

PRIOR AUTHORIZATION POLICY

POLICY: Immunologicals – Cinqair Prior Authorization Policy

- Cinqair® (reslizumab injection for intravenous use – Teva Respiratory)

REVIEW DATE: 02/17/2021

OVERVIEW

Cinqair, an interleukin-5 antagonist monoclonal antibody, is indicated for **severe asthma** as add-on maintenance treatment of patients ≥ 18 years of age who have an eosinophilic phenotype.¹ Limitations of Use: Cinqair is not indicated for the treatment of other eosinophilic conditions or for the relief of acute bronchospasm/status asthmaticus.

Clinical Efficacy

The Cinqair pivotal studies included adult and adolescent patients with moderate to severe asthma.²⁻⁴ In general, patients were required to have baseline blood eosinophil levels ≥ 400 cells/microliter despite therapy with a medium to high dose inhaled corticosteroid (ICS) with or without a second controller medication (two of the studies).²⁻⁴ In one study that did not require patients to have elevated eosinophils at baseline, clinical benefit in regard to forced expiratory volume in 1 second (FEV₁) was not statistically significant with Cinqair vs. placebo. However, a significant improvement was observed in a subgroup of patients with baseline eosinophil levels ≥ 400 cells/microliter.

Guidelines

The Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention (2020) proposes a step-wise approach to asthma treatment.⁵ Cinqair is listed as an option for add-on therapy in patients ≥ 18 years of age with difficult-to-treat, severe eosinophilic asthma (i.e., asthma that cannot be managed by therapy with an ICS/long-acting beta₂-agonist [LABA] combination with or without an additional controller). Higher blood eosinophil levels, more exacerbations in the previous year, adult-onset asthma, nasal polyposis, and maintenance oral corticosteroids at baseline may predict a good asthma response to Cinqair.

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.^{6,7} 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: FEV₁ $< 80\%$ predicted after appropriate bronchodilator withholding.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cinqair. 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 Cinqair as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Cinqair to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

- 1. Asthma.** Approve Cinqair 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 ≥ 18 years of age; AND
 - ii.** Patient has a blood eosinophil count ≥ 400 cells per microliter within the previous 4 weeks or within 4 weeks prior to treatment with any anti-interleukin-5 therapy; AND
Note: Examples of anti-interleukin-5 therapies include Cinqair, Fasentra[®] (benralizumab injection for subcutaneous use), and Nucala[®] (mepolizumab injection for subcutaneous use).
 - 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 beta₂-agonists, inhaled long-acting muscarinic antagonists, leukotriene receptor antagonists, anti-interleukin-5 therapies (e.g., Cinqair, Fasentra, Nucala), and theophylline. Use of a combination inhaler containing both an inhaled corticosteroid and a long-acting beta₂-agonist 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):
 - 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 hospitalization or an Emergency Department visit in the previous year; OR
 - c)** Patient has a forced expiratory volume in 1 second (FEV₁) $< 80\%$ predicted; OR
 - d)** Patient has an FEV₁/forced vital capacity (FVC) < 0.80 ; OR
 - e)** Patient has asthma that worsens upon tapering of oral corticosteroid therapy; AND
Note: “Baseline” is defined as prior to receiving any Cinqair or other anti-interleukin-5 therapies (i.e., Fasentra or Nucala).
 - v.** The medication is prescribed by or in consultation with an allergist, immunologist, or pulmonologist.
 - B) Patient is Currently Receiving Cinqair.** 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 Cinqair; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with Cinqair 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 Cinqair 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.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cinqair is not recommended in the following situations:

1. **Concurrent use of Cinqair with Another Anti-Interleukin Monoclonal Antibody.** The efficacy and safety of Cinqair used in combination other anti-interleukin monoclonal antibodies (e.g., Nucala® [mepolizumab injection for subcutaneous use], Fasena® [benralizumab subcutaneous injection], Dupixent® [dupilumab subcutaneous injection]) have not been established.
2. **Concurrent use of Cinqair with Xolair® (omalizumab injection for subcutaneous use).** Xolair is a recombinant humanized immunoglobulin G (IgG)1κ monoclonal antibody indicated for use in patients ≥ 6 years of age with moderate to severe persistent asthma and who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with ICSs.⁸ Xolair is also indicated for chronic idiopathic urticaria in adults and adolescents 12 years of age and older who remain symptomatic despite H₁ antihistamine treatment and for nasal polyps, as add-on maintenance treatment in patients ≥ 18 years of age with an inadequate response to nasal corticosteroids. The efficacy and safety of Cinqair in combination with Xolair have not been established.
3. **Eosinophilic Esophagitis, or Eosinophilic Gastroenteritis.** Cinqair is not indicated for the treatment of eosinophilic conditions other than asthma.¹ In addition to a small pilot study, one randomized, double-blind, placebo controlled study (n =226) evaluated the efficacy of Cinqair in pediatric and adolescent patients with eosinophilic esophagitis.^{9,10} In this study, patients were randomly assigned to receive Cinqair IV at varying doses for 12 weeks. At Week 15, peak esophageal eosinophil counts were reduced from baseline and all reductions with Cinqair were significant compared with placebo. Improvements in physician's global assessment scores were also observed in all groups (including placebo), but the difference between Cinqair and placebo was not statistically significant. 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.¹¹ Additional, well-controlled trials are needed to determine the role of Cinqair in the treatment of eosinophilic esophagitis and eosinophilic gastroenteritis.
4. **Hypereosinophilic Syndrome.** Cinqair is not indicated for the treatment of eosinophilic conditions other than asthma.¹ One very small pilot study (n = 4) evaluated the safety and efficacy of Cinqair in patients with hypereosinophilic syndrome who were refractory to or intolerant of treatment with conventional therapy.¹² A single dose of Cinqair resulted in a response in two of four patients. In the two responders, blood eosinophil counts dropped to within the normal range within 48 hours of the Cinqair infusion and this was accompanied by an improvement in clinical signs and symptoms. The 2019 World Health Organization (WHO)-defined eosinophilic disorders update on diagnosis, risk

stratification, and management notes that Cinqair has not been evaluated extensively for the treatment of hypereosinophilic syndrome; use of anti-interleukin-5 approaches for the treatment of hypereosinophilic syndrome remains investigational.¹³ Corticosteroids are the cornerstone of therapy for several forms of hypereosinophilic syndrome. In patients who have idiopathic hypereosinophilic syndrome and end organ damage, enrollment into an anti-interleukin-5/anti-interleukin-5 receptor antibody clinical trial is recommended as second-line therapy. Similarly, in patients with lymphocyte-variant hypereosinophilic syndrome, enrollment into an anti-interleukin-5/anti-interleukin-5 receptor antibody clinical trial is also recommended as second-line therapy. Additional, well-controlled trials are needed to determine the role of Cinqair in the treatment of hypereosinophilic syndrome.

5. **Nasal Polyps.** Cinqair is not indicated for the treatment of nasal polyps.¹ One double-blind, placebo-controlled, randomized safety and pharmacokinetic study (n = 24) evaluated the use of Cinqair in patients with nasal polyps.¹⁴ Patients received a single infusion of either Cinqair 3 mg/kg, Cinqair 1 mg/kg, or placebo. It was reported that blood eosinophil counts and concentrations of eosinophil cation protein were reduced for up to 8 weeks following the Cinqair infusion. Nasal polyp scores improved for approximately 4 weeks in one-half of patients receiving active treatment. Additionally, a pooled subgroup analysis from the two pivotal Cinqair asthma exacerbation trials found that in patients with inadequately controlled asthma and chronic sinusitis with nasal polyps (n = 150) Cinqair demonstrated enhanced efficacy. Patients in this subgroup experienced an 83% reduction the clinical asthma exacerbation rate with Cinqair vs. placebo.¹⁵ The magnitude of this reduction was greater than that observed with the overall study population. A 2014 Practice Parameter on the Diagnosis and Management of Rhinosinusitis and a 2020 Practice Parameter for the Management of Rhinitis from the from 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 note that Cinqair has shown benefit in the treatment of patients with chronic rhinosinusitis with nasal polyps.¹⁶⁻¹⁹ However, it is noted that Cinqair is not approved for this use. A 2015 Clinical Practice Guideline update on Adult Sinusitis from the American Academy of Otolaryngology (AAO) address the management of nasal polyps, but do not address Cinqair²⁰ Additional, well-designed, controlled trials are needed to determine the role of Cinqair in the treatment of patients with nasal polyps who do not have asthma.
6. 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. Cinqair[®] injection for intravenous use [prescribing information]. Frazer, PA: Teva Respiratory, LLC; February 2020.
2. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicenter, parallel, double-blind, randomized, placebo-controlled, phase 3 trials. *Lancet Respir Med.* 2015;3:355-366.
3. Bjermer L, Lemiere C, Maspero J, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: a randomized phase 3 study. *Chest.* 2016;150(4):789-798.
4. Corren J, Weinstein S, Janka L, et al. Phase 3 study of reslizumab in patients with poorly controlled asthma: effects across a broad range of eosinophil counts. *Chest.* 2016;150(4):799-810.
5. Global Initiative for Asthma. Global strategy for asthma management and prevention. Updated 2020. Available at: <http://www.ginasthma.org>. Accessed on February 5, 2021.
6. 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.
7. 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.
8. Xolair[®] subcutaneous injection [prescribing information]. South San Francisco, CA and East Hanover, NJ: Genentech, Inc. and Novartis Pharmaceuticals Corporation; November 2020.
9. Prussin C, James SP, Huber MM, et al. Pilot study of anti-IL-5 in eosinophilic gastroenteritis. *J Allergy Clin Immunol.* 2003;111:S275.

10. Spergel JM, Rothenberg ME, Collins MH, et al. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2012;129(2):456-463.
11. 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.
12. Klion AD, Law MA, Noel P, et al. Safety and efficacy of the monoclonal anti-interleukin-5 antibody SCH55700 in the treatment of patients with hypereosinophilic syndrome. *Blood*. 2004;103(8):2939-2941.
13. Shomali W, Gotlib J. World Health Organization-defined eosinophilic disorders: 2019 update on diagnosis, risk stratification, and management. *Am J Hematol*. 2019;94(10):1149-1167.
14. Gevaert P, Lang-Loidolt D, Lackner A, et al. Nasal IL-5 levels determine the response to anti-IL-5 treatment in patients with nasal polyps. *J Allergy Clin Immunol*. 2006;118(5):1133-1141.
15. Weinstein SF, Katial RK, Bardin P, et al. Effects of reslizumab on asthma outcomes in a subgroup of eosinophilic asthma patients with self-reported chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol Pract*. 2019;7(2):589-596.
16. Peters AT, Spector S, Hsu J, et al. Diagnosis and management of rhinosinusitis: a practice parameter update. *Ann Allergy Asthma Immunol*. 2014;347-385.
17. 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.
18. 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.
19. 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.
20. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update): adult sinusitis. *Otolaryngol Head Neck Surg*. 2015;152(2S):S1-S39.