CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761432Orig1s000

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	761432
PDUFA Goal Date	June 10, 2025
Nexus TTT #	2024-11253
Reviewer Name(s)	Timothy Bernheimer, Pharm.D
Team Leader	Naomi Boston, Pharm.D
Acting Division Director	Laura Zendel, Pharm.D
Review Completion Date	June 4, 2025
Subject	Evaluation of Need for a REMS
Established Name	Clerovimab-cfor
Trade Name	Enflonsia
Name of Applicant	Merck
Therapeutic Class	Human IgG1 monoclonal antibody
Formulation(s)	Prefilled syringe
Dosing Regimen	• 105 mg single intramuscular (IM) injection in neonates and infants born during or entering their first RSV season. For infants undergoing cardiac surgery with cardiopulmonary bypass during or entering their first RSV season, an additional 105 mg dose is recommended as soon as the infant is stable after surgery

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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 Enflonsia (clesrovimab-cfor) is necessary to ensure the benefits outweigh its risks. Merck submitted a Biologic Licensing Application (BLA) 761432 for Enflonsia with the proposed indication for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in neonates and infants who are born during or entering their first RSV season. The risks associated with Enflonsia include the class risk of hypersensitivity, including anaphylaxis and the risk of RSV Diagnostic Test Interference, and will be described in the *Warnings and Precautions* section of labeling. The applicant did not submit a REMS with this application.

DRM determined that a REMS is not needed to ensure the benefits of Enflonsia outweigh its risks. The likely prescribers are expected to be knowledgeable of the risks of hypersensitivity, including anaphylaxis, and risk of RSV diagnostic test interference as there are other approved products with similar indications and risks.

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) Enflonsia (clesrovimab-cfor) is necessary to ensure the benefits outweigh its risks. Merck submitted a Biologic Licensing Application (BLA) 761432 for Enflonsia with the proposed indication for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in neonates and infants who are born during or entering their first RSV season. This application is under review in the Division of Antivirals. The applicant did not submit a proposed REMS or risk management plan with this application, other than routine pharmacovigilance and labeling.

2. Background

2.1. Product Information

Enflonsia (clesrovimab-cfor), a new molecular entity,[a] is a respiratory syncytial virus (RSV) F protein-directed fusion inhibitor, that targets RSV fusion protein preventing RSV fusion with cells, proposed for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in neonates and infants who are born during or entering their first RSV season.[b] Enflonsia is proposed as 105 mg prefilled syringe by intramuscular injection. Enflonsia is not currently approved in any jurisdiction and is not part of a drug class that has a REMS or a Boxed Warning.

2.2. Regulatory History

The following is a summary of the regulatory history for BLA 761432 relevant to this review:

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

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- 10/11/2024: BLA 761432 submission received with proposed indication for the prevention of RSV lower respiratory tract disease in neonates and infants who are born during or entering their first RSV season
- 12/18/2024: Core Risk Management Plan for BLA 761432 received. The Applicant did not propose any risk management activities for Enflonsia beyond routine pharmacovigilance and labeling.
- 01/31/2025: 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 Enflonsia

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

RSV causes acute respiratory tract illness in persons of all ages. RSV is the most common cause of lower respiratory tract infection (LRTI) in children younger than one year and the most common cause of medically attended LRTI in children younger than five years. Almost all children are infected by two years of age, and reinfection is common.[1,c] RSV can cause severe lower respiratory tract disease, including bronchiolitis, bronchospasm, pneumonia, and acute respiratory failure in children. Severe apnea may be the presenting symptom in infants hospitalized with RSV. Small infants, especially those born prematurely or with bronchopulmonary dysplasia or congenital heart disease, are particularly susceptible to severe RSV disease.[d] In a prospective, population-based surveillance study in the U.S. from November 1, 2015, to June 30, 2016, the RSV hospitalization rate was 2.9 per 1000 children < 5 years of age, 6.3 per 1000 children < 2 years of age, and 14.7 per 1000 children < 6 months of age.[2] The estimated annual RSV-associated pneumonia mortality rate in the U.S. is 3.1 per 100,000 person-years in children < 1 year of age. In industrialized countries, most pediatric RSV deaths occur in children born prematurely and those with underlying cardiopulmonary disease or other chronic conditions.[1]

3.2. Description of Current Treatment Options

Three RSV vaccines are approved, none of which have a REMS. Arexvy (approved in 2023), Abrysvo (approved in 2023), and Mresvia (approved in 2024) are vaccines indicated for active immunization for the prevention of lower respiratory tract disease (LRTD) caused by RSV in individuals 60 years of age and older and for individuals 50 through 59 years of age who are at increased risk for LRTD caused by RSV. Abryso has an additional indication of active immunization of pregnant individuals at 32 through 36 weeks gestational age for the prevention of lower LTRD caused by RSV in infants through birth through 6

[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.*

months of age. No RSV vaccine is approved for use in children. Abrysvo carries the potential risk of preterm birth that is communicated through the *Warnings and Precautions* section of labeling.

There are two approved RSV treatments (Synagis (palivizumab) [BLA 103770] and Beyfortus (nirsevimab-alip) [BLA 761328], described below) that are recombinant, humanized IgG1 monoclonal antibodies against the RSV F protein. None of these treatments have a REMS.

Synagis (approved in 1998) is indicated for the prevention of serious RSV lower respiratory tract disease in children at high risk of RSV disease, including infants who were born preterm (at a gestational age of ≤ 35 weeks) and are younger than 6 months of age at the start of the RSV season. The product is also indicated in children younger than 2 years of age with chronic lung disease of prematurity or hemodynamically significant congenital heart disease. Synagis is administered intramuscularly once monthly throughout RSV season, typically for a maximum of five doses.[1,3] Use of Synagis carries the risks of hypersensitivity reactions, coagulation disorders, and RSV diagnostic test interference, which are communicated through the *Warnings and Precautions* section of labeling.[3]

Beyfortus (approved in 2023) is indicated for the prevention of RSV lower respiratory tract disease in neonates and infants born during or entering their first RSV season and children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. Beyfortus is administered intramuscularly once for patients born during the RSV starting from birth; and for patients born outside of the RSV season administered once prior to the start of the RSV season. For children up to 24 months of age who remain at increased risk for severe RSV disease, an additional dose is recommended for the second RSV season. Use of Beyfortus carries the risks of hypersensitivity reactions including anaphylaxis, and precaution in use in individuals with clinically significant bleeding disorders, which are communicated through the *Warnings and Precautions* section of labeling.[4]

4. Benefit Assessment

The evaluation of efficacy included two randomized trials (Trial 004 [NCT04767373] and Trial 007 [NCT04938830]).

Trial 004 was a Phase 2/3 randomized (2:1), double-blinded, placebo-controlled, trial where 3,632 subjects were randomized to received Enflonsia (n=2421) or placebo (n=1211) and were followed for at least 365 days. The primary efficacy endpoint was incidence of RSV-associated Medically Attended Lower Respiratory Infection (MALRI) from Days 1 through 150 post dose. The population in Trial 004 consisted of healthy infants ≥29 weeks gestational age (GA) from birth up to 1 year entering their first RSV season. Among subjects who received Enflonsia or placebo, the median age of infants was 3.1 months (range 0 to 12 months); 80% were less than 6 months; 16% were greater than or equal to 6 of less than 9 months, 4% were greater than or equal to 9 months of age, and 51% were male. A total of 3,614 subjects dosed, 98.8% of subjects finished Day 42 follow-up visit and 97% of subjects finished Day 150 follow up visit. Administration of Enflonsia reduced the incidence of RSV-associated MALRI (outpatient and inpatient) from Days 1 through 150 post dose compared with placebo, with the relative

risk reduction of 60.4% (95% CI: 44.1%, 71.9%; p<0.001).[e] The lower bound of the 95% CI was greater than 25%, thereby the statistical review team and the clinical reviewer concludes the trial met the statistical criterion for success.

Trial 007 is an ongoing Phase 3 randomized (1:1), partially blinded, open-label, active-controlled study with a primary objective of safety where 901 subjects were randomized to receive clesrovimab-cfor (n=450) or palivizumab (n=451). The secondary endpoint of Trial 007 is the same as the primary endpoint of Trial 004 explained above. The population in Trial 007 consisted of infants born at ≤35 weeks GA, or infants with chronic lung disease (CLD) of prematurity or hemodynamically significant chronic heart disease (CHD) from birth up to 1 year entering their first RSV season. Because Trial 007 was not fully powered to detect an efficacy difference between Enflonsia and palivizumab, the efficacy of Enflonsia of this population was extrapolated from healthy infants in Trial 004 by PK bridging. Among subjects who received Enflonsia or palivizumab, the median age of infants was 2.5 months (range: 0 to 12 months); 89% were less than 6 months; 9% were greater than or equal to 6 to less than 9 months, 2% were greater than or equal to 9 months of age; and 50% were male. Of these subjects, 28% had CLD, 11% had CHD, 6% were GA less than 29 weeks with neither CLD nor CHD and 55% were GA greater than or equal to 29 weeks with neither CLD nor CHD. For RSV-associated Outpatient and Inpatient MALRI from Days 1 to 150 post dose, the relative risk reduction of Enflonsia compared to palivizumab was -18.0% (95% CI: -155.5%, 45.5%) 15.9% (95% CI: -176.0%, 74.4%). The incidence rates of RSV-associated MALRI were generally comparable between Enflonsia and palivizumab arms from Days 1 through 150 in RSV Season 1.

The clinical reviewer concludes that the available efficacy data from the clinical trials have demonstrated that Enflonsia is effective for its intended use.[5]

5. Risk Assessment & Safe-Use Conditions

The safety database consists of a total of 2,947 pediatric subjects from the following clinical trials:

- 2,412 subjects from Trial 004 (NCT04767373)
- 446 subjects from Trial 007, Season 1 (NCT04938830)
- 64 subjects from Trial 002 (NCT03524118)
- 25 subjects from Trial 008 (NCT not provided)

Trial 002 was a phase 1b/2a, double blind, placebo concurrent, randomized (4:1) study where healthy preterm and full-term infants were randomized to receive Enflonsia (n=143) or placebo (n=38).

Trial 008 was a phase 1 pharmacokinetic (PK) and safety single arm, open label study in healthy males aged ≥ 18 to ≤ 55 years (N=25), healthy male or female children aged ≥ 2 to ≤ 8 years (n=25), and healthy male or female pre-term and full-term infants (n=25).

[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.*

No subjects discontinued treatment due to an adverse event, since Enflonsia is administered as a single dose.

There were 15 deaths among subjects who received Enflonsia (0.5%, N=2854) and 7 deaths among subjects who received the control (0.4%, N=1,652). All deaths occurred in Trials 004 and 007. The review team concludes that the numerical imbalance in the incidence of death does not appear to be related to the study drug.

The key safety concerns with Enflonsia are similar to those that are observed with other monoclonal antibodies, including the risk of serious hypersensitivity reactions such as anaphylaxis and serious skin reactions/rashes. Serious hypersensitivity reactions and serious skin reactions were not reported in the Enflonsia clinical trials.

An expanded analysis on the adverse event of special interest (AESI) of rash occurring within 14 days of study invention found that the proportion of subjects who experienced 1 or more rash AEs were 2.3% in the Enflonsia group and 1.9% in the placebo group. All events were non serious (Grade 1 or 2 toxicity) and were not considered to be related to study intervention.

One subject in an Enflonsia group experienced an anaphylaxis/hypersensitivity AESI of bronchospasm (grade 2) on Day 3 post dose, however the clinical reviewer agrees with the investigator's assessment that the event was not serious and not related to Enflonsia.

The clinical review team identified hypersensitivity including anaphylaxis and RSV Diagnostic Test interference as risks that will be detailed in the *Warnings and Precautions* section of labeling.[f] These risks and their management are detailed in the subsections below.

5.1. Hypersensitivity Including Anaphylaxis

Hypersensitivity including anaphylaxis, has been observed with other human immunoglobulin G1 (IgG1) monoclonal antibodies. Labeling will describe this class risk and advise health care providers to initiate appropriate medications and/or supportive therapy if signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur.

5.2. RSV Diagnostic Test Interference

Interference with immunologically-based RSV diagnostic assays (i.e., rapid antigen tests) by Enflonsia has been observed in laboratory studies. Labeling will recommend to healthcare providers to use an RT-PCR-

[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.*

based assay for confirmation when clinical observations are consistent with RSV infection and the rapid antigen assay results are negative.

6. Expected Postmarket Use

If approved, it is expected that Enflonsia will be administered in outpatient and inpatient settings and that the likely prescribers will include neonatologists, pediatricians, primary care providers, and other pediatric specialists.

7. Risk Management Activities Proposed by the Applicant

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

7.1. Other Proposed Risk Management Activities

The Agency proposes that based on the clinical development program and adverse events associated with monoclonal antibodies, prespecified adverse events of interest during postmarketing drug safety surveillance for Enflonsia include the following:

- Hypersensitivity reactions, including anaphylaxis and angioedema
- Immune complex disease, cytopenias (including thrombocytopenia)
- Injection Site Reactions, Serious Cutaneous Adverse Reactions

Additionally, the following postmarketing requirements (PMR) will be issued at the time of approval. The Applicant will:[6]

- ✓ Conduct a study in children up to 24 months of age with underlying conditions who are at increased risk for RSV disease.
- ✓ Conduct a surveillance study of current and emerging RSV variants from global locations, with F protein sequencing and identification of Enflonsia binding site substitutions and their frequency.
- ✓ Conduct a study to assess F protein substitutions in cell culture neutralization assays, in the background subtype in which they were identified based on non-clinical, surveillance, and clinical studies of Enflonsia.
- ✓ Conduct a study to assess the cell culture neutralization of Enflonsia against RSV with substitutions that confer > 100-fold reduction in susceptibility to Beyfortus, as reported in the Beyfortus prescribing information.

Reviewer's Comments: *We note that these other activities proposed by the applicant are outside of the scope of the REMS program and defer to Division of Pharmacovigilance and the Division of Epidemiology for review and input.*

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of Enflonsia on the basis of the efficacy and safety information currently available.

This reviewer recommends that, if Enflonsia is approved, a REMS is not necessary to ensure its benefits outweigh the risks. The risk of hypersensitivity, including anaphylaxis will be adequately described in the *Warnings and Precautions* section of labeling and further evaluated through an enhanced pharmacovigilance strategy with surveillance and PMRs. The risk of RSV diagnostic test interference will also be adequately described in the *Warnings and Precautions* section of labeling. None of these risks warrant a Boxed Warning. The clinicians who will prescribe Enflonsia are likely familiar by their experience and training in the management of the potential risks. There are products with similar indications and similar safety profiles as Enflonsia without a REMS. Additional risk mitigation measures beyond labeling are not necessary.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable, therefore, a REMS is not necessary for Enflonsia 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. Appendices

10.1. References

[1] Barr FE, Graham BS. Respiratory syncytial virus infection: Clinical features and diagnosis. In: Edwards MS, Torchia MM, eds. *UpToDate*. UpToDate; 2025.

[2] Rha B, Curns AT, Lively JY, et al. Respiratory Syncytial Virus-Associated Hospitalizations Among Young Children: 2015-2016. Pediatrics. July 202;146(1)doi:10.1542/peds.2019-3611

[3] Synagis (palivizumab) injection Prescribing Information. MedImmune, LLC. Gaithersburg, MD. Revised May 2017; accessed at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103770s5200lbl.pdf

[4] Beyfortus (nirsevimab-alip) injection Prescribing Information. AstraZeneca AB. Södertälje, Sweden. Revised August 2024; accessed at https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761328s005lbl.pdf

[5] Integrated Review: BLA 761432 clesrovimab-cfor intramuscular injection. Review in progress, Accessed May 1, 2025

[6] 6-Week Postmarketing Requirement Communication Letter for BLA 761432, DARRTS April 22, 2025.

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/s/

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