CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761328Orig1s000

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	761328
PDUFA Goal Date	July 26, 2023
OSE TT#	2022-1854
Reviewer Name	Bob Pratt, Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Associate Director for REMS Design and Evaluation	Laura Zendel, PharmD, BCPS
Subject	Evaluation of Need for a REMS
Review Completion Date	July 14, 2023
Established Name	Nirsevimab
Trade Name	Beyfortus
Name of Applicant	AstraZeneca AB
Therapeutic Class	Human IgG1κ monoclonal antibody
Formulation(s)	50 mg/0.5 mL single-dose pre-filled syringe 100 mg/1 mL single-dose pre-filled syringe
Dosing Regimen	• 50-100 mg single IM injection in neonates and infants entering their first RSV season • 200 mg single dose administered as two IM injections in children who remain vulnerable to severe RSV disease in their second RSV season

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Beyfortus (nirsevimab) is necessary to ensure the benefits outweigh its risks. AstraZeneca AB submitted a Biologics License Application (BLA) 761328 for nirsevimab with the proposed indication for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in neonates and infants entering or during their first RSV season and children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. The potential serious risks associated with nirsevimab are hypersensitivity reactions and thrombocytopenia. The applicant did not submit a proposed REMS but included a pharmacovigilance plan in the submission consisting of routine risk minimization measures.

The Division of Risk Management (DRM) and the Division of Antivirals (DAV) agree that a REMS is not needed to ensure the benefits of nirsevimab outweigh its risks. The efficacy of nirsevimab was supported by data from two randomized, placebo-controlled clinical trials in two pediatric patient populations entering their first RSV season. One study evaluated preterm infants born ≥ 29 to < 35 weeks gestational age (wGA), whereas the second study evaluated term and late preterm infants born ≥ 35 wGA. Nirsevimab significantly reduced the incidence of the primary endpoint, medically-attended RSV lower respiratory tract infection, in the two trials with a relative risk reduction (RRR) versus placebo of 70.1% and 74.9%, respectively. .The potential risks associated with nirsevimab of serious or severe hypersensitivity reactions and use in patients with clinically significant bleeding disorders will be described in the Warnings and Precautions of the Prescribing Information. At the time of this review, none of these risks warrant a Boxed Warning. The likely prescribers of nirsevimab will be neonatologists, pediatricians, primary care providers, and other pediatric specialists who should have experience managing the potential risks associated with nirsevimab.

1 Introduction

This review evaluates whether a REMS for the new molecular entity (NME)[a] nirsevimab is necessary to ensure the benefits outweigh its risks. AstraZeneca AB submitted a Biologics License Application (BLA) 761328 for nirsevimab with the proposed indication for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in neonates and infants entering or during their first RSV season and children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. This application is under review in the Division of Antivirals (DAV). The Applicant did not submit a proposed REMS but included a pharmacovigilance plan in the submission.

2 Background

2.1 PRODUCT INFORMATION

Nirsevimab is a monoclonal antibody that binds and locks the prefusion conformation of the RSV F glucoprotein to block viral entry into the host cell.[1] Nirsevimab has a modififed Fc region to prolong the serum half-life of the antibody. The duration of protection offered by a single dose extends through 5 months. Nirsevimab is proposed for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory

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

tract disease in neonates and infants entering or during their first RSV season and children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. Nirsevimab will be supplied as single-dose pre-filled syringes that contain 50 mg in 0.5 mL or 100 mg in 1 mL. The proposed dose in neonates and infants entering their first RSV season is 50 to 100 mg, depending on body weight, and is given as a single intramuscular (IM) injection. For children who remain vulnerable to severe RSV disease in the second RSV season, the proposed dose is 200 mg administered as a single dose using two IM injections.[b] Nirsevimab was approved by the European Medicines Agency in October 2022, and by the United Kingdom Medicines and Healthcare products Regulatory Agency in November 2022.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761328 relevant to this review:

- 3/27/2015: Fast Track designation granted.
- 2/1/2019: Breakthrough therapy designation granted.
- 9/26/2022: Submission of BLA 761328 for the prevention of RSV lower respiratory tract disease in neonates and infants entering or during their first RSV season and children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.
- 2/7/2023: The Mid-Cycle Communication meeting was held between the Agency and the Applicant via videoconference. The Agency informed the Appilcant that there are no major safety concerns identified at this time and there is currently no need for a REMS.
- 5/25/2023: The Late-Cycle meeting was held between the Agency and the Applicant via videoconference. The Applicant was informed that no issues relating to REMS have been identified at this time.
- 6/8/2023: The application was discussed at a meeting of the Antimicrobial Drugs Advisory Committee.

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.[2,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]

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

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.[3] 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.[2]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

No RSV vaccine is available for use in children, though infant and maternal RSV vaccines are in development. The Agency approved two RSV vaccines, Arexvy and Abrysvo, in May 2023 for use in patients 60 years of age and older. Challenges to development of an RSV vaccine for young infants include immature immunity, suppression of immune response by maternal antibody, and antigenically divergent virus strains, among other reasons. Palivizumab, BLA 103770, is a humanized monoclonal antibody against the RSV F glycoprotein that was approved in 1998 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. Palivizumab is administered intramuscularly once monthly throughout RSV season, typically for a maximum of five doses.[4]

4 Benefit Assessment

The efficacy of nirsevimab was evaluated in three clinical trials at Day 150 post dose, corresponding to a typical 5-month RSV season. Study D5290C00003 (Study 3) [NCT02878330] and Study D5290C00004 (Study 4) [NCT03979313] were randomized, double-blind, placebo-controlled trials that evaluated a single IM dose of nirsevimab or placebo in two pediatric patient populations entering their first RSV season. Patients were randomized 2:1 nirsevimab vs. placebo. The Study 3 population was comprised of very and moderately preterm infants born ≥ 29 to < 35 weeks gestational age (wGA) whereas the Study 4 population was comprised of term and late preterm infants born ≥ 35 wGA. The primary efficacy endpoint in each trial was medically attended (MA) RSV lower respiratory tract infection (bronchiolitis or pneumonia); the secondary efficacy endpoint was MA RSV lower respiratory tract infection with hospitalization. In addition to Studies 3 and 4, Study D5290C00005 (Study 5) [NCT03959488], was a randomized, double-blind, palivizumab-controlled clinical trial of nirsevimab in infants born less than 35 wGA and infants with chronic lung disease of prematurity or hemodynamically significant congenital heart disease. Study 5 was not powered for efficacy, but the incidence of MA RSV lower respiratory tract infection was assessed as a secondary efficacy endpoint.

In Study 3, 969 patients were randomized to receive nirsevimab 50 mg IM and 484 patients were randomized to receive placebo. The incidence of the primary endpoint, MA RSV lower respiratory tract infection, was 2.6% in the nirsevimab group compared with 9.5% in the placebo group, for a relative risk reduction (RRR) vs. placebo of 70.1% (95% CI 52.3, 81.2; $p < 0.001$). Nirsevimab reduced the incidence of the secondary endpoint, MA RSV lower respiratory tract infection with hospitalization, for an RRR vs. placebo of 78.4% (95% CI 51.9, 90.3; $p = 0.0002$).

In the primary cohort of Study 4, 994 patients received nirsevimab (50 mg IM for patients weighing < 5 kg or 100 mg IM for patients weighing ≥ 5 kg at the time of dosing) and 496 patients received placebo. The incidence of the primary endpoint, MA RSV lower respiratory tract infection, was 1.2% in the nirsevimab group compared with 5.0% in the placebo group, for an RRR versus placebo of 74.9% (95% CI 50.6, 87.3; p < 0.001). Nirsevimab also reduced the incidence of the secondary endpoint, MA RSV lower respiratory tract infection with hospitalization, with an RRR vs. placebo of 60.2%. However, this result did not reach statistical significance (95% CI -14.6, 86.2; p = 0.09).[e]

In Study 5, the incidence of MA RSV lower respiratory tract infection through 150 days post dose in patients during their first RSV season was 0.6% in the nirsevimab group and 1.0% in the palivizumab group. Although the study was not designed to demonstrate efficacy, the descriptive efficacy data demonstrated a similar proportion of events in the two treatment groups.

5 Risk Assessment & Safe-Use Conditions

The focus of the risk assessment for this review are the serious adverse events (SAEs) associated with nirsevimab in Study 3, Study 4, and Study 5. The safety population includes 968 patients who received nirsevimab in Study 3, 1,998 patients who received nirsevimab in Study 4, and 614 patients who received nirsevimab entering their first RSV season in Study 5.

5.1 SERIOUS ADVERSE EVENTS

In Study 3, SAEs occurred in 11% (N=108/968) of patients who received nirsevimab and 17% (81/479) of patients who received placebo. In Study 4, SAEs occurred in 6% (125/1,998) of patients who received nirsevimab and 7% (74/996) of patients who received placebo, and in Study 5, SAEs occurred in 13% (80/614) of patients who received nirsevimab and 13% (38/304) of patients who received palivizumab.[5]

Serious adverse events reported in at least 1% of patients of any of the three studies were either respiratory tract infections (pneumonia, bronchitis and bronchiolitis) or gastroenteritis. The percentages of patients in the nirsevimab and palivizumab arms with SAEs of pneumonia and bronchiolitis were low and similar in both groups. See Table 1 below for a comparison of the incidence of serious respiratory tract infections between treatment and control groups in the three studies. Gastroenteritis was reported as an SAE in 1% of patients who received nirsevimab in Study 5 and in less than 1% of patients in Studies 3 and 4. However, the overall incidence of gastroenteritis SAEs in the trials of nirsevimab was very low. Overall, the incidence of SAEs was low, and the types of SAEs reported are consistent with childhood illnesses.[f,6]

[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.*

Table 1. Studies 3, 4, 5 respiratory tract serious adverse events of bronchiolitis, bronchitis, and pneumonia

	Study 3		Study 4		Study 5	
Preferred Term	Nirsevimab N=968	Placebo N=479	Nirsevimab N=1998	Placebo N=996	Nirsevimab N=614	Palivizumab N=304
Bronchiolitis	20 (2%)	21 (4%)	24 (1%)	17 (2%)	12 (2%)	4 (1%)
Bronchitis	14 (1%)	11 (2%)	2 (0.1%)	4 (0.4%)	5 (1%)	2 (1%)
Pneumonia	13 (1%)	10 (2%)	9 (1%)	5 (1%)	5 (0.8%)	1 (0.3%)

Source: BLA 761328. Joint Assessment Meeting Slides, Clinical Safety Review, January 19, 2023; Study 4 Interim Clinical Study Report–Primary Analysis and Safety Analysis, Table 74, BLA 761328, September 26, 2022.

Deaths

Of the 2,966 patients who received nirsevimab in Study 3 and Study 4, there were six deaths (0.2%). Study 5 and an additional single-dose study reported a total of six deaths in patients who received nirsevimab. The clinical reviewer concluded that there is a plausible cause for each death and none of the deaths were likely related to nirsevimab.[7]

5.2 Adverse Events of Special Interest

No adverse events which were categorized as anaphylaxis, anaphylactic reaction, or hypersensitivity reaction were reported in any of the nirsevimab trials submitted with the BLA.[6] The Prescribing Information includes a proposed Warning and Precaution that states serious hypersensitivity reactions, including anaphylaxis, have been observed with other human immunoglobulin G1 (IgG1) monoclonal antibodies, and to initiate appropriate treatment if signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur. In addition, as with any other IM injections, the labeling includes recommendations to use with caution in individuals with thrombocytopenia or coagulation disorders is included as a potential risk in the Warnings and Precautions.[8]

6 Expected Postmarket Use

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

7 Risk Management Activities Proposed by the Applicant

The Applicant submitted a European Medicines Agency Risk Management Plan that asserts routine risk minimization measures for nirsevimab are considered adequate and are included in the labeling. The plan includes an adverse drug reaction follow-up form for postmarketing events of thrombocytopenia.

8 Discussion of Need for a REMS

The review team recommends approval of nirsevimab on the basis of the efficacy and safety information currently available. RSV can cause severe lower respiratory tract disease, including bronchiolitis, bronchospasm, pneumonia, and acute respiratory failure in children. Infants born prematurely or with bronchopulmonary dysplasia or congenital heart disease are particularly susceptible to severe disease. Nirsevimab reduced the incidence of MA RSV lower respiratory tract infection with a relative risk reduction versus placebo of 70.1% and 74.5% in Study 3 and Study 4, respectively.

The application was discussed by the Antimicrobial Drugs Advisory Committee on June 8, 2023. The committee voted 21-0 that the benefits of nirsevimab outweigh the risks for the prevention of RSV lower respiratory disease in neonates and infants born during or entering their first RSV season; the committee also voted 19-2 that the benefits of nirsevimab outweigh the risks for the prevention of RSV lower respiratory disease in children up to 24 months of age who remain vulnerable to severe RSV disease throughout their second RSV season.

The most common SAEs associated with nirsevimab were respiratory tract infections and gastroenteritis. The potential risks of hypersensitivity, anaphylaxis, and use in patients with clinically significant bleeding disorders will be communicated in Warnings and Precautions. The clinical reviewer concluded the potential risks can be appropriately managed through use of the labeling. In addition to standard postmarket pharmacovigilance practices for nirsevimab, the Agency plans to collaborate with the Centers for Disease Control and Prevention on safety data collection through use of an active surveillance platform with claims-based data sources.[6]

This reviewer recommends that, if nirsevimab is approved, a REMS is not necessary to ensure its benefits outweigh the risks. The potential risks will be adequately described in the labeling. None of these risks warrant a Boxed Warning. The clinicians who will prescribe nirsevimab are familiar by their experience and training in the management of the potential risks. Additional risk mitigation measures beyond labeling are not necessary.

9 Conclusion & Recommendations

Based on the integrated review, the benefit-risk profile is favorable, therefore, DRM and DAV agree that a REMS is not necessary for nirsevimab to ensure the benefits outweigh the risks. The availability of nirsevimab will provide a new, effective, and convenient single-dose administration option for the prevention of RSV lower respiratory tract disease in infants, including neonates, and in high-risk children up to 24 months of age.

10 Appendices

10.1 References

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5. Food and Drug Administration. Division of Antivirals. Beyfortus (nirsevimab) BLA 761328. Joint Assessment Meeting Slides: Clinical Safety Review. January 19, 2023.
6. Food and Drug Administration Briefing Document. Antimicrobial Drugs Advisory Committee Meeting. BLA 761328. Nirsevimab. June 8, 2023.
7. Food and Drug Administration. Beyfortus (nirsevimab). BLA 761328. Integrated Review. July 14, 2023.
8. Beyfortus (nirsevimab). BLA 761328. Draft Prescribing Information. June 23, 2023.

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