POLICY: Immunologicals – Cinqair® (reslizumab injection for intravenous use – Teva Respiratory)

APPROVAL DATE: 02/20/2019; selected revision 10/23/2019

OVERVIEW

Cinqair is indicated for add-on maintenance treatment of patients ≥18 years of age with severe asthma who have an eosinophilic phenotype.[1] Cinqair is not indicated for the treatment of other eosinophilic conditions or for the relief of acute bronchospasm/status asthmaticus. Cinqair should be administered as a 3 mg/kg intravenous (IV) infusion once every 4 weeks by a healthcare professional. Cinqair is a human interleukin (IL)-5 antagonist monoclonal antibody. IL-5 is the main cytokine involved in the growth, differentiation, recruitment, activation, and survival of eosinophils, a type of cell involved in asthmatic inflammation.

Clinical Efficacy

The efficacy of Cinqair was established in four randomized, double-blind, placebo-controlled, multicenter pivotal studies in patients with moderate to severe asthma.[2-4] In three of the studies, patients were required to have baseline blood eosinophil levels ≥ 400 cells/microliter despite therapy with a medium to high dose inhaled corticosteroid (ICS). Cinqair (at the FDA-approved dose) was found to reduce the rate of clinical asthma exacerbations per patient per year compared with placebo. Cinqair also significantly increased forced expiratory volume in 1 second (FEV_1) compared with placebo. In the fourth study that did not require patients to have elevated eosinophils at baseline, FEV_1 increased with Cinqair vs. placebo, but this improvement was not statistically significant. However, a significant improvement in this endpoint was observed in a subgroup of patients with baseline eosinophil levels ≥ 400 cells/microliter.

Guidelines

The 2019 Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention proposes a step-wise approach to asthma treatment.[5] Patients with persistent symptoms or exacerbations despite a medium-dose ICS/long-acting $beta_2$-agonist (LABA) combination with or without an additional controller, GINA recommends referral of the patient to a specialist with expertise in the management of severe asthma for phenotypic assessment and add-on treatment. Cinqair is listed as an option for add-on therapy in patients ≥ 18 years of age with difficult-to-treat, severe eosinophilic asthma. Higher blood eosinophil levels, more exacerbations in the previous year, adult-onset asthma, and nasal polyposis may predict a good asthma response to Cinqair.

According to the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines (2014), 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] Uncontrolled asthma is defined as asthma that meets one of the following four criteria: poor symptom control; frequent severe exacerbations; serious exacerbations; or airflow limitation. Additionally, patients may also have severe asthma if their asthma worsens upon tapering of corticosteroids.

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Cinqair. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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. All approvals are provided for the durations noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

RECOMMENDED AUTHORIZATION 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 Cinqair 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. Cinqair is prescribed by or in consultation with an allergist, immunologist, or pulmonologist; AND

iii. Patient has a blood eosinophil count of ≥ 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, Fasenra, and Nucala.

iv. 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/maintenance medication; AND

Note: An exception to the requirement for a trial of one additional asthma controller/maintenance medication (criterion b) can be made if the patient has already received anti-interleukin-5 therapy (e.g., Cinqair, Fasenra, Nucala) used concomitantly with an inhaled corticosteroid for at least 3 consecutive months. Use of a combination inhaler containing both an inhaled corticosteroid and a long-acting beta$_2$-agonist would fulfil the requirement for both criteria a and b. Examples of inhaled corticosteroids include Aerospan, Alvesco, ArmonAir RespiClick, Arnuity Ellipta, Asmanex Twisthaler/HFA, Flovent Diskus/HFA, Pulmicort Flexhaler, Qvar/Qvar RediHaler, and budesonide suspension for inhalation (Pulmicort Respules, generics). Examples of additional asthma controller/maintenance medications include long-acting beta$_2$-agonists (e.g., Serevent Diskus); inhaled long-acting muscarinic antagonists (e.g., Spiriva Respimat); leukotriene receptor antagonists (e.g., montelukast tablets/granules [Singulair, generics], zafirlukast tablets [Accolate, generics]); theophylline (e.g., Theo 24, TheoChron ER, generics). Examples of combination inhaled corticosteroid/long-acting beta$_2$-agonist inhalers include Advair Diskus (generic Wixela Inhub; authorized generics), Advair HFA, AirDuo RespiClick (authorized generics), Breo Ellipta, Dulera, Symbicort.

v. Patient's asthma is uncontrolled or was uncontrolled prior to starting any anti-interleukin therapy as defined by ONE of the following (a, b, c, d or e):

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

b) The patient experienced one or more asthma exacerbation requiring hospitalization or an Emergency Department (ED) visit in the previous year; OR
c) Patient has a forced expiratory volume in 1 second (FEV_1) < 80% predicted; OR
d) Patient has an FEV_1/forced vital capacity (FVC) < 0.80; OR
e) The patient's asthma worsens upon tapering of oral corticosteroid therapy.

Note: Examples of anti-interleukin therapies include Cinqair, Fasenra, and Nucala.

B) Patients Continuing Cinqair Therapy. Approve Cinqair for 1 year if the patient meets the following criteria (i, ii, and iii):

i. The patient has already received at least 6 months of therapy with Cinqair; AND
Note: Patients who have received < 6 months of therapy or those who are 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; AND
Note: Examples of an inhaled corticosteroid or an inhaled corticosteroid-containing combination inhaler include Flovent Diskus/HFA, ArmonAir RespiClick, Arnuity Ellipta, Asmanex Twisthaler/HFA, Aerospan, Alvesco, Pulmicort Flexhaler, budesonide suspension for inhalation (Pulmicort Respules, generics), Qvar/Qvar RediHaler, Advair Diskus (generic Wixela Inhub; authorized generics), Advair HFA, AirDuo RespiClick (authorized generics), Breo Ellipta, Dulera, and Symbicort.

iii. The patient has responded to Cinqair 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 (ED)/urgent care, or medical clinic visits due to asthma; and decreased requirement for oral corticosteroid therapy.

Dosing. Approve 3 mg/kg administered intravenously (IV) once every 4 weeks.

Conditions Not Recommended for Approval

Cinqair has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Concurrent use of Cinqair with Another Anti-Interleukin (IL) Monoclonal Antibody.** The efficacy and safety of Cinqair used in combination other anti-IL monoclonal antibodies (e.g., Nucala, Fasenra™ [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 IgG1κ 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.[7] The efficacy and safety of Cinqair in combination with Xolair have not been established.

3. **Eosinophilic Esophagitis (EoE) or Eosinophilic Gastroenteritis.** In addition to a small pilot study, one randomized, double-blind, placebo controlled study (published) [n =226] evaluated the efficacy of Cinqair in pediatric and adolescent patients with EoE.[8,9] In this study, patients were randomly assigned to receive Cinqair IV infusions of 1 mg/kg, 2 mg/kg, or 3 mg/kg, or placebo at Weeks 0, 4, 8, and 12. At Week 15, peak esophageal eosinophil counts were reduced by a median 24%, 59%, 67%, and 64%,

with placebo, Cinqair 1 mg/kg, 2 mg/kg, 3 mg/kg, respectively; 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. Additional, well-controlled trials are needed to determine the role of Cinqair in the treatment of EoE and eosinophilic gastroenteritis.

4. **Hypereosinophilic Syndrome (HES), Idiopathic.** One small pilot study (published) [n = 4] evaluated the safety and efficacy of Cinqair in patients with HES who were refractory to or intolerant of treatment with conventional therapy.[10] A single 1 mg/kg 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. Additional, well-controlled trials are needed to determine the role of Cinqair in the treatment of HES.

5. **Nasal Polyps.** Cinqair was studied in one double-blind, placebo-controlled, randomized safety and pharmacokinetic study (published) [n = 24] in patients with nasal polyps.[11] 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.[12] The magnitude of this reduction was greater than that observed with the overall study population. However, 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; January 2019.
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 2019. Available at: http://www.ginasthma.org. Accessed on October 18, 2019.
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. Xolair® subcutaneous injection [prescribing information]. South San Francisco, CA and East Hanover, NJ: Genentech, Inc. and Novartis Pharmaceuticals Corporation; May 2019.
8. Prussin C, James SP, Huber MM, et al. Pilot study of anti-IL-5 in eosinophilic gastroenteritis. *J Allergy Clin Immunol*. 2003;111:S275.
9. 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.
10. 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.
11. 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.

12. 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.

OTHER REFERENCES UTILIZED

- Brusselle G, Germinaro M, Weiss S, et al. Reslizumab in patients with inadequately controlled late-onset asthma and elevated blood eosinophils. *Pulm Pharmacol Ther*. 2017;43:39-45.
- Markowitz JE, Jobe L, Miller M, et al. Safety and efficacy of reslizumab for children and adolescents with eosinophilic esophagitis treated over nine years. *J Pediatr Gastroenterol Nutr*. 2018;66(6):893-897..
- Mukherjee M, Aleman Paramo F, Kjarsgaard M, et al. Weight-adjusted intravenous reslizumab in severe asthma with inadequate response to fixed-dose subcutaneous mepolizumab. *Am J Respir Crit Care Med*. 2018;197(1):38-46.
- Murphy K, Jacobs J, Bjermer L, et al. Long-term safety and efficacy of reslizumab in patients with eosinophilic asthma. *J Allergy Clin Immunol Pract*. 2017;5(6):1572-1581.

HISTORY

Type of Revision	Summary of Changes	Approval Date
New policy	--	09/26/2018
Early annual revision	• Updated initial therapy criteria for "Asthma in Patients with Severe Disease and an Eosinophilic Phenotype" to more concisely state the previous therapies required. Added the following: NOTE: An exception to the requirement for a trial of one additional asthma controller/maintenance medication (criterion b) can be made if the patient has already received anti-IL-5 therapy (e.g., Cinqair, Fasenra, Nucala) used concomitantly with an ICS for at least 3 consecutive months. • Updated dosing for "Asthma in Patients with Severe Disease and an Eosinophilic Phenotype". Removed the requirement that the Cinqair be infused over 20 to 50 minutes.	02/20/2019
Selected Revision	• Asthma: Approval indication was changed from "Asthma in Patients with Severe Disease and an Eosinophilic Phenotype" to "Asthma". Wording in reference to "according to the prescribing physician" was changed to "according to the prescriber". Added Wixela Inhub, a generic to Advair Diskus, to list of examples of asthma controller/maintenance medications.	10/23/2019

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