - **Relapsed or refractory follicular lymphoma (FL) who have received at least three prior lines of systemic therapy**
    - **These indications are approved under accelerated approval based on overall response rate. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial**
  - **Warnings and Precautions**
    - **Infections: Monitor for fever and any new or worsening signs and symptoms of infection. Evaluate promptly and treat as needed**
    - **Neutropenia: Monitor blood counts during treatment**
    - **Diarrhea or Non-infectious colitis: Monitor for the development of diarrhea or colitis and provide supportive care as appropriate**
    - **Hepatotoxicity: Monitor hepatic function**
  - **Dosage**
    - **Recommended dosage: 800 mg orally once daily with food**
    - **Manage toxicity using treatment interruption, dose reduction, or discontinuation**
  - **Availability**
    - **Tablets: 200 mg**

# Oncology, Oral- Hematological

- azacitidine (Onureg)
  - **September 2020: FDA approved this nucleoside metabolic inhibitor for continued treatment of adults with acute myeloid leukemia who achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy**
  - **Indication**
    - **For continued treatment of adult patients with acute myeloid leukemia who achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy**
  - **Warnings and Precautions**
    - **Risks of Substitution with Other Azacitidine Products: Do not substitute for intravenous or subcutaneous azacitidine**
    - **Myelosuppression: Monitor complete blood counts every other week for the first 2 cycles and prior to the start of each cycle thereafter. Increase monitoring to every other week for the 2 cycles after any dose reduction. Withhold and then resume at same or reduced dose or discontinue based on severity**
    - **Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of the potential risk to a fetus and use of effective contraception**
  - **Dosage**
    - **Do not substitute ONUREG for intravenous or subcutaneous azacytidine**
    - **The indications and dosing regimen for Onureg differ from that of intravenous or subcutaneous azacitidine**
    - **Administer 300 mg orally once daily on Days 1 through 14 of each 28-day cycle**
    - **Administer an antiemetic before each dose for at least the first 2 cycles**
  - **Availability**
    - **Tablets: 200 mg and 300 mg**

# Oncology, Oral- Hematological

- pomalidomide (Pomalyst)
  - **November 2020: Approval of shared pomalidomide REMS to include brand Pomalyst (original REMS approved 2013) and generic pomalidomide**
  - **December 2020: FDA approved Pomalyst for the treatment of adults with AIDS-related Kaposi sarcoma (KS) after failure of highly active antiretroviral therapy (HAART) or in patients with KS who are HIV-negative**
  - **Indication**
    - **Treatment of adult patients:**
      - In combination with dexamethasone, for patients with multiple myeloma (MM) who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy
      - **With AIDS-related Kaposi sarcoma (KS) after failure of highly active antiretroviral therapy (HAART) or in patients with KS who are HIVnegative. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s)**
  - **Warnings and Precautions**
    - Hematologic Toxicity: Neutropenia was the most frequently reported Grade 3/4 adverse event. Monitor patients for hematologic toxicities, especially neutropenia
    - Hepatotoxicity: Hepatic failure including fatalities; monitor liver function tests monthly
  - **Dosage**
    - MM: 4 mg per day taken orally on Days 1 through 21 of repeated 28-day cycles until disease progression
    - **KS: 5 mg per day taken orally on Days 1 through 21 of repeated 28-day cycles until disease progression or unacceptable toxicity**
  - **Availability**
    - **Capsules: 1 mg, 2 mg, 3 mg, and 4 mg**

# Oncology, Oral- Hematological

- selinexor (Xpovio)
  - **December 2020: Accelerated Approval for the new indication of treatment of adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy. Already indicated for use in combination with dexamethasone for the treatment of adults with relapsed or refractory multiple myeloma (RRMM) who have received at least 4 prior therapies and whose disease is refractory to at least 2 proteasome inhibitors, at least 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody**
  - **Indication**
    - A nuclear export inhibitor indicated:  In combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy
    - In combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody
    - **For the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy**
  - **Warnings and Precautions**
    - Thrombocytopenia: Monitor platelet counts throughout treatment. Manage with doseinterruption and/or reduction and supportive care
  - **Dosage**
    - **DLBCL: Recommended dosage of XPOVIO is 60 mg taken orally on Days 1 and 3 of each week**
  - **Availability**
    - **Tablets: 20 mg**

Magellan Rx MANAGEMENT℠

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# Oncology, Oral - Breast

# Oncology, Oral- Hematological - Overview of Disease State

- ONCOLOGY AGENTS : ANTIMETABOLITES – ORAL
  - Xeloda
  - Capecitabine
- ONCOLOGY AGENTS : PHOSPHATIDYLINOSITOL 3-KINASE (PI3K) INHIBITORS – ORAL
  - Piqray

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# Thrombopoiesis Stimulating Factors

# Thrombopoiesis Stimulating Proteins - Overview of Disease State

- **Platelets**
  - Small, circulating cell particles that do not contain a nucleus and are released into the bloodstream by megakaryocytes that reside in the bone marrow and function to maintain hemostasis by aggregating and forming platelet plugs at sites of injury to limit blood loss

- **Thrombocytopenia**
  - Generally defined as a platelet count of $< 100 \times 10^9/L$
  - Can result in bruising, bleeding, and fatal hemorrhaging
  - Causes of thrombocytopenia include decreased bone marrow production of megakaryocytes, splenic sequestration of platelets, and increased destruction of platelets

- **Immune Thrombocytopenia (ITP)**
  - Previously known as “immune thrombocytopenic purpura” and “idiopathic thrombocytopenic purpura”
  - Platelet count of $< 100 \times 10^9/L$
  - An immune-mediated disorder in which platelets are opsonized by autoreactive antibodies and prematurely destroyed by the reticuloendothelial system

# Thrombopoiesis Stimulating Proteins - Overview of Disease State

- **Immune Thrombocytopenia (ITP)**
  - In children, ITP is usually an acute, self-limiting disease that often occurs 2 to 3 weeks after a viral infection or immunization
    - Spontaneous remission in children typically occurs within 2 to 8 weeks
  - In adults, ITP has an insidious onset with no preceding viral or other illness and typically has a chronic course
    - Many adult cases of ITP are diagnosed incidentally after a routine complete blood count (CBC)
    - Signs and symptoms of ITP are highly variable and range from asymptomatic with mild bruising or mucosal bleeding to frank hemorrhage from any site
    - Severity of ITP in adults is dependent on the presence of active bleeding; platelet count; patient age; patient's lifestyle related to risk of bleeding; and presence of additional risk factors for bleeding, such as uremia or chronic liver diseases

- **Primary ITP**
  - Defined as an autoimmune disorder with isolated thrombocytopenia ($< 100 \times 10^9$/L) in the absence of other causes or disorders that might cause thrombocytopenia
  - Diagnosis of primary ITP remains one of exclusion; no robust clinical or laboratory parameters are currently available to establish its diagnosis with accuracy
    - Primary ITP is also defined by the length of time since diagnosis – newly diagnosed (< 3 months), persistent (between 3 and 12 months), and chronic (≥ 12 months)
  - The main clinical problem of primary ITP is an increased risk of bleeding, although bleeding symptoms may not always be present
  - Secondary causes of ITP include drug-induced, autoimmune diseases such as systemic lupus erythematosus (SLE), and viral infections such as human immunodeficiency virus (HIV) and Hepatitis C
  - Severe ITP, occurring at any time, indicates bleeding which requires treatment or the occurrence of new bleeding symptoms, which requires additional treatment or increased dose to control bleeding

# Thrombopoiesis Stimulating Proteins

- romiplostim (Nplate)
  - **February 2021: FDA approved new indication for Nplate to increase survival in adults and pediatric patients (including term neonates) acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [HS-ARS])**
  - **Indication**
    - Treatment of thrombocytopenia in:
      - Adult patients with immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy
      - Pediatric patients 1 year of age and older with ITP for at least 6 months who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy
    - **Nplate is indicated to increase survival in adults and in pediatric patients (including term neonates) acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [HS- myalgia, pain in extremity, abdominal pain, shoulder pain, dyspepsia, and ARS])**
  - **Warnings and Precautions**
    - Pregnancy: May cause fetal harm
    - Lactation: Advise not to breastfeed
  - **Dosage**
    - ITP: Recommended Initial Dose: 1 mcg/kg once weekly as a subcutaneous injection. Adjust dose based on platelet response
    - **Patients acutely exposed to myelosuppressive doses of radiation Recommended Dose: 10 mcg/kg administered once as a subcutaneous injection. Administer the dose as soon as possible after suspected or confirmed exposure to myelosuppressive doses of radiation**
  - **Availability**
    - For injection: 125 mcg, 250 mcg or 500 mcg of deliverable romiplostim as a lyophilized powder in single-dose vials

# Appendices

# Glucocorticoids, Inhaled – Guidelines

- Global Initiative for Asthma (GINA), 2020

| Characteristic | Well Controlled (all of the following) | Partly Controlled (any present in past week) | Uncontrolled |
|---|---|---|---|
| **A. Assessment of symptom control (preferably over 4 weeks)** | | | |
| **Daytime symptoms more than twice per week** | None of these criteria | 1 to 2 of these criteria | **≥ 3 of these criteria** |
| **Limitations of activities due to asthma** | | | |
| **Nocturnal symptoms/awakening due to asthma** | | | |
| **Need for reliever/rescue treatment with a SABA more than twice per week** | | | |
| **B. Risk factors for poor asthma outcomes** | | | |
| **Assess at diagnosis and periodically (and during exacerbations); assess forced expiratory volume in 1 second ($FEV_1$) after 3 to 6 months of controller treatment, and periodically thereafter** | | | |
| **Independent risk factors for exacerbations include (≥ 1 of these risk factors increases risk for exacerbations despite well controlled symptoms):**<br>▪ **Uncontrolled asthma symptoms, excessive short-acting beta2-agonist (SABA) use, inadequate ICS, low FEV1, exposure to cigarette smoke/allergens, major psychological or socioeconomic problems, comorbidities, pregnancy, sputum or blood eosinophilia, intensive care unit (ICU) admission or prior intubation for asthma, ≥ 1 severe exacerbation in past year, and higher bronchodilator reversibility** | | | |
| **Fixed air flow limitation risk factors include:**<br>▪ **Lack of ICS treatment, tobacco/chemical/occupational exposures, hypersecretion of mucus, low weight at birth/pre-term birth, and blood eosinophilia** | | | |
| **Risk factors for medication side effects include:**<br>▪ **Frequent oral corticosteroid use, long-term/high dose ICS, taking P450 inhibitors, and poor inhaler technique** | | | |

# Glucocorticoids, Inhaled – Guidelines

- Global Initiative for Asthma (GINA), 2020

| Step | Age Group | Preferred Controller | Other Controller Options |
|---|---|---|---|
| **Step 1:** **Symptom-driven or regular controller** | ≥ 12 years | ▪ **As-needed low dose ICS-formoterol (unlabeled indication)** | ▪ **Low dose ICS whenever SABA is taken (unlabeled indication)** |
| | 6 to 11 years | -- | ▪ **Low dose ICS whenever SABA is taken (unlabeled indication) or daily low dose ICS** |
| **Step 2:** **One controller AND an as-needed reliever medication** | ≥ 12 years | ▪ **Low dose ICS or as needed low dose ICS-formoterol (unlabeled indication)** | ▪ Leukotriene modifier or **low dose ICS whenever SABA is taken (unlabeled indication)** |
| | 6 to 11 years | ▪ Low dose ICS | ▪ Leukotriene modifier or **low dose ICS whenever SABA is taken (unlabeled indication)** |
| **Step 3:** **Two controllers and an as-needed reliever medication** | ≥ 12 years | ▪ Low dose ICS/LABA | ▪ Medium dose ICS OR low dose ICS + leukotriene modifier<br>▪ Sublingual immunotherapy (SLIT) may be considered in adults with allergic rhinitis, house dust mite sensitivity, and **FEV > 70% predicted** |
| | 6 to 11 years | ▪ **Low dose ICS/LABA or medium dose ICS** | ▪ Low dose ICS + leukotriene modifier |
| **Step 4:** **Two controllers and an as-needed reliever medication** | ≥ 12 years | ▪ Medium dose ICS/LABA | ▪ High dose ICS, add-on tiotropium, or **add-on leukotriene modifier**<br>▪ Sublingual immunotherapy (SLIT) may be considered in adults with allergic rhinitis, house dust mite sensitivity, and **FEV > 70% predicted** |
| | 6 to 11 years | ▪ Medium dose ICS/LABA; refer for expert advice | ▪ **High dose ICS/LABA, add-on tiotropium, or add-on leukotriene modifier** |
| **Step 5:** **Two controllers and an as-needed reliever medication** | ≥ 12 years | ▪ **High dose ICS/LABA; refer for phenotypic assessment with or without add-on therapy (e.g., tiotropium, anti-IgE [omalizumab], anti-interleukin-5[IL5]/5R [mepolizumab, reslizumab, benralizumab], anti-IL4R [dupilumab])** | ▪ **Add-on low dose oral corticosteroid, considering adverse effects** |
| | 6 to 11 years | ▪ **Refer for phenotypic assessment with or without add-on therapy (e.g., anti-IgE [omalizumab])** | ▪ **Add-on anti-IL-5 or add-on low dose oral corticosteroid, considering adverse effects** |

# Glucocorticoids, Inhaled – Guidelines

- Global Initiative for Asthma (GINA), 2020

| Age Group | Step | Preferred Reliever | Other Reliever Options |
|---|---|---|---|
| **≥ 12 years** | Steps 1 and 2 | ▪ As-needed low dose ICS-formoterol (unlabeled indication) | ▪ As needed SABA |
| | Steps 3 through 5 | ▪ As-needed low dose ICS-formoterol (unlabeled indication) | |
| **6 to 11 years** | Steps 1 through 5 | ▪ As needed SABA | -- |

# Colony Stimulating Factors - Guidelines

- **The National Comprehensive Cancer Network (NCCN) v1.2020 Practice Guidelines for Myeloid Growth Factors**
  - Safety data appear similar between Neupogen, Neulasta, and their biosimilars, and the subcutaneous (SC) route is preferred for all agents
    - Subcutaneous filgrastim and its biosimilars, Granix, 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
    - Filphila and Udenyca have been designated a category 2A (lower level evidence, there is uniform consensus that the intervention is appropriate)
    - Due to the recent approval, a recommendation for Ziextenzo is not currently provided by NCCN
    - To date, there are insufficient head-to-head comparative studies on the clinical benefits of G-CSFs and GM-CSFs
  - Filgrastim, filgrastim biosimilars, and tbo-filgrastim can be administered the day after chemotherapy, up to 3 to 4 days after chemotherapy, and through post-nadir recovery
  - Based on data from clinical trials, pegfilgrastim and its biosimilars should be administered the day after chemotherapy (category 1); however, administration up to 3 to 4 days after chemotherapy is also reasonable according to the NCCN guidelines
  - For patients unable to return to the clinic the next day for medication administration, a delivery device, (Neulasta Onpro®), is available that allows for the device to be applied to patient the same day as chemotherapy administration, but the device does not release the medication until approximately 27 hours after application
  - There is evidence to support the use of chemotherapy regimens every 3 weeks with pegfilgrastim or its biosimilars (category 1)
  - Efficacy data exist for pegfilgrastim products in chemotherapy regimens given every 2 weeks (category 2A)
  - There are insufficient data to support dose/schedule of weekly chemotherapy regimens; therefore, pegfilgrastim products should not be used
  - Leukine is no longer recommended for prophylactic use in patients with solid tumors receiving myelosuppressive chemotherapy

*National Comprehensive Cancer Network, 2020*

# Colony Stimulating Factors - Guidelines

- **<u>The updated v1.2020 NCCN Hematopoietic Growth Factors Guidelines</u>**
  - The guidelines note that a biosimilar is a biological product that is highly similar to the FDA-approved originator product with very small, clinically inactive differences but no difference in efficacy, safety, or purity
    - The first biosimilar, Zarxio, was approved in March 2015 with a second filgrastim biosimilar, Nivestym, being approved in 2018
    - However, Granix was approved in 2012 as a biologic rather than a biosimilar in the United States; in Europe, Granix is available as a biosimilar to filgrastim
    - The first pegfilgrastim biosimilars, Fulphila and Udenyca, were approved in 2018. Studies have shown these products have similar safety and efficacy profiles as the originator product
  - The guidelines state if overall safety and efficacy are equivalent, biosimilars may be substituted for the originator product
  - However, the guidelines note that current biosimilars are not interchangeable; therefore, alternating between a biosimilar and its originator in not recommended
  - The guidelines also note that the use of biosimilars may provide opportunities for cost containment
  - The panel endorses the use of Zarxio, Nivestym, Granix, Fulphila, and Udenyca for myelosuppressive doses of radiation
  - For mobilization of hematopoietic progenitor cells in the autologous setting, the use of concurrent filgrastim (or 1 of its biosimilars) with sargramostim (category 2B) or single agent filgrastim, Zarxio, Nivestym, or Granix is recommended (category 2A)
  - Filgrastim, Granix, or filgrastim biosimilars (filgrastim-sndz, filgrastim-aafi) are all NCCN category 1 G-CCF options for prophylaxis of febrile neutropenia and maintenance of scheduled dose delivery
  - According to the guidelines, the World Marrow Donor Association (WMDA) recommends filgrastim (NCCN category 2A; preferred) or filgrastim biosimilars (NCCN category 2B) for the mobilization of peripheral blood progenitor cells in healthy donors in the allogeneic setting
  - The NCCN Panel does not recommend Neulasta or its biosimilars for mobilization at this time

*National Comprehensive Cancer Network, 2020*