PRIOR AUTHORIZATION POLICY

POLICY: Immunologicals – Nucala Prior Authorization Policy
- Nucala® (mepolizumab subcutaneous injection – GlaxoSmithKline)

REVIEW DATE: 03/16/2022; selected revision 07/20/2022

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** 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 an inhaled corticosteroid [ICS]/long-acting beta$_2$-agonist [LABA] combination 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 (ERS)/American Thoracic Society (ATS) 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.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Nucala. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Nucala as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Nucala to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nucala is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. Asthma. Approve Nucala for the duration noted if the patient meets one of the following conditions (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, iv, and v):

i. Patient is ≥ 6 years of age; AND

ii. Patient has a blood eosinophil level ≥ 150 cells per microliter within the previous 6 weeks or within 6 weeks prior to treatment with Nucala or another monoclonal antibody therapy that may lower blood eosinophil levels; AND

Note: Examples of monoclonal antibody therapies that may lower blood eosinophil levels include Nucala, Adbry (tralokinumab-ldrm subcutaneous injection), Cinqair (reslizumab intravenous infusion), Dupixent (dupilumab subcutaneous injection), Fasenra (benralizumab subcutaneous injection), Tezspire (tezepelumab-ekko subcutaneous injection), Xolair (omalizumab subcutaneous injection).

iii. Patient has received at least 3 consecutive months of combination therapy with BOTH of the following (a and b):

a) An inhaled corticosteroid; AND

b) At least one additional asthma controller or asthma maintenance medication; AND

Note: Examples of additional asthma controller or asthma maintenance medications are inhaled long-acting beta$_2$-agonists, inhaled long-acting muscarinic antagonists, leukotriene receptor antagonists, and monoclonal antibody therapies for asthma (e.g., Cinqair, Dupixent, Fasenra, Nucala, Tezspire, and Xolair). Use of a combination inhaler containing both an inhaled corticosteroid and additional asthma controller/maintenance medication(s) would fulfil the requirement for both criteria a and b.

iv. Patient has asthma that is uncontrolled or was uncontrolled at baseline as defined by ONE of the following (a, b, c, d, or e):

Note: "Baseline" is defined as prior to receiving Nucala or another monoclonal antibody therapy for asthma. Examples of monoclonal antibody therapies for asthma include Nucala, Cinqair, Dupixent, Fasenra, Tezspire, and Xolair.

a) Patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR

b) Patient experienced one or more asthma exacerbation(s) requiring a hospitalization, an emergency department visit, or an urgent care visit in the previous year; OR

c) Patient has a forced expiratory volume in 1 second (FEV_1) < 80% predicted; OR

d) Patient has an FEV_1/forced vital capacity (FVC) < 0.80; OR

e) Patient has asthma that worsens upon tapering of oral (systemic) corticosteroid therapy; AND

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

B) Patient is Currently Receiving Nucala. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):

i. Patient has already received at least 6 months of therapy with Nucala; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with Nucala should be considered under criterion 1A (Asthma, Initial Therapy).

ii. Patient continues to receive therapy with one inhaled corticosteroid or one inhaled corticosteroid-containing combination inhaler; AND

iii. Patient has responded to therapy as determined by the prescriber.

Note: Examples of a 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) [formerly known as Churg-Strauss Syndrome].** Approve Nucala for the duration noted if the patient meets one of the following conditions (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets the following conditions (i, ii, iii, iv and v):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has active, non-severe disease; AND
       Note: Non-severe disease is defined as vasculitis without life- or organ-threatening manifestations. Examples of symptoms in patients with non-severe disease include rhinosinusitis, asthma, mild systemic symptoms, uncomplicated cutaneous disease, mild inflammatory arthritis.
     - **iii.** Patient has/had a blood eosinophil level ≥ 150 cells per microliter within the previous 6 weeks or within 6 weeks prior to treatment with any monoclonal antibody therapy that may lower blood eosinophil levels; AND
       Note: Examples of monoclonal antibody therapies that may lower blood eosinophil levels include Nucala, Adbry (tralokinumab-ldrm subcutaneous injection), Cinqair (reslizumab intravenous infusion), Dupixent (dupilumab subcutaneous injection), Fasenra (benralizumab subcutaneous injection), Tezspire (tezepelumab-ekko subcutaneous injection), and Xolair (omalizumab subcutaneous injection).
     - **iv.** Patient has tried therapy with a corticosteroid (e.g., prednisone) for a minimum of 4 weeks; AND
     - **v.** The medication is prescribed by or in consultation with an allergist, immunologist, pulmonologist, or rheumatologist.
   - **B)** Patient is Currently Receiving Nucala. Approve for 1 year if the patient meets the following criteria (i and ii):
     - **i.** Patient has already received at least 6 months of therapy with Nucala; AND
       Note: A patient who has received < 6 months of therapy or who is restarting therapy with Nucala should be considered under criterion 2A (Eosinophilic Granulomatosis with Polyangiitis, Initial Therapy).
     - **ii.** Patient has responded to therapy as determined by the prescriber.
       Note: Examples of a response to Nucala therapy are reduced rate of relapse, corticosteroid dose reduction, and reduced eosinophil levels.

3. **Hypereosinophilic Syndrome.** Approve Nucala for the duration noted if the patient meets one of the following conditions (A or B):
   - **A)** Initial Therapy. Approve for 8 months if the patient meets the following conditions (i, ii, iii, iv, v, vi, and vii):
     - **i.** Patient is ≥ 12 years of age; AND;
     - **ii.** Patient has had hypereosinophilic syndrome for ≥ 6 months; AND
     - **iii.** Patient has FIP1L1-PDGFRα-negative disease; AND
     - **iv.** Patient does NOT have an identifiable non-hematologic secondary cause of hypereosinophilic syndrome according to the prescriber; AND
       Note: Examples of secondary causes of hypereosinophilic syndrome include drug hypersensitivity, parasitic helminth infection, human immunodeficiency virus infection, non-hematologic malignancy.
     - **v.** Patient has/had a blood eosinophil level ≥ 1,000 cells per microliter prior to treatment with any monoclonal antibody therapy that may lower blood eosinophil levels; AND

Note: Examples of monoclonal antibody therapies that may lower blood eosinophil levels include Nucala, Adbry (tralokinumab-ldrm subcutaneous injection), Cinqair (reslizumab intravenous infusion), Dupixent (dupilumab subcutaneous injection), Fasenra (benralizumab subcutaneous injection), Tezspire (tezepelumab-ekko subcutaneous injection), and Xolair (omalizumab subcutaneous injection).

vi. Patient has tried at least one other treatment for hypereosinophilic syndrome for a minimum of 4 weeks; AND
Note: Example of treatments for hypereosinophilic syndrome include systemic corticosteroids, hydroxyurea, cyclosporine, imatinib, or pegylated-interferon.

vii. Nucala is prescribed by or in consultation with an allergist, immunologist, pulmonologist, or rheumatologist.

B) Patient is Currently Receiving Nucala. Approve for 1 year if the patient meets the following criteria (i and ii):

i. Patient has already received at least 8 months of therapy with Nucala; AND
Note: A patient who has received < 8 months of therapy or who is restarting therapy with Nucala should be considered under criterion 3A (Hypereosinophilic Syndrome, Initial Therapy).

ii. Patient has responded to therapy as determined by the prescriber.
Note: Examples of a response to Nucala therapy are decreased number of flares, improved fatigue, reduced corticosteroid requirements, and decreased eosinophil levels.

4. Nasal Polyps. Approve Nucala for the duration noted if the patient meets one of the following conditions (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, iv, v, and vi):

i) Patient is ≥ 18 years of age; AND

ii) Patient has chronic rhinosinusitis with nasal polyposis as evidenced by direct examination, endoscopy, or sinus computed tomography (CT) scan; AND

iii) Patient has experienced two or more of the following symptoms for at least 6 months: nasal congestion, nasal obstruction, nasal discharge, and/or reduction/loss of smell; AND

iv) Patient meets BOTH of the following (a and b):

a) Patient has received at least 3 months of therapy with an intranasal corticosteroid; AND

b) Patient will continue to receive therapy with an intranasal corticosteroid concomitantly with Nucala; AND

v) Patient meets ONE of the following (a, b, or c):

a) Patient has received at least one course of treatment with a systemic corticosteroid for 5 days or more within the previous 2 years; OR

b) Patient has a contraindication to systemic corticosteroid therapy; OR

c) Patient has had prior surgery for nasal polyps; AND

vi) Nucala is prescribed by or in consultation with an allergist, immunologist, or an otolaryngologist (ear, nose and throat [ENT] physician specialist).

B) Patient is Currently Receiving Nucala. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):

i) Patient has already received at least 6 months of therapy with Nucala; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with Nucala should be considered under criterion 4A [Nasal Polyps, Initial Therapy]).

ii) Patient continues to receive therapy with an intranasal corticosteroid; AND

iii) Patient has responded to therapy as determined by the prescriber.
Note: Examples of a response to Nucala therapy are reduced nasal polyp size, improved nasal congestion, reduced sinus opacification, decreased sino-nasal symptoms, improved sense of smell.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Nucala is not recommended in the following situations:

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 . 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 (2022) 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 with another Monoclonal Antibody Therapy.** The efficacy and safety of Nucala used in combination with other monoclonal antibody therapies (e.g., Adbry, Cinqair, Dupixent, Fasenra, Tezspire, Xolair) 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.[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.

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Nucala® subcutaneous injection [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; January 2022.
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 Apr 16. [Online ahead of print].
8. Global Initiative for Asthma. Global strategy for asthma management and prevention. Updated 2021. Available at: http://www.ginasthma.org. Accessed on: February 21, 2022.
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. Joint Task Force on Practice Parameters: American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of rhinitis: An updated practice parameter. *J Allergy Clin Immunol*. 2008;122(2):S1-S84.
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 February21, 2022.
24. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2022 report. Global Initiative for Chronic Obstructive Lung Disease. Available from: http://goldcopd.org/. Accessed on February 21, 2022.

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.