CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761458Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEWS

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	761458
PDUFA Goal Date	December 16, 2025
Nexus TTT #	2025-12443
Reviewer Name(s)	Celeste Will, PharmD, MPH
Team Leader	Carolyn Tieu, PharmD, MPH
Division Director	Laura Zendel, PharmD
Review Completion Date	December 15, 2025
Subject	Evaluation of Need for a REMS
Established Name	depemokimab
Trade Name	Exdensur
Name of Applicant	GlaxoSmithKline
Therapeutic Class	Interleukin-5 (IL-5) antagonist monoclonal antibody
Formulation(s)	Single-Dose Pre-Filled Pen 100 mg/mL
	Single-Dose Pre-Filled Syringe with Needle Guard 100 mg/mL
Dosing Regimen	100 mg administered subcutaneously once every 6 months

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Exdensur (depemokimab) is necessary to ensure the benefits outweigh its risks.

GlaxoSmithKline submitted a Biologics License Application (BLA) 761458 for depemokimab with the proposed indication of add-on maintenance treatment of severe asthma characterized by an eosinophilic phenotype in adult and pediatric patients aged 12 years and older (b) (4) This application is under review in the DPACC. The efficacy for the proposed asthma indication was demonstrated in the pivotal trials, SWIFT-1 and SWIFT-2, where there was a statistically significant reduction in the annualized rate of exacerbations compared to placebo, with rate ratios of 0.42 (95% CI: 0.3, 0.6) and 0.52 (95% CI: 0.36, 0.73), respectively. The review team concluded that this demonstrates substantial evidence of effectiveness. (b) (4) .

The risks associated with depemokimab include hypersensitivity reactions, acute asthma symptoms or deteriorating disease, risks associated with abrupt reduction of corticosteroid dosage, and parasitic (helminth) infection. The Applicant did not submit a proposed REMS or risk management plan with this application.

DRM has determined that a REMS is not needed to ensure the benefits of depemokimab outweigh its risks. There are various other approved biologics for severe asthma with the same risks, therefore the likely prescribers will be familiar with managing the risks associated with depemokimab. Overall, depemokimab has a favorable benefit-risk profile, and the risks will be addressed in the warnings and precautions section of the labeling.

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) Exdensur (depemokimab) is necessary to ensure the benefits outweigh its risks.[a] GlaxoSmithKline submitted a Biologics License Application (BLA) 761458 for depemokimab with the proposed indication of add-on maintenance treatment of asthma in adult and pediatric patients aged 12 years and older with type 2 inflammation characterized by an eosinophilic phenotype on medium- to high-dose inhaled corticosteroids (ICS) plus another asthma controller (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

Depemokimab is a humanized, YTE-modified, monoclonal antibody (IgG1, kappa) that binds and inhibits IL-5, an integral cytokine involved in the growth, survival, differentiation, activation, and recruitment of eosinophils. Depemokimab is not currently approved in any jurisdiction.

The proposed dose and route of administration is 100 mg subcutaneously (SC) once every six months administered by healthcare professionals. It is proposed as a prefilled syringe with safety syringe device.

2.2. Regulatory History

The following is a summary of the regulatory history for BLA 761458 relevant to this review:

- 12/15/2024: BLA 761458 was received.
- 05/30/2025: Midcycle meeting occurred, and the Applicant was notified that (b) (4)
- 06/10/2025: Midcycle communication sent in which the Agency stated that we have not identified any major safety concerns that would warrant a risk management or mitigation strategy at this time; however, our review remains ongoing.
- 09/15/2025: Late cycle meeting occurred during which the Agency reiterated what was stated in the mid-cycle communication (b) (4) .

[a] Section 505-1 (a) of the FD&C Act: FDAAA factor (F): *Whether the drug is a new molecular entity*.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Asthma is a disease of the lower respiratory tract that affects over 300 million people worldwide and causes about 1,000 deaths each day (Brusselle, 2022; GINA, 2024). In the United States, the current asthma population estimate in thousands among adults and children is 24,964 and the lifetime asthma population estimate in thousands among adults and children is 41,892 (CDC NHIS Data, 2023). Asthma is a heterogenous, chronic lower airway respiratory disease consisting of airway hyperresponsiveness, inflammation, and bronchodilator associated reversible expiratory airflow. Clinical symptoms include cough, wheezing, and shortness of breath among others.

Severe asthma is characterized by ongoing inflammation which causes airflow restriction that can improve with inhaled medications and the inability to maintain adequate symptom control in the absence of high-dose inhaled therapies including inhaled corticosteroids and long-acting beta agonists (Kavanagh et al, 2020). Patients with severe asthma experience frequent exacerbations and may require daily maintenance oral corticosteroids when maximal inhaled therapy proves insufficient to reduce exacerbation risk or to control day to day symptoms. Patients with severe eosinophilic asthma are a distinct subgroup associated with the greatest risks of severe exacerbation, critical care admission, and poor lung function along with the inflammatory signature of elevated eosinophil counts.[b]

Of the severe asthma subgroup, at least 50% of patients have an eosinophilic phenotype characterized by elevated serum eosinophils or elevated fractional exhaled nitric oxide, and predominant cytokines such as interleukin (IL)-4, IL-5, and IL-13.[c] The local presence of persistent inflammatory cells, such as eosinophils, causes significant morbidity and mortality attributed to its association with an increased exacerbation risk, airway remodeling, and chronic obstruction (Brusselle, 2022; Rupani, 2024).[e]

3.2. Description of Current Treatment Options

Asthma treatment for adults and adolescents over 12 years old follows a stepwise approach described in the Global Initiative for Asthma (Global Initiative for Asthma, 2024). In this approach, ICS are gradually increased with or without the addition of other therapeutics. Biologics are considered as add-on therapy at Step 5, of which there are currently six approved treatments shown in Table 1. There is limited data to suggest the optimal duration of treatment for patients initiated on biologic therapies for asthma in the published literature although Global Initiative for Asthma guidelines recommend between 3-to-6-month treatment trials to determine efficacy depending on the specific therapy (Sutherland et al. 2023).[d]

[b] 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*.

[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 (D): *The expected or actual duration of treatment with the drug*.

Studies that evaluated specific approved biologic therapies reveal no tolerability concerns among patients treated for up to 2, 4.5, or even 6 years, depending on the specific therapy (Khatri et al. 2019, Menzella et al. 2024, and Deeks and Brusselle 2017 and Vennera et al. 2018).[g] Approved biologics that target IL-5 are generally dosed once every 2 weeks to once every 8 weeks. If approved, the extended half-life of depemokimab offers a favorable alternative for injection-averse patients, reduces the burden of frequent treatment administration, and may promote therapeutic compliance.

Table 1. Summary of Biologic Therapies for Asthma

Product Name	Relevant Indication	Initial Year of Approval	Dosing/ Administration	Warnings & Precautions
Tezepelumab	Add-on maintenance treatment of asthma patients ≥12 years-old with severe asthma	2021	210 mg SC once every 4 weeks	W&P for Hypersensitivity Reactions, Acute Asthma Symptoms or Deteriorating Disease, Risk Associated with Abrupt Reduction of Corticosteroid Dosage, Parasitic (Helminth) Infection, Concomitant use with Live Attenuated Vaccines
Benralizumab	Add-on maintenance treatment of asthma patients ≥6 years-old with severe asthma and with an eosinophilic phenotype	2017	Patients 6-11 years-old and <35 kg: 10 mg SC every 4 weeks for the first 3 doses followed by once every 8 weeks Patients 6-11 years-old and ≥35 kg: 30 mg SC every 4 weeks for the first 3 doses followed by once every 8 weeks Patients ≥12 years-old: 30 mg every 4 weeks for the first 3 doses followed by once every 8 weeks	W&P for Hypersensitivity Reactions, Acute Asthma Symptoms or Deteriorating Disease, Reduction of Corticosteroid Dosage, Parasitic (Helminth) Infection
Dupilumab	Add-on maintenance treatment of patients ≥6 years-old with moderate to severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma	2017	Patients 6 to 11 years-old and 15 to <30 kg: 300 mg SC every 4 weeks Patients 6 to 11 years-old and ≥30 kg: 200 mg every other week Patients ≥12 years-old: 400 mg SC loading dose followed by 200 mg SC once every 2 weeks or 600 mg SC loading	W&P for Hypersensitivity, Conjunctivitis and Keratitis, Eosinophilic Conditions, Acute Symptoms of Asthma or Chronic Obstructive Pulmonary Disease or Acute Deteriorating Disease, Risk Associated with Abrupt Reduction of Corticosteroid Dosage, Patients with Co-morbid Asthma, Psoriasis, Arthralgia and Psoriatic

			dose followed by 300 mg SC once every 2 weeks. Dosing and dosing regimen may be different for patients with additional co-morbidities.	Arthritis, Parasitic (Helminth) Infections, Vaccinations
Reslizumab	Add-on maintenance treatment of adults ≥18 years-old with severe asthma and with an eosinophilic phenotype	2016	3 mg/kg IV once every 4 weeks	Black Box Warning for anaphylaxis; W&P for Anaphylaxis, Acute Asthma Symptoms or Deteriorating Disease, Malignancy, Reduction of Corticosteroid Dosage, Parasitic (Helminth) Infection
Mepolizumab	Add-on maintenance treatment of asthma patients ≥6 years-old with severe asthma and with an eosinophilic phenotype	2015	Patients 6-11 years-old: 40 mg SC once every 4 weeks Patients ≥12 years-old: 100 mg SC once every 4 weeks	W&P for Hypersensitivity Reactions, Acute Symptoms of Asthma or Chronic Obstructive Pulmonary Disease or Acute Deteriorating Disease, Opportunistic Infections: Herpes Zoster, Reduction of Corticosteroid Dosage, Parasitic (Helminth) Infection
Omalizumab	Treatment of moderate to severe persistent asthma in patients ≥6 years-old with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms inadequately controlled with an inhaled corticosteroid	2003	75 mg to 375 mg SC once every 2 or 4 weeks based on weight (kg) and serum total IgE level (IU/mL)	Black Box Warning for anaphylaxis; W&P for Anaphylaxis, Malignancy, Acute Asthma Symptoms and Deteriorating Disease, Corticosteroid Reduction, Eosinophilic Conditions, Fever, Arthralgia, and Rash, Parasitic (Helminth) Infection, Laboratory Tests, Potential Medication Error Related to Emergency Treatment of Anaphylaxis

Adapted from the table in the Multi-Disciplinary Review and Evaluation created by the clinical reviewer based on product labeling for currently approved biologics for asthma.

4. Benefit Assessment

(b) (4)

[redacted]

The efficacy of depemokimab for the treatment of add-on maintenance treatment of severe asthma characterized by an eosinophilic phenotype in adult and pediatric patients aged 12 years and older was

demonstrated in two pivotal phase 3 trials (SWIFT-1 [NCT04719832] and SWIFT-2 [NCT04718103]). The two trials consisted of the same design: replicated, 52-week, global, randomized, double-blind, parallel-group, placebo-controlled. Participants were randomized 2:1 to receive depemokimab 100 mg or matching placebo, on top of background asthma maintenance therapy. The efficacy population consisted of 762 patients who were randomized and received at least 1 dose of depemokimab or placebo (SWIFT-1, depemokimab=250, placebo=132, total=382 and SWIFT-2, depemokimab=252, placebo=128, total=380). Both trials had the same primary efficacy endpoint: annualized rate of clinically significant exacerbations over the 52 weeks. Both trials met statistical significance for the primary endpoint. In SWIFT-1, the annualized exacerbation rate ratio of the depemokimab treatment group compared to the placebo treatment group was 0.42 ($p<0.001$, 95% CI 0.30, 0.6) with a 58% reduction (95% CI 40%, 70%) in the annual rate.[e] In SWIFT-2, the annualized exacerbation rate ratio of the depemokimab treatment group compared to the placebo treatment group was 0.52 ($p<0.001$, 95% CI 0.36, 0.73) with a 48% reduction (95% CI 27%, 64%) in the annual rate. The clinical reviewer concluded that the Applicant provided substantial evidence of effectiveness for the proposed asthma indication (FDA Multi-Disciplinary Review and Evaluation for Asthma, 2025).

5. Risk Assessment & Safe-Use Conditions

The primary safety population for depemokimab consists of 762 participants treated in the pivotal trials SWIFT-1 and SWIFT-2, of which there were 501 participants in the depemokimab group and 261 in the placebo group (FDA Multi-Disciplinary Review and Evaluation for Asthma, 2025). There were 33 (6.6%) serious adverse events (SAEs) in the depemokimab group compared to 35 (13.4%) in the placebo group.[f] In the depemokimab treatment group, one subject had treatment interrupted for acute sinusitis. AEs leading to study drug discontinuation in the depemokimab group were for increased ALT, myasthenia gravis, mental health issue following bereavement, elevated ALT, abnormal total bilirubin, and bilateral ovarian cancer with peritoneal metastases. There were no deaths in SWIFT-1 or SWIFT-2.

The draft labeling will include warnings and precautions for the following risks: hypersensitivity reactions, acute asthma symptoms or deteriorating disease, risk associated with abrupt reduction of corticosteroid dosage, and parasitic (helminth) infection (GlaxoSmithKline Draft Prescribing Information, 2025). These risks are known risks among the approved biologics that target IL-5 for asthma and labeling for depemokimab will be similar to the other biologics that target IL-5. Safe use conditions for managing the risks include monitoring and specific interventions such as prophylaxis treatment, discontinuing depemokimab if hypersensitivity reactions or parasitic infection occur, avoiding use of depemokimab to treat acute asthma symptoms or acute exacerbations, and gradually reducing corticosteroid dose if appropriate.

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[e] Section 505-1 (a) of the FD&C Act: FDAAA factor (C): *The expected benefit of the drug with respect to such disease or condition.*

[f] Section 505-1 (a) of the FD&C Act: FDAAA factor (E): *The seriousness of any 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*.

The clinical reviewer concluded the safety data did not identify any concerning safety signal that would preclude approval or require narrowing of the indicated target population (FDA Multi-Disciplinary Review and Evaluation for Asthma, 2025).

6. Expected Postmarket Use

Severe asthma is typically diagnosed outpatient in ambulatory care settings such as urgent care, emergency departments, telemedicine visits, or physician offices. The likely prescribers will be primary care providers, such as internal medicine practitioners including nurse practitioners and physician assistants, family physicians, emergency medicine physicians, pediatricians, along with asthma specialists such as pulmonologists and allergists (Global Initiative for Asthma, 2024). If approved, depemokimab will likely be stocked in pharmacies and healthcare settings. Depemokimab should be administered by a healthcare provider every six months. Based on the anticipated medication use process and experience from other biologics that target IL-5 for the treatment of asthma, monitoring for the risks discussed in section 5 should be a collaborative effort between the prescriber, other members of the care team, and the patient or patient's caregiver.

The use of the Patient Information may facilitate patient education and instruct patients when to seek additional medical attention. Labeling is sufficient to ensure the safe use conditions for the risks of depemokimab described in Section 5 are mitigated in the expected postmarket setting.

7. Discussion of Need for a REMS

Based on the efficacy and safety information currently available, FDA determined that a REMS is not necessary to ensure the benefits of depemokimab outweigh the risks. FDA expects the labeling to be sufficient to communicate the risks.

Patients with severe eosinophilic asthma are a distinct subgroup associated with the greatest risks of severe exacerbation, critical care admission, and poor lung function along with the inflammatory signature of elevated eosinophil counts. For patients with persistently uncontrolled asthma, anti-IL-5 biologics can facilitate tapering off systemic glucocorticoids (Sharma S and Carr TF, 2025). If approved, the extended half-life of depemokimab offers a favorable alternative for injection-averse patients, reduces the burden of frequent treatment administration, and may promote therapeutic compliance.

Further risk mitigation beyond labeling to ensure that depemokimab is administered by a healthcare provider is not necessary. Both mepolizumab and reslizumab are indicated for use in a similar patient population to depemokimab and are administered by a healthcare provider. We expect that depemokimab will likely be prescribed by a similar prescribing population who have experience on the administration of SC biologic therapies for asthma.

In summary, we expect the depemokimab labeling to be sufficient to communicate the risks of hypersensitivity reactions, acute asthma symptoms or deteriorating disease, risks associated with abrupt reduction of corticosteroid dosage, and parasitic (helminth) infection. In addition, there are various other approved biologics for severe asthma with the same risks, therefore the likely prescribers will be

familiar with managing the risks associated with depemokimab. Furthermore, none of the risks associated with depemokimab rise to the level of a boxed warning. Overall, depemokimab has a favorable safety profile, and risks will be adequately addressed in the warnings and precautions section of the labeling.

Based on the available data, this reviewer has determined that a REMS is not necessary to ensure the benefits of depemokimab outweigh the risks.

8. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities beyond labeling and routine pharmacovigilance.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for depemokimab to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. References

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