CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761328Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: July 7, 2023

To: Saebyeol Jang, Project Manager
Division of Antivirals (DAV)

From: L. Sheneé Toombs, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for BEYFORTUS (nirsevimab-alip) injection, for intramuscular use

NDA: BLA 761328

In response to DAV's consult request dated October 12, 2022, OPDP has reviewed the proposed product labeling (PI) and Patient Package Insert (PPI) for the original BLA submission for BEYFORTUS (nirsevimab-alip) injection, for intramuscular use.

PI/PPI: OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on June 23, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI, and comments were sent under separate cover on July 5, 2023.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on June 20, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Sheneé Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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/s/

LATOYA S TOOMBS
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	June 29, 2023
To:	Saebyeol Jang, PhD, RAC Regulatory Project Manager **Division of Antivirals (DAV)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** LaToya Sheneé Toombs, PharmD, CPH Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	BEYFORTUS (nirsevimab-alip)
Dosage Form and Route:	injection for intramuscular use
Application Type/Number:	BLA 761328
Applicant:	AstraZeneca AB

1 INTRODUCTION

On September 26, 2022, AstraZeneca AB submitted for the Agency's review an original Biologic License Application (BLA) 761328 for BEYFORTUS (nirsevimab-alip) injection. BEYFORTUS is a long-acting Respiratory Syncytial Virus (RSV) F protein inhibitor monoclonal antibody with a proposed indication for the prevention of the RSV lower respiratory tract disease in:

- Neonates and infants entering or during their first RSV season.
- Children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antivirals (DAV) on October 12, 2022, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for BEYFORTUS (nirsevimab-alip) injection for intramuscular use.

2 MATERIAL REVIEWED

- Draft BEYFORTUS (nirsevimab-alip) injection PPI received on September 26, 2022, and received by DMPP and OPDP on June 23, 2023.
- Draft BEYFORTUS (nirsevimab-alip) Prescribing Information (PI) received on September 26, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 23, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
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BARBARA A FULLER
06/29/2023 02:40:56 PM

LASHAWN M GRIFFITHS
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Clinical Inspection Summary

Date	May 18, 2023
From	Tina Chang, M.D., Medical Officer Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Melisse Baylor, M.D., Clinical Reviewer Mary Singer, M.D., Ph.D., Clinical Team Leader Saebyeol Jang, Ph.D., RAC-US Regulatory Project Manager Division of Antiviral (DAV)
BLA #	761328
Applicant	AstraZeneca AB
Drug	MEDI8897 (nirsevimab)
NME (Yes/No)	Yes
Proposed Indication(s)	Indicated for 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.
Consultation Request Date	November 22, 2022
Summary Goal Date	June 26, 2023
Action Goal Date	July 26, 2023
PDUFA Date	September 26, 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Madhi, Talosi, Saenz Llorens, and Domachowske were inspected in support of BLA 761328 covering three clinical studies, D5290C00003, D5290C00004, and D5290C00005. Despite some minor protocol deviations, the studies appear to have been conducted adequately, and the data generated by these clinical investigator (CI) sites appear acceptable in support of this BLA.

II. BACKGROUND

BLA 761328 was submitted in support of the use of MEDI8897 (nirsevimab) for the indication of 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. According to the sponsor, nirsevimab is a recombinant human IgG monoclonal antibody to RSV fusion protein, blocking cell entry of RSV. The sponsor submitted one Phase IIb study, D5290C00003, and two Phase 3 studies, D5290C00004 and D5290C00005 to support this BLA. The following briefly describes the three protocols:

D5290C00003, "A Phase 2b Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of MEDI8897, a Monoclonal Antibody With an Extended Half-life Against Respiratory Syncytial Virus, in Healthy Preterm Infants."

Protocol D5290C00003 was a Phase IIb, multicenter, randomized, double-blind, placebo-controlled safety, PK, and efficacy study. The primary objective was to assess the efficacy of nirsevimab when administered as a single 50 mg intramuscular (IM) dose to healthy preterm infants that had been born between 29 weeks 0 days and 34 weeks 6 days gestational age and entering their first RSV season for the reduction of medically attended (MA) lower respiratory tract infection (LRTI) caused by reverse-transcriptase polymerase chain reaction (RT-PCR) confirmed RSV, compared to placebo.

Sites: The study was conducted at 164 sites in 23 countries: 136 sites in 17 countries (Belgium, Bulgaria, Canada, Czech Republic, Estonia, Finland, France, Hungary, Italy, Latvia, Lithuania, Poland, Spain, Sweden, Turkey, United Kingdom, and US) in the northern hemisphere and 28 sites in 6 countries (Argentina, Australia, Brazil, Chile, New Zealand, and South Africa) in the southern hemisphere.

Subjects: A total of 1453 subjects were randomized (i.e., 966 subjects received nirsevimab and 481 subjects received placebo) and 1367 subjects completed the study (i.e., 913 who received nirsevimab and 454 who received placebo completed the study).

Study initiation and completion dates: 3 November 2016 (first patient, first visit); 6 December 2018 (last patient, last visit)

Database lock date: 12 February 2019

Subjects were randomly assigned in a 2:1 ratio to receive a single 50 mg intramuscular (IM) dose, pre-filled syringe of nirsevimab or placebo (0.9% saline). Randomization was stratified by temperate zones in the northern and southern hemisphere and by subject age at the time of randomization (i.e., ≤ 3 months, > 3 to ≤ 6 months, > 6 months). Subjects were monitored throughout the study for LRTI. All subjects who sought medical attention for a respiratory illness (inpatient or outpatient setting) were evaluated for the occurrence of LRTI. Subjects who had a primary hospitalization for a respiratory illness, a respiratory deterioration during a hospitalization, or who sought outpatient medical attention, including emergency room (ER) visits for a respiratory illness, were assessed for RSV by diagnostic testing of respiratory secretions and clinical assessment of the presence of LRTI. The study was conducted over two years. Efficacy was followed until Day 151 (5-month RSV season) and safety followed for 360 days after dosing (Day 361).

Key inclusion criteria: Healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days GA who did not receive RSV prophylaxis (palivizumab) based on the AAP (American Academy of Pediatrics Committee on Infectious Diseases, 2014) or other local or national guidelines. Please see protocol for full details pertaining to eligibility criteria.

Primary Efficacy Endpoint: Incidence of medically attended (MA) RSV LRTI (inpatient and

outpatient) over the duration of the 5-month RSV season (i.e., through 150 days post dose).

The diagnosis of RSV LRTI required having a respiratory sample positive for RSV performed centrally via reverse-transcriptase polymerase chain reaction (RT PCR) and objective clinical LRTI criteria, which are described below. Respiratory secretions for RSV testing must have been collected within two days of diagnosis for medically attended outpatient lower respiratory tract infections or hospital admission for, or new onset in hospital of, a respiratory illness.

Definition of LRTI: Documented at least one of the physical exam findings of rhonchi, rales, crackles, or wheeze AND at least one of the clinical signs:

- ↑ RR at rest (age < 2 months ≥ 60 breaths/min, age 2-6 months ≥ 50 breaths/min, age >6 months-2 years ≥ 40 breaths/min), or
- Hypoxemia (in room air: O2 saturation <95% at altitudes ≤ 1800 meters or <92% at altitudes >1800 meters), or
- Clinical signs of severe respiratory disease (e.g., acute hypoxic or ventilator failure; new onset apnea; nasal flaring; intercostal, subcostal, or supraclavicular retractions; or grunting), or
- Dehydration secondary to inadequate oral intake due to respiratory distress (need for intravenous fluid).

D5290C00004, "A Phase 3 Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of MEDI8897, a Monoclonal Antibody With an Extended Half-life Against Respiratory Syncytial Virus, in Healthy Late Preterm and Term Infants (MELODY)"

The study is an ongoing Phase 3, multicenter, randomized, double-blind, placebo-controlled, safety, PK, and efficacy study to assess the efficacy of nirsevimab when administered as a single fixed IM dose to infants that had been born at 35 weeks gestational age or later and entering their first respiratory syncytial virus (RSV) season, in reducing medically attended (MA) lower respiratory tract infection (LRTI) due to RT-PCR confirmed RSV, compared to placebo.

Sites: 211 sites in 31 countries

Subjects: A total of 3012 subjects were randomized (i.e., 2009 subjects received nirsevimab and 1003 received placebo) and 1357 subjects completed the study as of 31 March 2022 (i.e., 907 who received nirsevimab and 450 who received placebo completed the study).

Study initiation and completion dates: 23 July 2019 (first patient, first visit); study is still ongoing in the follow-up period.

Data cut-off date (database lock date): 11 March 2021 (14 April 2021) for Primary Analysis complete to Day 361; 9 August 2021 (10 September 2021) for Primary Analysis complete to Day 510; 31 March 2022 (29 April 2022) for Safety Analysis complete to Day 151.

Subjects were randomly assigned in a 2:1 ratio to receive a single IM dose of nirsevimab or placebo. The dose level was based on the infant's body weight: 50-mg for infants weighing <5 kg or 100-mg for infants weighing ≥5 kg. Randomization was stratified by hemisphere (northern, southern) and by subject age at the time of randomization (≤ 3 months, > 3 to ≤ 6 months, > 6 months). A total of approximately 3,000 infants were randomized. However, the impact of the coronavirus disease 2019 (COVID-19) pandemic on RSV circulation led to a protocol amendment, in consultation with regulatory authorities (Type B meeting, December 2020), to analyze the primary endpoint of MA RSV LRTI based on the first 1500 subjects enrolled to the Primary Cohort. This resulted in two study phases or two study cohorts, a Primary Cohort, and a Safety Cohort:

1) The Primary Cohort (1490 randomized subjects): The primary objective was met based on the Primary Cohort data. The primary analysis was conducted after all randomized subjects from the Northern Hemisphere (NH) 2019/2020 and Southern Hemisphere (SH) 2020 enrollment seasons (with South Africa being the only SH country). Subjects had been followed through 360 days post dose and included all efficacy data collected as of 11 March 2021.

2) The Safety Cohort (1522 randomized subjects) was to include subjects from the NH 2020/2021 and SH 2021 enrollment seasons. Although efficacy data was collected for the safety cohort, only descriptive summaries were provided. All subjects were followed for approximately 510 days after dosing. For the evaluation of safety, the study included all available safety data from both cohorts through 30 days post dose at the time of data cut-off for the Safety Analysis of 31 March 2022.

Subjects were monitored throughout the study for LRTI. All subjects seeking medical attention for a respiratory illness (in either the inpatient or outpatient setting) would be evaluated for the occurrence of LRTI. All subjects found to have an LRTI and all subjects who required hospitalization for a respiratory infection, even if there is not a diagnosis of LRTI, should have had respiratory samples obtained and respiratory assessment forms completed. Samples were collected for all these events (even those not meeting the protocol definition of LRTI). Subjects who had a primary hospitalization for a respiratory infection (i.e., upper or lower tract), or a respiratory deterioration during a hospitalization, or who sought outpatient medical attention (including ER visits) for a lower respiratory illness, would be assessed clinically for the presence of LRTI and for RSV by central laboratory diagnostic testing of respiratory secretions. In addition to the clinical assessment of LRTI, there was a protocol definition using objective criteria for the determination of a medically attended LRTI, the same as in -003.

Key inclusion criteria: Healthy late preterm and term infants who had been born ≥ 36 weeks 0 days GA who would not receive RSV prophylaxis based on the American Academy of Pediatrics (AAP) or other local or national guidelines and are entering their first RSV season at the time of screening. Please see protocol for full details pertaining to the eligibility criteria, which were similar between study -003 and -004, except for the differences in criteria for GA at birth.

Primary Efficacy Endpoint: Same primary efficacy endpoint as Protocol D5290C00003, with same definition of medically attended RSV LRTI.

D5290C00005, "A Phase 2/3 Randomized, Double-blind, Palivizumab-controlled Study to Evaluate the Safety of MEDI8897, a Monoclonal Antibody With an Extended Half-life Against Respiratory Syncytial Virus, in High-risk Children (MEDLEY)"

The study is an ongoing Phase II/III, multicenter, randomized, double-blind, palivizumab-controlled, safety, PK study in infants at higher risk for RSV severe disease eligible to receive palivizumab when entering their first or second RSV season. The primary objective was to evaluate the safety and tolerability of nirsevimab compared to palivizumab when administered to preterm infants entering their first RSV season and children with chronic lung disease (CLD) or congenital heart disease (CHD) entering their first and second RSV season.

Sites: For Season 1, 126 sites in 25 countries. For season 2, 58 sites in 18 countries.

Subjects: A total of 925 subjects were randomized (i.e., 616 subjects received nirsevimab and 309 received palivizumab), including 615 in the preterm cohort and 310 in the CLD/CHD cohort. 806 subjects completed the efficacy follow-up through 360 days post first dose (i.e., 543 who received nirsevimab and 263 who received palivizumab).

Only the CLD/CHD subjects proceeded to Season 2. Subjects from the CLD/CHD cohort who received nirsevimab in Season 1 were assigned to receive nirsevimab again in Season 2. Subjects from the CLD/CHD cohort who were randomized to palivizumab in Season 1 were re-randomized 1:1 to nirsevimab or palivizumab. A total of 262 subjects from the Season 1 CLD/CHD cohort proceeded into Season 2 and 104 subjects completed the efficacy follow-up through 360 days post first dose (69/180 subjects received nirsevimab during Seasons 1 and 2, 18/40 subjects received palivizumab during Season 1 and nirsevimab during Season 2, and 17/42 subjects received palivizumab during Seasons 1 and 2).

Study initiation and completion dates: July 30, 2019 (first patient, first visit)

Data cut-off date (database lock date): 30 April 2022 (31 May 2022) for Season 2 Analysis

Palivizumab eligible infants entering their first RSV season were enrolled into 1 of 2 cohorts: 1) preterm cohort, which included infants who had been preterm ≤ 35 weeks gestational age without CLD/CHD or 2) CLD/CHD cohort, which included infants with chronic lung disease of prematurity or hemodynamically significant chronic heart disease.

In Season 1, within each cohort, all subjects were randomized 2:1 to either nirsevimab or palivizumab. Subjects in the nirsevimab group received a single fixed IM dose of nirsevimab followed by 4 once-monthly IM doses of placebo while subjects in the palivizumab group received 5 once-monthly IM doses of 15 mg/kg palivizumab.

The Season 2 study population included subjects from the CLD/CHD cohort who had already participated in Season 1. Subjects from the CLD/CHD cohort who received nirsevimab in Season 1 were assigned to receive nirsevimab again in Season 2. Subjects from the CLD/CHD cohort who were randomized to palivizumab in Season 1 were re-randomized 1:1 to

nirsevimab or palivizumab. Subjects in the Season 2 nirsevimab groups received a single fixed IM dose of 200 mg nirsevimab followed by 4 once-monthly IM doses of placebo. Subjects in the palivizumab group received 5 once-monthly IM doses of 15 mg/kg palivizumab.

Key inclusion criteria for the preterm cohort: preterm infants in their first year of life and born ≤ 35 weeks 0 days GA eligible to receive palivizumab in accordance with national or local guidelines, including those with uncomplicated small atrial or ventricular septal defects or patent ductus arteriosus, or aortic stenosis, pulmonic stenosis, or coarctation of the aorta alone.

Key inclusion criteria for the CLD/CHD cohort included subjects with CLD - infants in their first year of life and a diagnosis of CLD of prematurity requiring medical intervention/management (i.e., supplemental oxygen, bronchodilators, or diuretics) within the 6 months prior to randomization and subjects with CHD - infants in their first year of life and documented, hemodynamically significant CHD (must be unoperated or partially corrected CHD). Please see protocol for full details pertaining to eligibility criteria.

Note: Infants with hemodynamically significant acyanotic cardiac lesions must have pulmonary hypertension (≥40 mmHg measured pressure in the pulmonary artery) or the need for daily medication to manage CHD.

Primary Safety Endpoint: Safety and tolerability of nirsevimab as assessed by the occurrence of all treatment-emergent adverse events, treatment-emergent serious adverse events, adverse events of special interest, and new onset chronic disease.

Rationale for Site Selection

- Dr. Shabir Madhi (Site #2002937) was selected for GCP inspection for all three studies D5290C00003, D5290C00004, and D5290C00005 since this site was one of the top enrolling sites with the greatest influence on the primary efficacy results.

- Dr. Gyula Talosi (Site #2002894) was selected for GCP inspection for study D5290C00003 since this site was one of the top enrolling sites with the greatest influence on the primary efficacy results for study D5290C00003.

- Dr. Xavier Saenz Llorens (Site #2004872) was chosen for GCP inspection for study D5290C00004 since this site was one of the top enrolling sites with the greatest influence on the primary efficacy results for study D5290C00004.

- Dr. Joseph Domachowske (Site # 2004169) was selected for GCP inspection for study D5290C00005 based on number of enrolled subjects for study D5290C00005.

III. RESULTS (by site):

1. Dr. Shabir A. Madhi
Site #2002937 (Protocol D5290C00003)
Site #2004109 (Protocol D5290C00004)
Site #2004078 (Protocol D5290C00005)
New Nurses Residence, Chris Hani
Baragwanath, Academic Hospital, Chris
Hani Road, Diepkloof, Wits Vida
Research Unit, 11th Floor West Wing
Soweto, South Africa
PDUFA Inspection Dates: February 20 – March 3, 2023

For Protocol D5290C00003, 92 subjects were screened, 78 subjects were randomized, and 77 subjects had completed the study. Per the applicant's data line listings, Subject - (b) (6) (randomized to placebo) died on Day 26.

For Protocol D5290C00004, 191 subjects were screened, 171 subjects were randomized, and 151 subjects had completed the study. Per the applicant's data line listings, eight subjects were withdrawn by their parent/guardian for unspecified reasons, and ten subjects were lost to follow-up. Subject - (b) (6) (randomized to nirsevimab) died on Day 143, and Subject - (b) (6) (randomized to nirsevimab) died on Day 338.

For Protocol D5290C00005, 45 subjects were screened, 39 subjects were randomized and completed the study. Per the applicant's data line listings, four subjects were withdrawn by their parent/guardian for unspecified reasons, one subject was lost to follow-up, and one subject relocated.

An audit of the study records was conducted for 23 of the 78 randomized subjects for study D5290C00003, 7 of the 171 randomized subjects for study D5290C00004, and 6 of the 41 randomized subjects for study D5290C00005. Records reviewed included, but were not limited to, protocol versions, eligibility, informed consent, protocol adherence, protocol deviations, monitoring reports, case report forms, ethics committee approvals, delegation records, medical histories, financial disclosures, adverse event reporting, source records including those related to verification of the primary efficacy endpoint of incidence of medically attended lower respiratory tract infection (MA RSV LRTI) over the duration of the 5-month RSV season in studies D5290C00003 and D5290C00004. All source records were in paper format.

Source records were reviewed for missed cases of MA RSV LRTI as well as comparing the dates of respiratory sample collection, central laboratory results, visit settings, exam findings, and clinical signs in the source documents at the site against the sponsor's data line listings for 23 of the 78 randomized subjects in study D5290C00003 and 7 of the 171 randomized subjects in study D5290C00004. No discrepancies or missed cases of MA RSV LRTI were noted.

For study D5290C000003, there were unreported adverse events of cough, nasal congestion and runny nose for Subject - (b) (6) (randomized to nirsevimab on (b) (6)) documented

in the adverse event (AE) log. The adverse events started on (b) (6), was treated with amoxicillin and saline drops, and resolved by (b) (6).

For study D5290C00005, there were three unreported adverse events for two subjects. Subject - (b) (6) (randomized to nirsevimab on (b) (6)) was documented on the AE log and progress notes as having a mild heat rash on (b) (6), and mild nasal congestion on (b) (6). Stop dates are unknown for the heat rash and nasal congestion. Per the AE log and progress notes, Subject - (b) (6) (randomized to palivizumab on (b) (6)) was documented as having an upper respiratory tract infection (URTI) that was then deleted and upgraded to a moderate lower respiratory tract infection (LRTI), which ended on (b) (6). No start date was recorded in the source documents for this adverse event.

Reviewer's comment: Rash is already included in the sponsor's draft label. The unreported adverse events of cough and nasal congestion that occurred in Subject - (b) (6) and the unreported adverse event of URTI/LRTI that occurred in Subject - (b) (6) did not meet criteria for MA RSV LRTI and are otherwise isolated events unlikely to impact the safety profile of the drug.

2. **Dr. Joseph Domachowske**
   Site #2004169 (Protocol D5290C00005)
   SUNY Upstate Medical University
   750 East Adams Street, Room 5802
   Syracuse, NY 13210
   PDUFA Inspection Dates: January 9-12, 2023

At this site for Protocol D5290C00005, Dr. Domachowske screened and randomized 20 subjects. Out of 20 randomized subjects, 14 subjects had completed one season of the study. Per the applicant's data line listings, three subjects withdrew consent, two subjects were lost to follow-up, and one subject was removed from the study due to a family move.

Records were reviewed for all 20 screened subjects at this site. Records reviewed included, but were not limited to, protocol versions, eligibility, informed consent, adverse events reporting, protocol adherence, protocol deviations, IRB approvals/acknowledgments, sponsor/IRB correspondence, monitoring reports, investigational product accountability records, and financial disclosures. All source records were in paper format.

The primary endpoint of study D5290C00005 was safety. There was no evidence of underreporting of adverse events or of unreported protocol deviations.

3. **Dr. Xavier Saenz Llorens**
   Site # 2004872 (Protocol D5290C00004)
   Calle 1 Y 2 Edificio Plaza Nuevo
   Urbanizacion Nuevo
   Tocumen, Panama
   PDUFA Inspection Dates: February 13-17, 2023

At this site for Protocol D5290C00004, 228 subjects were screened, 181 subjects were randomized, and 171 subjects had completed the study at the time of inspection as the study was still in the follow-up period. Per the source records, two subjects withdrew from the study after moving, two subjects withdrew consent, and six subjects were lost to follow-up.

An audit of the study records was conducted for 135 subjects for adverse events reporting, 51 subjects for reporting of protocol deviations, eligibility, concomitant medications, and informed consent, and 32 subjects for efficacy endpoint data verification. Records reviewed included, but were not limited to, protocol versions, eligibility, informed consent, protocol adherence, protocol deviations, monitoring reports, investigational product accountability records, case report forms, ethics committee approvals, delegation records, medical histories, financial disclosures, adverse event reporting, source records including those related to verification of the primary efficacy endpoint of incidence of medically attended RSV LRTI over the duration of the 5-month RSV season. Source records for subjects consisted of paper copies and electronic medical records.

Subject - (b) (6) was enrolled despite meeting exclusion criterion #5 in protocol amendment #1, dated (b) (6), which stated that a subject would be excluded from study participation if the subject was on any drug (chronic or other) within 7 days prior to randomization or expected receipt during the study with the exception of multivitamins and iron as well as infrequent use of over-the-counter (OTC) medications for the systemic treatment of common childhood symptoms (e.g., pain relievers) that may be permitted according to the judgment of the investigator. The subject was taking isoniazid from (b) (6), to (b) (6), and was randomized to placebo on (b) (6).

Reviewer's comment: This protocol deviation was documented during routine monitoring visits and is in the sponsor's protocol deviation data line listing. Enrolling a single ineligible subject is unlikely to affect the overall efficacy and safety results of the study.

The source records documenting dates of respiratory sample collection, central laboratory results, visit settings, exam findings, and clinical signs for the primary efficacy endpoint data (incidence MA RSV LRTI cases over the duration of the 5-month RSV season) were reviewed and verified against the sponsor's data line listings for 32 of the 181 randomized subjects. No discrepancies or missed cases of MA LRTI were noted. There was no evidence of underreporting of adverse events or of unreported protocol deviations.

4. **Dr. Gyula Talosi**
   Site #2002894 (Protocol D5290C00003)
   Gyermekosztaly (Pediatric Department)
   Bacs-Kiskun Megyei Oktatokorhaz, Nyiri Ut 38
   Kecskemet, Bacs-Kiskun, 6000
   Hungary
   PDUFA Inspection dates: February 6-9, 2023

At this site for Protocol D5290C00003, 23 subjects were screened and randomized. All

randomized subjects had completed the study.

An audit of the study records was conducted for all 23 randomized subjects. Records reviewed included, but were not limited to, protocol versions, eligibility, informed consent, protocol adherence, protocol deviations, monitoring reports, case report forms, ethics committee approvals, delegation records, medical histories, financial disclosures, adverse event reporting, source records including those related to verification of the primary efficacy endpoint of incidence of medically attended RSV LRTI over the duration of the 5-month RSV season. All source records for subjects consisted of paper copies of electronic hospital records.

The source records documenting dates of respiratory sample collection, central laboratory results, visit settings, exam findings, and clinical signs for the primary efficacy endpoint data (incidence of MA RSV LRTI cases over the duration of the 5-month RSV season) were reviewed and verified against the sponsor's data line listings for all 23 randomized subjects. No discrepancies or missed cases of MA LRTI were noted. There was no evidence of underreporting of adverse events or of unreported protocol deviations.

{See appended electronic signature page}

Suyoung Tina Chang, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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CONCURRENCE: {See appended electronic signature page}

Jenn Sellers, M.D., Ph.D.
Branch Chief
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Office of Scientific Investigations

CC:

Central Doc. Rm.
Review Division /Division Director/
Review Division /Medical Team Leader/
Review Division /Project Manager/
Review Division/MO/
OSI/Office Director/
OSI/DCCE/ Division Director/
OSI/DCCE/Branch Chief/
OSI/DCCE/Team Leader/
OSI/DCCE/GCP Reviewer/
OSI/ GCP Program Analysts/
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	February 6, 2023
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	BLA 761328
Product Name and Strength:	Beyfortus (nirsevimab-xxxx)[a] injection, 50 mg/0.5 mL and 100 mg/mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	AstraZeneca Pharmaceuticals LP
FDA Received Date:	September 26, 2022
TTT ID #:	2022-1853
DMEPA 1 Safety Evaluator:	Melina Fanari, R.Ph
Acting DMEPA 1 Team Leader:	Madhuri R. Patel, PharmD

[a] The non-proprietary name suffix for this product has not yet been determined; therefore, the placeholder nirsevimab-xxxx is used throughout this review to refer to the non-proprietary name and suffix for this product.

1 REASON FOR REVIEW

As part of the approval process for Beyfortus (nirsevimab-xxxx) injection, the Division of Antivirals (DAV) requested that we review the proposed Beyfortus prescribing information (PI), patient prescribing information (PPI), container labels and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
ISMP Newsletters*	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D-N/A
Other	E-N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed PI, container labels and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for AstraZeneca Pharmaceuticals LP. We do not have any recommendations for the proposed PPI at this time.

4 RECOMMENDATIONS FOR ASTRAZENECA PHARMACEUTICALS LP

Table 2. Identified Issues and Recommendations for AstraZeneca Pharmaceuticals LP (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	Once approved ensure that the four-letter suffix is applied appropriately to proper names across all labeling pieces for proper product naming and identification.		

Table 2. Identified Issues and Recommendations for AstraZeneca Pharmaceuticals LP (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	Revise the '100 mg/1 mL' concentration statement to '100 mg/mL' in accordance with USP General Chapter <7>.		
3.	Revise [redacted] (b) (4) so that either the strength or the proprietary name appears [redacted] (b) (4) and the color does not overlap with any other colors utilized in highlighting the strengths. [redacted] (b) (4) minimizes the difference between the strengths, which may lead to wrong strength selection errors.		
IDENTIFIED ISSUE		RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s)			
1.	'Rx Only' statement is too prominent.	Distracts from other important information on the label.	Decrease the prominence of the "Rx Only" statement as this information appears more prominent than the established name on the principal display panel.
Carton Labeling			
1.	'Must be administered by Healthcare providers' statement is missing.	The statement will help alert patients and healthcare providers.	Consider adding such a statement to the carton (must be administered by a healthcare provider).
2.	Net quantity statement missing strength designation.	Prevent wrong dose medication errors.	Revise the net quantity statements on the Principal Display Panel (PDP) from "(1 or 5) Single-dose prefilled syringe" to read "(One or Five) 0.5 mL single-dose prefilled syringe" or "(One or Five) 1 mL single-dose prefilled syringe" to clarify the net quantity statement.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Beyfortus that AstraZeneca Pharmaceuticals LP submitted on September 26, 2022.

Table 3. Relevant Product Information for Beyfortus	
Initial Approval Date	N/A
Active Ingredient	nirsevimab-xxxx
Indication	For the prevention of RSV lower respiratory tract disease in 1) Neonates and infants entering or during their first RSV season and 2) Children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season
Route of Administration	intramuscular
Dosage Form	injection
Strength	50 mg/0.5 mL in a single-dose pre-filled syringe 100 mg/ mL in a single-dose pre-filled syringe
Dose and Frequency	Infants (< 5 kg)- One 50 mg dose entering their first RSV season and Infants (≥5kg)- One 100 mg dose entering their first RSV season and for children who remain vulnerable through their second RSV season- a single fixed dose of 200 mg (2 x 100 mg)
How Supplied	Commercial packs of 1 or 5 single-use pre-filled syringes
Storage	Store refrigerated between 36°F to 46°F (2°C to 8°C). May be kept at room temperature 68°F to 77°F (20°C to 25°C) for a maximum of 8 hours. After removal from the refrigerator, must be used within 8 hours or discarded

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Beyfortus labels and labeling submitted by AstraZeneca Pharmaceuticals LP.

- Container labels and carton labeling received on September 26, 2022
- Prescribing Information and Patient Prescribing Information (Image not shown) received on September 26, 2022, available from \\CDSESUB1\evsprod\BLA761328\0001\m1\us

F.2 Label and Labeling Images

Container labels

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

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