Policy Number	**RX501.143**
Policy Effective Date	**04/15/2025**
Policy End Date	**12/31/2025**

Tezepelumab-ekko

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

NOTE 1: Tezepelumab-ekko (Tezspire™) may be self-administered. For self-administered medications, please refer to applicable pharmacy benefit plan.

Tezepelumab-ekko (Tezspire™) **may be considered medically necessary** for the add-on maintenance treatment of severe asthma when the following criteria are met:

- Individual is 12 years of age and older; AND
- There is documented and current use of an inhaled corticosteroid (ICS) in combination with a long acting beta2-agonist (LABA), leukotriene receptor antagonist (LTRA), theophylline or long-acting muscarinic antagonist (LAMA) for at least 3 months; AND
- The individual has uncontrolled asthma while on control therapy as evidenced by two or more exacerbations requiring systemic glucocorticoids, frequent emergency room visits, or hospitalizations; AND
- Will not be used in combination with another antiasthmatic monoclonal antibody agent (e.g., Reslizumab [Cinqair], omalizumab [Xolair], mepolizumab [Nucala], dupilumab [Dupixent], benralizumab [Fasenra]).

NOTE 2: Individuals who do not meet the criteria for uncontrolled asthma, but whose asthma worsens on tapering off corticosteroids, will also meet this definition of moderate to severe asthma. For definition of uncontrolled asthma, see Description section.

Tezepelumab-ekko (Tezspire™) **is considered experimental, investigational and/or unproven** for all other indications.

NOTE 3: Tezepelumab-ekko (Tezspire™) is NOT indicated for the relief of acute bronchospasm or status asthmaticus.

Self-Administration

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage of a formulation that cannot be self-administered **may be considered medically necessary** when:

- Patient or caregiver is unable to recognize symptoms of anaphylaxis; OR
- Patient or caregiver is unable to treat anaphylaxis appropriately; OR
- Patient or caregiver is unable to perform subcutaneous injections with a prefilled syringe or autoinjector with proper technique according to the prescribed dosing regimen and Instructions for Use; OR

- The patient has a physical or cognitive limitation that makes the utilization of a self-administered formulation unsafe or otherwise not feasible, as demonstrated by BOTH of the following:
  - Inability to self-administer the medication; and
  - Lack of caregiver or support system for assistance with administration of self-administered products

Coverage of a formulation that cannot be self-administered **is considered not medically necessary** if the above criteria are not met.

Policy Guidelines

None.

Description

Asthma is a chronic condition that affects the airways in the lungs. The airways become inflamed and narrow at times, making it hard for air to flow out of the airways when exhaling. About 8% of the adults in the United States has asthma according to the Center for Disease Control and Prevention (CDC). It affects people of all ages and often starts in childhood. Certain things or triggers can set off or worsen asthma symptoms, such as pollen, exercise, viral infections, or cold air. There is no cure for asthma, but treatment and an asthma action plan can help individuals manage their symptoms. (1)

Symptoms of asthma may include chest tightness; coughing, especially at night or early morning; shortness of breath; and wheezing, which is a whistling sound when exhaling. While other conditions can cause these symptoms, in asthma, they often follow a pattern:

- They come and go over time or within the same day.
- They start or get worse with viral infection, such as a cold.
- They are triggered by exercise, allergies, cold air, or breathing too fast from laughing or crying.
- They are worse at night or in the morning.

An asthma attack happens when the airways swell and narrow, making it harder to breathe. During an asthma attack, symptoms get much worse. Attacks can come on fast or gradually and may be life-threatening. People with severe asthma get attacks more often.

Treatment of asthma can include daily medications to control and prevent symptoms, as well as medication to use during an asthma attack, such as a rescue inhaler. Long-term medications may be used to help prevent asthma attacks and control symptoms. This may include oral or inhaled corticosteroids to reduce inflammation; biologics for severe asthma; leukotriene modifiers to reduce swelling and keep the airways open; or inhaled long-acting bronchodilators to prevent the airways from narrowing.

Definition of Uncontrolled Asthma
At least one of the following:

- Asthma Control Questionnaire (ACQ) score consistently >1.5, Asthma Control Test (ACT) score <20 (or ''not well controlled'' by National Asthma Education and Prevention Program (NAEPP) /Global Initiative for Asthma (GINA) guidelines);
- Frequent severe exacerbations: ≥2 bursts of systemic corticosteroids (CS) (>3 days each) in the previous year;
- Serious exacerbations: at least 1 hospitalization, intensive care unit (ICU) stay, or mechanical ventilation in the previous year;
- Airflow limitation: after appropriate bronchodilator withhold, forced expiratory volume in 1 second (FEV1) <80% predicted (in the face of reduced FEV1/forced vital capacity (FVC) defined as less than the lower limit of normal). (3)

Tezepelumab-ekko (Tezspire™)
Thymic stromal lymphopoietin (TSLP) is an epithelial cell-derived cytokine that participates in asthma inflammation. Tezepelumab is a human monoclonal immunoglobulin G2-lambda antibody (AMG 157) that binds TSLP and prevents its interaction with the TSLP receptor complex. (4)

Regulatory Status
The U.S. Food and Drug Administration (FDA) approved tezepelumab-ekko (Tezspire™) in 2021 for the add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma. Tezspire is not indicated for the relief of acute bronchospasm or status asthmaticus. (2)

Rationale

This medical policy was developed in 2022 and is based on the clinical studies provided to the U.S. Food and Drug Administration (FDA) for approval. The most recent literature update was performed through January 30, 2024.

Tezepelumab-ekko (Tezspire) (2)
The efficacy of Tezspire was evaluated in two randomized, double-blind, parallel group, placebo-controlled clinical trials (PATHWAY [NCT02054130] and NAVIGATOR [NCT03347279]) of 52 weeks duration. The two trials enrolled a total of 1609 patients 12 years of age and older with severe asthma.

PATHWAY was a 52-week dose-ranging exacerbation trial that enrolled 550 adult patients with severe asthma who received treatment with tezepelumab-ekko 70 mg subcutaneously every 4 weeks, Tezspire 210 mg subcutaneously every 4 weeks, tezepelumab-ekko 280 mg subcutaneously every 2 weeks, or placebo subcutaneously. Patients were required to have a

history of 2 or more asthma exacerbations requiring oral or injectable corticosteroid treatment or 1 asthma exacerbation resulting in hospitalization in the past 12 months.

NAVIGATOR was a 52-week exacerbation trial that enrolled 1061 patients (adult and pediatric patients 12 years of age and older) with severe asthma who received treatment with Tezspire 210 mg subcutaneously every 4 weeks or placebo subcutaneously every 4 weeks. Patients were required to have a history of 2 or more asthma exacerbations requiring oral or injectable corticosteroid treatment or resulting in hospitalization in the past 12 months.

In both PATHWAY and NAVIGATOR, patients were required to have an Asthma Control Questionnaire 6 (ACQ-6) score of 1.5 or more at screening and reduced lung function at baseline [pre-bronchodilator forced expiratory volume in 1 second (FEV1) below 80% predicted in adults, and below 90% predicted in adolescents]. Patients were required to have been on regular treatment with medium or high-dose inhaled corticosteroids (ICS) and at least one additional asthma controller, with or without oral corticosteroids (OCS). Patients continued background asthma therapy throughout the duration of the trials. In both trials, patients were enrolled without requiring a minimum baseline level of blood eosinophils or FeNO.

The results summarized below are for the recommended Tezspire 210 mg subcutaneously every 4 weeks dosing regimen.

Exacerbations

The primary endpoint for PATHWAY and NAVIGATOR was the rate of clinically significant asthma exacerbations measured over 52 weeks. Clinically significant 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 both PATHWAY and NAVIGATOR, patients receiving Tezspire had significant reductions in the annualized rate of asthma exacerbations compared to placebo. There were also fewer exacerbations requiring emergency room visits and/or hospitalization in patients treated with Tezspire compared with placebo (Table 1).

Table 1. Rate of Clinically Significant Exacerbations Over 52 Weeks in PATHWAY and NAVIGATOR

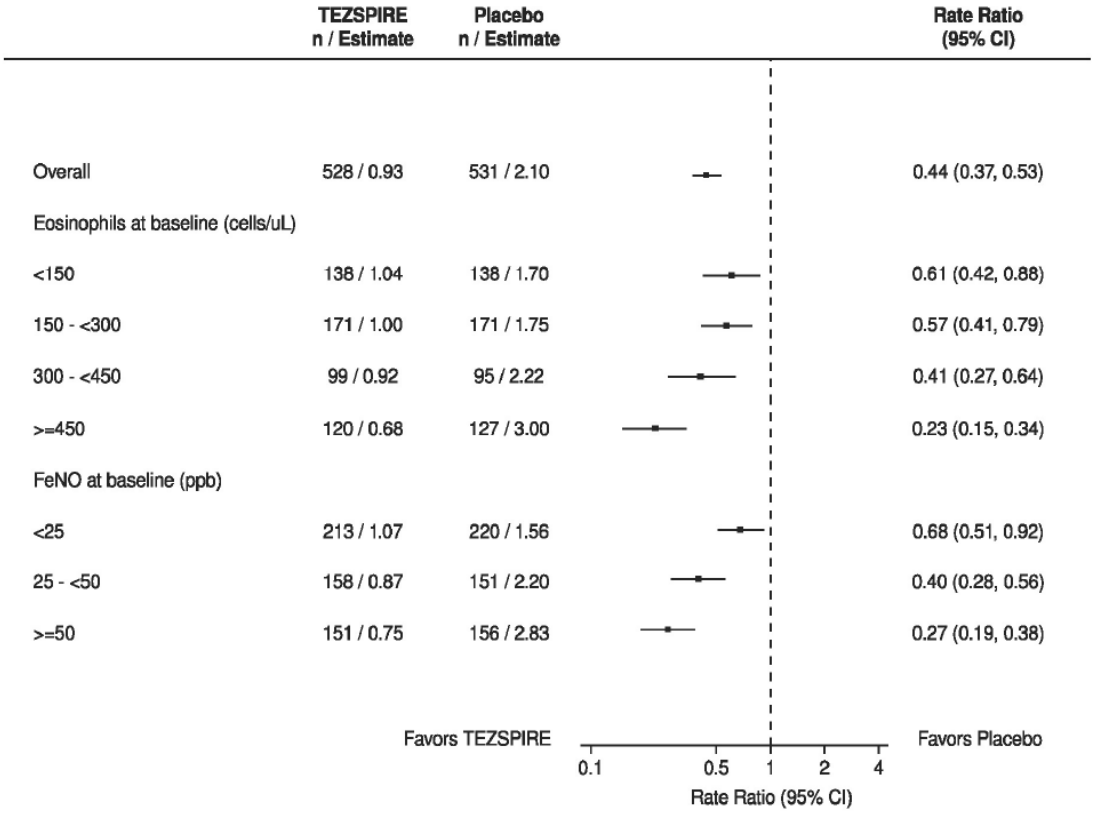
Trial	**Treatment**	**Exacerbations per year**	
		Rate	**Rate Ratio (95% CI)**
Annualized Asthma Exacerbation Rate			
PATHWAY	Tezspire (N=137)	0.20	0.29 (0.16, 0.51)
	Placebo (N=138)	0.72	
NAVIGATOR	Tezspire (N=528)	0.93	0.44 (0.37, 0.53)
	Placebo (N=531)	2.10	

Exacerbations requiring emergency room visit/hospitalization			
PATHWAY	Tezspire (N=137)	0.03	0.15 (0.04, 0.58)
	Placebo (N=138)	0.18	
NAVIGATOR	Tezspire (N=528)	0.06	0.21 (0.12, 0.37)
	Placebo (N=531)	0.28	
Exacerbations requiring hospitalization			
PATHWAY	Tezspire (N=137)	0.02	0.14 (0.03, 0.71)
	Placebo (N=138)	0.14	
NAVIGATOR	Tezspire (N=528)	0.03	0.15 (0.07, 0.22)
	Placebo (N=531)	0.19	

CI: confidence interval.

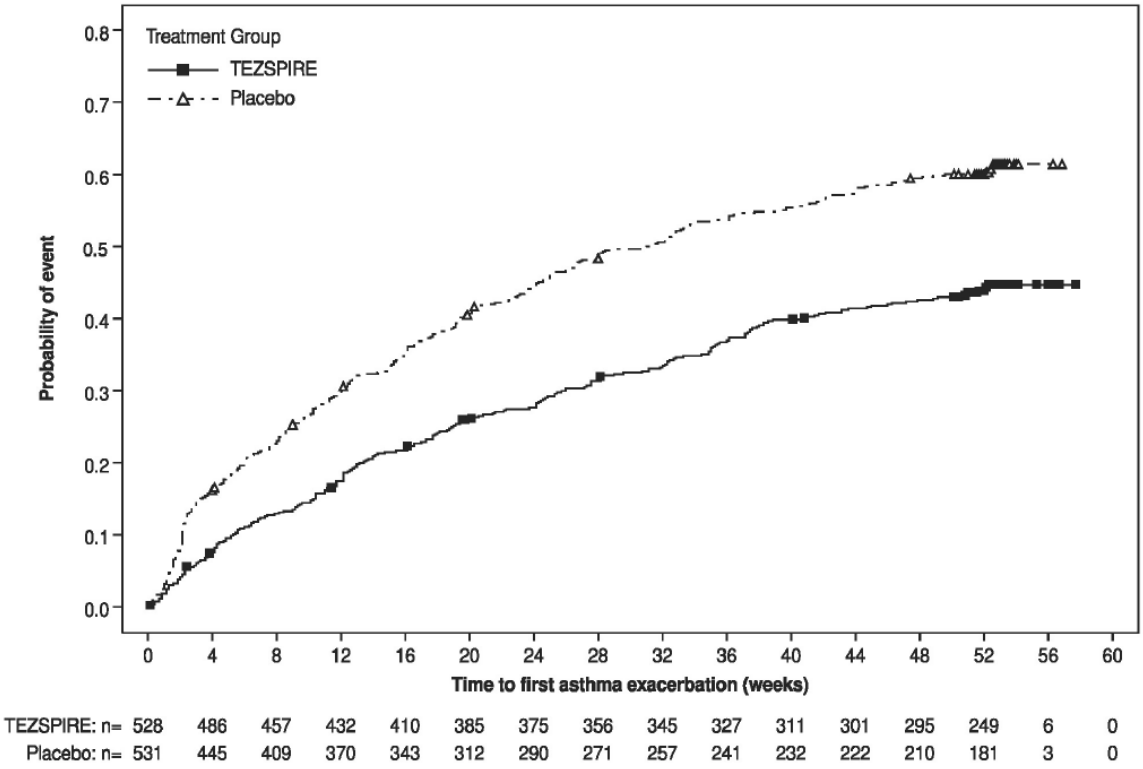
In NAVIGATOR, patients receiving TEZSPIRE experienced fewer exacerbations than those receiving placebo regardless of baseline levels of blood eosinophils or FeNO (Figure 1). Similar results were seen in PATHWAY.

Figure 1. Annualized Asthma Exacerbation Rate Ratio Over 52 Weeks Across Different Baseline Biomarkers in NAVIGATOR



The time to first exacerbation was longer for the patients receiving TEZSPIRE compared with placebo in NAVIGATOR (Figure 2). Similar findings were seen in PATHWAY.

Figure 2. Kaplan-Meier Cumulative Incidence Curves for Time to First Exacerbation in NAVIGATOR



Lung Function

Change from baseline in FEV1 was assessed as a secondary endpoint in PATHWAY and NAVIGATOR. Compared with placebo, Tezspire provided clinically meaningful improvements in the mean change from baseline in FEV1 in both trials (Table 2).

Table 2. Mean Change from Baseline in Pre-Bronchodilator FEV1 at End of Trial in PATHWAY and NAVIGATOR*

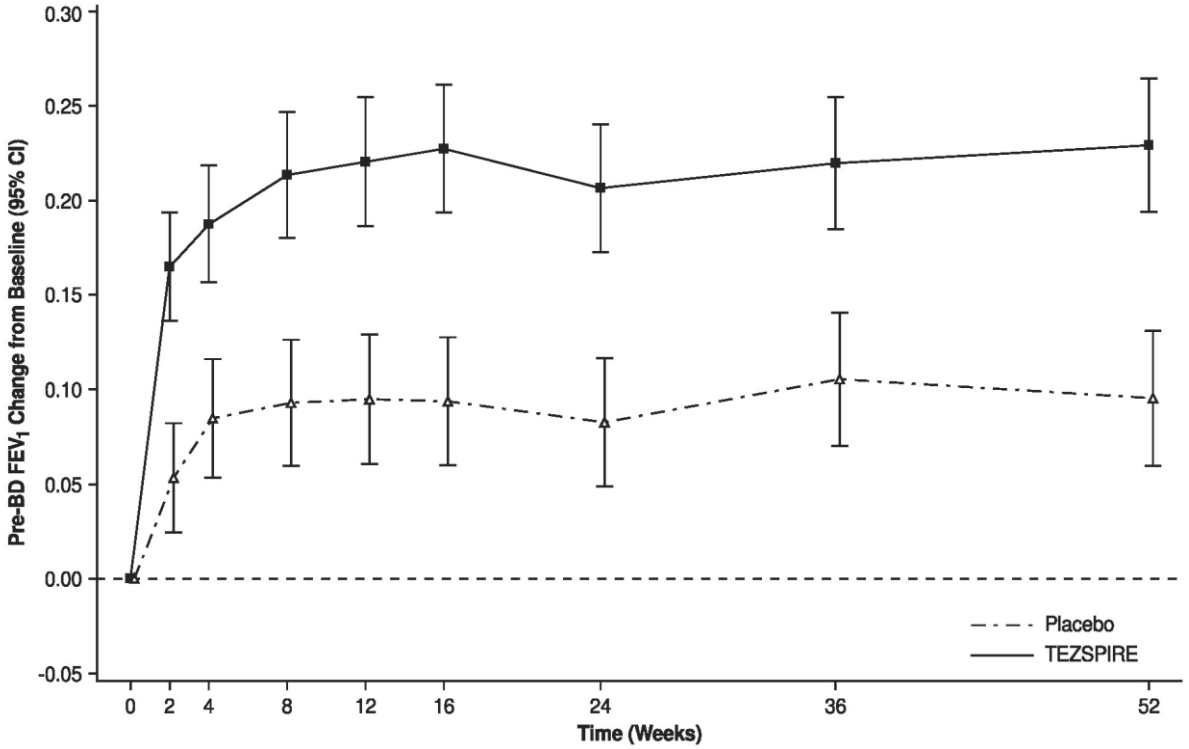
Trial	Treatment	LS Mean Change from Baseline (L)	Difference from Placebo (95% CI)
PATHWAY	Tezspire (N=133)[a]	0.08	0.13 (0.03, 0.23)
	Placebo (N=138)[a]	-0.06	
NAVIGATOR	Tezspire (N=527)[a]	0.23	0.13 (0.08, 0.18)
	Placebo (N=531)[a]	0.10	

*Week 52 in PATHWAY, Week 52 in NAVIGATOR

[a] Number of patients contributing to the full analysis (FA) with at least 1 change from baseline value.

In NAVIGATOR, improvement in FEV1 was seen as early as 2 weeks after initiation of treatment and was sustained through week 52 (Figure 3).

Figure 3. Mean Change (95% CI) from Baseline in Pre-Bronchodilator FEV1 (L) in NAVIGATOR



Number of subjects with a change from baseline value at each time point

TEZSPIRE	527	514	523	518	510	510	497	483	471
Placebo	531	507	516	517	514	509	490	475	453

Patient Reported Outcomes

Changes from baseline in Asthma Control Questionnaire 6 (ACQ-6) and Standardized Asthma Quality of Life Questionnaire for ages 12 and older [AQLQ(S)+12] were also assessed as secondary endpoints in PATHWAY and NAVIGATOR. In both trials, more patients treated with Tezspire compared to placebo had a clinically meaningful improvement in ACQ-6 and AQLQ(S)+12. Clinically meaningful improvement (responder rate) for both measures was defined as improvement in score of 0.5 or more at end of trial. In NAVIGATOR, the ACQ-6 responder rate for Tezspire was 86% compared with 77% for placebo (OR=1.99; 95% CI 1.43, 2.76) and the AQLQ(S)+12 responder rate for Tezspire was 78% compared with 72% for placebo (OR=1.36; 95% CI 1.02, 1.82). Similar findings were seen in PATHWAY.

Additional Trial

In a randomized, double-blind, parallel group, placebo-controlled clinical trial, the effect of Tezspire (210 mg subcutaneously every 4 weeks) on reducing the use of maintenance OCS was evaluated. The trial enrolled 150 adult patients with severe asthma who required treatment with daily OCS (7.5 mg to 30 mg per day) in addition to regular use of high-dose ICS and a long-acting beta-agonist with or without additional controller(s). 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 compared with placebo (cumulative OR=1.28; 95% CI 0.69, 2.35). (2, 5)

Summary of Evidence

Based on the clinical studies provided to the U.S. Food and Drug Administration, tezepelumab-ekko (Tezspire™) may be considered medically necessary for the add-on maintenance treatment of severe asthma for individuals 12 years of age and older meeting the definition of severe asthma as defined by the following: documented and current use of an inhaled corticosteroid (ICS) in combination with a long acting beta2-agonist (LABA), leukotriene receptor antagonist (LTRA), theophylline or long-acting muscarinic antagonist (LAMA) for at least 3 months; and the individual has uncontrolled asthma while on control therapy as evidenced by two or more exacerbations requiring systemic glucocorticoids, frequent emergency room visits, or hospitalizations; and tezepelumab will not be used in combination with another antiasthmatic monoclonal antibody agent (e.g., Reslizumab [Cinqair], omalizumab [Xolair], mepolizumab [Nucala], dupilumab [Dupixent], benralizumab [Fasenra]). Tezepelumab-ekko (Tezspire™) is experimental, investigational and/or unproven for all other indications.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J2356

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

References

1. National Center for Environmental Health. Asthma Data, Statistics, and Surveillance. March 29, 2023. Available at: < https://www.cdc.gov> (accessed February 14, 2023).
2. U.S. Food and Drug Administration, Drugs@FDA. Highlights of prescribing information: Tezspire™ (Tezepelumab-ekko) (May 2023). Available at: <https://www.accessdata.fda.gov> (accessed January 30, 2024).
3. 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. PMID 24337046
4. Wenzel S. Treatment of severe asthma in adolescents and adults. In: UpToDate, Kraft M (Ed), UpToDate, Waltham, MA. Available at: <https://www.uptodate.com> (Accessed January 29, 2024).

5. Wechsler ME, Menzies-Gow A, Brightling CE, et al. Evaluation of the oral corticosteroid-sparing effect of tezepelumab in adults with oral corticosteroid-dependent asthma (SOURCE): a randomised, placebo-controlled, phase 3 study. Lancet Respir Med. July 2022; 10(7):650-660. PMID 35364018

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
04/15/2025	Document updated. The following change was made to Coverage: Added "The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage of a formulation that cannot be self-administered is considered not medically necessary unless the patient has a physical or cognitive limitation that makes the utilization of a self-administered formulation unsafe or otherwise not feasible, as demonstrated by BOTH of the following: Inability to self-administer the medication, AND lack of caregiver or support system for assistance with administration of self-administered products." No new references added.
04/01/2024	Document updated with literature review. The following changes were made to Coverage: 1) Modified the criteria on inhaled corticosteroids from 12 months to 3 months; and 2) Clarified exacerbation episodes to include frequent ER visits or hospitalizations. Reference 1 added; others updated.
07/01/2023	Reviewed. No change to coverage criteria. NOTEs added/modified.
07/01/2022	New medical document. Tezepelumab-ekko (Tezspire™) may be considered medically necessary for the add-on maintenance treatment of severe asthma when the following criteria are met: Patient is 12 years of age and older; AND Patient meets the definition of severe asthma as defined by the following: 12-months of treatment with high-dose inhaled corticosteroids (ICS) in combination with long-acting beta2-agonist (LABA) or leukotriene receptor antagonist (LTRA)/theophylline for the previous year or systemic corticosteroids for 50% or more of the previous year to prevent asthma from

	becoming uncontrolled or remaining uncontrolled (see NOTE 1); AND History of 2 or more exacerbations requiring systemic glucocorticoids while being treated with fluticasone propionate 880µg or more, or its equivalent in the last year; AND Will not be used in combination with another antiasthmatic monoclonal antibody agent (e.g., Reslizumab [Cinqair], omalizumab [Xolair], mepolizumab [Nucala], dupilumab [Dupixent], benralizumab [Fasenra]). NOTE 1: Patients who do not meet the criteria for uncontrolled asthma, but whose asthma worsens on tapering off corticosteroids, will also meet this definition of moderate to severe asthma. For definition of uncontrolled asthma, see Description section. Tezepelumab-ekko (Tezspire™) is experimental, investigational and/or unproven for all other indications.