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Policy Number: 003.005

Title: Coverage Determination Policy for Asthma Medications:

- **Xolair (Omalizumab); Cinqair (Reslizumab); Nucala (Mepolizumab); Fasenra (Benralizumab); Tezspire (Tezepelumab-ekko)**

Regions: ☒ Texas ☒ New Mexico

Impacted Areas:

☐ Network Management/Provider Services	☒ Utilization Management
☐ Member services	☐ Case management
☐ Quality Management	☐ Disease management
☐ Credentialing	☒ Claims
☐ IT	☐ Human resources
☐ Administration	☐ Finance
☐ Compliance/delegation	☒ Pharmacy
	☐ ALL

Available LCD/NCD/LCA: None

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Coverage Policy Number: 003.005

Line of Business: Medicare Part B

Policy Type: Prior Authorization

Coverage Determination:

Initial/New Requests

Xolair

Xolair for provider administration is proven for patients with **moderate to severe persistent asthma**. WellMed Medical Management will cover **Xolair (Omalizumab)** for provider administration as medically necessary when **ALL** of the following criteria are met:

A. Diagnosis of moderate or severe asthma

B. Classification of asthma as uncontrolled or inadequately controlled as defined by ONE of the following:

I. Poor symptom control (e.g., Asthma Control Questionnaire [ACQ] score consistently greater than 1.5 or Asthma Control Test [ACT] score consistently less than 20)

II. Two or more bursts of systemic corticosteroids for at least 3 days each in the previous 12 months

III. Asthma-related emergency treatment (e.g., emergency room visit, hospital admission, or unscheduled physician's office visit for nebulizer or other urgent treatment)

IV. Airflow limitation (e.g., after appropriate bronchodilator withhold forced expiratory volume in 1 second [FEV1] less than 80% predicted [in the face of reduced FEV1/forced vital capacity [FVC] defined as less than the lower limit of normal])

V. Patient is currently dependent on maintenance therapy with oral corticosteroids for the treatment of asthma

C. Baseline (pre-omalizumab treatment) serum total IgE level greater than or equal to 30 IU/mL and less than or equal to 1300 IU/mL

D. There is a positive skin test or in vitro reactivity to a perennial aeroallergen

E. Xolair will be used in combination with ONE of the following:

I. One maximally-dosed (appropriately adjusted for age) combination inhaled corticosteroid (ICS)/long-acting beta2- agonist (LABA) product [e.g., Advair/AirDuo Respiclick (fluticasone propionate/salmeterol), Symbicort (budesonide/formoterol), Breo Ellipta (fluticasone furoate/vilanterol)]

II. Combination therapy including BOTH of the following:

a. One high-dose (appropriately adjusted for age) ICS product [e.g., ciclesonide (Alvesco), mometasone furoate (Asmanex), beclomethasone dipropionate (QVAR)

b. One additional asthma controller medication [e.g., LABA - olodaterol (Striverdi) or indacaterol (Arcapta); leukotriene receptor antagonist – montelukast (Singulair); theophylline]

F. Patient is not receiving Xolair in combination with any of the following

I. Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]

II. Anti-interleukin 5 therapy [e.g., Nucala (mepolizumab), Cinqair (reslizumab), Fasenra (benralizumab)]

III. Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

G. Xolair is dosed in accordance with FDA approved labeling for this indication.

H. Prescribed by allergist/immunologist or pulmonologist

Xolair (omalizumab) for provider administration is proven for patients with **Chronic Urticaria**. WellMed Medical Management will cover **Xolair (Omalizumab)** for provider administration as medically necessary when **ALL** of the following criteria are met:

**Note: Patients 65 years of age and older in whom first generation H1-antihistamines are considered high risk medications to be avoided (e.g., Beers criteria, HEDIS) should be directed to try alternatives that are not considered high risk.*

A. Diagnosis of chronic urticaria

B. Patient meets ONE of the following:

I. Patient remains symptomatic despite at least a 2-week trial of, or history of contraindication or intolerance to**,** two H1- antihistamines [e.g., Allegra (fexofenadine), Benadryl (diphenhydramine), Claritin (loratadine)]

II. Patient remains symptomatic despite at least a 2-week trial of, or history of contraindication or intolerance to both of the following taken in combination

a. A second generation H1-antihistamine [e.g., Allegra (fexofenadine), Claritin (loratadine), Zyrtec (cetirizine)

b. ONE of the following:

i. Different second generation H1-antihistamine [e.g., Allegra (fexofenadine), Claritin (loratadine), Zyrtec (cetirizine)]

ii. First generation H1-antihistamine [e.g., Benadryl (diphenhydramine), Chlor-Trimeton (chlorpheniramine), Vistaril (hydroxyzine)

iii. H2-antihistamine [e.g., Pepcid (famotidine), Tagamet HB (cimetidine), Zantac (ranitidine)]

iv. Leukotriene modifier [e.g., Singulair (montelukast)]

C. Patient is NOT receiving Xolair in combination with ANY of the following:

I. Anti-interleukin 5 therapy [e.g., Cinqair (reslizumab), Fasenra (benralizumab)]

II. Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]

III. Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

D. Xolair is dosed in accordance with FDA approved labeling for this indication

E. Prescribed by an allergist/immunologist or dermatologist

Xolair (Omalizumab) for provider administration is proven for patients with **Nasal Polyps**, WellMed Medical Management will cover **Xolair (Omalizumab)** for provider administration as medically necessary when **ALL** of the following criteria are met :

A. Diagnosis of nasal polyps

B. TWO or more of the following symptoms for longer than 12 weeks duration:

I. Nasal mucopurulent discharge

II. Nasal obstruction, blockage, or congestion

III. Facial pain, pressure, and/or fullness

IV. Reduction or loss of sense of smell

C. ONE of the following findings using physical exam, nasal endoscopy OR sinus computed tomography (CT)

I. Purulent mucus or edema in the middle meatus or ethmoid regions

II. Polyps in the nasal cavity or the middle meatus

III. Radiographic imaging demonstrating mucosal thickening or partial or complete opacification of nasal paranasal sinuses.

D. ONE of the following:

I. Patient has been unable to obtain symptom relief after trial of both of the following:

a. Intranasal corticosteroids (e.g., fluticasone, mometasone, triamcinolone)

b. One other therapy used in the management of nasal polyps [i.e., nasal saline irrigations. antileukotriene agents (e.g., montelukast, zafirlukast, zileuton)]

II. Patient has required systemic corticosteroids (e.g., prednisone, methylprednisolone) for chronic rhinosinusitis with nasal polyposis (CRSwNP) in the previous 2 years

III. Patient has required prior sinus surgery

E. Patient will receive Xolair as add-on maintenance therapy in combination with intranasal corticosteroids (e.g., fluticasone, mometasone, triamcinolone)

F. Patient is NOT receiving Xolair in combination with ANY of the following:

I. Anti-interleukin 5 therapy [e.g., Cinqair (reslizumab), Fasenra (benralizumab), Nucala (mepolizumab)]

II. Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]

III. Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

G. Xolair is dosed in accordance with FDA approved labeling for this indication.

H. Prescribed by an allergist/immunologist/otolaryngologist/pulmonologist

Note: Xolair is <u>unproven and not medically necessary</u> for the following conditions:

A. Seasonal allergic rhinitis
B. Perennial allergic rhinitis
C. Atopic dermatitis
D. Peanut allergy
E. Acute bronchospasm or status asthmaticus

Cinqair

WellMed Medical Management will cover **Cinqair (Reslizumab)** for ***intravenous*** use as medically necessary **when used as an add-on maintenance treatment of severe asthma in patients with an Eosinophilic Phenotype** when **ALL** of the following criteria are met:

A. Diagnosis of severe asthma

B. Classification of asthma as uncontrolled or inadequately controlled as defined by at least ONE of the following:

I. Poor symptom control (e.g., ACQ score consistently greater than 1.5 or ACT score consistently less than 20)

II. Two or more bursts of systemic corticosteroids for at least 3 days each in the previous 12 months

III. Asthma-related emergency treatment (e.g., emergency room visit, hospital admission, or unscheduled physician's office visit for nebulizer or other urgent treatment)

IV. Airflow limitation (e.g., after appropriate bronchodilator withhold FEV1 less than 80% predicted [in the face of reduced FEV1/FVC defined as less than the lower limit of normal])

V. Patient is currently dependent on maintenance therapy with oral corticosteroids for the treatment of asthma

C. Asthma is an eosinophilic phenotype as defined by a baseline (pre-reslizumab) peripheral blood eosinophil level of ≥ 150 cells/µL

D. Used in combination with ONE of the following:

I. One maximally-dosed (appropriately adjusted for age) combination ICS/LABA product [e.g., Advair/AirDuo Respiclick (fluticasone propionate/salmeterol), Symbicort (budesonide/formoterol), Breo Ellipta (fluticasone furoate/vilanterol)];

II. Combination therapy including BOTH of the following:

a. One high-dose (appropriately adjusted for age) ICS product [e.g., ciclesonide (Alvesco), mometasone furoate (Asmanex), beclomethasone dipropionate (QVAR)

b. One additional asthma controller medication [e.g., LABA - olodaterol (Striverdi) or indacaterol (Arcapta), leukotriene receptor antagonist – montelukast (Singulair), theophylline] BOTH of the following:

I. ONE of the following:

a. History of failure to a 4 month trial of Fasenra or Nucala; or

b. Contraindication or intolerance to Fasenra or Nucala

AND

II. ONE of the following:

a. History of failure to a 4 month trial of Tezspire; or

b. Contraindication or intolerance to Tezspire

E. Patient is NOT receiving Cinqair in combination with ANY of the following:

I. Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]

II. Anti-interleukin 5 therapy [e.g., Nucala (mepolizumab), Fasenra (benralizumab)]

III. Anti-IgE therapy [e.g., Xolair (omalizumab)]

IV. Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

F. Cinqair is dosed in accordance with FDA approved labeling for this indication.

G. Prescribed by a pulmonologist or allergist/immunologist

Nucala

WellMed Medical Management will cover **Nucala (Mepolizumab)** for provider administration as proven and medically necessary for **add-on maintenance treatment of severe asthma in patients with an Eosinophilic Phenotype** when **ALL** of the following criteria are met:

A. Diagnosis of severe asthma

B. Classification of asthma as uncontrolled or inadequately controlled as defined by at least ONE of the following:

I. Poor symptom control (e.g., Asthma Control Questionnaire [ACQ] score consistently greater than 1.5 or Asthma Control Test [ACT] score consistently less than 20)

II. Two or more bursts of systemic corticosteroids for at least 3 days each in the previous 12 months

III. Asthma-related emergency treatment (e.g., emergency room visit, hospital admission, or unscheduled physician's office visit for nebulizer or other urgent treatment)

IV. Airflow limitation (e.g., after appropriate bronchodilator withhold forced expiratory volume in 1 second (FEV1) less than 80% predicted [in the face of reduced FEV1/forced vital capacity (FVC) defined as less than the lower limit of normal]

V. Patient is currently dependent on maintenance therapy with oral corticosteroids for the treatment of asthma

C. Asthma is an eosinophilic phenotype as defined by a baseline (pre-treatment) peripheral blood eosinophil level of ≥ 150 cells/µL

D. Used in combination with ONE of the following:

I. One maximally-dosed (appropriately adjusted for age) combination ICS/ LABA product [e.g., Advair/AirDuo Respiclick (fluticasone propionate/salmeterol), Symbicort (budesonide/formoterol), Breo Ellipta (fluticasone furoate/vilanterol)]

II. Combination therapy including BOTH of the following:

a. One high-dose (appropriately adjusted for age) ICS product [e.g., ciclesonide (Alvesco), mometasone furoate (Asmanex), beclomethasone dipropionate (QVAR)]

b. One additional asthma controller medication [e.g., LABA - olodaterol (Striverdi) or indacaterol (Arcapta); leukotriene receptor antagonist – montelukast (Singulair); theophylline]

E. Patient is NOT receiving Nucala in combination with ANY of the following

I. Anti-interleukin 5 therapy [e.g., Cinqair (reslizumab), Fasenra (benralizumab)]

II. Anti-IgE therapy [e.g., Xolair (omalizumab)]

III. Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]

IV. Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

F. Nucala is dosed in accordance with FDA approved labeling for this indication

G. Prescribed by a pulmonologist or allergist/immunologist

WellMed Medical Management will cover **Nucala (Mepolizumab)** for provider administration as medically necessary for the treatment of **Eosinophilic granulomatosis with polyangiitis (EGPA)** when **ALL** of the following are met:

A. Diagnosis of relapsing or refractory EGPA as defined by ALL of the following:

I. Diagnosis of EGPA

II. Past medical history or presence of asthma

III. Presence of at least TWO of the following characteristics typical of EGPA

a. Histopathological evidence of:

i. Eosinophilic vasculitis

ii. Perivascular eosinophilic infiltration

iii. Eosinophil-rich granulomatous inflammation

b. Neuropathy, mono or poly (motor deficit or nerve conduction abnormality)

c. Pulmonary infiltrates, non-fixed

d. Sino-nasal abnormality

e. Cardiomyopathy (established by echocardiography or MRI)

f. Glomerulonephritis (hematuria, red cell casts, proteinuria)

g. Alveolar hemorrhage

h. Palpable purpura

i. Anti-neutrophil cytoplasmic antibody (ANCA) positive

IV. History of relapsing or refractory disease defined as ONE of the following:

a. Relapsing disease as defined as a past history (within the past 2 years) of at least one EGPA relapse (requiring additional or dose escalation of corticosteroids or immunosuppressant, or hospitalization)

b. Refractory disease as defined as failure to attain remission within the prior 6 months following induction treatment with standard therapy regimens

B. Patient is currently taking standard therapy (corticosteroids with or without immunosuppressive therapy)

C. Patient is NOT receiving Nucala in combination with ANY of the following:

I. Anti-interleukin 5 therapy [e.g., Cinqair (reslizumab), Fasenra (benralizumab)]

II. Anti-IgE therapy [e.g., Xolair (omalizumab)]

III. Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]

IV. Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

D. Dosing is in accordance with the U. S. Food and Drug Administration approved labeling; **AND**

E. Prescribed by a pulmonologist, rheumatologist, or allergist/immunologist; **AND**

F. Initial authorization will be for no more than 12 months

WellMed Medical Management will cover **Nucala (Mepolizumab)** for provider administration as proven and medically necessary for diagnosis of **Hypereosinophilic Syndrome (HES)** when **ALL** of the following are met:

A. Diagnosis of HES for ≥ 6 months

B. BOTH of the following:

I. There is no identifiable non-hematologic secondary cause of the patient's HES (e.g., drug hypersensitivity, parasitic helminth infection, HIV infection, non-hematologic malignancy)

II. HES is not FIP1L1-PDGFRα kinase-positive

C. Submission of medical records (e.g., chart notes, laboratory values, etc.) documenting BOTH of the following:

I. Baseline (pre-mepolizumab treatment) blood eosinophil level ≥ 1000 cells/µL within the past 4 weeks

II. Patient is currently receiving a stable dose of background HES therapy (e.g., oral corticosteroid, immunosuppressor, or cytotoxic therapy)

D. Patient is NOT receiving Nucala in combination with ANY of the following:

I. Anti-interleukin 5 therapy [e.g., Cinqair (reslizumab), Fasenra (benralizumab)]

II. Anti-IgE therapy [e.g., Xolair (omalizumab)]

III. Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]

IV. Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

E. Nucala is dosed in accordance with FDA approved labeling for this indication

F. Prescribed by an allergist, immunologist, hematologist, cardiologist, or pulmonologist

WellMed Medical Management will cover **Nucala (Mepolizumab)** for provider administration as proven and medically necessary for diagnosis of **Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)** when **ALL** of the following are met:

A. Diagnosis of chronic rhinosinusitis with nasal polyps (CRSwNP) defined by ALL of the following:

I. TWO or more of the following symptoms for longer than 12 weeks duration

a. Nasal mucopurulent discharge

b. Nasal obstruction, blockage, or congestion

c. Facial pain, pressure, and/or fullness

d. Reduction or loss of sense of smell

II. ONE of the following findings using nasal endoscopy OR sinus computed tomography (CT):

a. Purulent mucus or edema in the middle meatus or ethmoid regions

b. Polyps in the nasal cavity or the middle meatus

c. Radiographic imaging demonstrating mucosal thickening or partial or complete opacification of paranasal sinuses

III. ONE of the following:

a. Presence of bilateral nasal polyposis

b. Patient has previously required surgical removal of bilateral nasal polyps

IV. ONE of the following

a. Patient has required prior sinus surgery

b. Patient has required systemic corticosteroids (e.g., prednisone, methylprednisolone) for CRSwNP in the previous 2 years

c. Patient has been unable to obtain symptom relief after trial of two of the following classes of agents

i. Nasal saline irrigations

ii. Intranasal corticosteroids (e.g., fluticasone, mometasone, triamcinolone)

iii. Antileukotriene agents (e.g., montelukast, zafirlukast, zileuton)

B. Patient will receive Nucala as add-on maintenance therapy in combination with intranasal corticosteroids (e.g., fluticasone, mometasone, triamcinolone)

C. Patient is NOT receiving Nucala in combination with ANY of the following:

I. Anti-interleukin 5 therapy [e.g., Cinqair (reslizumab), Fasenra (benralizumab)]

II. Anti-IgE therapy [e.g., Xolair (omalizumab)]

III. Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]

IV. Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

D. Nucala is dosed in accordance with FDA approved labeling for this indication

E. Prescribed by an allergist/immunologist/otolaryngologist/pulmonologist

Fasenra

WellMed Medical Management will cover **Fasenra (Benralizumab)** for provider administration as proven and medically necessary as **add-on maintenance therapy in the treatment of severe asthma of Eosinophilic Phenotype** when **ALL** of the following are met:

A. Patient has a diagnosis of severe asthma

B. Classification of asthma as uncontrolled or inadequately controlled as defined by at least ONE of the following:

I. Poor symptom control (e.g., Asthma Control Questionnaire [ACQ] score consistently greater than 1.5 or Asthma Control Test [ACT] score consistently less than 20)

II. Two or more bursts of systemic corticosteroids for at least 3 days each in the previous 12 months

III. Asthma-related emergency treatment (e.g., emergency room visit, hospital admission, or unscheduled physician's office visit for nebulizer or other urgent treatment)

IV. Airflow limitation (e.g., after appropriate bronchodilator withhold forced expiratory volume in 1 second (FEV1) less than 80% predicted [in the face of reduced FEV1/forced vital capacity (FVC) defined as less than the lower limit of normal]

III. Patient is currently dependent on maintenance therapy with oral corticosteroids for the treatment of asthma

C. Asthma is an eosinophilic phenotype as defined by a baseline (pre-treatment) peripheral blood eosinophil level of ≥ 150 cells/µL

D. Used in combination with ONE of the following:

I. One maximally-dosed (appropriately adjusted for age) combination ICS/ LABA product [e.g., Advair/AirDuo Respiclick (fluticasone propionate/salmeterol), Symbicort (budesonide/formoterol), Breo Ellipta (fluticasone furoate/vilanterol)]

II. Combination therapy including BOTH of the following:

a. One high-dose (appropriately adjusted for age) ICS product ([e.g., ciclesonide (Alvesco), mometasone furoate (Asmanex), beclomethasone dipropionate (QVAR)]

b. One additional asthma controller medication [e.g., LABA - olodaterol (Striverdi) or indacaterol (Arcapta); leukotriene receptor antagonist – montelukast (Singulair); theophylline]

E. Patient is NOT receiving Fasenra in combination with ANY of the following:

I. Anti-interleukin 5 therapy [e.g., Nucala (mepolizumab), Cinqair (reslizumab)]

II. Anti-IgE therapy [e.g., Xolair (omalizumab)]

III. Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]

IV. Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

F. Fasenra is dosed in accordance with FDA approved labeling for this indication

G. Prescribed by a pulmonologist or allergist/immunologist;

Tezspire

WellMed Medical Management will cover **Tezspire (Tezepelumab-ekko)** for provider administration is proven and medically necessary for add-on maintenance treatment for patients that meet **ALL** of the following criteria:

A. Diagnosis of severe asthma

B. Classification of asthma as uncontrolled or inadequately controlled as defined by at least ONE of the following:

I. Poor symptom control (e.g., ACQ score consistently greater than 1.5 or ACT score consistently less than 20)

II. Two or more bursts of systemic corticosteroids for at least 3 days each in the previous 12 months

III. Asthma-related emergency treatment (e.g., emergency room visit, hospital admission, or unscheduled physician's office visit for nebulizer or other urgent treatment)

IV. Airflow limitation (e.g., after appropriate bronchodilator withhold FEV1 less than 80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal)

V. Patient is currently dependent on maintenance therapy with oral corticosteroids for the treatment of asthma

C. Used in combination with ONE of the following:

I. One maximally-dosed (appropriately adjusted for age) combination inhaled corticosteroid (ICS)/long-acting beta2 agonist (LABA) product [e.g., Advair/AirDuo Respiclick (fluticasone propionate/salmeterol), Symbicort (budesonide/formoterol), Breo Ellipta (fluticasone furoate/vilanterol)]

II. Combination therapy including BOTH of the following:

a. One maximally-dosed (appropriately adjusted for age) ICS product [e.g., ciclesonide (Alvesco), mometasone furoate (Asmanex), beclomethasone dipropionate (QVAR)]

b. One additional asthma controller medication [e.g., LABA - olodaterol (Striverdi) or indacaterol (Arcapta), leukotriene receptor antagonist – montelukast (Singulair®), theophylline]

D. Patient is NOT receiving Tezspire in combination with ANY of the following:

a. Anti-interleukin 5 therapy [e.g., Cinqair (reslizumab), Fasenra (benralizumab), Nucala (mepolizumab]

b. Anti-IgE therapy [e.g., Xolair (omalizumab)]

c. Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]

E. Tezspire is dosed in accordance with FDA approved labeling for this indication

F. Tezspire is prescribed by a pulmonologist or allergist/immunologist

Renewal/Continuation of Therapy Requests

Xolair for provider administration, for the treatment of the following conditions is medically necessary when **ALL** of the following criteria are met:

I. Asthma

A. Documentation of positive clinical response as demonstrated by at least ONE of the following

i. Reduction in the frequency of exacerbations

ii. Decreased utilization of rescue medications

iii. Increase in percent predicted FEV1 from pretreatment baseline

iv. Reduction in severity or frequency of asthma-related symptoms (e.g., wheezing, shortness of breath, coughing, etc.)

B. Used in combination with an ICS-containing controller medication

C. Patient is NOT receiving Xolair in combination with ANY of the following:

i. Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]

ii. Anti-interleukin 5 therapy [e.g., Nucala (mepolizumab), Cinqair (resilizumab), Fasenra (benralizumab)]

iii. Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

D. Dosing is in accordance with the United States Food and Drug Administration approved labeling

II. Chronic Urticaria

A. Documentation of positive clinical response (e.g., reduction in exacerbations, itch severity, hives)

B. Patient is NOT receiving Xolair in combination with ANY of the following:

i. Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]

ii. Anti-interleukin 5 therapy [e.g., Nucala (mepolizumab), Cinqair (resilizumab), Fasenra (benralizumab)]

iii. Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

C. Dosing is in accordance with the United States Food and Drug Administration approved labeling;

III. <u>Nasal Polyps</u>

A. Documentation of positive clinical response

B. Patient will receive Xolair as add-on maintenance therapy in combination with intranasal corticosteroids (e.g., fluticasone, mometasone, triamcinolone);

C. Patient is NOT receiving Xolair in combination with ANY of the following:

i. Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]

ii. Anti-interleukin 5 therapy [e.g., Nucala (mepolizumab), Cinqair (resilizumab), Fasenra (benralizumab)]

iii. Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

D. Dosing is in accordance with the United States Food and Drug Administration approved labeling; and

Continued treatment with **Cinqair (Reslizumab), Fasenra (Benralizumab), or Nucala (Mepolizumab) for the treatment of severe Eosinophilic Asthma** is considered medically necessary when **ALL** of following criteria are met:

A. There is documentation of positive clinical response as demonstrated by at least ONE of the following:

I. Reduced frequency of exacerbations

II. Decreased utilization of rescue medications

III. Increased percent predicted FEV1 from pretreatment baseline

IV. Reduced severity or frequency of asthma-related symptoms (e.g., wheezing, shortness of breath, coughing, etc.)

B. Used in combination with an ICS-containing maintenance medication [e.g., Advair/AirDuo (fluticasone/salmeterol), Breo Ellipta (fluticasone furoate/vilanterol), Symbicort (budesonide/ formoterol), Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol)]; and

C. Patient is NOT receiving the product in combination with ANY of the following:

I. Another anti-interleukin 5 therapy [e.g., Cinqair (reslizumab), Fasenra (benralizumab), Nucala (mepolizumab], respectively

II. Anti-IgE therapy [e.g., Xolair (omalizumab)]

III. Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]

IV. Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

D. Dosing is in accordance with the United States Food and Drug Administration approved labeling

E. For **Cinqair** reauthorization/continuation, BOTH of the following:

I. ONE of the following:

a. History of failure to a 4 month trial of Fasenra or Nucala; or

b. Contraindication or intolerance to Fasenra or Nucala

II. ONE of the following:

a. History of failure to a 4 month trial of Tezspire; or

b. Contraindication or intolerance to Tezspire

Nucala, for provider administration, for the treatment of **EGPA**, authorization for continued use will be approved based on **ALL** of the following criteria:

A. Documentation of positive clinical response as demonstrated by at least ONE of the following:

I. Reduction in the frequency and/or severity of relapses

II. Reduction or discontinuation of doses of corticosteroids and/or immunosuppressant

III. Disease remission

IV. Reduction in severity or frequency of EGPA-related symptoms

B. Patient is NOT receiving Nucala in combination with ANY of the following:

I. Anti-interleukin 5 therapy [e.g., Cinqair (reslizumab), Fasenra (benralizumab)]

II. Anti-IgE therapy [e.g., Xolair (omalizumab)]

III. Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]

IV. Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

C. Dosing is in accordance with the U. S. Food and Drug Administration approved labeling

Nucala, for provider administration, for the treatment of **HES**, authorization for continued use will be approved based on **ALL** of the following criteria:

A. Documentation of positive clinical response as demonstrated by at least ONE of the following:

I. Reduction in frequency of HES flares; or

II. Maintenance or reduction in background HES therapy requirements

and

B. Patient is NOT receiving Nucala in combination with ANY of the following:

I. Anti-interleukin 5 therapy [e.g., Cinqair (resilizumab), Fasenra (benralizumab)]

II. Anti-IgE therapy [e.g., Xolair (omalizumab)]

III. Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]

IV. Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

AND

C. Dosing is in accordance with the United States Food and Drug Administration approved labeling

For patients currently on **Nucala** for the treatment of **CRSwNP** authorization for continued use will be approved based on **ALL** of the following criteria:

A. Documentation of positive clinical response to Nucala therapy; and

B. Patient will continue to receive Nucala as add-on maintenance therapy in combination with intranasal corticosteroids (e.g., fluticasone, mometasone, triamcinolone); and

C. Patient is NOT receiving Nucala in combination with ANY of the following:

I. Anti-interleukin 5 therapy [e.g., Cinqair (resilizumab), Fasenra (benralizumab)]

II. Anti-IgE therapy [e.g., Xolair (omalizumab)]

III. Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]

IV. Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

D. Dosing is in accordance with the United States Food and Drug Administration approved labeling

Continued treatment with **Tezspire (Tezepelumab-ekko)** is considered medically necessary when the **ALL** of the following criteria are met:

A. Documentation of a positive clinical response as demonstrated by at least ONE of the following:

I. Reduction in the frequency of exacerbations

II. Decreased utilization of rescue medications

III. Increase in percent predicted FEV1 from pretreatment baseline

IV. Reduction in severity or frequency of asthma-related symptoms (e.g., wheezing, shortness of breath, coughing, etc.)

B. Used in combination with an ICS-containing controller medication

C. Patient is NOT receiving Tezspire in combination with ANY of the following:

I. Anti-interleukin 5 therapy [e.g., Cinqair (reslizumab), Fasenra (benralizumab), Nucala (mepolizumab]

II. Anti-IgE therapy [e.g., Xolair (omalizumab)]

III. Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]

D. Tezspire dosing is in accordance with the United States Food and Drug Administration approved labeling

Unproven

Cinqair, Fasenra, and Nucala are unproven and NOT medically necessary in the following:

A. Acute bronchospasm
B. Chronic obstructive pulmonary disease (COPD)
C. Granulomatosis with polyangiitis (Wegener's)
D. Microscopic polyangiitis
E. Organ or Life-threatening EGPA
F. Other eosinophilic conditions
G. Status asthmaticus

FDA Approved Dose and Indication

FDA Approved Indications	Xolair (Omalizumab)	Cinqair (Reslizumab)	Nucala (Mepolizumab)	Fasenra (Benralizumab)	Tezspire (Tezepelumab-ekko)
Asthma	X (moderate to severe persistent)	X (severe)	X (severe)	X (severe)	X (severe)
Nasal Polyps	X (polyps)				
Chronic Idiopathic Urticaria	X				
Eosinophilic granulomatosis with polyangiitis			X		
Hypereosinophilic Syndrome			X		
Chronic Rhinosinusitis with Nasal Polyps			X		

Product	FDA Approved Dosing
Xolair (Omalizumab)	**1. Moderate to severe persistent asthma:** given SubQ. Dose is based on body weight and IgE level **Pretreatment serum IgE ≥30 to 100 units/mL:** 30 to 90 kg: 150 mg every 4 weeks >90 to 150 kg: 300 mg every 4 weeks **Pretreatment serum IgE >100 to 200 units/mL:** 30 to 90 kg: 300 mg every 4 weeks >90 to 150 kg: 225 mg every 2 weeks **Pretreatment serum IgE >200 to 300 units/mL:** 30 to 60 kg: 300 mg every 4 weeks >60 to 90 kg: 225 mg every 2 weeks >90 to 150 kg: 300 mg every 2 weeks **Pretreatment serum IgE >300 to 400 units/mL:** 30 to 70 kg: 225 mg every 2 weeks >70 to 90 kg: 300 mg every 2 weeks >90 kg: **Do not administer dose** **Pretreatment serum IgE >400 to 500 units/mL:** 30 to 70 kg: 300 mg every 2 weeks >70 to 90 kg: 375 mg every 2 weeks >90 kg: **Do not administer dose** **Pretreatment serum IgE >500 to 600 units/mL:** 30 to 60 kg: 300 mg every 2 weeks >60 to 70 kg: 375 mg every 2 weeks >70 kg: **Do not administer dose** **Pretreatment serum IgE >600 to 700 units/mL:** 30 to 60 kg: 375 mg every 2 weeks >60 kg: **Do not administer dose** **2. Chronic Idiopathic Urticaria:** 150 or 300 mg SubQ every 4 weeks. **3.Nasal Polyps:** given SubQ. Dose is based on body weight and IgE level **Pretreatment serum IgE ≥30 to 100 units/mL:** >30 to 40 kg: 75 mg every 4 weeks >40 to 90 kg: 150 mg every 4 weeks >90 to 150 kg: 300 mg every 4 weeks **Pretreatment serum IgE >100 to 200 units/mL:** >30 to 40 kg: 150 mg every 4 weeks >40 to 90 kg: 300 mg every 4 weeks >90 to 125 kg: 450 mg every 4 weeks >125 to 150 kg: 600 mg every 4 weeks **Pretreatment serum IgE >200 to 300 units/mL:** >30 to 40 kg: 225 mg every 4 weeks

	>40 to 60 kg: 300 mg every 4 weeks >60 to 90 kg: 450 mg every 4 weeks >90 to 125 kg: 600 mg every 4 weeks >125 to 150 kg: 375 mg every 2 weeks **Pretreatment serum IgE >300 to 400 units/mL:** >30 to 40 kg: 300 mg every 4 weeks >40 to 70 kg: 450 mg every 4 weeks >70 to 90 kg: 600 mg every 4 weeks >90 to 125 kg: 450 mg every 2 weeks >125 to 150 kg: 525 mg every 2 weeks **Pretreatment serum IgE >400 to 500 units/mL:** >30 to 50 kg: 450 mg every 4 weeks >50 to 70 kg: 600 mg every 4 weeks >70 to 90 kg: 375 mg every 2 weeks >90 to 125 kg: 525 mg every 2 weeks >125 to 150 kg: 600 mg every 2 weeks **Pretreatment serum IgE >500 to 600 units/mL:** >30 to 40 kg: 450 mg every 4 weeks >40 to 60 kg: 600 mg every 4 weeks >60 to 70 kg: 375 mg every 2 weeks >70 to 90 kg: 450 mg every 2 weeks >90 to 125 kg: 600 mg every 2 weeks **Pretreatment serum IgE >600 to 700 units/mL:** >30 to 40 kg: 450 mg every 4 weeks >40 to 50 kg: 600 mg every 4 weeks >50 to 60 kg: 375 mg every 2 weeks >60 to 80 kg: 450 mg every 2 weeks >80 to 90 kg: 525 mg every 2 weeks **Pretreatment serum IgE >700 to 800 units/mL:** >30 to 40 kg: 300 mg every 2 weeks >40 to 50 kg: 375 mg every 2 weeks >50 to 70 kg: 450 mg every 2 weeks >70 to 80 kg: 525 mg every 2 weeks >80 to 90 kg: 600 mg every 2 weeks **Pretreatment serum IgE >800 to 900 units/mL:** >30 to 40 kg: 300 mg every 2 weeks >40 to 50 kg: 375 mg every 2 weeks >50 to 60 kg: 450 mg every 2 weeks >60 to 70 kg: 525 mg every 2 weeks >70 to 80 kg: 600 mg every 2 weeks **Pretreatment serum IgE >900 to 1000 units/mL:** >30 to 40 kg: 375 mg every 2 weeks >40 to 50 kg: 450 mg every 2 weeks >50 to 60 kg: 525 mg every 2 weeks >60 to 70 kg: 600 mg every 2 weeks **Pretreatment serum IgE >1000 to 1100 units/mL:** >30 to 40 kg: 375 mg every 2 weeks >40 to 50 kg: 450 mg every 2 weeks

	>50 to 60 kg: 600 mg every 2 weeks **<u>Pretreatment serum IgE >1100 to 1200 units/mL:</u>** >30 to 40 kg: 450 mg every 2 weeks >40 to 50 kg: 525 mg every 2 weeks >50 to 60 kg: 600 mg every 2 weeks **<u>Pretreatment serum IgE >1200 to 1300 units/mL:</u>** >30 to 40 kg: 450 mg every 2 weeks >40 to 50 kg: 525 mg every 2 weeks **<u>Pretreatment serum IgE >1300 to 1500 units/mL:</u>** >30 to 40 kg: 525 mg every 2 weeks >40 to 50 kg: 600 mg every 2 weeks
Cinqair (Reslizumab)	**Severe Asthma:** 100 mg SubQ once every 4 weeks **Eosinophilic granulomatosis with polyangiitis:** 300 mg (given as 3 separate 100-mg injections) SubQ once every 4 weeks **Hypereosinophilic syndrome:** 300 mg subQ every 4 weeks **Chronic Rhinosinusitis with Nasal Polyps:** 100 mg once every 4 weeks
Cinqair (Reslizumab)	**Severe asthma:** 3 mg/kg IV once every 4 weeks
Fasenra (Benralizumab)	**Severe asthma:** 30 mg subQ once every 4 weeks for the first 3 doses, and then once every 8 weeks
Tezspire (Tezepelumab-ekko)	**Severe asthma:** 210 mg subQ every 4 weeks

General Background

Asthma is a common chronic inflammatory disease of the airways that affects an estimated 24 million adults and children and is associated with significant morbidity and mortality.
Although the disease is well controlled with inhaled therapy in most patients, approximately 1.2 to 2.4 million people have severe asthma (i.e., 5 to 10% of the asthma population) that is associated with substantial morbidity, mortality, and economic effects.
Key asthma phenotypes include allergic asthma, eosinophilic asthma, and non-eosinophilic asthma.
Eosinophilic asthma is characterized by an increase in the blood and sputum eosinophil (EOS) levels; fractional exhaled nitric oxide (FeNO) also provides an indication of level of eosinophilic inflammation in the lung. In contrast, allergic asthma is characterized by a positive perennial aeroallergen skin test and/or increased levels of serum IgE. In current clinical practice, such phenotypic biomarkers are central to the management of severe, uncontrolled asthma as existing asthma biologic therapies are targeted at either eosinophilic or allergic asthma. Approximately one-half of patients may present with overlapping or changing phenotypes, and almost 30% may not have a defined inflammatory pathway
Omalizumab is a monoclonal antibody that binds to human immunoglobulin E (IgE)'s high affinity Fc receptor, thereby preventing the binding of IgE to a variety of cells associated with the allergic response. Preventing the bridging between IgE and cells associated with allergic response prevents degranulation of such cells and, thereby, the release of inflammatory mediators. Omalizumab has been found in clinical trials to reduce free serum IgE concentrations by more than 90%, considerably suppress eosinophils in induced sputum, and blunt both early and late phase allergic reactions.
Asthma has been divided into subtypes, some of which are associated with airway inflammation with eosinophils. It is estimated that about half of individuals with severe asthma exhibit the eosinophilic phenotype with elevated eosinophil levels (a marker of inflammation) in both the blood and airways. Activated eosinophils can increase airway smooth muscle contraction and mucous secretion, which are hallmarks of asthma. Interleukin-5 (IL-5) is an important cellular signal in eosinophilic inflammation. Therapies that decrease IL-5 levels, such as Nucala (mepolizumab) and Cinqair (reslizumab), may decrease eosinophils in lung tissue. Fasenra (benralizumab) directly binds to the human IL-5 receptor on the surface of eosinophils and basophils, leading to the apoptosis of these cells through antibody-dependent cell mediated cytotoxicity
Eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss syndrome) is characterized by asthma, sinusitis, pulmonary infiltrates, neuropathy, and eosinophilic vasculitis of one or more end organs. It is thought that eosinophils mediate the effects in patients with EGPA by infiltrating tissue and vasculature, causing inflammation. Systemic glucocorticoids are currently the standard of treatment for EGPA, however, some patients do not have sufficient response to therapy. Mepolizumab, by inhibiting IL-5 signaling, reduces the production and survival of eosinophils; however, the mechanism of mepolizumab action in asthma and EGPA has not been definitively established.

Hypereosinophilic Syndrome (HES) is a disorder marked by the sustained overproduction of eosinophils associated with damage to one or more organs due to eosinophilic infiltration and mediator release. HES is rare and the true prevalence is unknown. One study that used clinician coding of eosinophilia to identify patients with HES in the Surveillance, Epidemiology, and End Results (SEER) database, concluded the estimated prevalence was between 0.36 to 6.3 per 100,000. Most patients are between 20 and 50 years of age at the time of diagnosis, although HES can develop in children. One study suggested that the frequencies of clinical HES variants (including myeloproliferative variants) were similar in children and adults. Certain variants of HES (i.e., those associated with aberrations in the gene for tyrosine kinase receptor platelet-derived growth factor receptor alpha [PDGFRA] and platelet-derived growth factor beta [PDGFRB]) occur almost exclusively in males, whereas others (lympcytic variant HES [L-HES] and HES of unknown etiology) appear to be equally distributed between the sexes. Patients with HES usually have more than 1500 eosinophils/µL in their blood for 6 months or more, and the cause cannot be identified. The eosinophils disperse to various tissues, causing inflammation and eventually organ dysfunction. Mepolizumab binds to IL-5 inhibiting the production of eosinophils, thereby reducing inflammation.

Chronic rhinosinusitis with nasal polyps is an inflammatory condition involving the paranasal sinuses and linings of the nasal passages, which persists for 12 weeks or longer, and affects approximately 2-4% of the population. Symptoms include mucopurulent drainage, nasal obstruction, facial pain/pressure/fullness and decreased sense of smell. CRSwNP cannot be cured in most patients and therapy is intended to reduce symptoms and improve quality of life. Standard treatment includes therapies to minimize inflammation such as intranasal corticosteroids and antileukotriene agents. If intranasal and oral corticosteroids fail to reduce polyp tissue sufficiently and the patient has persistent blockage, sinus surgery or therapy with a biologic recommended. Mepolizumab binds to IL-5, inhibiting the production of eosinophils, thereby reducing inflammation.

Tezepelumab is a human monoclonal antibody that acts at the top of the inflammatory cascade by specifically binding TSLP, blocking TSLP from interacting with its receptor. Blocking TSLP with tezepelumab reduces downstream markers of inflammation, including blood EOS, immunoglobulin E (IgE), fractional exhaled nitric oxide (FeNO), interleukin 5 (IL-5), and interleukin 13 (IL-13). Unlike other FDA-approved biologic therapies for severe asthma that target downstream inflammatory pathways and are indicated for specific patient phenotypes, because of its upstream activity early in the inflammatory cascade, tezepelumab is suitable for a broad spectrum of severe asthma patients irrespective of asthma phenotype.

Clinical Evidence

Allergic Asthma

Omalizumab is indicated for treatment of adults and adolescents 6 years of age and older, who have moderate to severe persistent asthma and a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.3

Deschildre et al. evaluated omalizumab efficacy and safety in a real-life setting in children aged 6 to 18 years (n = 104) with severe asthmas followed up in pediatric pulmonary tertiary care centers.28 Asthma control levels, exacerbations, inhaled corticosteroid dose, lung function and adverse events were evaluated over 1 year. Children were characterized by allergic sensitization to three or more allergens (66%), high IgE levels (mean 1125 kU L(-1)), high rate of exacerbations (4.4 per year) and healthcare use during the previous year, and high inhaled corticosteroid dose (mean 703 µg equivalent fluticasone per day). Asthma control levels defined as good, partial, or poor, improved from 0%, 18% and 82% at entry to 53%, 30% and 17% at week 20, and to 67%, 25% and 8% at week 52, respectively ($p < 0.0001$). Reported exacerbation and hospitalization rates decreased by 72% and 88.5%, respectively. At 12 months, forced expiratory volume in 1 s (FEV1) improved by 4.9% ($p = 0.023$), and inhaled corticosteroid dose decreased by 30% ($p < 0.001$). Six patients stopped omalizumab for related significant adverse events. Omalizumab improved asthma control in children with severe allergic asthma and was generally well tolerated. Authors concluded that he observed benefit was greater than that reported in clinical trials.

Sorkness et al conducted a post-hoc analyses which examined patient characteristics of those eligible and ineligible for omalizumab; described onset of effect after initiation of omalizumab and offset of treatment effect after stopping therapy; and determined whether the efficacy differs by age, asthma severity, dosing regimen, and pre-specified biomarkers.27 Inner-city children and adolescents with persistent allergic asthma enrolled in the Inner-City Anti-IgE Therapy for Asthma (ICATA) trial that compared omalizumab with placebo added to guidelines-based therapy for 60 weeks were eligible for the evaluation (a significant portion of children and adolescents particularly suited for omalizumab because of asthma severity status were ineligible due to IgE > 1300 IU/mL). Two hundred ninety-three of 889 participants (33%) clinically suitable for omalizumab were ineligible for dosing according to a modified dosing table specifying IgE level and body weight criteria. Baseline symptoms were comparable among those eligible and ineligible to receive omalizumab, but other characteristics (rate of health care utilization and skin test results) differed. Patients receiving biweekly injections experienced a greater reduction in both exacerbations (OR = 2.54) and inhaled corticosteroids (ICS) usage (−204.8 µg/day) compared to patients receiving monthly injections (1.42 and −50.2 µg/day; $p = 0.08$ and $p = 0.02$, respectively). Omalizumab efficacy for symptom days per 2 weeks did not differ by dosing regimen ($p = 0.62$). Patients with total IgE ≥ 700 IU/mL had the greatest reduction in ICS usage (−504.6 µg/day) because of treatment with omalizumab. The time of onset of omalizumab effect was < 30 days and time of offset was between 30 and 120 days. No difference in efficacy was

noted by age or asthma severity, but high exhaled nitric oxide, blood eosinophils, and body mass index predicted efficacy. Researchers concluded that results of this analysis showed that efficacy for exacerbations and ICS treatment was comparable in children 6 to 12 years of age compared with older children (> 12 years). Additionally, the data suggested that omalizumab may be efficacious in both severe disease (steps 5-6 treatments) and more moderate disease (steps 1-4). Certain subgroups of persons, for example, those with higher exhaled nitric oxide, blood eosinophils, and BMI were more likely to benefit from omalizumab according to the secondary analysis.

The Inner-City Anti-IgE Therapy for Asthma (ICATA) Study was a 60-week, randomized, double-blind, placebo-controlled, parallel-group trial (n = 419) which evaluated the effectiveness of omalizumab (75 to 375 mg subcutaneously every 2 to 4 weeks), as compared with placebo, when added to guidelines-based therapy.21 The primary outcome was reduction in symptoms and exacerbations of asthma. Inner-city patients 6 to 20 years of age with persistent asthma (receiving long-term therapy for disease control and having symptoms of persistent asthma or evidence of uncontrolled disease as indicated by hospitalization or unscheduled urgent care in the 6 to 12 months preceding study entry), at least one positive skin test for a perennial allergen, weight between 20 and 150 kg, and having total serum levels of IgE between 30 and 1300 IU per milliliter were eligible for enrollment. Additionally, patients not receiving long-term control therapy were eligible for enrollment only if they had both persistent symptoms and uncontrolled asthma. The primary outcome defined as reduction in symptoms (number of days with symptoms during the previous two weeks) and exacerbations of asthma was evaluated every 4 weeks. Omalizumab as compared with placebo significantly reduced the number of days with asthma symptoms, from 1.96 to 1.48 days per 2-week interval, a 24.5% decrease ($p < 0.001$). Similarly, the percentage of participants with exacerbations (one or more) during the study was 48.8% in the placebo group as compared with 30.3% in the omalizumab group ($p < 0.001$), and the percentage who were hospitalized because of asthma was 6.3% as compared with 1.5%, respectively ($p = 0.02$). Improvements occurred with omalizumab despite reductions in the use of inhaled glucocorticoids and long-acting beta-agonists.

In a further pre-specified, subgroup [Lanier 2009] analysis, Kulus et al. evaluated efficacy and safety of omalizumab as compared to placebo in children (n = 235) with severe, persistent allergic asthma.24 Over the 24-week fixed-steroid phase, omalizumab reduced the rate of clinically significant asthma exacerbations (worsening symptoms requiring doubling of baseline inhaled corticosteroid dose and/or systemic steroids) by 34% versus placebo (0.42 vs 0.63, $p = 0.047$). Over 52 weeks, the exacerbation rate was reduced by 50% ($p < 0.001$). The overall incidence of adverse events (AEs) was similar in both omalizumab and placebo groups (93.4% vs 95.0%, $p = 0.779$), serious AEs were less frequent in the omalizumab group (3.6% vs 10.0%, $p = 0.073$), and no new safety concerns were evident. Researchers noted that the sample size was not based on providing statistical power in the severe subgroup, and no corrections were made for multiple comparisons; however, outcomes consistently favored omalizumab.
Milgrom et al. evaluated the safety of omalizumab in children (n = 926) ages 6 to 12 with allergic (IgE-mediated) asthma in a pooled analysis of two double-blind, placebo-controlled studies [Milgrom 2001 and Lanier 2009].22 Children on optimized asthma care were randomized (2:1) to omalizumab (75-375 mg every 2 or 4 weeks) or placebo. Adverse events (AEs) were more frequently reported in the placebo (91.7%) than omalizumab (89.7%) group. The most common AEs were nasopharyngitis, upper respiratory

tract infection and headache. Suspected treatment-related AEs included headache, erythema and urticaria; none of which were reported by ≥ 2% of patients receiving omalizumab. Serious adverse effects were reported by 3.4% and 6.6% of patients receiving omalizumab and placebo, respectively; the most common were appendicitis, pneumonia, and bronchitis; no deaths were reported.

Allergic Asthma with IgE Levels > 700 IU/ml

A retrospective study evaluated the response of asthmatic patients treated with omalizumab with IgE levels greater than 700 IU/mL.29 Emergency department (ED) visits, hospitalizations, change in forced expiratory volume in 1 second (FEV1), corticosteroid bursts, and Asthma Control Test (ACT) scores were recorded for a period of 6 months before and after treatment with omalizumab in patients with elevated IgE levels or treatment length of ≥ 6 months. Twenty-six patients with an IgE level > 700 IU/mL (group 1) were matched by age, sex, and severity of asthma to patients with an IgE of 30 to 700 IU/mL (group 2). The mean numbers of ED visits before and after treatment was 0.96 vs 0.23 ($p = 0.008$) in group 1 and 0.65 vs 0.15 ($p = 0.02$) in group 2. Both groups had an improvement in asthma control based on the mean ACT score before and after treatment (15.6 vs 18.9 [$p = 0.02$] and 15.4 vs 19 [$p = 0.006$], respectively). Additionally, there was a significant reduction in the frequency of systemic corticosteroid use during the 6 months before and after treatment (2.58 vs 0.96 [$p < 0.001$] and 2.62 vs 1.23 [$p < 0.001$] systemic steroid treatments, respectively). Researchers concluded that omalizumab was just as effective in reducing ED visits, controlling asthma symptoms, and reducing the need for systemic corticosteroids in patients with IgE levels > 700 IU/mL compared with patients with levels within 30 to 700 IU/mL.

A multicenter, randomized, double-blind, parallel-group, placebo-controlled study evaluated use of high dose omalizumab in adult patients with IgE levels > 700 IU/ml.25 Fifty asthmatic patients (pre-bronchodilator forced expiratory volume in 1 second (FEV1) ≥ 65% predicted; had been asthma exacerbation-free for ≥ 4 weeks; and skin reactivity to a specific allergen within 2 years before screening) with an age range of 18 to 65 years and a body weight range of 40 to 150 kg were divided into two groups according to IgE levels (group 1: 30-300 IU/ml and group 2: 700-2000 IU/ml) and randomized 2:1 to receive either omalizumab or placebo every 2 or 4 weeks. Allergen bronchoprovocation (ABP) testing was performed at baseline, week 8 and week 16. The primary efficacy endpoint measured was the early-phase allergic response (EAR; defined as the maximum percentage drop in forced expiratory volume in 1 second during the first 30 minute after ABP). Secondary outcome evaluated with the late-phase allergic response (LAR; defined as maximum percentage drop in FEV1 over 3-8 hours after ABP). Additional outcomes assessed included serum free IgE (as a pharmacodynamic endpoint) and the exhaled fractional concentration of nitric oxide (FENO; as an exploratory endpoint). At week 8, EAR was 23.1% for placebo and treatment with omalizumab reduced it to 9.3% in in group 1 ($p = 0.018$ vs placebo) and 5.6% in group 2 ($p < 0.001$ vs placebo). Additionally, at week 16, reported EAR was 20%, 11.8% ($p = 0.087$) and 5.1% ($p < 0.001$), respectively. LAR analysis was not performed due to the small number of patients studied. Serum free IgE levels decreased in groups 1 and 2 and remained < 50 ng/ml in all patients during weeks 6-16. Treatment with omalizumab suppressed FENO increases after ABP in both groups. Authors conclude that the outcomes of this study demonstrated that the protective effects of omalizumab against allergen-induced bronchoconstriction in patients with allergic asthma and baseline IgE up to 2000 IU/ml.

Researchers conducted a post-marketing observational surveillance trial to evaluate the efficacy and tolerability of omalizumab in a real-life setting in Spain, particularly in those patients with immunoglobulin E (IgE) levels out of range.26 Patients were recruited if they had a diagnosis of uncontrolled severe, persistent, allergic asthma while on high-dose inhaled corticosteroids (ICSs) plus long-acting β2-agonist (LABA); had an age ≥ 12 years; and had received at least one dose of omalizumab between May 2006 and November 2009, Main efficacy outcomes evaluated included asthma exacerbation rate (AER), asthma control test (ACT), and global evaluation of treatment effectiveness (GETE). Of the 266 patients enrolled, 7 patients had IgE levels < 30 IU/mL, and 46 patients has IgE levels > 700 IU/ml. Average AER reported for all groups showed a reduction from 3.6 in previous year to 0.67 at 4 months ($p < 0.05$) and to 1.04 at 2

years ($p < 0.05$). Average ACT increased from 14.3 at baseline to 18.4 at 4 months ($p < 0.05$) and to 20.3 $p < 0.05$) at 2 years. After 4 months, 74.6% of patients had reached a good or excellent rate on the GETE scale ($p < 0.05$) and this rate continued to increase to 81.6% at 2 years. Similarly, in the IgE > 700 IU/ml group, researchers reported an increased ACT from 13.6 at baseline to 20.9 at the 2-year visit ($p < 0.05$) and a decrease in exacerbations from 3.58 at baseline to 0.72 at the 2-year visit ($p < 0.05$). At follow-up, maintenance treatment with oral steroids was reduced from 89 patients to 19 patients ($p < 0.05$). Omalizumab was discontinued because of lack of efficacy in 28/266 (10.5%) patients and 30 patients (11.4%) reported adverse events (none were severe). Researchers conclude that this observational study confirms that omalizumab is efficacious and well tolerated in patients with uncontrolled severe asthma, including those patients with IgE levels > 700 IU/ml.

Chronic Urticaria

Omalizumab is indicated for treatment of chronic idiopathic urticaria in adults and adolescents (12 years of age and above) who remain symptomatic despite H1 antihistamine treatment.3

Saini et al conducted a 40-week, randomized, double-blind, placebo-controlled trial (ASTERIA I) to evaluate the efficacy and safety of subcutaneous omalizumab as add-on therapy for 24 weeks in patients (n = 319) with chronic idiopathic urticaria/spontaneous urticaria (CIU/CSU) who remained symptomatic despite H1 antihistamine treatment.1 Eligible patients aged 12 to 75 years with CIU/CSU who remained symptomatic despite treatment with approved doses of H1 antihistamines were randomized (1:1:1:1) in a double-blind manner to subcutaneous omalizumab 75 mg (n = 78), 150 mg (n = 80), or 300 mg (n = 81) or placebo (n = 80) every 4 weeks for 24 weeks followed by 16 weeks of follow-up. The primary outcome measured was change from baseline in weekly itch severity score (ISS) at week 12. Secondary outcomes evaluated at week 12, included changes from baseline in UAS7 and weekly number of hives score; time to MID response (≥ 5-point decrease) in weekly ISS; the proportion of patients with UAS7 ≤ 6; the proportion of weekly ISS MID responders; changes from baseline in weekly size of largest hive score and overall DLQI score; the proportion of angioedema-free days during weeks 4 to 12; and the proportion of patients with complete response (UAS7 = 0). Compared with placebo mean weekly ISS was reduced from baseline to week 12 by an additional 2.96 points (95% confidence interval (CI): −4.71 to −1.21; $p = 0.0010$), 2.95 points (95% CI: −4.72 to −1.18; $p = 0.0012$), and 5.80 points (95% CI: −7.49 to −4.10; $p < 0.0001$) in the omalizumab 75-mg, 150-mg, and 300-mg groups, respectively. The omalizumab 300-mg group met all nine secondary end points, including a significant decrease in the duration of time to reach minimally important difference response (≥ 5-point decrease) in weekly ISS ($p < 0.0001$) and higher percentages of patients with well-controlled symptoms (urticaria activity score over 7 days (UAS7) ≤ 6: 51.9% vs. 11.3% $p < 0.0001$) and complete response (UAS7 = 0: 35.8% vs. 8.8% $p < 0.0001$) versus placebo. During the 24-week treatment period, the proportions of patients who experienced one or more treatment-emergent adverse events (AEs) ranged from 57 to 69% in the omalizumab groups versus 51% in the placebo group. Additionally, 2 (2.9%), 3 (3.4%), 0, and 4 (5.0%) patients in the omalizumab 75-mg, 150-mg, 300-mg, and placebo groups, respectively, experienced a serious adverse event. Omalizumab 300 mg administered every 4 weeks reduced weekly ISS and other symptom scores versus placebo in CIU/CSU patients who remained symptomatic despite treatment with approved doses of H1 antihistamines. Additionally, the results of this study showed a sustained treatment effect of omalizumab 300 mg for up to 24 weeks on CIU/CSU symptom scores in patients with H1 antihistamine-refractory CIU/CSU. The safety profile for omalizumab over 24 weeks of treatment in patients with CIU/CSU receiving approved doses of H1 antihistamines was consistent with the established safety profile in allergic asthma and with previous observations in CIU/CSU.

Nasal Polyps

Omalizumab is indicated for nasal polyps in adult patients 18 years of age and older with inadequate response to nasal corticosteroids, as add-on maintenance treatment.

The safety and efficacy of omalizumab was evaluated in two, randomized, multicenter, double-blind, placebo-controlled clinical trials that enrolled patients with nasal polyps with inadequate response to nasal corticosteroids (Nasal Polyps Trial 1, n = 138; Nasal Polyps Trial 2, n = 127). Patients received omalizumab or placebo subcutaneously every 2 or 4 weeks, for 24 weeks followed by a 4-week follow-up period. All patients received background nasal mometasone therapy during both the treatment period and during a 5-week run-in period. Prior to randomization, patients were required to have evidence of bilateral polyps as determined by a nasal polyp score (NPS) ≥ 5 with NPS ≥ 2 in each nostril, despite use of nasal mometasone during the run-in period. NPS was measured via endoscopy and scored (range 0 to 4 per nostril: 0 = no polyps; 1 = small polyps in the middle meatus not reaching below the inferior border of the middle turbinate; 2 = polyps reaching below the lower border of the middle turbinate; 3 = large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate; 4 = large polyps causing complete obstruction of the inferior nasal cavity) for a total NPS (range 0 to 8). Patients were furthermore required to have a weekly average of nasal congestion score (NCS) > 1 prior to randomization, despite use of nasal mometasone. Nasal congestion was measured by a daily assessment on a 0 to 3-point severity scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Prior sino-nasal surgery or prior systemic corticosteroid usage were not required for inclusion in the trials and sinus CT scans were not performed to evaluate for sinus opacification.

The co-primary endpoints in Trials 1 and 2 were NPS and average daily NCS at Week 24. In both trials, patients who received omalizumab had a statistically significant greater improvement from baseline at Week 24 in NPS and weekly average NCS, than patients who received placebo. The greater improvements in NPS and NCS in the omalizumab group compared to the placebo group were observed as early as the first assessment at Week 4 in both studies.

Omalizumab had statistically significant improvements on sense of smell score compared to placebo. Sense of smell was measured by a daily assessment on a 0 to 3-point severity scale (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = severe symptoms). The LS mean difference for change from baseline at Week 24 in sense of smell score in omalizumab compared to placebo was -0.3 (95% CI: -0.6, -0.1) in Trial 1 and -0.5 (95% CI: -0.7, -0.2) in Trial 2. Omalizumab had statistically significant improvements on post-nasal drip compared to placebo. The LS mean difference for change from baseline at Week 24 in post-nasal drip score in omalizumab compared to placebo was -0.6 (95% CI: -0.8, -0.3) in Trial 1 and -0.5 (95% CI: - 0.8, -0.3) in Trial 2. Omalizumab had statistically significant improvements on runny nose compared to placebo. The LS mean difference for change from baseline at Week 24 in runny nose score in omalizumab compared to placebo was -0.4 (95% CI: -0.7, -0.2) in Trial 1 and -0.6 (95% CI: - 0.9, -0.4) in Trial 2. In a pre-specified pooled analysis of systemic corticosteroid use during the 24-week treatment period, there was no significant reduction in systemic corticosteroid use between the treatment arms. The proportion of patients taking systemic corticosteroid in omalizumab was 2.3% compared to 6.2% in placebo. The odds-ratio of systemic corticosteroid use with omalizumab compared to placebo was 0.4 (95% CI: 0.1, 1.5). There were no sino-nasal surgeries reported, in either placebo or omalizumab arms, in either trial.

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

Mepolizumab is indicated for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA). In a post hoc analysis of the phase III clinical trial, Steinfeld et al, investigated the clinical benefit of mepolizumab in patients with EGPA that factors in remission, oral glucocorticoid (OGC) dose reduction, and EGPA relapses.14 The post hoc clinical benefit was defined as: remission at any time (2 definitions used), 50% or greater OGC dose reduction during weeks 48 to 52, or no EGPA relapses. The 2 remission definitions were Birmingham Vasculitis Activity Score of 0 plus OGC dose of 4 mg/d or less (remission 1/clinical benefit 1) or 7.5 mg/d or

less (remission 2/clinical benefit 2). Clinical benefit was assessed in all patients and among subgroups with a baseline blood eosinophil count of less than 150 cells/µL, baseline OGC dosage of greater than 20 mg/d, or weight of greater than 85 kg. With mepolizumab versus placebo, 78% versus 32% of patients experienced clinical benefit 1, and 87% versus 53% of patients experienced clinical benefit 2 (both $p < .001$). Significantly more patients experienced clinical benefit 1 with mepolizumab versus placebo in the blood eosinophil count less than 150 cells/µL subgroup (72% vs 43%, $p = .033$) and weight greater than 85 kg subgroup (68% vs 23%, $p = .005$); in the OGC greater than 20 mg/d subgroup, results were not significant but favored mepolizumab (60% vs 36%, $p = .395$). The authors concluded that the majority of patients with EGPA experienced benefit with mepolizumab.

In a multicenter, double-blind, parallel-group, phase 3 trial, Wechsler et al, evaluated the efficacy and safety mepolizumab versus placebo for eosinophilic granulomatosis with polyangiitis (EGPA).13 Patients with relapsing or refractory EGPA were randomly assigned to receive 300 mg of mepolizumab (n = 68) or placebo (n = 68) subcutaneously every 4 weeks, plus standard care, for 52 weeks. Patients had to have received treatment for at least 4 weeks and were taking stable corticosteroid dosing for at least 4 weeks. The two primary end points were the accrued weeks of remission over the 52 week period, and the proportion of participants in remission at both week 36 and week 48. Secondary endpoints included: time to first relapse and average daily glucocorticoid use at weeks 48 through 52). Patients receiving mepolizumab had significantly more accrued weeks of remission than placebo (28% vs. 3% had 24 weeks of accrued remission; odds ratio, 5.91; 95% confidence interval [CI], 2.68 to 13.03; $p < 0.001$) and a higher percentage of patients were in remission at both week 36 and week 48 (32% vs. 3%; odds ratio, 16.74; 95% CI, 3.61 to 77.56; $p < 0.001$). Remission did not occur in 47% of the patients in the mepolizumab group versus 81% of those in the placebo group. The annualized relapse rate was 1.14 in the mepolizumab group, as compared with 2.27 in the placebo group (rate ratio, 0.50; 95% CI, 0.36 to 0.70; $p < 0.001$). A total of 44% of the patients in the mepolizumab group, as compared with 7% of those in the placebo group, had an average daily dose of prednisolone or prednisone of 4.0 mg or less per day during weeks 48 through 52 (odds ratio, 0.20; 95% CI, 0.09 to 0.41; $p < 0.001$). The authors concluded that in patients with EGPA, mepolizumab resulted in significantly more weeks in remission and a higher proportion of patients in remission than placebo, although only half of the patients treated with mepolizumab had protocol-defined remission.

Severe Eosinophilic Asthma

Benralizumab is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.10

Mepolizumab is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.1

Reslizumab is indicated for the add-on maintenance treatment of patients with severe asthma aged 18 years and older, and with an eosinophilic phenotype.2

Hypereosinophilic Syndrome

Mepolizumab is indicated for 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.

In a multicenter, randomized, placebo-controlled, 32-week treatment trial. Patients with non-hematologic secondary HES (e.g., drug hypersensitivity, parasitic helminth infection, HIV infection, non-hematologic malignancy) or FIP1L1-PDGFRα kinase-positive HES were excluded from the trial. Patients received 300 mg of Nucala (n = 54) or placebo (n = 54) subcutaneously once every 4 weeks. Patients were required to have been on a stable dose of background HES therapy (oral corticosteroids, immunosuppressive, or cytotoxic therapy) for 4 weeks prior to randomization and continue their therapy throughout the trial. Patients entering the trial had experienced at least 2 HES flares within the past 12 months and blood eosinophil count of 1,000 cells/mcL or higher during screening. The primary endpoint was percentage of patients who experienced ≥ 1 HES flare during the 32-week treatment period or who withdrew from the study. A HES flare was defined as a HES related clinical manifestation based on a physician-documented change in clinical signs or symptoms which resulted in need for an increase in the maintenance oral corticosteroid dose by at least 10 mg per day for 5 days or an increase in or addition of any cytotoxic or immunosuppressive HES therapy. HES flare was also defined as receipt of two or more courses of blinded active oral corticosteroid during the treatment period. The secondary endpoints included time to first flare, proportion of patients who experienced flares during Week 20 to Week 32, and number of HES flares per participant per year. Over the 32-week treatment period, the incidence of HES flare was 56% for the placebo group and 28% for the Nucala group (odds ratio, 0.28; 95% CI 0.12 to 0.64; p = 0.002). The risk of first HES flare over the treatment period was 66% lower for patients treated with Nucala compared to placebo (hazard ratio: 0.34; 95% CI 0.18 to 0.72; p = 0.002). From Week 20 through Week 32, significantly fewer patients experienced a HES flare or withdrew from the trial when treated with Nucala compared with placebo (17% versus 35%, respectively; p = 0.02; odds ratio, 0.33; 95% CI: 0.13 to 0.85). Patients who received Nucala experienced significantly fewer HES flares during a 32-week treatment period compared with the placebo group (rate ratio, 0.35; 95% CI 0.19 to 0.63; Wilcoxon p value (unadjusted/adjusted) 0.002/0.02).1

Chronic Rhinosinusitis with Nasal Polyps

Mepolizumab is indicated for add-on maintenance treatment of adult patients 18 years and older with chronic rhinosinusitis with nasal polyps (CRSwNP) and an inadequate response to nasal corticosteroids.

A total of 407 adult patients with CRSwNP were evaluated in a randomized, double-blind, placebo-controlled, multicenter, 52-week trial (NCT03085797). Patients received NUCALA 100 mg or placebo administered subcutaneously once every 4 weeks while continuing nasal corticosteroid therapy. Patients must have received background nasal corticosteroid for = 8 weeks pre-screening. Patients had recurrent and symptomatic CRSwNP and had at least 1 surgery for the removal of nasal polyps within the previous 10 years. Patients were required to have nasal obstruction symptoms with a visual analog scale (VAS) score of > 5 out of a maximum score of 10. Patients were also required to have an endoscopic bilateral nasal polyp score (NPS) of = 5 out of 8 with NPS = 2 in each nasal cavity. Patients reported nasal obstruction VAS scores daily by placing a single mark on a continuous line labeled from 0 (none) to 100 (as bad as you can imagine). The distance along the line was converted to a 0 to 10 point scale for scoring. For NPS, polyps on each side of the nose were graded on a categorical scale (0 = no polyps, 1 = small polyps in the middle meatus not reaching below the inferior border of the middle concha, 2 = polyps reaching below the lower border of the middle turbinate, 3 = large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle concha, 4 = large polyps causing almost complete congestion/obstruction of the inferior meatus) for a total score of 0 to 8. Sinus CT scans were not performed at baseline nor during treatment to evaluate for sinus opacification.

The co-primary endpoints were change from baseline to Week 52 in total endoscopic NPS (0 to 8 scale) as graded by independent blinded assessors and change from baseline in nasal obstruction VAS score (0 to 10 scale) during Weeks 49 to 52. The key secondary endpoint was the time to first nasal surgery (nasal polypectomy) up to Week 52 in this trial. Other secondary endpoints were change from baseline in loss of smell VAS score during Weeks 49 to 52, and proportion of patients requiring systemic steroids for nasal

polyps up to Week 52. All VAS scores were collected daily by the patients and reported on a 0 to 10 scale (0 = none, 10 = as bad as you can imagine).
Patients who received NUCALA 100 mg had a statistically significant improvement (decrease) in bilateral NPS at Week 52 and nasal obstruction VAS score from Weeks 49 to 52 at the end of the 52 week treatment period. The key secondary endpoint was the time to first nasal surgery (nasal polypectomy) up to Week 52. The proportion of patients who had surgery was significantly reduced by 57% (hazard ratio: 0.43, 95% CI: 0.25, 0.76) in the group treated with NUCALA 100 mg compared with the placebo group. By Week 52, 18 (9%) patients who received NUCALA 100 mg had surgery compared with 46 (23%) patients in the placebo group. For patients who received NUCALA 100 mg, statistically significant improvement was observed in loss of smell compared to placebo and improvements were also observed in the individual VAS symptom scores compared with patients in the placebo group in the 4-weeks prior to the end of the 52-week treatment period. Treatment with NUCALA 100 mg significantly reduced the need for systemic steroids for nasal polyps vs. placebo up to Week 52 (odds ratio: 0.58, 95% CI: 0.36, 0.92). In patients who received NUCALA 100 mg, 52 (25%) required = 1 course of systemic steroids compared with 74 (37%) in the placebo group throughout the 52-week treatment period.

Tezepelumab is indicated for the add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma.

The efficacy of tezepelumab was established in two randomized, double-blind, placebo-controlled studies in 1,609 patients 12 years of age and older with severe asthma. PATHWAY was a 52-week dose-ranging study in which patients received tezepelumab-ekko 70 mg every 4 weeks, Tezspire 210 mg every 4 weeks, tezepelumab-ekko 280 mg every 2 weeks, or placebo. NAVIGATOR was a 52-week study in which patients received Tezepelumab 210 mg every 4 weeks or placebo. The primary endpoint in both studies was the rate of clinically significant asthma exacerbations measured over 52 weeks. Asthma exacerbations were defined as worsening of asthma requiring the use of or increase in oral or injectable corticosteroids for at least 3 days, or a single depo-injection of corticosteroids, and/or emergency department visits requiring use of oral or injectable corticosteroids and/or hospitalization. In PATHWAY, the annualized rate of asthma exacerbations was 0.20 with tezepelumab vs. 0.72 with placebo (rate ratio 0.29, 95% CI: 0.16, 0.51). In NAVIGATOR, the annualized rate of asthma exacerbations was 0.93 with tezepelumab vs. 2.10 with placebo (rate ratio 0.44, 95% CI: 0.37, 0.53). In NAVIGATOR, patients receiving tezepelumab experienced fewer exacerbations than those receiving placebo regardless of baseline levels of blood eosinophils or fractional exhaled nitric oxide (FeNO). Similar results were seen in PATHWAY.

Tezepelumab was also evaluated in a randomized, double-blind, placebo-controlled clinical study in 150 adult patients with severe asthma requiring treatment with daily oral corticosteroids (OCS). Patients received tezepelumab 210 mg every 4 weeks or placebo. The primary endpoint was categorized percent reduction from baseline of the final OCS dose at week 48 (≤ 90% reduction, < 75% to < 90% reduction, ≥ 50% to < 75% reduction, > 0% to < 50% reduction, and no change or no decrease in OCS), while maintaining asthma control. Tezspire did not demonstrate a statistically significant reduction in maintenance OCS dose vs. placebo (cumulative odds ratio 1.28, 95% CI: 0.69, 2.35)

Professional Societies

Allergic Asthma

The Global Initiative for Asthma (GINA, 2023) defines uncontrolled, difficult-to-treat and severe asthma as follows:

- Uncontrolled asthma is asthma with poor symptom control (frequent symptoms or reliever use, activity limited by asthma, night waking due to asthma) and/or frequent exacerbations (≥ 2/year) requiring OCS, or serious exacerbations (≥ 1/year) requiring hospitalization.
- Difficult-to-treat asthma is asthma that is uncontrolled despite prescribing of medium- or high-dose ICS with a second controller (usually a LABA) or maintenance OCS, or that requires high-dose treatment to maintain good symptom control and reduce the risk of exacerbations.
- Severe asthma is asthma that is uncontrolled despite adherence with maximal optimized high-dose ICS-LABA treatment and management of contributory factors, or that worsens when high-dose treatment is decreased. Asthma is not classified as severe if it markedly improves when contributory factors such as inhaler technique and adherence are addressed.

The Global Initiative for Asthma (GINA, 2023) recommends add-on biologic therapy for treatment of adults, adolescents and children with uncontrolled severe asthma despite optimized maximal therapy as follows:

- Add-on anti-immunoglobulin E (anti-IgE) treatment (omalizumab) for patients aged ≥ 6 years) with severe allergic asthma (Evidence A).
- Add-on anti-interleukin 5/5R treatment (subcutaneous mepolizumab for patients aged ≥ 6 years; intravenous reslizumab for ages ≥ 18 years; subcutaneous benralizumab for ages ≥ 12 years) with severe eosinophilic asthma (Evidence A).
- Add-on anti-interleukin-4R α treatment (subcutaneous dupilumab) for patients aged ≥ 6 years with severe eosinophilic/Type 2 asthma, or for adults or adolescents requiring treatment with maintenance OCS (Evidence A).
- Add-on anti-thymic stromal lymphopoietin (anti-TSLP) treatment (subcutaneous tezepelumab for patients aged ≥ 12 years with severe asthma (Evidence A).

The Global Initiative for Asthma (GINA, 2023) recommends that low dose oral corticosteroids (≤ 7.5 mg/day prednisone equivalent) should only be considered as last resort in adult patients with severe asthma with poor symptom control and/or frequent exacerbations despite good inhaler technique and adherence with Step 5 treatment, and after exclusion of other contributory factors and other add-on treatments including biologics where available and affordable. (Evidence D). Oral corticosteroids are often associated with substantial side effects (Evidence A).

The first European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines on severe asthma were published in 2014.31 Severe asthma was defined as that which requires treatment with high-dose ICSs plus a second controller (or systemic corticosteroids) to prevent progression to uncontrolled disease status or continuing uncontrolled disease status despite this therapy.3 Emphasis was placed on the necessity to confirm the diagnosis of asthma and exclude other conditions that may mimic asthma. In addition, the guidelines recognized that severe asthma is a heterogeneous condition consisting of phenotypes such as severe eosinophilic asthma, and specific recommendations were made on the use of sputum eosinophil count and exhaled nitric oxide fraction (FENO) to guide therapy. Recommendations were also made for the use of methotrexate, macrolide antibiotics, antifungal agents, bronchial thermoplasty and the anti-IgE antibody omalizumab in severe asthma.

In 2020, the European Respiratory Society (ERS)/American Thoracic Society (ATS) published updated guidelines for the management of asthma.33 Six specific and important questions were formulated using the PICO (Patient population, Intervention, Comparison and Outcome) format. The GRADE (Grading of

Recommendations, Assessment, Development and Evaluation) approach was used to assess the strength of evidence and develop recommendations. These recommendations are summarized below:

- An anti-interleukin (IL)-5 and anti-IL-5 receptor α for severe uncontrolled adult eosinophilic asthma phenotypes.
- A blood eosinophil cut-point ≥ 150 µL-1 to guide anti-IL-5 initiation in adult patients with severe asthma.
- Specific eosinophil (≥ 260 µL-1) and exhaled nitric oxide fraction (≥ 19.5 ppb) cut-offs to identify adolescents or adults with the greatest likelihood of response to anti-IgE therapy.
- Inhaled tiotropium for adolescents and adults with severe uncontrolled asthma despite Global Initiative for Asthma (GINA) step 4-5 or National Asthma Education and Prevention Program (NAEPP) step 5 therapies.
- A trial of chronic macrolide therapy to reduce asthma exacerbations in persistently symptomatic or uncontrolled patients on GINA step 5 or NAEPP step 5 therapies, irrespective of asthma phenotype.
- Anti-IL-4/13 for adult patients with severe eosinophilic asthma and for those with severe corticosteroid-dependent asthma regardless of blood eosinophil levels.

Nasal Polyps

In 2023, the Joint Task Force on Practice Parmeters (JTFPP) published GRADE guidelines for the medical management of chronic rhinosinusitis with nasal polyposis.34 The guideline panel used the Grading of Recommendations Assessment, Development and Evaluation approach to inform and develop recommendations. The task force recommended the use of biologics rather than no biologics (conditional recommendation based on moderate certainty of evidence) in the following patients:

• For patients using inhaled corticosteroid (INCS for at least 4 weeks and who continue to have high disease burden, biologics may be preferred over other medical treatment choices.

• For patients who have higher disease severity at presentation, biologics may be preferred over other medical treatment choices.

• There is variability in efficacy among the biologics and this may influence the overall choice. Dupilumab and omalizumab are the most beneficial for most patient-important outcomes when comparing with other biologics.

• Patients with comorbid diseases that led to a dual indication for biologic treatment (e.g., asthma) may be a reason to choose biologics in general and even specific biologics.

Chronic Urticaria

In 2014, the Joint Task Force on Practice Parameters (JTFPP), representing the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology updated the practice parameter for the diagnosis and management of acute and chronic urticaria (CU). The practice parameter established a step-care approach to the treatment of chronic urticaria and angioedema. The task force recommended the following step-care treatment approach:20

- Monotherapy with second-generation antihistamines: H1-antagonists are effective in the majority of patients with CU but might not achieve complete control in all patients.
- Dose advancement of H1-antihistamine therapy, combining first- and second-generation agents and adding an H2-antihistamine and/or an antileukotriene agent: Higher doses of second-generation antihistamines can provide greater efficacy when control is not achieved with conventional doses of these agents.
- Therapeutic trial of potent antihistamine (e.g., hydroxyzine or doxepin): First-generation antihistamines should be prescribed cautiously in the elderly or patients with occupations (e.g., machine operators, airline pilots, or alpine skiers) for which alertness is essential.

- Add an immunosuppressant or biologic agent: Omalizumab and cyclosporine have the greatest published experience documenting efficacy in patients with CU compared with all other alternative agents.

Institute for Clinical and Economic Review (ICER)

On March 14, 2016, the Institute for Clinical and Economic Review (ICER) released a clinical report entitled, "Mepolizumab (Nucala®, GlaxoSmithKline plc.) for the Treatment of Severe Asthma with Eosinophilia: Effectiveness, Value, and Value-Based Price Benchmarks." ICER recommendations are as follows: 4

- ICER judges the current body of evidence on mepolizumab to be "comparable or better."
- For adult patients with severe eosinophilic asthma, ICER judges there to be moderate certainty of a comparable or better net benefit for mepolizumab 100mg SC every four weeks as add-on maintenance treatment compared with standard of care including high dose ICS, LABA, and additional controller medications. There is moderate certainty because both the MENSA trial, which demonstrated a significant reduction in asthma exacerbations, and the SIRIUS trial, which demonstrated a significant reduction in oral corticosteroids dosage, were relatively small studies of short duration. There remains uncertainty about the long-term durability of the benefits of the therapy and about the potential harms from modulation of the immune system. Ongoing post-marketing trials and extension studies evaluating mepolizumab may demonstrate a wide variety of outcomes, from substantial net health benefit to a comparable net benefit given the potential harms associated with the monoclonal antibody (opportunist infection, anaphylaxis).

HCPCS Codes

HCPCS Code	Description	Availability	Route
J2357	Omalizumab (Xolair), 5 mg	75 mg/150 mg/300 mg single dose prefilled syringe/autoinjector 150 mg single dose vial	SQ*
J2786	Cinqair (Reslizumab), 1 mg	100 mg single use vial	IV**
J2182	Nucala (Mepolizumab), 1 mg	100 mg single dose vial 100 mg single dose prefilled autoinjector or syringe	SQ*
J0517	Fasenra (Benralizumab), 1 mg	30 mg single dose prefilled syringe or autoinjector	SQ*
J2356	Tezspire (Tezepelumab-ekko), 10 mg	210 mg solution in single dose vial, prefilled syringe/pen	SQ*

***subcutaneous ** intravenous**

Acronyms

NCD = National Coverage Determination

LCD = Local Coverage Determination

CMS = Centers for Medicare and Medicaid Services

FDA = Food and Drug Administration

IgE = Immunoglobulin E

IL-5 = interleukin-5

NAEPP = National Asthma Education and Prevention Program

ACT = Asthma Control Test

ICS = Inhaled corticosteroid

LABA = Long-acting beta agonist

EPGA = Eosinophilic granulomatosis with polyangiitis

FEV1 = Forced expiratory volume in one second

HES = Hypereosinophilic Syndrome

TSLP = Thymic stromal lymphopoietin

CRSwNP = Chronic Rhinosinusitis with Nasal Polyps

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