Effective Date **8/1/2023**
Next Review Date… **8/1/2024**
Coverage Policy Number **IP0422**

Mepolizumab

Table of Contents

Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for **Nucala®** (mepolizumab) subcutaneous injection.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Medical Necessity Criteria

Mepolizumab (Nucala) is considered medically necessary when ONE of the following is met (1, 2, 3, or 4):

1. **Asthma.** Individual meets **ALL** of the following criteria (A, B, C, D, E, and F):
   A. Individual is 6 years of age or older
   B. Diagnosis of asthma is confirmed by **BOTH** of the following (i and ii):
      i. Pre-bronchodilator FEV1 below the lower limits of normal for age in the setting of reduced FEV1/FVC (usually less than 80% in adults and 90% in children)

ii. Variable expiratory airflow obstruction as documented by **ONE** of the following (a, b or c):
    a. Increase of at least 12% AND 200 mL in FEV1 after the administration of 200 to 400 mcg albuterol or levalbuterol
    b. Increase of at least 12% AND 200 mL in FEV1 from baseline between visits or after 4 weeks of treatment
    c. Positive exercise or bronchial challenge testing

C. Eosinophilic phenotype defined as **EITHER** of the following (i or ii):
    i. Blood eosinophils greater than or equal to 150 cells/mcl within the previous 6 weeks or within 6 weeks prior to treatment with any anti-interleukin-5 therapy (for example, Fasenra, Cinqair or Nucala)
    ii. History of blood eosinophils greater than or equal to 300 cells/mcl

D. Individual has received at least 3 consecutive months of combination therapy with **BOTH** of the following (i and ii):
    i. An inhaled corticosteroid
    ii. At least one additional asthma controller or asthma maintenance medication (for example, inhaled long-acting beta2-agonists, inhaled long-acting muscarinic antagonists, leukotriene receptor antagonists, and theophylline)

    Note: Use of a combination inhaler containing both an inhaled corticosteroid and a long-acting beta2-agonist would fulfill the requirement for both criteria [i] and [ii].

E. Individual has asthma that is uncontrolled or was uncontrolled at baseline as defined by **ONE** of the following (i, ii, iii, or iv):
    i. Poor symptom control as defined by Asthma Control Questionnaire consistently greater than 1.5 or Asthma Control Test less than 20
    ii. Individual experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year
    iii. Individual experienced one or more asthma exacerbation(s) requiring hospitalization, an Emergency Department visit, or an urgent care visit in the previous year
    iv. Daily or every other day oral corticosteroids are required to prevent asthma exacerbations

    Note: "Baseline" is defined as prior to receiving any Tezspire, anti-interleukin-5 therapies (i.e., Cinqair, Fasenra, or Nucala), Dupixent, or Xolair.

F. The medication is prescribed by, or in consultation with, an allergist, immunologist, or pulmonologist

2. **Eosinophilic Granulomatosis with Polyangiitis (EGPA).** Individual meets **ALL** of the following criteria (A, B, C, D, and E):
    A. Individual is 18 years of age or older
    B. Individual has active, non-severe disease
    Note: Non-severe disease is defined as vasculitis without life- or organ-threatening manifestations. Examples of symptoms in individuals with non-severe disease include rhinosinusitis, asthma, mild systemic symptoms, uncomplicated cutaneous disease, mild inflammatory arthritis.
    C. Blood eosinophil count which meet **ONE** of the following (i, ii, or iii):
        i. Absolute eosinophil counts (AEC) greater than or equal to 1000 cells/mcl prior to daily corticosteroid use
        ii. Eosinophils greater than or equal to 10% of total leukocytes prior to daily corticosteroid use
        iii. Absolute eosinophil counts (AEC) greater than or equal to 150 cells/mcl while on a stable oral corticosteroid dose for at least 4 weeks
    D. Medication is being prescribed by, or in consultation with, an allergist, immunologist, pulmonologist, or rheumatologist
    E. Documentation of **ONE** of the following (i or ii):
        i. Individual has had an inadequate response to a corticosteroid (for example, oral prednisone greater than or equal to 7.5 mg/day) for at least 4 weeks

ii. Individual has a contraindication per FDA label, significant intolerance, or is not a candidate for a corticosteroid (for example, oral prednisone greater than or equal to 7.5 mg/day) for at least 4 weeks

3. **Hypereosinophilic Syndrome.** Individual meets **ALL** of the following criteria (A, B, C, D, E, F and G):
   A. Individual is 12 years of age or older
   B. Individual has had hypereosinophilic syndrome for at least 6 months
   C. Documentation of FIP1L1-PDGFRα-negative disease
   D. According to the prescriber, the individual does **NOT** have an identifiable non-hematologic secondary cause of hypereosinophilic syndrome (for example, drug hypersensitivity, parasitic helminth infection, human immunodeficiency virus infection, non-hematologic malignancy)
   E. Prior to initiating therapy with any anti-interleukin-5 therapy (for example, Cinqair, Fasenra or Nucala), the individual has/had a blood eosinophil level of 1,000 cells per microliter or greater
   F. Medication is being prescribed by, or in consultation with, an allergist, immunologist, pulmonologist, hematologist or rheumatologist
   G. Documentation of **ONE** of the following:
      i. Individual has had an inadequate response to at least **ONE** other treatment for hypereosinophilic syndrome for a minimum of 4 weeks (for example, systemic corticosteroids, hydroxyurea, cyclosporine, imatinib, methotrexate, tacrolimus, azathioprine)
      ii. Individual has a contraindication per FDA label, significant intolerance, or is not a candidate for **ALL** of the following (a, b, c, d, e, f, and g):
         a. azathioprine
         b. cyclosporine
         c. hydroxyurea
         d. imatinib
         e. methotrexate
         f. systemic corticosteroids
         g. tacrolimus

4. **Nasal Polyps.** Individual meets **ALL** of the following criteria (A, B, C, D, E, and F):
   A. Individual is 18 years of age or older
   B. Individual has evidence of chronic rhinosinusitis with nasal polyposis by direct examination, endoscopy, or sinus computed tomography (CT) scan
   C. Individual has experienced **TWO** or more of the following symptoms for at least 6 months:
      i. Nasal congestion
      ii. Nasal obstruction
      iii. Rhinorrhea
      iv. Reduction/loss of smell
   D. Individual meets **BOTH** of the following (i and ii):
      i. Individual has received at least 3 months of therapy with an intranasal corticosteroid
      ii. Individual will continue intranasal corticosteroid therapy unless contraindicated per FDA label
   E. Individual meet **ONE** of the following (i or ii):
      i. Individual has received treatment with a systemic corticosteroid within the previous two years or has a contraindication per FDA label to systemic corticosteroid therapy
      ii. Individual has had prior surgery for nasal polyps
   F. Medication is being prescribed by, or in consultation with, an allergist, immunologist, or an otolaryngologist (ear, nose and throat [ENT] physician specialist)

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Reauthorization Criteria

Mepolizumab (Nucala) is considered medically necessary for continued use when **ONE** of the following is met (1, 2, 3, or 4):

1. **Asthma.** Individual meets **BOTH** of the following criteria (A and B):
   A. Initial criteria are met **AND** there is documentation of beneficial response
   B. Individual continues to receive therapy with one inhaled corticosteroid OR one inhaled corticosteroid-containing combination

   Note: Examples of a beneficial response to Nucala therapy are decreased asthma exacerbations; decreased asthma symptoms; decreased hospitalizations, emergency department/urgent care, or medical clinic visits due to asthma; and decreased requirement for oral corticosteroid therapy.

2. **Eosinophilic Granulomatosis with Polyangiitis (EGPA).** Individual meets the following criteria:
   A. Initial criteria are met **AND** there is documentation of beneficial response (for example, reduced rate of relapse, corticosteroid dose reduction, and reduced eosinophil levels)

3. **Hypereosinophilic Syndrome.** Individual meets the following criteria:
   A. Initial criteria are met **AND** there is documentation of beneficial response (for example, decreased number of flares, improved fatigue, reduced corticosteroid requirements, and decreased eosinophil levels)

4. **Nasal Polyps.** Individual meets **BOTH** of the following criteria (A and B):
   A. Initial criteria are met **AND** there is documentation of beneficial response (for example, reduced nasal polyp size, improved nasal congestion, reduced sinus opacification, decreased sino-nasal symptoms, and/or improved sense of smell)
   B. Continued concomitant therapy with an intranasal corticosteroid

Authorization Duration

Initial approval duration:

- Asthma: up to 12 months
- Eosinophilic Granulomatosis with Polyangiitis (EGPA) [Nucala only]: up to 12 months
- Hypereosinophilic Syndrome [Nucala only]: up to 12 months
- Nasal Polyps [Nucala only]: up to 6 months

Reauthorization approval duration:

- Asthma: up to 12 months
- Eosinophilic Granulomatosis with Polyangiitis (EGPA) [Nucala only]: up to 12 months
- Hypereosinophilic Syndrome [Nucala only]: up to 12 months
- Nasal Polyps [Nucala only]: up to 12 months

Conditions Not Covered

Mepolizumab (Nucala) is considered experimental, investigational or unproven for **ANY** other use including the following (this list may not be all inclusive):

1. **Atopic Dermatitis.** Nucala is not indicated for the treatment of atopic dermatitis.[1] In one small study, intravenous (IV) mepolizumab significantly reduced peripheral blood eosinophil counts in patients with moderate to severe atopic dermatitis.[19,20] However, mepolizumab IV therapy did not result in clinical success as assessed by Physician's Global Assessment of Improvement scores compared with placebo. Other clinical outcomes were also not significantly improved with mepolizumab IV. Another small study evaluated subcutaneous Nucala in patients with moderate to severe atopic dermatitis.[21] Following 16 weeks of

therapy, Nucala did not demonstrate efficacy, with 11% (n = 2/11) of patients meeting the primary endpoint of treatment success with Nucala vs. 0 with placebo.

2. **Chronic Obstructive Pulmonary Disease (COPD).** Nucala is not indicated for the treatment of COPD.[1] Two Phase III studies, METREX (n = 836) and METREO (n = 675) evaluated Nucala in patients with COPD who had a history of moderate or severe exacerbations despite treatment with inhaled triple therapy (inhaled corticosteroid/long-acting muscarinic antagonist/long-acting beta$_2$-agonist).[22] METREX included patients regardless of eosinophil counts, but did include a subgroup of patients who were considered to have an eosinophilic phenotype (eosinophil count ≥ 150 cells/microliter) [n = 462]. METREO only included patients with an eosinophilic phenotype (defined as an eosinophil count ≥ 150 cells/microliter at screening or ≥ 300 cells/microliter within the previous year). Overall, lower COPD exacerbation rates were observed with Nucala vs. placebo; however, none of these reductions were statistically significant in either the METREX overall modified intent to treat (mITT) population or the METREO mITT population (which included all eosinophilic phenotype patients). In the subgroup of patients in the METREX study with an eosinophilic phenotype, the COPD exacerbation rates were statistically lower with Nucala vs. placebo, as was the difference in the time to first exacerbation. In July 2018, the FDA's Pulmonary Allergy Drugs Advisory Committee voted against approval of Nucala as an add-on treatment to inhaled corticosteroid-based maintenance treatments to reduce flare-ups in patients with COPD.[23] The Committee had concerns about the defining criteria for the eosinophilic phenotype of COPD as well as the lack of data on patient asthma history. Subsequently, in September 2018, the FDA rejected the approval of Nucala for COPD citing the need for additional clinical data. Current COPD guidelines from the Global Initiative for Chronic Lung Disease (GOLD) [2021] note the mixed data with Nucala.[24] The guidelines state that further studies are needed to determine if Nucala may have a role in a highly selected subgroup of patients with eosinophilic COPD.

3. **Concurrent use of Nucala with another Monoclonal Antibody Therapy (i.e., Cinqair, Fasenra, Dupixent, Tezspire, Xolair, or Adbry).** The efficacy and safety of Nucala used in combination with other monoclonal antibody therapies (e.g., Cinqair, Fasenra, Dupixent, Tezspire, Xolair or Adbry) have not been established. A small number of case reports detailing combination use of Nucala and Xolair are available for both FDA-approved and off-label uses.[14,25-28] Further investigation is warranted.

4. **Eosinophilic Esophagitis, Eosinophilic Gastroenteritis, or Eosinophilic Colitis.** Nucala is not indicated for the treatment of eosinophilic esophagitis, eosinophilic gastroenteritis or eosinophilic colitis.[1] A few small studies have reported IV mepolizumab to be efficacious in these conditions.[29-31] Of note, Nucala is not approved for IV administration.[1] Guidelines for the management of eosinophilic esophagitis from the American Gastroenterological Association (AGA) and the Joint Task Force on Allergy-Immunology Practice Parameters (2020) only recommend using anti-interleukin-5 therapies in the context of a clinical trial.[32] Further research is warranted to determine if Nucala has a place in therapy in the treatment of these conditions.

Coding / Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J2182	Injection, mepolizumab, 1 mg

Background

OVERVIEW
Nucala, an interleukin (IL)-5 antagonist monoclonal antibody, is indicated for the following uses:[1]

- **Asthma**, as add-on maintenance treatment of patients ≥ 6 years of age with severe disease with an eosinophilic phenotype. Limitations of Use: Nucala is not indicated for the relief of acute bronchospasm or status asthmaticus.
- **Chronic rhinosinusitis with nasal polyposis** (CRSwNP), as an add-on maintenance treatment in patients ≥ 18 years of age with an inadequate response to nasal corticosteroids.
- **Eosinophilic granulomatosis with polyangiitis** (EGPA) [formerly known as Churg-Strauss Syndrome] in adult patients.
- **Hypereosinophilic syndrome** (HES) in patients ≥ 12 years of age who have had HES for ≥ 6 months without an identifiable non-hematologic secondary cause.

Clinical Efficacy
Asthma
In the pivotal asthma studies of Nucala, patients were generally required to have elevated eosinophils at baseline (e.g., peripheral blood eosinophil count ≥ 150 cells/microliter at screening or ≥ 300 cells/microliter at some time during the previous year). Across the studies, efficacy was assessed as early as 24 weeks.[1-4]

Eosinophilic Granulomatosis with Polyangiitis
One study evaluated the efficacy of Nucala in patients ≥ 18 years of age with relapsing or refractory EGPA who had received ≥ 4 weeks of a stable oral corticosteroid dose (i.e., prednisolone, prednisone).[5] Patients were also required to have a baseline relative eosinophil level of 10% or an absolute eosinophil level > 1,000 cells per microliter; however, the baseline mean absolute eosinophil level was approximately 175 cells per microliter across both treatment groups. While remission benefit of Nucala was demonstrated in the overall patient population, the magnitude of improvements observed with Nucala were larger in patients with baseline eosinophil levels ≥ 150 cells per microliter than in patients with lower baseline levels.

Hypereosinophilic Syndrome
One study evaluated the efficacy of Nucala in patients ≥ 12 years of age with hypereosinophilic syndrome for ≥ 6 months.[6] Patients with non-hematologic secondary hypereosinophilic syndrome and those with FIP1L1-PDGFRα kinase-positive hypereosinophilic syndrome were excluded. All patients had a baseline blood eosinophil count ≥ 1,000 cells per microliter. Additionally, all patients had been on stable therapy for their hypereosinophilic syndrome (e.g., oral corticosteroids, immunosuppressive agents, or cytotoxic therapy) for 4 weeks or more prior to randomization. Efficacy was assessed following 32 weeks of therapy.

Nasal Polyps
In one pivotal study involving adult patients with chronic rhinosinusitis with nasal polyposis, the primary efficacy endpoints were assessed at 52 weeks.[1,7] However, improvements in nasal polyp size and symptoms compared with placebo were observed much earlier on in the course of treatment (i.e., between 9 and 24 weeks).
Guidelines
Asthma Guidelines
The Global Initiative for Asthma Global Strategy for Asthma Management and Prevention (2022) proposes a step-wise approach to asthma treatment.[8] Nucala is listed as an option for add-on therapy in patients ≥ 6 years of age with difficult-to-treat, severe eosinophilic asthma (i.e., asthma that cannot be managed by therapy with medium- to high-dose inhaled corticosteroid [ICS]/formoterol [as both maintenance and reliever therapy] or medium- to high-dose ICS/long-acting beta$_2$-agonist [LABA] combination therapy with an as needed short-acting beta$_2$-agonist reliever, with or without an additional controller). Higher blood eosinophil levels, more exacerbations in the previous year, adult-onset asthma, nasal polyposis, maintenance corticosteroid requirements, and low lung function may predict a good asthma response to Nucala.

According to the European Respiratory Society/American Thoracic Society guidelines (2014; updated in 2020), severe asthma is defined as asthma which requires treatment with a high-dose ICS in addition to a second controller medication (and/or systemic corticosteroids) to prevent it from becoming uncontrolled, or asthma which

remains uncontrolled despite this therapy.[9,10] Uncontrolled asthma is defined as asthma that worsens upon tapering of high-dose ICS or systemic corticosteroids or asthma that meets one of the following four criteria:

1) Poor symptom control: Asthma Control Questionnaire consistently ≥ 1.5 or Asthma Control Test < 20;
2) Frequent severe exacerbations: two or more bursts of systemic corticosteroids in the previous year;
3) Serious exacerbations: at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year;
4) Airflow limitation: forced expiratory volume in 1 second (FEV_1) < 80% predicted after appropriate bronchodilator withholding.

EGPA Guidelines

The American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis (2021) includes recommendations regarding the management of EGPA.[11] For patients with active, non-severe EGPA, combination therapy with Nucala and corticosteroids is recommended over other traditional treatments such as methotrexate, azathioprine, or mycophenolate mofetil in the setting of remission induction. Non-severe EGPA is defined as vasculitis in the absence of life- or organ-threatening manifestations. In general, the clinical profile includes rhinosinusitis, asthma, mild systemic symptoms, uncomplicated cutaneous disease, and mild inflammatory arthritis. Nucala, in combination with corticosteroids, is also a recommended therapy for patients who have relapsed and are experiencing non-severe disease manifestations (i.e., asthma and/or sinonasal disease) while receiving either low-dose corticosteroids alone, methotrexate, azathioprine, or mycophenolate mofetil. In this same setting, Nucala therapy is preferred over Xolair (off-label use), even in patients with high serum immunoglobulin E (IgE) levels. For patients with severe EGPA, cyclophosphamide or rituximab is preferred over Nucala for remission induction. Similarly, for remission induction, methotrexate, azathioprine, or mycophenolate mofetil are recommended over Nucala in patients with severe disease. Severe EGPA is defined as vasculitis with life- or organ-threatening manifestations, such as alveolar hemorrhage, glomerulonephritis, central nervous system vasculitis, mononeuritis multiplex, cardiac involvement, mesenteric ischemia, or limb/digit ischemia.

Hypereosinophilia Guidelines

The World Health Organization-defined eosinophilic disorders update on diagnosis, risk stratification, and management (2022) notes that corticosteroids remain first-line therapy for the treatment of HES.[12] Nucala, hydroxyurea, pegylated-interferon, imatinib, and hematopoietic stem cell transplantation are listed as second-line treatment options.

Nasal Polyps Guidelines

A Practice Parameter on the Diagnosis and Management of Rhinosinusitis (2014), a Practice Parameter for the Management of Rhinitis (2020) from the Joint Task Force on Practice Parameters (JTFPP), and a Clinical Practice Guideline update on Adult Sinusitis (2015) from the American Academy of Otolaryngology (AAO) make similar recommendations regarding the diagnosis and management of CRSwNP.[13-17] The presence of two or more signs and symptoms of chronic rhinosinusitis (CRS) [e.g., rhinorrhea, postnasal drainage, anosmia, nasal congestion, facial pain, headache, fever, cough, and purulent discharge] that persist for an extended period of time makes the diagnosis CRS likely. However, this requires confirmation of sinonasal inflammation, which can either be done via direct visualization or computed tomography scan. Nasal corticosteroids are recommended for the management of CRSwNP, as they decrease nasal polyp size, prevent regrowth of nasal polyps following surgical removal, and improve nasal symptoms. Short courses of oral corticosteroids are also recommended. Endoscopic surgical intervention may be considered as an adjunct to medical therapy in patients with chronic rhinosinusitis that is not responsive or is poorly responsive to medical therapy. In the JTFPP practice parameter, Nucala is noted to have demonstrated benefit for the treatment of CRSwNP, but specific recommendations were not made. The AAO guidelines do not address Nucala.

The European Forum for Research and Education in Allergy expert board on uncontrolled severe CRSwNP and biologics (2021) recommends these agents, including Nucala, only be used for severe uncontrolled CRSwNP when Type 2 inflammation is present.[18] Severe CRSwNP is defined as bilateral CRSwNP with a nasal polyp score (NPS) ≥ 4 and persistent symptoms (e.g., loss of smell/taste, nasal obstruction, secretion or postnasal drip, facial pain or pressure) with the need for add-on treatment to supplement intranasal corticosteroids. Severe CRSwNP is considered to be uncontrolled if the patient has received continuous treatment with an intranasal

corticosteroid and has needed at least one course of systemic corticosteroids in the previous 2 years (or has a medical contraindication or intolerance) and/or has a previous sinonasal surgery.

References

1. Nucala® subcutaneous injection [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; March 2023.
2. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet*. 2012;380:651-659.
3. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med.* 2014;371:1198-1207.
4. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 2014;371(13):1189-1197.
5. Wechsler ME, Akuthota P, Jayne D. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. *N Engl J Med*. 2017;376(20):1921-1932.
6. Roufosse F, Kahn JE, Rothenberg ME, et al. Efficacy and safety of mepolizumab in hypereosinophilic syndrome: a phase III, randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2020;146(6):1397-1405.
7. Han JK, Bachert C, Fokkens W, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2021;9(10):1141-1153.
8. Global Initiative for Asthma. Global strategy for asthma management and prevention. Updated 2022. Available at: http://www.ginasthma.org. Accessed on: March 15, 2023.
9. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43:343-373.
10. Holguin F, Cardet JC, Chung KF, *et al*. Management of severe asthma: a European Respiratory Society/American Thoracic Society Guideline. *Eur Respir J.* 2020;55:1900588.
11. Chung SA, Langford CA, Maz M, et al. 2021 American College of Rheumatology/Vasculitis Foundation guideline for the management of antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheumatol.* 2021;73(8):1088-1105).
12. Shomali W, Gotlib J. World Health Organization-defined eosinophilic disorders: 2022 update on diagnosis, risk stratification, and management. *Am J Hematol*. 2022;97(1):129-148.
13. Peters AT, Spector S, Hsu J, et al. Diagnosis and management of rhinosinusitis: a practice parameter update. *Ann Allergy Asthma Immunol.* 2014:347-385.
14. Baccelli A, Kocwin M, Parazzini EM, et al. Long-term outcomes of combination biologic therapy in uncontrolled severe asthma: a case study. *J Asthma*. 2022 Sept 13. [Online ahead of print].
15. Dykewicz MS, Wallace DV, Baroody F, et al. Treatment of seasonal allergic rhinitis: an evidenced-based focused 2017 guideline update. *Ann Allergy Asthma Immunol.* 2017;119(6):489-511.
16. Joint Task Force on Practice Parameters: American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology. Rhinitis 2020: a practice parameter update. *J Allergy Clin Immunol.* 2020;146:721-767.
17. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update): adult sinusitis. *Otolaryngol Head Neck Surg*. 2015;152(2S):S1-S39.
18. Bachert C, Han JK, Wagenmann, et al. EUFOREA expert board meeting on uncontrolled severe chronic rhinosinusitis with nasal polyps (CRSwNP) and biologics: definitions and management. *J Allergy Clin Immunol*. 2021;147(1):29-36.
19. Oldhoff JM, Darsow U, Werfel T, et al. Anti-IL-5 recombinant humanized monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis. *Allergy*. 2005;60(5):693-696.
20. Oldhoff JM, Darsow U, Werfel T, et al. No effect of anti-interleukin-5 therapy (mepolizumab) on the atopy patch test in atopic dermatitis patients. *Int Arch Allergy Immunol*. 2006;141(3):290-294.
21. Kang EG, Narayana PK, Pouliguen IJ, et al. Efficacy and safety of mepolizumab administered subcutaneously for moderate to severe atopic dermatitis. *Allergy*. 2020;75(4):950-953.
22. Pavord ID, Chanez P, Criner GJ, et al. Mepolizumab for eosinophilic chronic obstructive pulmonary disease. *N Engl J Med*. 2017;377(17):1613-1629.
23. GSK reports on outcome of the FDA Advisory Committee on mepolizumab for the treatment of COPD patients on maximum inhaled therapy [press release]. London, UK: GlaxoSmithKline; July 25, 2018.

Available at: https://www.gsk.com/en-gb/media/press-releases/gsk-reports-on-outcome-of-the-fda-advisory-committee-on-mepolizumab-for-the-treatment-of-copd-patients-on-maximum-inhaled-therapy/. Accessed on March 15, 2023.
24. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2023 report. Global Initiative for Chronic Obstructive Lung Disease. Available from: http://goldcopd.org/. Accessed on March 15, 2023.
25. Fox HM, Rotolo SM. Combination anti-IgE and anti-IL-5 therapy in a pediatric patient with severe persistent asthma. *J Pediatr Pharmacol Ther*. 2021;26(3):306-310.
26. Dedaj R, Unsel L. Case study: a combination of mepolizumab and omalizumab injections for severe asthma. *J Asthma*. 2019;56(5):473-474.
27. Altman MC, Lenington J, Bronson S, et al. Combination omalizumab and mepolizumab therapy for refractory allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol Pract*. 2017;5(4):1137-1139.
28. Han D, Lee JK. Severe asthma with eosinophilic gastroenteritis effectively managed by mepolizumab and omalizumab. *Ann Allergy Asthma Immunol*. 2018;121(6):742-743.
29. Stein ML, Collins MH, Villanueva JM, et al. Anti-IL-5 (mepolizumab) therapy for eosinophilic esophagitis. *J Allergy Clin Immunol*. 2006;118(6):1312-1319.
30. Straumann A, Conus S, Grzonka P, et al. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic esophagitis: a randomized, placebo-controlled, double-blind trial. *Gut*. 2010;59:21-30.
31. Assa'ad AH, Gupta SK, Collins MH, et al. An antibody against IL-5 reduces numbers of esophageal intraepithelial eosinophils in children with eosinophilic esophagitis. *Gastroenterology*. 2011;141(5):1593-1604.
32. Hirano I, Chan ES, Rank MA, et al. AGA Institute and Joint Task Force on Allergy-Immunology Practice Parameters Clinical Guidelines for the Management of Eosinophilic Esophagitis. *Gastroenterology*. 2020;158(6):1776-1786.