Beyfortus® (nirsevimab-alip) | 50 mg 100 mg Injection

Beyfortus® Formulary Kit

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INDICATION AND IMPORTANT SAFETY INFORMATION

Indication

Beyfortus® is indicated for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in:

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

Important Safety Information

Contraindication

Beyfortus is contraindicated in infants and children with a history of serious hypersensitivity reactions, including anaphylaxis, to nirsevimab-alip or to any of the excipients.

Warnings and Precautions

- **Hypersensitivity Reactions Including Anaphylaxis:** Serious hypersensitivity reactions have been reported following Beyfortus administration. These reactions included urticaria, dyspnea, cyanosis, and/or hypotonia. Anaphylaxis has been observed with human immunoglobulin G1 (IgG1) monoclonal antibodies. If signs and symptoms of anaphylaxis or other clinically significant hypersensitivity reactions occur, initiate appropriate treatment.
- **Use in Individuals with Clinically Significant Bleeding Disorders:** As with other IM injections, Beyfortus should be given with caution to infants and children with thrombocytopenia, any coagulation disorder or to individuals on anticoagulation therapy.

Most common adverse reactions with Beyfortus were rash (0.9%) and injection site reactions (0.3%).

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PRODUCT MONOGRAPH

Executive Summary

Respiratory syncytial virus (RSV) is a highly contagious virus that affects people of all ages, but is most common in infants and children.[1,2] Although RSV typically manifests as an upper respiratory infection, it can cause lower respiratory tract infections (LRTIs) like bronchiolitis and pneumonia.[1,3] RSV is a seasonal virus that typically manifests as an annual epidemic starting in the fall and peaking in winter in the United States.[1]

RSV affects 68% of all infants before the age of 1 year,[3] and it is the leading cause of hospitalization in infants younger than 12 months.[4]*

Beyfortus® is a long-acting monoclonal antibody designed to provide protection against RSV lower respiratory tract disease in infants and high risk children aged <24 months.[5] Based on clinical and pharmacokinetic data, the duration of protection offered by a single dose of Beyfortus extends through 5 months.[5]

Beyfortus demonstrated efficacy in reducing the risk of medically attended (MA) LRTIs and hospitalizations across a broad range of infant populations. In clinical trials, the safety of Beyfortus was established vs placebo and palivizumab.[5-8]

*Based on leading primary diagnosis (RSV bronchiolitis, October 2015 to December 2019, rank 1, 165,930 cases [9.3%]).[4]

Overview of RSV

Seasonality of RSV

RSV is a highly contagious virus that affects people of all ages, but is most common in infants and children.[1,2] It causes a variety of respiratory illnesses that manifest as annual epidemics starting in the fall and peaking in winter.[1]

The circulation of RSV typically starts in the fall and ends in the spring. In states with a tropical climate (eg, parts of Florida and Hawaii), RSV can start earlier and last longer.[9] In states with a temperate climate, the seasonal pattern of RSV is generally persistent, with peaks occurring regularly each year during the winter months.[10] The precise start of the RSV season may vary slightly from year to year and between regions of the United States.[11,12]

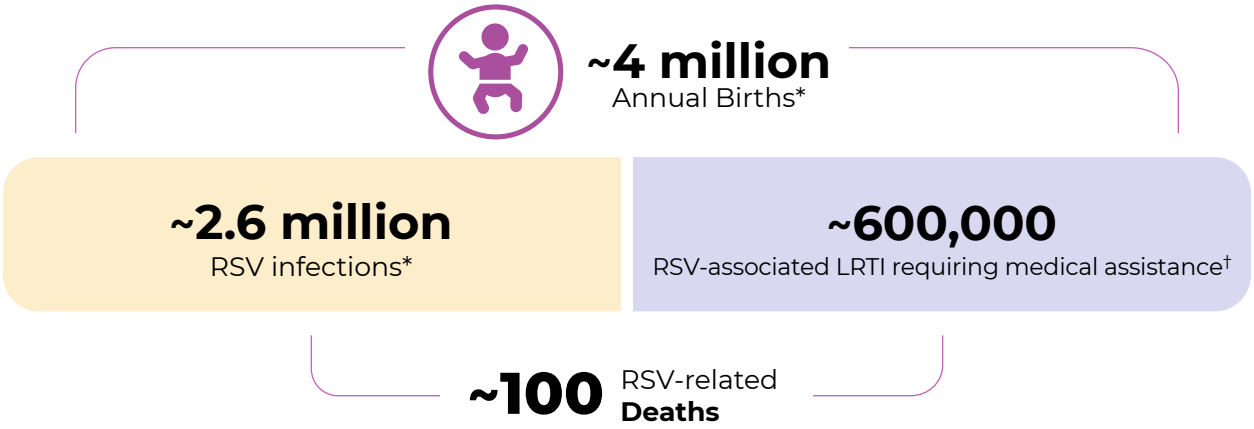
RSV is classified as a pneumovirus that has two different subtypes, A and B, which co-circulate during the same season.[2]

Burden of RSV

Approximately 2 out of 3 infants will become infected with RSV by the age of 1 year and nearly all children in the United States will have been infected with RSV by their second birthday.[3] While RSV typically manifests as an upper respiratory infection, it can cause LRTIs like bronchiolitis and pneumonia.[1,3] LRTI rates are higher in infants aged <1 year and annually during peak season.[13] Annually, approximately 20% of infants will develop an LRTI due to RSV.[3]

Several studies have shown that out of the nearly 4 million annual births in the United States, an estimated 2.6 million infants will be infected with RSV.[3,14,15]* Nearly 600,000 infants will have RSV-associated LRTIs that will need medical assistance, resulting in substantial RSV morbidity.[15]† This burden leads to about 100 annual infant deaths due to RSV.[16]

Annual Burden of RSV in US infants[3,14-16]



*Numbers estimated based on annual birth rate from 2017 birth certificates.[14]

†From a US study designed to estimate the impact of immunization strategies on RSV-associated MA LRTI in various healthcare settings among infants aged <12 months, based on the average proportion of lab-confirmed RSV visits in a national vaccine surveillance network from 2002 to 2009.[15]

Overview of RSV (continued)

Economic Burden of RSV

RSV affects 68% of all infants before the age of 1 year,[3] and it is the leading cause of infant hospitalization in infants aged <12 months.[4]*

~75% **Among children hospitalized due to RSV, ~75%** were born at full term with no underlying conditions[17,18]†‡

16x **Infants younger than 1 year are on average 16x** more likely to be hospitalized due to RSV compared with influenza[19]§

In a widely cited study, RSV was reported to cause an estimated 50% to 80% of infant bronchiolitis hospitalizations and an estimated 30% to 60% of pediatric pneumonia hospitalizations annually between November and April.[20]

Estimated Annual Burden of Medically Attended (MA) RSV LRTIs for US Infants (aged <12 months)[15,21]

~590,000
Total MA RSV LRTIs

~400,000	~150,000	~33,000 to 80,000
Other office/clinic visits	Emergency department visits	Hospitalizations

In a modeling study based on a US birth cohort, RSV was found to contribute substantially to healthcare resource utilization. It was estimated that RSV resulted in 529,915 annual MA RSV LRTIs, of which 353,563 (67%) led to primary care visits, 129,070 (24%) led to emergency department visits, and 47,281 (9%) led to hospitalizations.[22]||

*Based on leading primary diagnosis (RSV bronchiolitis, October 2015 to December 2019, rank 1, 165,930 cases [9.3%]).[4]

†Data based on a total of 1554 laboratory-confirmed RSV cases in children aged <2 years from 4 Influenza Hospitalization Surveillance Network (FluSurv-NET) sites between October 2014 and April 2015.[17]

‡Full-term infants were defined as being ≥37 weeks' gestational age (wGA) at birth. Data based on infants born April 2016 to February 2020 in the MarketScan Commercial (644,116), MarketScan Medicaid (1,025,286), and Optum Clinformatics (460,426) data sets.[18]

§Based on data for 13 states from 1993–1994 through 2007–2008 of estimated influenza and RSV hospitalizations in 5 age categories (<1, 1–4, 5–49, 50–64, and ≥65 years).[19]

||Study evaluated the health and cost outcomes associated with the use of Beyfortus® compared with the standard of care in the prevention of MA RSV-associated LRTIs in entire US birth cohort in their first RSV season in the United States.[22]

Overview of RSV (continued)

The economic burden of RSV infection is high for all infants in their first year of life, including full-term infants.[23]

Cost of Hospitalization for RSV in Full-term Infants in the US (USD 2014)[23]*

	Full-term infants (aged <12 months), N	Mean cost (SD)
First-year cost of hospitalizations for RSV		
Medicaid insured	24,487	$8,324 ($39,112)
Commercially insured	13,885	$10,570 ($30,860)
RSV ICU hospitalization costs		
Medicaid insured	1954	$35,623 ($133,320)
Commercially insured	1179	$35,864 ($79,869)
RSV ICU hospitalization costs with mechanical ventilation		
Medicaid insured	381	$69,381 ($144,109)
Commercially insured	151	$89,464 ($151,715)

*Data based on Truven Health MarketScan Multi-State Medicaid and Commercial Claims and Encounters, which contained a combined 4 million births from 2003 to 2013.[23]

ICU, intensive care unit; SD, standard deviation; USD, United States dollar.

In a systematic literature review of 17 studies published between 2014 and 2020, an episode of RSV in infants in the United States incurred an average cost of $11,973 for inpatient care (cost year not reported).[24]

- Average inpatient hospitalization costs were 68% higher for infants with commercial coverage ($15,289) compared with those covered by Medicaid ($10,394)[24]
- Of RSV discharges (N=39,407), the majority were for full-term infants (82.0%), who made up 69.9% of the $471.8 million in aggregate costs; however, extremely preterm infants incurred average inpatient costs that were more than 5x those incurred by full-term infants[24]

Overview of RSV (continued)

Current Management Strategy

Supportive care is the primary objective of disease management to ensure sufficient hydration and nutrition, with additional oxygen and mechanical ventilation as required.[25,26]

There is limited evidence for the efficacy of antiviral treatment for mild or moderate RSV infection.[25] The aerosolized antiviral agent ribavirin is approved by the FDA for the treatment of severe LRTIs due to RSV in infants and young children.[27] However, the efficacy of this treatment remains unclear.[25]

For the last decade, standard of care has been prophylaxis for the prevention of serious LRTIs caused by RSV in a small subset of the infant population.[28,29]

About Beyfortus®

Indication

Beyfortus is indicated for the prevention of respiratory syncytial virus (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.[5]

Contraindication

Beyfortus is contraindicated in infants and children with a history of serious hypersensitivity reactions, including anaphylaxis, to nirsevimab-alip or to any of the excipients.[5]

Dosing and Administration

The recommended dosage of Beyfortus in neonates and infants born during or entering their first RSV season is based on body weight and is administered as one single intramuscular (IM) injection.[5]

Recommended Dosage of Beyfortus for the First RSV Season[5]

Body Weight at Time of Dosing	Recommended Dosage
Less than 5 kg	50 mg by IM injection
5 kg and greater	100 mg by IM injection

50 mg by IM injection

100 mg by IM injection

About Beyfortus® (continued)

Dosing for children undergoing cardiac surgery with cardiopulmonary bypass[5]

For children undergoing cardiac surgery with cardiopulmonary bypass, an additional dose of Beyfortus is recommended as soon as the child is stable after surgery to ensure adequate nirsevimab-alip serum levels. The recommended dosage of Beyfortus is administered as a single IM injection.

During the first RSV season, if surgery is within 90 days after receiving Beyfortus, the additional dose should be based on body weight at the time of the additional dose, as per the table on the previous page. If more than 90 days have elapsed since receiving Beyfortus, the additional dose should be 50 mg regardless of body weight.

During the second RSV season, if surgery is within 90 days after receiving Beyfortus, the additional dose should be 200 mg, regardless of body weight. If more than 90 days have elapsed since receiving Beyfortus, the additional dose should be 100 mg, regardless of body weight.

Second RSV season: Dosing for children who remain vulnerable to severe RSV disease[5]

For children up to 24 months of age, regardless of body weight, who remain at increased risk for severe RSV disease in their second RSV season, the recommended dosage of Beyfortus is a single 200-mg dose administered as 2 IM injections (2 x 100 mg).

About Beyfortus® (continued)

The ideal timing for Beyfortus dosing is just before or near the start of the RSV season, or from birth for infants born shortly before or during the RSV season[5]*

Beyfortus Administration at the Hospital or Office Based on the Infant Birth Month and RSV Season[5]

Administration of a single dose of Beyfortus

Born	Setting	Timing	Outside the RSV season	RSV season
Before the RSV season	Office	Prior to the start of their first RSV season	For infants born before the RSV season, Beyfortus should be administered once just before or at the start of the RSV season.	
During the RSV season	Hospital	From birth		For infants born shortly before or during the RSV season, Beyfortus should be administered starting from birth.

Duration of protection of Beyfortus (extending through 5 months) | Baby birth month | Immunization with Beyfortus

If the Infant Is Born Before RSV Season	If the Infant Is Born During RSV Season
• Beyfortus may be administered at the regularly scheduled 2-, 4-, or 6-month well-baby visit closest to the start of RSV season[5]	• Administer Beyfortus in the hospital at birth, prior to discharge[5] • If not given prior to discharge, administer Beyfortus at the first office visit, within 1 week of birth[30]

- For children undergoing cardiac surgery with cardiopulmonary bypass, an additional dose of Beyfortus is recommended as soon as the child is stable after surgery; please consult the Prescribing Information for complete information on dosing in these circumstances
- Second season: for children up to 24 months of age, regardless of body weight, who remain at increased risk for severe RSV, the recommended dosage of Beyfortus is a single 200 mg dose administered as 2 IM injections (2 x 100 mg)

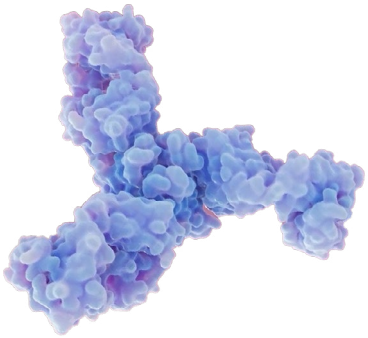
Administration and storage[5]

Beyfortus is available in a 50-mg and a 100-mg prefilled syringe. Beyfortus must be administered by a healthcare provider.

Beyfortus injection is a sterile, preservative-free, clear to opalescent, colorless to yellow solution for IM injection. It should be stored refrigerated between 36 °F and 46 °F (2 °C and 8 °C). Beyfortus 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, Beyfortus must be used within 8 hours or discarded.

Beyfortus should be stored in the original carton to protect it from light until the time of use. Do not freeze, shake, or expose Beyfortus to heat.

About Beyfortus® (continued)



Mechanism of Action

Beyfortus is a long-acting monoclonal antibody with anti-RSV activity that provides passive immunity by targeting the prefusion conformation of the RSV F protein to prevent entry of the virus into cells.[5]

- Based on clinical data, the duration of protection offered by a single dose of Beyfortus extends through 5 months

Clinical Pharmacology

Following the recommended dose, Beyfortus serum exposures were similar in patient populations across all clinical trials. This includes[5]

- Neonates and infants born during or entering their first RSV season
- Neonates and infants born at <35 wGA (including <29 wGA) in their first RSV season
- Children aged up to 24 months with chronic lung disease (CLD) of prematurity or hemodynamically significant congenital heart disease (CHD) in their first and second RSV seasons

Drug interactions[5]

No formal drug interaction studies have been performed with Beyfortus.

In clinical trials, when Beyfortus was given concomitantly with routine childhood vaccines, the safety and reactogenicity profile of the coadministered regimen was similar to the childhood vaccines given alone. However, there is limited experience with coadministration of Beyfortus with vaccines. Beyfortus should not be mixed with any vaccine in the same syringe or vial. When Beyfortus and injectable vaccines are administered concomitantly, they should be given with separate syringes and at different injection sites.

Clinical Studies

Beyfortus® has been studied in 3 pivotal trials across a broad range of infant populations (healthy infants and those at risk for severe RSV disease).[5]

Beyfortus Clinical Trial Summary

	Healthy infants born preterm	Healthy infants born term and late preterm	Infants at higher risk of severe RSV disease (season 1)*
	Phase 2b[5,6,31] Trial 03	Phase 3 (MELODY)[5,7,32] Trial 04	Phase 2/3 (MEDLEY)[5,8,33] Trial 05
Number of subjects	N=1453 (Beyfortus n=969, placebo n=484)	N=3012 Primary cohort†: n=1490 (Beyfortus n=994, placebo n=496) Safety cohort‡: n=1522 (Beyfortus n=1015, placebo n=507)	N=925§ (Beyfortus n=616, palivizumab n=309)
Study population	Infants born at ≥29 to <35 wGA entering their first RSV season	Infants born at ≥35 wGA entering their first RSV season	**2 cohorts of infants entering their first RSV season:** • Preterm infants (<35 wGA) • Infants with CLD or CHD Infants from the CLD or CHD cohort entering their second RSV season
Randomized double-blind	2:1 Beyfortus:placebo		2:1 Beyfortus:palivizumab (First RSV season only)
Beyfortus dosage (single IM dose)	50 mg for all weights*	50 mg if <5 kg weight* 100 mg if ≥5 kg weight*	50 mg if <5 kg weight* 100 mg if ≥5 kg weight*
Primary endpoint	Incidence of MA RSV LRTI through 150 days post dose		Safety and tolerability through 360 days post dose
Secondary endpoint	Hospitalization for MA RSV LRTI through 150 days post dose		• Serum concentrations and PK parameters

Trial 04 continued monitoring for the primary cohort and an additional 1522 subjects to include all subjects[32]

*For neonates and infants in their first season, the recommended dosage is 50 mg for infants <5 kg or 100 mg for infants ≥5 kg via IM injection. For children up to 24 months of age who remain at increased risk for severe RSV disease in their second season, the recommended dosage is a single 200-mg dose administered as 2 IM injections (2 x 100 mg).[5]

†The primary efficacy analysis for Trial 04 is based on subjects from the primary cohort.[5]

‡Trial 04 safety analysis included both primary and safety cohorts.[5]

§Included 128 preterm infants born at <29 wGA.[5]

‖Incidence of RSV LRTI (inpatient or outpatient) due to confirmed RSV through 150 days (descriptive).[8]

PK, pharmacokinetics.

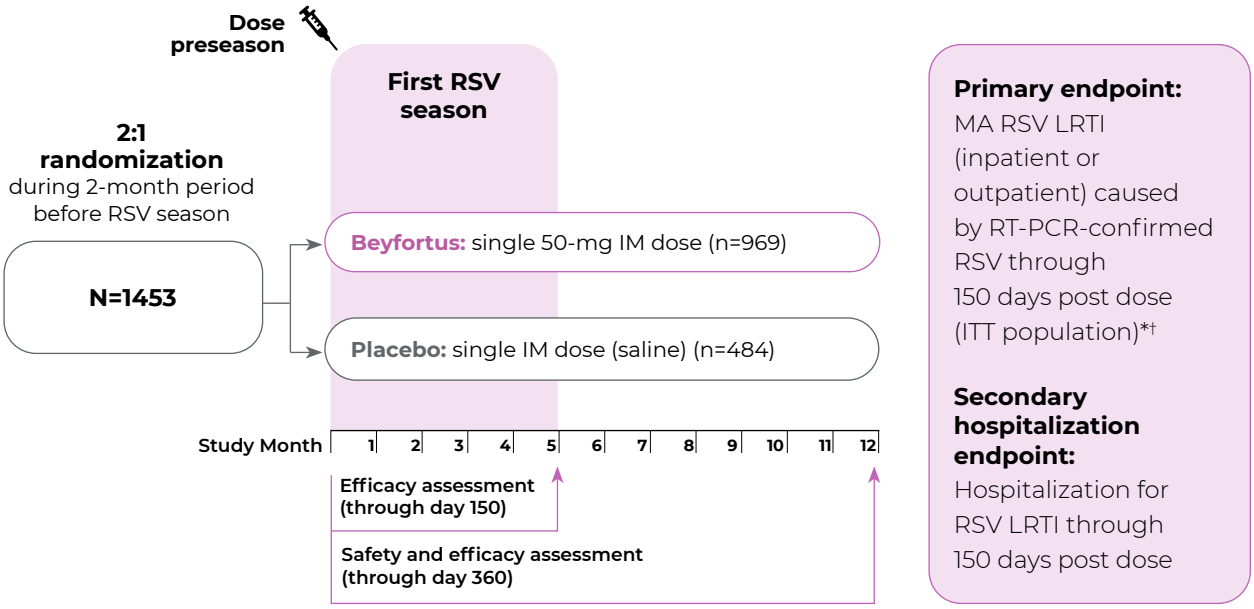
Clinical Studies (continued)

Clinical Trial 03

Phase 2b trial in term and preterm healthy infants

Trial 03 [NCT02878330] was a phase 2b, randomized, double-blind, placebo-controlled multicenter trial that evaluated Beyfortus® for the prevention of MA RSV LRTI in healthy infants born preterm (≥29 to <35 wGA) who were aged ≤1 year.[5,6,31]

Trial 03 Study Design[5,6]



- At randomization, 20% of subjects were ≥29 to <32 wGA and 80% were ≥32 to <35 wGA[5]

*Efficacy analysis conducted in ITT population (1453 infants who underwent randomization).[6]

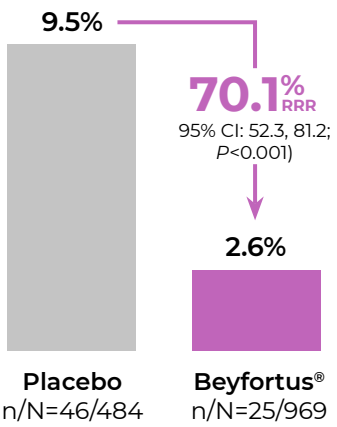
†Signs of LRTI involvement included rhonchi, rales, crackles, or wheezing, and at least 1 sign of worsening clinical severity, including at least 1 of the following: increased respiratory rate, hypoxemia, acute hypoxic or ventilatory failure, new onset apnea, nasal flaring, retractions, grunting, or dehydration due to respiratory distress.[5]

ITT, intention-to-treat; RT-PCR, reverse transcription–polymerase chain reaction.

Clinical Studies (continued)

Trial 03 Results[5,6]

Incidence of MA* RSV LRTI 150 days post dose
(primary endpoint)



The RRR of MA RSV LRTI with hospitalization was **78.4%** (95% CI: 51.9, 90.3; *P*<0.001) through 150 days post dose (secondary endpoint)

*Medically attended is comprehensive and included all healthcare provider visits such as physician's office, urgent care, emergency room, and hospitalizations.[5]

- Beyfortus demonstrated efficacy against MA LRTIs, with 70.1% relative risk reduction (RRR) compared with placebo (*P*<0.001)[5,6]
- Beyfortus was efficacious in preventing RSV LRTI hospitalizations during the study (78.4% RRR compared with placebo, *P*<0.001)[5,6]

- A post hoc analysis of Trial 03 evaluated the incidence of MA RSV LRTI through day 150 for infants who received 50 mg of Beyfortus consistent with the recommended weight-based dose (n=570) vs infants who received placebo (n=290). All infants in this analysis weighed <5 kg[34]
- The RRR comparison was based on MA RSV LRTI in 7 infants receiving Beyfortus (1.2%) and in 26 infants receiving placebo (9.0%)[34]

The RRR of MA RSV LRTI was **86.2%** (95% CI: 68.0, 94.0) through 150 days post dose (secondary endpoint)[5]

Clinical Studies (continued)

Clinical Trial 04

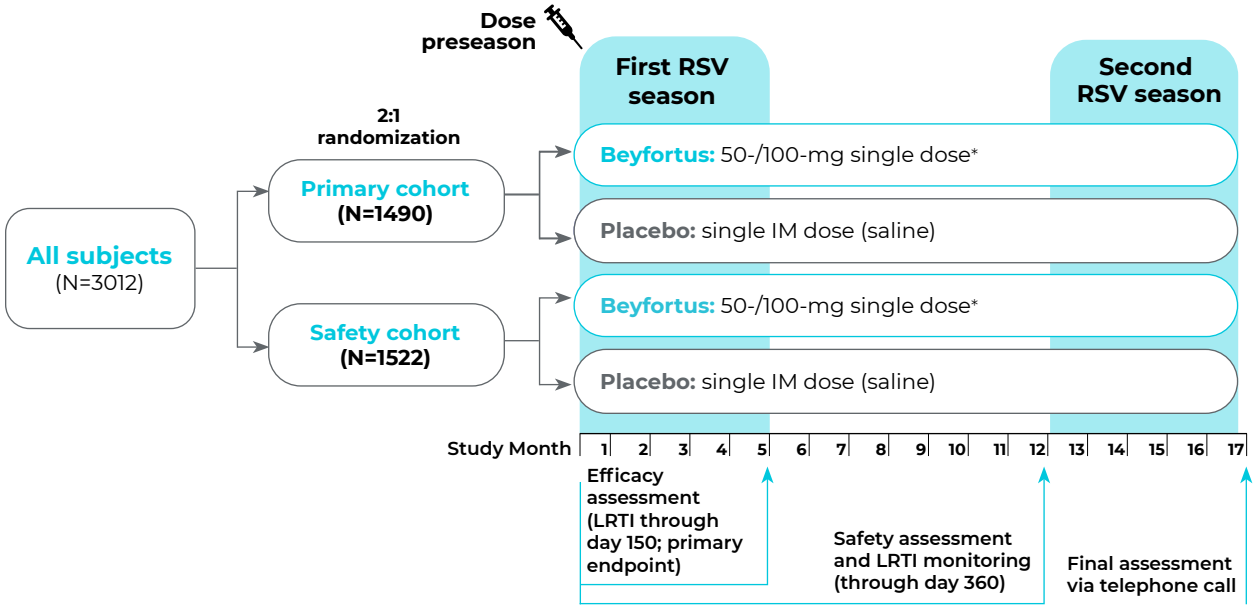
Phase 3 trial (primary cohort) study in term and preterm healthy infants

Trial 04 [NCT03979313] was a phase 3, randomized, double-blind, placebo-controlled multicenter trial that evaluated Beyfortus® for the prevention of MA RSV LRTI in term and late preterm infants born at ≥35 wGA who were aged ≤1 year and entering their first RSV season.[5,7]

As a result of the COVID-19 pandemic, the original target enrollment was not reached, which meant the trial had reduced power to evaluate the impact of Beyfortus on hospitalizations or in prespecified subgroups. After consultation with the FDA and European Medicines Agency, the decision was made to analyze the primary endpoint after the first 1490 participants were enrolled (primary cohort).[35]

- Study enrollment resumed in 2021 when operationally feasible, and as RSV cases were observed again.. This second cohort collected additional safety data as well as efficacy data as an exploratory endpoint; efficacy results for the full study are referred to as "All Subjects" representing the results for the full enrollment (N=3012)

Trial 04 Study Design[5,7,31,32]



- At randomization, 14% of subjects were ≥35 wGA and <37 wGA and 86% were ≥37 wGA[5]

Primary endpoint: MA RSV LRTI (inpatient or outpatient) caused by RT-PCR-confirmed RSV through 150 days post dose (ITT population)†

Secondary hospitalization endpoint: Hospitalization for RSV LRTI through 150 days post dose

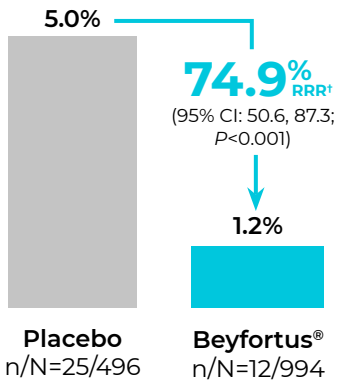
*50 mg if <5 kg weight, 100 mg if ≥5 kg weight.[5,7]

†Signs of LRTI involvement included rhonchi, rales, crackles, or wheezing, and at least 1 sign of worsening clinical severity, including at least 1 of the following: increased respiratory rate, hypoxemia, acute hypoxic or ventilatory failure, new onset apnea, nasal flaring, retractions, grunting, or dehydration due to respiratory distress.[5]

Clinical Studies (continued)

Trial 04 Primary Cohort Results[5]

Incidence of MA* RSV LRTI 150 days post dose
(primary endpoint)



The RRR of MA RSV LRTI with hospitalization was **60.2%** (95% CI: -14.6, 86.2; *P*=0.09) through 150 days post dose (secondary endpoint)

*Medically attended is comprehensive and included all healthcare provider visits such as physician's office, urgent care, emergency room, and hospitalizations.[5]

†RRR calculated as 1 minus the relative risk, where the relative risk was estimated with the use of a Poisson regression model with robust variance.[7]

- Through 150 days post-injection, Beyfortus demonstrated efficacy against MA RSV LRTIs, with a 74.9% RRR compared with placebo (*P*<0.001)[5]
- The efficacy of Beyfortus in preventing MA RSV LRTI with hospitalization in terms of RRR was 60.2% compared with placebo (*P*=0.09)[5]

- Trial 04 continued to enroll infants following the primary analysis. The full study cohort included 3012 infants randomized to receive Beyfortus (n=2009) or placebo (n=1003) in this post hoc analysis[36]

The RRR of MA RSV LRTI with hospitalization was **76.8%** (95% CI: 49.4, 89.4) through 150 days post dose (exploratory post hoc analysis of the full cohort)[36]

Based on the prespecified number need to treat (NNT) analyses for the primary and secondary efficacy endpoints, the NNT for MA RSV LRTIs was 12 based on any RSV test result (95% CI: 10-17).[7‡§]

‡The number needed to treat to avert 1 case of RSV-associated LRTI was calculated as the reciprocal of the difference in risk between the Beyfortus group and the placebo group.[7]

§When using any RSV test result (central lab or local).[7]

Clinical Studies (continued)

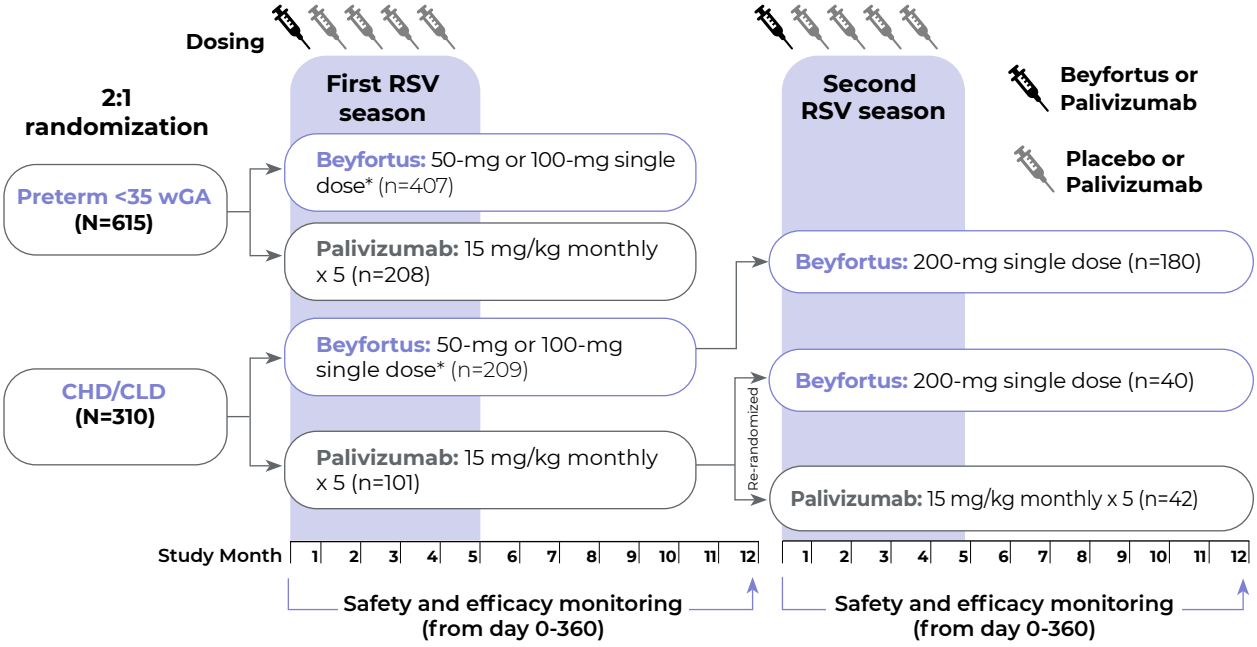
Clinical Trial 05

Phase 2/3 safety study in infants and children at higher risk of severe RSV disease

The safety of Beyfortus® was evaluated in a phase 2/3, randomized, double-blind, palivizumab-controlled multicenter trial in infants and children born at <35 wGA and in infants with CLD of prematurity or hemodynamically significant CHD.[5,8]

- Participants were randomized 2:1 to receive one IM injection of Beyfortus 50 mg (if they weighed <5 kg) or 100 mg (if they weighed ≥5 kg) or palivizumab 15 mg/kg. Beyfortus was administered once on Study Day 1, followed by 4 monthly IM doses of placebo, and palivizumab was administered IM monthly for 5 months
- The trial was not powered for efficacy, but efficacy was assessed as a secondary endpoint

Trial 05 Study Design[5,8,33]



- At randomization, in the preterm cohort, 77 infants (13%) were <29 wGA and 499 (81%) were ≥29 wGA to <35 wGA. In the CLD/CHD cohort, 70% had CLD of prematurity; 34% had hemodynamically significant CHD; 123 infants (40%) were <29 wGA, 28% were ≥29 wGA to <35 wGA, and 32% were ≥35 wGA[5]

Primary endpoint: Safety and tolerability through 360 days post dose

Secondary endpoint: Serum concentrations and PK parameters; incidence of ADAs; incidence of RSV LRTI (inpatient and outpatient) due to confirmed RSV through 150 days (descriptive)†

*50 mg if <5 kg weight, 100 mg if ≥5 kg weight, followed by 4 monthly doses of placebo.[5]

†Signs of LRTI involvement included rhonchi, rales, crackles, or wheezing, and at least 1 sign of worsening clinical severity, including at least 1 of the following: increased respiratory rate, hypoxemia, acute hypoxic or ventilatory failure, new onset apnea, nasal flaring, retractions, grunting, or dehydration due to respiratory distress.[5]

Clinical Studies (continued)

Trial 05 RSV season 1

In the first RSV season of Trial 05, the incidence of MA RSV LRTI through 150 days post dose was 0.6% (4/616) in the Beyfortus® group and 1.0% (3/309) in the palivizumab group.[5]

Efficacy was established based on extrapolation of the efficacy from Trials 04 and 03 to the population enrolled in Trial 05 based on similar Beyfortus exposures among infants enrolled in Trials 04 and 05.[5]

Trial 05 was not powered for efficacy, but efficacy was assessed as a secondary endpoint. The clinical significance of these data is unknown.[5]

Trial 05 RSV season 2

In the second RSV season of Trial 05, there were no cases of MA RSV LRTI through Day 150 post dose in children who received either Beyfortus or palivizumab.[5]

Safety Profile

Clinical Trial Experience

Trial 03 and Trial 04

Infants who received the recommended dose in Trial 03 and Trial 04 were pooled to evaluate the safety of Beyfortus® (n=2570) compared with placebo (n=1284). At randomization, in this pooled Safety Population, 22% of infants were born at <35 wGA, 10% of infants were born at ≥35 and <37 wGA, and 68% were born at ≥37 wGA.[5]

In both trials, infants received a single dose of IM Beyfortus or placebo on Study Day 1 and were monitored for at least 60 minutes post dose. Infants were followed for 360 days post dose to assess safety. Adverse reactions were reported in 1.2% of infants who received Beyfortus; adverse reactions were mild to moderate in intensity.[5]

Trial 03 and Trial 04 Adverse Reactions (Pooled)[5]*

Adverse Reaction	Beyfortus n=2570	Placebo n=1284
Rash (occurring within 14 days post dose)†	0.9%	0.6%
Injection site reaction (occurring within 7 days post dose)‡	0.3%	0.0%

*The Safety Population included all infants who received the recommended dose of Beyfortus in Trial 03 and Trial 04: Primary and Safety cohorts from Trial 04 and infants who weighed <5 kg and who received the recommended dose of Beyfortus (single 50-mg IM dose) in Trial 03.

†Rash was defined by the following grouped preferred terms: rash, rash macular, rash maculo-papular, rash papular.

‡Injection site reaction was defined by the following grouped preferred terms: injection site reaction, injection site pain, injection site induration, injection site edema, injection site swelling.

Trial 05

Trial 05 was a randomized, double-blind, palivizumab-controlled multicenter trial in infants at high risk for severe RSV disease that evaluated the safety of Beyfortus (primary endpoint).[5]

- Adverse reactions for infants who received Beyfortus in their first RSV season were similar to those reported in infants who received Beyfortus in Trial 03 and Trial 04
- Children with CLD of prematurity or hemodynamically significant CHD could continue in Trial 05 and receive Beyfortus or palivizumab prior to their second RSV season
- The safety profile of Beyfortus in these children during their second RSV season was consistent with the safety profile of Beyfortus observed during their first RSV season

Summary

Approximately 2 out of 3 infants will become infected with RSV by age 1 year[3]

- Infants aged <1 year are on average 16x more likely to be hospitalized due to RSV than for influenza[19]

Beyfortus® is a long-acting, monoclonal antibody designed to protect the vast majority of infants against RSV for 5 months with a single dose, based on weight[5]*

- The ideal timing for Beyfortus dosing is just before or near the start of the RSV season, or from birth for infants born during the RSV season[5]
- For example, Beyfortus should be administered to infants born during the RSV season within 1 week of birth, preferably in the hospital prior to discharge.[30] For infants born outside of RSV season, Beyfortus should be administered during regularly scheduled well-baby visits prior to the start of their first RSV season

Beyfortus demonstrated efficacy in reducing the risk of MA LRTIs and hospitalizations across a broad range of infant populations[5-7]

- In Trial 03, Beyfortus demonstrated efficacy in reducing the risk of MA LRTIs in healthy infants who were born preterm, with 70.1% RRR compared with placebo (95% CI: 52.3, 81.2; *P*<0.001). Beyfortus was efficacious in preventing RSV LRTI hospitalizations during the study compared with placebo (78.4% RRR [95% CI: 51.9, 90.3; *P*<0.001])[5,6†]
- In Trial 04, Beyfortus demonstrated efficacy against MA RSV LRTIs in healthy infants who were born late preterm or at term, with a 74.9% RRR compared with placebo (95% CI: 50.6, 87.3; *P*<0.001) through 150 days post injection. Beyfortus demonstrated a 60.2% RRR in preventing RSV LRTI hospitalization compared with placebo (95% CI: -14.6, 86.2; *P*=0.09)[5‡]
  - The NNT[§] for MA RSV LRTIs was 12 based on any RSV test result (95% CI: 10-17)[7||]

In clinical trials, the safety of Beyfortus was established vs placebo (Trial 03 and Trial 04) and palivizumab (Trial 05)[5]

- In Trial 03 and Trial 04, the most common adverse events in healthy term and preterm infants (born at ≥29 wGA) were rash (0.9%) and injection site reactions (0.3%)[5]
- In Trial 05, the safety of Beyfortus was comparable with that reported in Trial 03 and Trial 04 in infants born at <35 wGA and infants with CLD or hemodynamically significant CHD[5#]

*For children undergoing cardiac surgery with cardiopulmonary bypass, an additional dose of Beyfortus is recommended as soon as the child is stable after surgery; please consult the Prescribing Information for complete information on dosing in these circumstances. For children up to 24 months of age who remain vulnerable in their second RSV season, the recommended dose is a single 200 mg dose administered as 2 IM injections (2 x 100 mg).[5]

†Trial 03 was a phase 2b, randomized, double-blind, placebo-controlled multicenter trial that evaluated Beyfortus for the prevention of MA RSV LRTI in healthy infants born preterm (≥29 to <35 wGA) who were aged ≤1 year. Primary endpoint was incidence of MA RSV LRTI 150 days post dose (Beyfortus [n/N=25/969] compared with placebo [n/N=46/484]). Secondary endpoint was incidence of RSV LRTI with hospitalizations 150 days post dose (Beyfortus [n/N=8/969] compared with placebo [n/N=20/484]).[5,6,31]

‡Trial 04 was a phase 3, randomized, double-blind, placebo-controlled multicenter trial that evaluated Beyfortus for the prevention of MA RSV LRTI in term and late preterm infants born at ≥35 wGA who were aged ≤1 year and entering their first RSV season. Primary endpoint was incidence of MA RSV LRTI 150 days post dose (Beyfortus [n/N=12/994] compared with placebo [n/N=25/496]). Secondary endpoint was incidence of RSV LRTI with hospitalizations 150 days post dose (Beyfortus [n/N=6/994] compared with placebo [n/N=8/496]).[5,7]

§The number needed to treat to avert 1 case of RSV-associated LRTI was calculated as the reciprocal of the difference in risk between the Beyfortus group and the placebo group.[7]

||When using any RSV test result (central lab or local).[7]

#Trial 05 was a phase 2/3, randomized, double-blind, palivizumab-controlled multicenter trial in infants and children born at <35 wGA and infants with CLD of prematurity or hemodynamically significant CHD. The trial was not powered for efficacy, but efficacy was assessed as a secondary endpoint. Primary endpoint was safety and tolerability. Secondary endpoint was serum concentrations and PK parameters; incidence of ADAs; and incidence of RSV LRTI (inpatient and outpatient) due to confirmed RSV through 150 days (descriptive).[5,8,33]

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INDICATION AND IMPORTANT SAFETY INFORMATION

Indication

Beyfortus® is indicated for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in:

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

Important Safety Information

Contraindication

Beyfortus is contraindicated in infants and children with a history of serious hypersensitivity reactions, including anaphylaxis, to nirsevimab-alip or to any of the excipients.

Warnings and Precautions

- **Hypersensitivity Reactions Including Anaphylaxis:** Serious hypersensitivity reactions have been reported following Beyfortus administration. These reactions included urticaria, dyspnea, cyanosis, and/or hypotonia. Anaphylaxis has been observed with human immunoglobulin G1 (IgG1) monoclonal antibodies. If signs and symptoms of anaphylaxis or other clinically significant hypersensitivity reactions occur, initiate appropriate treatment.
- **Use in Individuals with Clinically Significant Bleeding Disorders:** As with other IM injections, Beyfortus should be given with caution to infants and children with thrombocytopenia, any coagulation disorder or to individuals on anticoagulation therapy.

Most common adverse reactions with Beyfortus were rash (0.9%) and injection site reactions (0.3%).

CODING AND BILLING INFORMATION

Beyfortus® CPT® Codes			
	CPT® Code	**Description**	**Suggested Use**
Product[1]	90380	RSV, monoclonal antibody, seasonal dose; 0.5 mL dosage, for intramuscular use	Bill 1 unit of 90380 when a 0.5-mL (50-mg) dose is provided.
	90381	RSV, monoclonal antibody, seasonal dose; 1 mL dosage, for intramuscular use	Bill 1 unit of 90381 when a 1-mL (100-mg) dose is provided; Bill 2 units of 90381 when a 2-mL dose is provided.
Administration[2,3]	96380	Administration of RSV antibody, seasonal dose by intramuscular injection, with counseling by physician or other qualified health care professional (Report 96380 for administration of RSV, monoclonal antibody, seasonal dose [90380, 90381])	For the administration service, when counseling is performed by a provider who independently bills, such as a physician or other qualified health care professional, report 96380 with the Beyfortus product code 90380 or 90381. Bill 96380 when any size dose of Beyfortus is administered and the counseling requirement is met.
	96381	Administration of RSV, monoclonal antibody, seasonal dose by intramuscular injection (Report 96381 for administration of RSV, monoclonal antibody, seasonal dose [90380, 90381])	For the administration service, when counseling is not performed by a provider who independently bills, report 96381 with the Beyfortus product code 90380 or 90381. Bill 96381 when any size dose of Beyfortus is administered and the counseling requirement is not met.
	96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular	For the administration service, until your payers update their systems to add the 2 new codes, you may need to report CPT 96372 with the Beyfortus product code 90380 or 90381. Check with your payers for their coding guidance. Bill 96372 when any size dose of Beyfortus is administered until your payers update their systems to add CPT codes 96380 and 96381.

CPT, *Current Procedural Terminology®*.

Coding and Billing Information (continued)

Beyfortus® National Drug Codes (NDCs)[4]	
Carton NDC	**Description**
49281-575-15	Five 50 mg/0.5 mL single-dose prefilled syringes in a carton
49281-574-15	Five 100 mg/mL single-dose prefilled syringes in a carton
Unit of Use NDC	**Description**
49281-575-00	One 50 mg/0.5 mL single-dose prefilled syringe in a carton
49281-574-88	One 100 mg/mL single-dose prefilled syringe in a carton

When NDCs are required, use the N4 qualifier, followed by the correct 11-digit Carton NDC or Unit of Use NDC and the unit of measure in the actual amount of milliliters administered (eg, ML0.5, ML1.0, or ML2.0). To convert the Beyfortus NDC to the required 11-digit format, add a leading zero in the middle section of numbers (eg, 49281-575-00 → 49281-0575-00).[5]

Diagnosis Codes[6]		
ICD-10-CM Code	**Code Description**	**Suggested Use**
Z29.11	Encounter for prophylactic immunotherapy for RSV	When a dose of RSV passive immunization is administered

When a dose of RSV passive immunization is administered due to a high-risk condition, use Z29.11 and add the applicable ICD-10 code that describes the patient's specific high-risk condition.

ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.

Coding and Billing References

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INDICATION AND IMPORTANT SAFETY INFORMATION

Indication

Beyfortus® is indicated for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in:

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

Important Safety Information

Contraindication

Beyfortus is contraindicated in infants and children with a history of serious hypersensitivity reactions, including anaphylaxis, to nirsevimab-alip or to any of the excipients.

Warnings and Precautions

- **Hypersensitivity Reactions Including Anaphylaxis:** Serious hypersensitivity reactions have been reported following Beyfortus administration. These reactions included urticaria, dyspnea, cyanosis, and/or hypotonia. Anaphylaxis has been observed with human immunoglobulin G1 (IgG1) monoclonal antibodies. If signs and symptoms of anaphylaxis or other clinically significant hypersensitivity reactions occur, initiate appropriate treatment.
- **Use in Individuals with Clinically Significant Bleeding Disorders:** As with other IM injections, Beyfortus should be given with caution to infants and children with thrombocytopenia, any coagulation disorder or to individuals on anticoagulation therapy.

Most common adverse reactions with Beyfortus were rash (0.9%) and injection site reactions (0.3%).

ACIP AND AAP RECOMMENDATIONS

ACIP and AAP Recommend the Use of Beyfortus® for All Infants[1,2]

First RSV Season

All infants aged <8 months born during or entering their first RSV season are recommended to receive 1 dose of Beyfortus (50 mg for infants weighing <5 kg and 100 mg for infants weighing ≥5 kg, administered as 1 IM injection).[1]

- Beyfortus should be administered shortly before the start of the RSV season for infants aged <8 months[1,2]
- For infants born during or entering their first RSV season, Beyfortus should be administered within 1 week of birth, either during the birth hospitalization or in the outpatient setting[1,2]
- Refer to the most current CDC immunization schedule for additional immunization considerations

Second RSV Season

Infants and children aged 8 to 19 months who are at increased risk of severe RSV disease and entering their second RSV season are recommended to receive 1 dose of Beyfortus (200 mg administered as two 100-mg IM injections).[1]

- Beyfortus should be administered shortly before the start of the season for infants and children aged 8 to 19 months who are at increased risk of severe RSV disease[1,2]

AAP, American Academy of Pediatrics; ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; IM, intramuscular; RSV, respiratory syncytial virus.

ACIP and AAP Recommendations References

1. Jones JM, Fleming-Dutra KE, Prill MM, et al. Use of nirsevimab for the prevention of respiratory syncytial virus disease among infants and young children: recommendations of the Advisory Committee on Immunization Practices – United States, 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(34):920-925. doi:10.15585/mmwr.mm7234a4
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INDICATION AND IMPORTANT SAFETY INFORMATION

Indication

Beyfortus® is indicated for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in:

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

Important Safety Information

Contraindication

Beyfortus is contraindicated in infants and children with a history of serious hypersensitivity reactions, including anaphylaxis, to nirsevimab-alip or to any of the excipients.

Warnings and Precautions

- **Hypersensitivity Reactions Including Anaphylaxis:** Serious hypersensitivity reactions have been reported following Beyfortus administration. These reactions included urticaria, dyspnea, cyanosis, and/or hypotonia. Anaphylaxis has been observed with human immunoglobulin G1 (IgG1) monoclonal antibodies. If signs and symptoms of anaphylaxis or other clinically significant hypersensitivity reactions occur, initiate appropriate treatment.
- **Use in Individuals with Clinically Significant Bleeding Disorders:** As with other IM injections, Beyfortus should be given with caution to infants and children with thrombocytopenia, any coagulation disorder or to individuals on anticoagulation therapy.

Most common adverse reactions with Beyfortus were rash (0.9%) and injection site reactions (0.3%).

Beyfortus®
(nirsevimab-alip)
50 mg
100 mg
Injection

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