CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761224Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761224
PDUFA Goal Date	January 7, 2022
OSE RCM #	2021-1006
Reviewer Name(s)	Donella Fitzgerald, PharmD
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	December 14, 2021
Subject	Evaluation of Need for a REMS
Established Name	tezepelumab
Trade Name	Tezspire
Name of Applicant	AstraZeneca
Therapeutic Class	Thymic stromal lymphopoietin blocker
Formulation(s)	210 mg/1.91 mL (110 mg/mL) solution for subcutaneous injection
Dosing Regimen	210 mg once every 4 weeks

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1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] Tezspire (tezepelumab) is necessary to ensure the benefits outweigh its risks. AstraZeneca (AZ) submitted a New Biologic Licensing Application (BLA) 761224 for tezepelumab with the proposed indication for the add-on maintenance treatment of patients aged 12 years and older with (b) (4) severe asthma (b) (4) (b) (4) This application is under review in the Division of Pulmonology, Allergy and Critical Care (DPACC). The applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Tezepelumab (TPM), a new molecular entity, is an anti-thymic stromal lymphopoietin human immunoglobulin monoclonal antibody proposed for add-on maintenance[b] treatment of patients aged 12 years and older with (b) (4) severe asthma (b) (4) (b) (4) Thymic stromal lymphopoietin (TSLP) is an epithelial cell-derived cytokine that plays a central role in the inflammatory cascade leading to the initiation and persistence of airway inflammation in asthma.[1] Tezepelumab binds to human TSLP with high affinity and prevents its interaction with the TSLP receptor. The receptor blockade reduces levels of a broad spectrum of biomarkers and cytokines associated with inflammation.

AstraZeneca proposes a prefilled syringe and single-dose vial of TPM, each 210 mg in 1.91 mL (110 mg/mL), for subcutaneous (SC) administration by providers in a healthcare setting. The recommended dose is 210 mg to be injected every four weeks. Tezepelumab was granted breakthrough therapy in September 2018 and received priority review status in July 2021. It is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for BLA 761224 relevant to this review:

- **09/05/2018:** Tezepelumab granted breakthrough therapy designation as add-on maintenance treatment for patients with severe asthma without an eosinophilic phenotype.
- **05/07/2021:** BLA 761224 submission for the add-on maintenance treatment of patients aged 12 years and older with (b) (4) severe asthma (b) (4) (b) (4)
- **07/07/2021:** Priority review granted for BLA 761224.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): Whether the Drug Is a New Molecular Entity*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): Expected or Actual Duration of Treatment With the Drug*

- **11/09/2021:** A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for tezepelumab.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Asthma is a chronic heterogeneous inflammatory airway disease affecting approximately 25 million Americans.[2c] It is characterized by bronchial hyperresponsiveness and airflow limitation. Associated symptoms include wheezing, breathlessness, chest tightness and coughing. There is considerable variability in patterns of airway inflammation and disease severity as well as response to treatment and disease control. Severe, uncontrolled disease can lead to oral corticosteroid dependence with long term use and increased risk of emergency room (ER) visits and hospitalizations. Asthma exacerbations result in approximately 1.3 million ER visits, 439,000 hospitalizations and more than 3,500 deaths annually.[3d]

3.2. Description of Current Treatment Options

Treatment of asthma includes rescue treatments for asthma exacerbation, namely inhaled short-acting β-agonists, and maintenance treatments to prevent asthma exacerbations. Current therapies for the maintenance treatment of asthma include inhaled corticosteroids, combination inhaled corticosteroids and long-acting β-agonists. For asthmatic patients who remain symptomatic despite these treatments, inhaled long-acting muscarinic antagonists, leukotriene receptor antagonists and systemic corticosteroids are often used.[4] Biologics provide an additional treatment option for patients with uncontrolled eosinophilic phenotype asthma. A summary of the approved biologic treatment options for asthma is outlined below in Table 1:

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (*A*): The estimated size of the population likely to use the drug involved*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug*

Table 1 - Summary of the Approved Biologic Treatment Options for Asthma

Product Trade Name (Generic) **Year of Approval**	**Indication**	**Dosing/ Administration**	**Important Safety and Tolerability Issues**	**Risk Management Approaches/ Boxed Warning, Medication Guide**
FDA Approved Biologic Treatments for Asthma				
Omalizumab 2003	Moderate to severe persistent asthma in patients ≥6 years of age with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids	75 mg to 375 mg SC every 2 to 4 weeks, depending on weight and serum IgE	anaphylaxis, malignancy	Boxed warning for anaphylaxis, Medication guide
Mepolizumab 2015	Add-on maintenance treatment in patients ≥12 years of age with severe asthma with an eosinophilic phenotype	100 mg SC every 4 weeks	hypersensitivity reactions, Herpes zoster infections	Patient labeling and Instructions for Use
Reslizumab 2016	Add-on maintenance therapy in patients ≥18 years old with severe asthma with an eosinophilic phenotype	3 mg/kg IV every 4 weeks	anaphylaxis	Boxed warning, Patient labeling
Benralizumab 2017	Add-on maintenance treatment in patients ≥12 years of age with severe asthma with an eosinophilic phenotype	30 mg SC every 4 weeks x 3 doses, then every 8 weeks	hypersensitivity reactions	Patient labeling and Instructions for use
Other Treatments: trigger avoidance, immunotherapy, bronchial thermoplasty				

The currently approved biologic therapies are specific to the eosinophilic phenotype. There is an unmet medical need for biologic treatments indicated for both eosinophilic and non-eosinophilic asthma.

4. Benefit Assessment

Tezepelumab efficacy for the add-on maintenance treatment of patients aged 12 years and older with (b) (4) severe asthma, (b) (4) was demonstrated in two trials:

NAVIGATOR (D5180C00007/NCT03347279) [pivotal study]: Phase 3, randomized, double-blind, placebo-controlled study of TPM 210 mg every 4 weeks administered SC in adult and adolescent subjects aged 12 to 80 years with inadequately controlled asthma, with a 52-week treatment period (N = 1061 randomized, 1059 treated)

PATHWAY (D5180C00001/NCT02054130): Phase 2b, randomized, double-blind, placebo-controlled dose-ranging study of TPM administered SC in adults aged 18 to 75 years with inadequately controlled asthma, with a 52-week treatment period (N = 550 randomized and treated)

The primary endpoint for both studies was annualized asthma exacerbation rate (AAER) reduction over 52 weeks for TPM versus placebo. The applicant reported that TPM treatment resulted in significant reductions in the AAER as indicated below in Table 2[5].

Table 2

Rate of Clinically Significant (p<0.001) 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	

The clinical reviewer concluded that the primary endpoint was met for both trials[e] and that the results are supported by the key secondary endpoints of increased pre-bronchodilator forced expiratory volume in one second at Week 12 and patient reported outcomes such as Asthma Control Questionnaire-6, Asthma Quality of Life Questionnaire and Asthma Symptom diary score.[6,f]

Based on evaluation of the clinical trial data, the DPACC has determined that the proposed indication, for the add-on maintenance treatment of patients aged 12 years and older with (b) (4)

[e] Based on the revised indication for the add-on maintenance treatment of patients aged 12 years and older with severe asthma

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): Expected Benefit of the Drug With Respect to the Disease or Condition*

(b) (4) severe asthma (b) (4) must be revised (b) (4) If TPM is approved, the indication will be for the add-on maintenance treatment of patients aged 12 years and older with severe asthma.

5. Risk Assessment & Safe-Use Conditions

The safety analysis of TPM was based on the pooled safety population from the NAVIGATOR and PATHWAY trials and includes data from 1334 subjects with severe asthma, including 665 subjects who received at least one dose of TPM 210 mg SC once every 4 weeks.

Two deaths were reported in the primary safety pool; both were secondary to cardiac failure and occurred in the placebo group. One death secondary to a cerebrovascular accident occurred in the TPM group of the PATHWAY trial. The subject was a 74-year-old female with severe asthma, hypertension and hypertensive encephalopathy who experienced a cerebral infarction 67 days after her last active dose.

The incidence of serious adverse events (SAEs) reported in the on-treatment period was 8.6% in the TPM treated group and 13.0% in the placebo treated subjects. The most common SAEs by system organ class was Respiratory, Thoracic and Mediastinal Disorders (3% TPM, 8% placebo), and Infections and Infestations (2% TPM, 3% placebo).[7] Adverse reactions with incidence greater than or equal to 3% and more common with TPM than placebo included pharyngitis, arthralgia and back pain. Each of these occurred in 4% of TPM subjects and 3% of placebo subjects.[8]

5.1. Hypersensitivity

Hypersensitivity, including anaphylaxis, was identified as an adverse event of special interest in the clinical trial program due to well-documented concerns associated with immunomodulatory therapy and biologics. In the primary safety pool, hypersensitivity reactions (rash, dermatitis, allergic conjunctivitis, pruritis, etc.) were reported in a total of 56 (8.4%) subjects in the TPM group and 58 (8.7%) in the placebo group. Of these reports, 1 (0.2%) in the TPM group was considered a SAE and 2 (0.3%) in the placebo group. No anaphylactic or serious allergic reactions causally related to TPM were reported,[9] though one incident of anaphylactic food reaction occurred in the placebo group[g]. Hypersensitivity reactions are included in Section 5.1 of the Warnings and Precautions of the draft TPM Prescribing Information. The label informs providers that these reactions can occur within hours or days of administration and that prescribers should consider the benefits and risks of continued TPM treatment for patients who experience a hypersensitivity reaction.

[g] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): Seriousness of Known or Potential Adverse Events That May Be Related to the Drug and the Background Incidence of Such Events in the Population Likely to Use the Drug*

6. Expected Postmarket Use

Tezepelumab is to be administered as a SC injection by a healthcare provider in a healthcare setting, such as a clinic or hospital. In most cases TPM will be prescribed by specialists, such as allergists or pulmonologists who have experience managing the adverse effects of biologic asthma therapies. Hypersensitivity reactions are a well-documented risk with the use of biologics. Healthcare providers can counsel patients at the point of care regarding the risk of hypersensitivity reactions which can include rash, urticaria, fever or anaphylaxis in serious cases. The adolescent and adult asthma patient population will likely be able to recognize these side effects and take necessary actions to manage them.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for TPM beyond routine pharmacovigilance and labeling. AstraZeneca stated that the risks of treatment with TPM are expected based on the drug class and mechanism of action and are considered to be manageable and without negative impact on the benefit-risk assessment.

8. Discussion of Need for a REMS

Based on the efficacy and safety information currently available, the Clinical Reviewer recommends approval of TPM for the add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma.

Asthma is a chronic heterogeneous inflammatory airway disease that is characterized by bronchial hyperresponsiveness and airflow limitation. For asthmatic patients who remain symptomatic despite currently approved treatments such as corticosteroids and β-agonists, biologics provide an additional treatment option. The benefit of TPM for the treatment of severe asthma was demonstrated in two randomized, double-blind, placebo-controlled studies of TPM SC administered in subjects with inadequately controlled asthma over a 52-week treatment period with a primary endpoint of annualized asthma exacerbation rate reduction. The clinical reviewer concluded that the primary endpoint for the revised indication was met for both trials and that the results are supported by key secondary endpoints.

Hypersensitivity reactions were reported in patients treated with TPM. One report was classified as a serious adverse reaction, however there were no incidents of anaphylaxis. Draft labeling includes hypersensitivity reactions in the Warnings and Precautions and instructs prescribers to use clinical judgement to determine continued use in patients who experience a reaction. The likely prescribers (allergists and pulmonologists) of TPM should be familiar with the hypersensitivity risks, as they are associated with other biosimilar products and the need to counsel patients about the risk of hypersensitivity reactions and the symptoms. The hypersensitivity risk associated with TPM will be communicated in labeling. This reviewer is not recommending a REMS for management of the risk of hypersensitivity with TPM therapy.

9. Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. The safety concerns associated with TPM are well characterized and in general, healthcare providers who treat severe asthma should be familiar with the risk of hypersensitivity reactions with the use of biologics and the importance of patient monitoring.

Should DPACC have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10. Appendices

10.1. References

[1] Cianferoni A, Spergel J. The importance of TSLP in allergic disease and its role as a potential therapeutic target. Expert Rev Clin Immunol. 2014 Nov; 10(11): 1463-1474

[2] American College of Allergy, Asthma & Immunology. Asthma Facts. Retrieved from https://www.acaai.org

[3] American College of Allergy, Asthma & Immunology. Asthma Facts. Retrieved from https://www.acaai.org

[4] Cianferoni A, Spergel J. The importance of TSLP in allergic disease and its role as a potential therapeutic target. Expert Rev Clin Immunol. 2014 Nov; 10(11): 1463-1474

[5] Division of Pulmonary, Allergy and Critical Care. Section 14 of Draft Prescribing Information: Labeling Correspondence for Tezepelumab, BLA 761224, December 10, 2021

[6] Division of Pulmonary, Allergy and Critical Care. Draft Multidisciplinary Review and Evaluation for Tezepelumab, BLA 761224, November 22, 2021

[7] Division of Pulmonary, Allergy and Critical Care. Draft Multidisciplinary Review and Evaluation for Tezepelumab, BLA 761224, December 13, 2021

[8] Division of Pulmonary, Allergy and Critical Care. Labeling Correspondence for Tezepelumab, BLA 761224, December 10, 2021

[9] Division of Pulmonary, Allergy and Critical Care. Draft Multidisciplinary Review and Evaluation for Tezepelumab, BLA 761224, November 22, 2021

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/s/

DONELLA A FITZGERALD
12/14/2021 11:51:29 AM

JACQUELINE E SHEPPARD
12/14/2021 06:04:27 PM

CYNTHIA L LACIVITA
12/14/2021 06:14:06 PM