NEW DRUG APPROVAL

Brand Name	Tezspire™
Generic Name	tezepelumab-ekko
Drug Manufacturer	Astrazeneca AB

New Drug Approval

FDA Approval Date: December 17, 2021

Review Designation: Priority

Type of review: Biologic License Application (BLA): 761224

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Asthma is one of the most common major non-communicable diseases and for many, has a substantial impact on quality of life. Globally, asthma is ranked 16th among the leading causes of years lived with disability and 28th among the leading causes of burden of disease, as measured by disability-adjusted life years. Around 300 million people have asthma worldwide, and it is likely that by 2025 a further 100 million may be affected.

Asthma causes the airways of the lungs to narrow or become blocked, making it hard to breathe. Many processes contribute to the narrowing, including tightening of the muscles around the airways, inflamed tissue lining the airways, and mucous plugging of the airways. The disease follows a waxing and waning course with exacerbations initiated by allergens, cold weather, exercise, pollution, and other triggers. This leads to approximately 10 million office visits, 1.6 million emergency room visits, 180,000 hospitalizations, and 3,500 deaths each year in the US.1,2 The societal costs are estimated to be $82 billion including $50 billion in direct medical costs, $29 billion from asthma-related mortality, and $3 billion from missed work and school. In the US, asthma is more than twice as common among Black children as among white children (13.5% and 6.4%, respectively), and remains somewhat more common among Black adults.

Asthma has been divided into different phenotypes with some overlap. T helper 2 (Th2) cells secrete interleukin (IL)-4, IL-5, and IL-13, which increase the proliferation, survival and recruitment of eosinophils and increase IgE levels. About half of individuals with mild-to-moderate asthma exhibit the type 2 phenotype with increases in Th2 cells, and the proportion with this phenotype is believed to be larger in severe asthma. Allergic asthma, which is associated with allergic rhinitis, atopy, and elevated IgE levels, is characteristic of approximately half of all patients with asthma and is generally a form of type 2 asthma. The ICER report in 2018 reviewed five monoclonal antibodies that primarily targeted pathways involved in the allergic or type 2 inflammatory phenotypes of asthma. At that time, none of the biologic therapies appeared to be effective for patients who had neither allergic asthma nor eosinophilia.

Efficacy

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.

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.

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 3 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	

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 4 Mean Change from Baseline in Pre-Bronchodilator FEV_1 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)†	0.08	0.13 (0.03, 0.23)
	Placebo (N=138)†	-0.06	
NAVIGATOR	TEZSPIRE (N=527)†	0.23	0.13 (0.08, 0.18)
	Placebo (N=531)†	0.10	

*Week 52 in PATHWAY, Week 52 in NAVIGATOR
†Number of patients contributing to the full analysis (FA) with at least 1 change from baseline value

Safety

ADVERSE EVENTS

Most common adverse reactions (incidence ≥ 3%) are pharyngitis, arthralgia, and back pain.

WARNINGS & PRECAUTIONS

- Hypersensitivity Reactions: Hypersensitivity reactions (e.g., rash, allergic conjunctivitis) can occur after administration of Tezspire™. Initiate appropriate treatment as clinically indicated in the event of a hypersensitivity reaction.
- Risk Associated with Abrupt Reduction in Corticosteroid Dosage: Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with Tezspire™. Decrease corticosteroids gradually, if appropriate.
- Parasitic (Helminth) Infection: Treat patients with pre-existing helminth infections before therapy with Tezspire™. If patients become infected while receiving Tezspire™ and do not respond to antihelminth treatment, discontinue Tezspire™ until the parasitic infection resolves.
- Vaccination: Avoid use of live attenuated vaccines.

CONTRAINDICATIONS

Known hypersensitivity to tezepelumab-ekko or excipient.

Clinical Pharmacology

MECHANISMS OF ACTION

Tezepelumab-ekko is a thymic stromal lymphopoietin (TSLP) blocker, human monoclonal antibody IgG2λ that binds to human TSLP with a dissociation constant of 15.8 pM and blocks its interaction with the heterodimeric TSLP receptor. TSLP is a cytokine mainly derived from epithelial cells and occupies an upstream position in the asthma inflammatory cascade.

Airway inflammation is an important component in the pathogenesis of asthma. Multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes, ILC2 cells) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) are involved in airway inflammation. Blocking TSLP with tezepelumab-ekko reduces biomarkers and cytokines associated with inflammation including blood eosinophils, airway submucosal eosinophils, IgE, FeNO, IL-5, and IL-13; however, the mechanism of tezepelumab-ekko action in asthma has not been definitively established.

Dose & Administration

ADULTS

Recommended dosage is 210 mg administered once every 4 weeks.

PEDIATRICS

- For age 12 years and older: Refer to adult dosing.
- The safety and effectiveness in patients younger than 12 years of age have not been established.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

No formal clinical studies have been conducted to investigate the effect of renal impairment on tezepelumab-ekko.

HEPATIC IMPAIRMENT

No formal clinical studies have been conducted to investigate the effect of renal impairment on tezepelumab-ekko.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection:

- 210 mg/1.91 mL (110 mg/mL) solution in a single-dose glass vial.
- 210 mg/1.91 mL (110 mg/mL) solution in a single-dose pre-filled syringe.