NAME OF THE MEDICINAL PRODUCT

Beyfortus solution for injection in pre-filled syringe 50 mg/ 0.5 mL
Beyfortus solution for injection in pre-filled syringe 100 mg/ 1.0 mL

QUALITATIVE AND QUANTITATIVE COMPOSITION

Beyfortus 50 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains 50 mg of nirsevimab in 0.5 mL (100 mg/mL).

Beyfortus 100 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains 100 mg of nirsevimab in 1 mL (100 mg/mL).

Nirsevimab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Excipients with known effect

This medicine contains 0.1 mg of polysorbate 80 (E433) in each 50 mg (0.5 mL) dose and 0.2 mg in each 100 mg (1 mL) dose (see section Special warnings and precautions for use).

For the full list of excipients, see section list of excipients.

PHARMACEUTICAL FORM

Solution for injection (injection).

Clear to opalescent, colourless to yellow, pH 6.0 solution.

CLINICAL PARTICULARS

Therapeutic indications

Beyfortus is indicated for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in neonates and infants during their first RSV season.

Beyfortus should be used in accordance with official recommendations.

Posology and method of administration

Posology

The recommended dose is a single dose of 50 mg administered intramuscularly for infants with body weight <5 kg and a single dose of 100 mg administered intramuscularly for infants with body weight ≥5 kg.

Beyfortus should be administered prior to commencement of the RSV season, or from birth for infants born during the RSV season.

Dosing in infants with a body weight from 1.0 kg to <1.6 kg is based on extrapolation, no clinical data are available. Exposure in infants <1 kg is anticipated to yield higher exposures than in those weighing more. The benefits and risks of nirsevimab use in infants <1 kg should be carefully considered.

There are limited data available in extremely preterm infants (Gestational Age [GA] <29 weeks) less than 8

weeks of age. No clinical data available in infants with a postmenstrual age (gestational age at birth plus chronological age) of less than 32 weeks (see section Pharmacodynamic properties).

For infants undergoing cardiac surgery with cardiopulmonary bypass, an additional dose may be administered as soon as the infant is stable after surgery to ensure adequate nirsevimab serum levels. If within 90 days after receiving the first dose of Beyfortus, the additional dose should be 50 mg or 100 mg according to body weight. If more than 90 days have elapsed since the first dose, the additional dose could be a single dose of 50 mg regardless of body weight, to cover the remainder of the RSV season.

There are no safety and efficacy data available on repeat dosing.

The safety and efficacy of nirsevimab in children aged 2 to 18 years have not been established. No data are available.

Method of administration

Beyfortus is for intramuscular injection only.

It is administered intramuscularly, preferably in the anterolateral aspect of the thigh. The gluteal muscle should not be used routinely as an injection site because of the risk of damage to the sciatic nerve.

Instructions for administration

Beyfortus is available in a 50 mg and a 100 mg pre-filled syringe. Check the labels on the carton and pre-filled syringe to make sure you have selected the correct 50 mg or 100 mg presentation as required.

Beyfortus 50 mg (50 mg/0.5 mL) pre-filled syringe with a purple plunger rod.

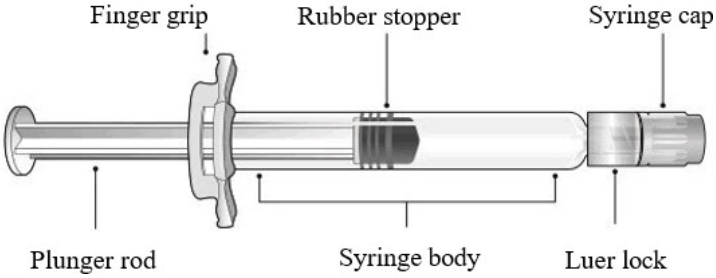
Beyfortus 100 mg (100 mg/1 mL) pre-filled syringe with a light blue plunger rod.

Purple

Light Blue

Refer to Figure 1 for pre-filled syringe components.

Figure 1: Luer lock syringe components



Step 1: Holding the Luer lock in one hand (avoid holding the plunger rod or syringe body), unscrew the syringe cap by twisting it counter clockwise with the other hand.

Step 2: Attach a Luer lock needle to the pre-filled syringe by gently twisting the needle clockwise onto the pre-filled syringe until slight resistance is felt.

Step 3: Hold the syringe body with one hand and carefully pull the needle cover straight off with the other hand. Do not hold the plunger rod while removing the needle cover or the rubber stopper may move. Do not touch the needle or let it touch any surface. Do not recap the needle or detach it from the syringe.

Step 4: Administer the entire contents of the pre-filled syringe as an intramuscular injection, preferably in the anterolateral aspect of the thigh. The gluteal muscle should not be used routinely as an injection site because of the risk of damage to the sciatic nerve.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section list of excipients.

Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity including anaphylaxis

Serious hypersensitivity reactions have been reported following Beyfortus administration. Anaphylaxis has been observed with human immunoglobulin G1 (IgG1) monoclonal antibodies. If signs and symptoms of anaphylaxis or other clinically significant hypersensitivity reaction occur, immediately discontinue administration and initiate appropriate medicinal products and/or supportive therapy.

Clinically significant bleeding disorders

As with any other intramuscular injections, nirsevimab should be given with caution to infants with thrombocytopenia or any coagulation disorder.

Immunocompromised children

In some immunocompromised children with protein-losing conditions, a high clearance of nirsevimab has been observed in clinical trials (see section Pharmacokinetic Properties), and nirsevimab may not provide the same level of protection in those individuals.

Polysorbate 80 (E433)

This medicine contains 0.1 mg of polysorbate 80 in each 50 mg (0.5 mL) dose and 0.2 mg in each 100 mg (1 mL) dose. Polysorbates may cause allergic reactions.

Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Monoclonal antibodies do not typically have significant interaction potential, as they do not directly affect cytochrome P450 enzymes and are not substrates of hepatic or renal transporters. Indirect effects on cytochrome P450 enzymes are unlikely as the target of nirsevimab is an exogenous virus.

Nirsevimab does not interfere with reverse transcriptase polymerase chain reaction (RT-PCR) or rapid antigen detection RSV diagnostic assays that employ commercially available antibodies targeting antigenic

site I, II, or IV on the RSV fusion (F) protein.

Concomitant administration with vaccines

Since nirsevimab is a monoclonal antibody, a passive immunisation specific for RSV, it is not expected to interfere with the active immune response to co-administered vaccines.

There is limited experience of co-administration with vaccines. In clinical trials, when nirsevimab was given with routine childhood vaccines, the safety and reactogenicity profile of the co-administered regimen was similar to the childhood vaccines given alone. Nirsevimab can be given concomitantly with childhood vaccines.

Nirsevimab should not be mixed with any vaccine in the same syringe or vial (see section Incompatibilities). When administered concomitantly with injectable vaccines, they should be given with separate syringes and at different injection sites.

Fertility, pregnancy and lactation

Not applicable.

Effects on ability to drive and use machines

Not applicable.

Undesirable effects

Summary of the safety profile

The most frequent adverse reaction was rash (0.7%) occurring within 14 days post dose. The majority of cases were mild to moderate in intensity. Additionally, pyrexia and injection site reactions were reported at a rate of 0.5% and 0.3% within 7 days post dose, respectively. Injection site reactions were non-serious.

Tabulated list of adverse reactions

Table 1 presents the adverse reactions reported in 2 966 term and preterm infants (GA ≥29 weeks) who received nirsevimab in clinical trials, and in post-marketing setting (see section Special warnings and precautions for use).

Adverse reactions reported from controlled clinical trials are classified by MedDRA System Organ Class (SOC). Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000) and not known (cannot be estimated from available data).

Table 1: Adverse reactions

MedDRA SOC	MedDRA Preferred Term	Frequency
Immune system disorders	Hypersensitivity[a]	Not known
Skin and subcutaneous tissue disorders	Rash[b]	Uncommon
General disorders and administration site conditions	Injection site reaction[c]	Uncommon
	Pyrexia	Uncommon

[a] Adverse reaction from spontaneous reporting

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

[c] Injection site reaction was defined by the following grouped preferred terms: injection site reaction, injection site pain, injection site induration, injection site oedema, injection site swelling.

Infants at higher risk for severe RSV disease

Safety was also evaluated in MEDLEY in 918 infants at higher risk for severe RSV disease, including 196 extremely preterm infants (GA <29 weeks) and 306 infants with chronic lung disease of prematurity, or haemodynamically significant congenital heart disease entering their first RSV season, who received nirsevimab (614) or palivizumab (304). The safety profile was comparable to the palivizumab comparator and consistent with the safety profile in term and preterm infants GA ≥29 weeks (D5290C00003 and MELODY).

Term and Preterm Infants entering their first RSV season

Safety of nirsevimab was also evaluated in HARMONIE, a randomised open-label multicentre trial in 8 034 term and preterm infants (GA ≥29 weeks) entering their first RSV season (not eligible for palivizumab), who received nirsevimab (n=4 016) or no intervention (n=4 018) for the prevention of RSV LRTI hospitalisation. The safety profile of nirsevimab administered in the first RSV season was consistent with the safety profile of nirsevimab in the placebo-controlled trials (D5290C00003 and MELODY)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

Overdose

There is no specific treatment for an overdose with nirsevimab. In the event of an overdose, the individual should be monitored for the occurrence of adverse reactions and provided with symptomatic treatment as appropriate.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Immune sera and immunoglobulins, antiviral monoclonal antibodies, ATC code: J06BD08

Mechanism of action

Nirsevimab is a recombinant neutralising human IgG1κ long-acting monoclonal antibody to the prefusion conformation of the RSV F protein which has been modified with a triple amino acid substitution (YTE) in the Fc region to extend serum half-life. Nirsevimab binds to a highly conserved epitope in antigenic site Ø on the prefusion protein with dissociation constants K_D = 0.12 nM and K_D = 1.22 nM for RSV subtype A and B strains, respectively. Nirsevimab inhibits the essential membrane fusion step in the viral entry process, neutralising the virus and blocking cell-to-cell fusion.

Pharmacodynamic effects

Antiviral activity

The cell culture neutralisation activity of nirsevimab against RSV was measured in a dose-response model using cultured Hep-2 cells. Nirsevimab neutralised RSV A and RSV B isolates with median EC_{50} values of 3.2 ng/mL (range 0.48 to 15 ng/mL) and 2.9 ng/mL (range 0.3 to 59.7 ng/mL), respectively. The clinical RSV isolates (70 RSV A and 49 RSV B) were collected between 2003 and 2017 from subjects across the United States, Australia, Netherlands, Italy, China and Israel and encoded the most common RSV F sequence polymorphisms found among circulating strains.

Nirsevimab demonstrated *in vitro* binding to immobilised human FcγRs (FcγRI, FcγRIIA, FcγRIIB, and FcγRIII) and equivalent neutralising activity compared to parental monoclonal antibodies, IG7 and IG7- TM (Fc region modified to reduce FcR binding and effector function). In a cotton rat model of RSV infection, IG7 and IG7-TM exhibited comparable dose-dependent reduction in RSV replication in the lungs and nasal turbinates, strongly suggesting that protection from RSV infection is dependent on nirsevimab neutralisation activity rather than Fc-mediated effector function.

Antiviral resistance

In cell culture

Escape variants were selected following three passages in cell culture of RSV A2 and B9320 strains in the presence of nirsevimab. Recombinant RSV A variants that showed reduced susceptibility to nirsevimab included those with identified substitutions N67I+N208Y (103-fold). Recombinant RSV B variants that showed reduced susceptibility to nirsevimab included those with identified substitutions N208D (>90,000-fold), N208S (>24,000-fold), K68N+N201S (>13,000-fold), or K68N+N208S (>90,000-fold). All resistance-associated substitutions identified among neutralisation escape variants were located in the nirsevimab binding site (amino acids 62-69 and 196-212) and were shown to reduce binding affinity to RSV F protein.

In clinical trials

In MELODY and MEDLEY, no subject with medically attended RSV lower respiratory tract infection (MA RSV LRTI) had an RSV isolate containing nirsevimab resistance-associated substitutions in any treatment group.

In D5290C00003 (subjects who received a single dose of 50 mg nirsevimab irrespective of weight at time of dosing), 2 of 25 subjects in the nirsevimab group with MA RSV LRTI had an RSV isolate containing nirsevimab resistance-associated substitutions (RSV A: 0 of 11 subjects and RSV B: 2 of 14 subjects). No subjects in the placebo group had an RSV isolate containing nirsevimab resistance-associated substitution. Recombinant RSV B variants harbouring the identified I64T+K68E+I206M+Q209R (>447.1-fold) or N208S (>386.6-fold) F protein sequence variations in the nirsevimab binding site conferred reduced susceptibility to nirsevimab neutralisation.

Nirsevimab retained activity against recombinant RSV harbouring palivizumab resistance-associated substitutions identified in molecular epidemiology studies and in neutralisation escape variants of palivizumab. It is possible that variants resistant to nirsevimab could have cross-resistance to other monoclonal antibodies targeting the F protein of RSV.

Immunogenicity

Anti-drug antibodies (ADA) were commonly detected.

The employed immunogenicity assay has limitations in detecting ADAs at early onset (prior to Day 361) in the presence of high concentrations of drug, therefore, the incidence of ADA might not have been conclusively determined. The impact on clearance of nirsevimab is uncertain. Subjects who were ADA positive at Day 361 had reduced nirsevimab concentrations at Day 361 compared to subjects who received nirsevimab and were ADA-negative.

The impact of ADA on the efficacy of nirsevimab has not been determined. No evidence of ADA impact on safety was observed.

Clinical efficacy

The efficacy and safety of nirsevimab were evaluated in two randomised, double-blind, placebo controlled

multicentre trials (D5290C00003 [Phase IIb] and MELODY [Phase III]) for the prevention of MA RSV LRTI in term and preterm infants (GA ≥29 weeks) entering their first RSV season. Safety and pharmacokinetics of nirsevimab were also evaluated in a randomised, double-blind, palivizumab-controlled multicentre trial (MEDLEY [Phase II/III]) in infants GA <35 weeks at higher risk for severe RSV disease, including extremely preterm infants (GA <29 weeks) and infants with chronic lung disease of prematurity, or haemodynamically significant congenital heart disease, entering their first RSV season.

Efficacy and safety of nirsevimab were also evaluated in one randomised open-label multicentre trial (HARMONIE, Phase IIIb), compared to no intervention, for the prevention of RSV LRTI hospitalisation in term and preterm infants (GA ≥29 weeks) born during or entering their first RSV season (not eligible to palivizumab).

Efficacy against MA RSV LRTI, MA RSV LRTI hospitalisation, and very severe MA RSV LRTI in term and preterm infants (D5290C00003 and MELODY)

D5290C00003 randomised a total of 1 453 very and moderately preterm infants (GA ≥29 to <35 weeks) entering their first RSV season (2:1) to receive a single intramuscular dose of 50 mg nirsevimab or placebo. At randomisation, 20.3% were GA ≥29 to <32 weeks; 79.7% were GA ≥32 to <35 weeks; 52.4% were male; 72.2% were White; 17.6% were of African origin; 1.0% were Asian; 59.5% weighed <5 kg (17.0% <2.5 kg); 17.3% of infants were ≤1.0 month of age, 35.9% were >1.0 to ≤3.0 months, 32.6% were >3.0 to ≤6.0 months, and 14.2% were >6.0 months.

MELODY (Primary cohort) randomised a total of 1 490 term and late preterm infants (GA ≥35 weeks) entering their first RSV season (2:1) to receive a single intramuscular dose of nirsevimab (50 mg nirsevimab if <5 kg weight or 100 mg nirsevimab if ≥5 kg weight at the time of dosing) or placebo. At randomisation, 14.0% were GA ≥35 to <37 weeks; 86.0% were GA ≥37 weeks; 51.6% were male; 53.5% were White; 28.4% were of African origin; 3.6% were Asian; 40.0% weighed <5 kg (2.5% <2.5 kg); 24.5% of infants were ≤1.0 month of age, 33.4% were >1.0 to ≤3.0 months, 32.1% were >3.0 to ≤6.0 months, and 10.0% were >6.0 months.

The trials excluded infants with a history of chronic lung disease/bronchopulmonary dysplasia or congenital heart disease (except for infants with uncomplicated congenital heart disease).

Demographic and baseline characteristics were comparable between the nirsevimab and placebo group in both trials.

The primary endpoint for D5290C00003 and MELODY (Primary cohort) was the incidence of medically attended lower respiratory tract infection (inclusive of hospitalisation) caused by RT-PCR-confirmed RSV (MA RSV LRTI), characterised predominantly as bronchiolitis or pneumonia, through 150 days after dosing. Signs of LRTI were defined by having one of the following findings at physical examination indicating lower respiratory tract involvement (e.g., rhonchi, rales, crackles, or wheeze); and at least one sign of clinical severity (increased respiratory rate, hypoxemia, acute hypoxic or ventilatory failure, new onset apnoea, nasal flaring, retractions, grunting, or dehydration due to respiratory distress). The secondary endpoint was the incidence of hospitalisation in infants with MA RSV LRTI. RSV hospitalisation was defined as hospitalisation for LRTI with a positive RSV test, or worsening of respiratory status and positive RSV test in an already hospitalised patient. Very severe MA RSV LRTI was also evaluated, defined as MA RSV LRTI with hospitalisation and requirement for supplemental oxygen or intravenous fluids.

The efficacy of nirsevimab in term and preterm infants (GA ≥29 weeks) entering their first RSV season against MA RSV LRTI, MA RSV LRTI with hospitalisation and very severe MA RSV LRTI are shown in Table 2.

Table 2: Efficacy in term and preterm infants against MA RSV LRTI, MA RSV LRTI with hospitalisation and very severe MA RSV LRTI through 150 days post dose, D5290C00003 and MELODY (Primary cohort)

Group	Treatment	N	Incidence % (n)	Efficacy[a] (95% CI)
Efficacy in infants against MA RSV LRTI through 150 days post dose				
Very and moderately preterm GA ≥29 to <35 weeks (D5290C00003)[b]	Nirsevimab	969	2.6 (25)	70.1% (52.3, 81.2)[c]
	Placebo	484	9.5 (46)	
Term and late preterm GA ≥35 weeks (MELODY Primary cohort)	Nirsevimab	994	1.2 (12)	74.5% (49.6, 87.1)[c]
	Placebo	496	5.0 (25)	
Efficacy in infants against MA RSV LRTI with hospitalisation through 150 days post dose				
Very and moderately preterm GA ≥29 to <35 weeks (D5290C00003)[b]	Nirsevimab	969	0.8 (8)	78.4% (51.9, 90.3)[c]
	Placebo	484	4.1 (20)	
Term and late preterm GA ≥35 weeks (MELODY Primary cohort)	Nirsevimab	994	0.6 (6)	62.1% (-8.6, 86.8)
	Placebo	496	1.6 (8)	
Efficacy in infants against very severe MA RSV LRTI through 150 days post dose				
Very and moderately preterm GA ≥29 to <35 weeks (D5290C00003)[b]	Nirsevimab	969	0.4 (4)	87.5% (62.9, 95.8)[d]
	Placebo	484	3.3 (16)	
Term and late preterm GA ≥35 weeks (MELODY Primary cohort)	Nirsevimab	994	0.5 (5)	64.2% (-12.1, 88.6)[d]
	Placebo	496	1.4 (7)	

[a] Based on relative risk reduction versus placebo.

[b] All subjects who received 50 mg irrespective of weight at the time of dosing.

[c] Prespecified multiplicity controlled; p-value =<0.001.

[d] Not multiplicity controlled.

Subgroup analyses of the primary efficacy endpoint by gestational age, gender, race and region showed results were consistent with the overall population.

The severity of breakthrough cases of subjects hospitalised for MA RSV LRTI was assessed. The percentage of subjects who required supplementary oxygen was 44.4% (4/9) vs. 81.0% (17/21), subjects who required continuous positive airway pressure [CPAP]/high flow nasal cannula [HFNC] was 11.1% (1/9) vs. 23.8% (5/21), and 0% (0/9) vs. 28.6% (6/21) subjects were admitted to intensive care unit, for nirsevimab vs. placebo, respectively.

MELODY continued to enrol infants following the primary analysis, and overall, 3 012 infants were randomised to receive Beyfortus (2 009) or placebo (1 003). Efficacy of nirsevimab against MA RSV LRTI, MA RSV LRTI with hospitalisation, and very severe MA RSV LRTI through 150 days post dose was a relative risk reduction of 76.4% (95% CI 62.3, 85.2), 76.8% (95% CI 49.4, 89.4) and 78.6% (95% CI 48.8, 91.0), respectively.

Efficacy against MA RSV LRTI in infants at higher risk for severe RSV disease (MEDLEY)

MEDLEY randomised a total of 925 infants at higher risk for severe RSV disease including infants with chronic lung disease or congenital heart disease and preterm infants GA <35 weeks, entering their first RSV season. Infants received a single intramuscular dose (2:1) of nirsevimab (50 mg nirsevimab if <5 kg weight or 100 mg nirsevimab if ≥5 kg weight at the time of dosing) or 5 monthly intramuscular doses of 15 mg/kg palivizumab. At randomisation, 21.6% were GA <29 weeks; 21.5% were GA≥29 to <32 weeks; 41.9% were GA ≥32 to <35 weeks; 14.9% were GA ≥35 weeks. Of these infants 23.6% had chronic lung disease; 11.2% had congenital heart disease; 53.5% were male; 79.2% were White; 9.5% were of African origin; 5.4% were Asian; 56.5% weighed <5 kg (9.7% were <2.5 kg); 11.4% of infants were ≤1.0 month of age, 33.8% were >1.0 to ≤3.0 months 33.6% were >3.0 months to ≤6.0 months, and 21.2% were >6.0 months.

The efficacy of nirsevimab in infants at higher risk for severe RSV disease is extrapolated from the efficacy

of nirsevimab in D5290C00003 and MELODY (Primary cohort) based on pharmacokinetic exposure (see section Pharmacokinetic properties). In MEDLEY, the incidence of MA RSV LRTI through 150 days post dose was 0.6% (4/616) in the nirsevimab group and 1.0% (3/309) in the palivizumab group.

Efficacy against RSV LRTI hospitalisation in term and pre-term infants (HARMONIE)

HARMONIE randomised a total of 8 058 in term and preterm infants (GA ≥29) born during or entering their first RSV season to receive a single IM dose of nirsevimab (50 mg if <5 kg weight or 100 mg if ≥5 kg weight at the time of dosing) or no intervention. At randomisation, the median age was 4 months (range: 0 to 12 months). 48.6% of infants were aged ≤3 months; 23.7% were aged >3 to ≤6 months; and 27.7% were aged >6 months. Of these infants, 52.1% were male and 47.9% were female. Half of the infants were born during the RSV season. Most participants were term infants, with a gestational age at birth of ≥37 weeks (85.2%).

The primary endpoint for HARMONIE was the overall incidence of RSV LRTI hospitalisation through the RSV season in term and preterm infants caused by confirmed RSV infection. The efficacy of nirsevimab in preventing RSV LRTI hospitalisation compared to no intervention was estimated accounting for the follow-up time to emulate use in real world conditions. The median follow-up time of participants was 2.3 months (range: 0 to 7.0 months) in the nirsevimab group and 2.0 months (range: 0 to 6.8 months) in the no intervention group.

RSV LRTI hospitalisations occurred in 11 of 4 037 infants in the nirsevimab group (incidence rate = 0.001) and in 60 of 4 021 infants in the no intervention group (incidence rate = 0.006), corresponding to an efficacy of 83.2% (95% CI, 67.8 to 92.0) in preventing RSV LRTI hospitalisations through the RSV season, and the efficacy sustained through 180 days post-dosing/randomisation (82.7%; 95% CI, 67.8 to 91.5).

Duration of protection

Based on clinical and pharmacokinetic data, the duration of protection afforded by nirsevimab is at least 5 to 6 months.

Pharmacokinetic properties

The pharmacokinetic properties of nirsevimab are based on data from individual studies and population pharmacokinetic analyses. The pharmacokinetics of nirsevimab were dose-proportional in infants and adults following administration of clinically relevant intramuscular doses over a dose range of 25 mg to 300 mg.

Absorption

Following intramuscular administration, the maximum concentration was reached within 6 days (range 1 to 28 days) and the estimated absolute bioavailability was 85%.

Distribution

The estimated central and peripheral volume of distribution of nirsevimab were 249 mL and 241 mL, respectively, for an infant weighing 5 kg. The volume of distribution increases with increasing body weight.

Biotransformation

Nirsevimab is a human IgG1κ monoclonal antibody that is degraded by proteolytic enzymes widely distributed in the body and not metabolised by hepatic enzymes.

Elimination

As a typical monoclonal antibody, nirsevimab is eliminated by intracellular catabolism and there is no evidence of target-mediated clearance at the doses tested clinically.

The estimated clearance of nirsevimab was 3.38 mL/day for an infant weighing 5 kg and the terminal half-life was approximately 69 days. Nirsevimab clearance increases with increasing body weight.

Special populations

Race

There was no clinically relevant effect of race.

Renal impairment

As a typical IgG monoclonal antibody, nirsevimab is not cleared renally due to its large molecular weight, change in renal function is not expected to influence nirsevimab clearance. However, in one individual with nephrotic syndrome, an increased clearance of nirsevimab was observed in clinical trials.

Hepatic impairment

IgG monoclonal antibodies are not primarily cleared via the hepatic pathway. However, in some individuals with chronic liver disease which may be associated with protein loss, an increased clearance of nirsevimab was observed in clinical trials.

Infants at higher risk for severe RSV disease

There was no significant influence of chronic lung disease or congenital heart disease on the pharmacokinetics of nirsevimab.

Pharmacokinetic/pharmacodynamic relationship(s)

In D5290C00003 and MELODY (Primary cohort) a positive correlation was observed between a serum AUC (Area Under the Curve), based on clearance at baseline above 12.8 mg*day/mL and a lower incidence of MA RSV LRTI. The recommended dosing regimen consisting of a 50 mg or 100 mg intramuscular dose for infants in their first RSV season was selected on the basis of these results.

In MEDLEY, >80% of infants at higher risk for severe RSV disease, including infants born extremely preterm (GA <29 weeks) and infants with chronic lung disease or congenital heart disease, achieved nirsevimab exposures associated with RSV protection (serum AUC above 12.8 mg*day/mL) following a single dose (see section Pharmacodynamic properties).

Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity and tissue cross-reactivity studies.

PHARMACEUTICAL PARTICULARS

List of excipients

L-histidine
L-histidine hydrochloride L-arginine hydrochloride Sucrose
Polysorbate 80 (E433)
Water for injections

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

36 Months

Beyfortus may be kept at room temperature (20°C - 25°C) when protected from light for a maximum of 8 hours. After this time, the syringe must be discarded.

Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze. Do not shake or expose to direct heat.
Keep the pre-filled syringe in the outer carton in order to protect from light. For storage conditions of the medicinal product, see section shelf life.

Nature and contents of container

Siliconised Luer lock Type I glass pre-filled syringe with a FluroTec-coated plunger stopper. Each pre-filled syringe contains 0.5 mL or 1 mL solution.

Pack sizes:

- 1 or 5 pre-filled syringe(s) without needles.
- 1 pre-filled syringe packaged with two separate needles of different sizes.

Not all pack sizes may be marketed.

Special precautions for disposal and other handling

This medicinal product should be administered by a trained healthcare professional using aseptic techniques to ensure sterility.

Visually inspect the medicinal product for particulate matter and discolouration prior to administration. The medicinal product is a clear to opalescent, colourless to yellow solution. Do not inject if the liquid is cloudy, discoloured, or it contains large particles or foreign particulate matter.

Do not use if the pre-filled syringe has been dropped or damaged or the security seal on the carton has been broken.

Disposal

Each pre-filled syringe is for single-use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

MANUFACTURER
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USA

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