▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION BEYFORTUS™ (NIRSEVIMAB) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Nirsevimab

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

BEYFORTUS 50 mg solution for injection in prefilled syringe

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

BEYFORTUS 100 mg solution for injection in prefilled syringe

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

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Solution for injection

Clear to opalescent, colourless to yellow, pH 6.0 solution in a prefilled syringe

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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.

BEYFORTUS should be used in accordance with official recommendations.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosing recommendations

Neonates and Infants: First RSV Season

For neonates and infants born during or entering the RSV season, administer BEYFORTUS starting from birth. For infants born outside the RSV season, administer BEYFORTUS once prior to the start of the RSV season considering duration of protection provided by BEYFORTUS (see Section 5.1).

The recommended dosage of BEYFORTUS for neonates and infants born during or entering their first RSV season is based on body weight (see Table 1) and is administered as a single intramuscular (IM) injection.

Table 1 - Recommended Dosage of BEYFORTUS in Neonates and Infants Born During or Entering Their First RSV Season

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

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 (see Section 4.8, 5.1 and 5.2). No clinical data are available in infants with a postmenstrual age (gestational age at birth plus chronological age) of less than 32 weeks.

Children Who Remain at Increased Risk for Severe RSV Disease: Second RSV Season

For children up to 24 months of chronological age 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 two IM injections (2 x 100 mg) at the same visit.

Children Undergoing Cardiac Surgery with Cardiopulmonary Bypass

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 serum levels. The recommended dosage of BEYFORTUS is administered as an IM injection.

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. Refer to Table 1 for weight-based dosing.
- If more than 90 days have elapsed since receiving BEYFORTUS, the additional dose should be 50 mg regardless of body weight.

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.

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

Limited data or no data are available in infants with a range of underlying conditions, e.g. Down syndrome (n=13), Cystic fibrosis (n=5), Congenital airway anomalies (n=9), and Neuromuscular disease (n=0; not evaluated in clinical trials).

Method of administration

BEYFORTUS is for IM injection intended for administration by a healthcare professional.

BEYFORTUS 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. If two injections are required, different injection sites should be used.

Instructions for administration

BEYFORTUS prefilled syringe is for single use in one patient only. Contains no antimicrobial preservative.

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

Do not use if the BEYFORTUS prefilled syringe has been dropped or damaged, the security seal on the carton has been broken, or the expiry date (EXP) has passed.

BEYFORTUS is available in a 50 mg in 0.5 mL and a 100 mg in 1 mL prefilled syringe. Check the labels on the BEYFORTUS carton and prefilled syringe to make sure you have selected the correct 50 mg in 0.5 mL and a 100 mg in 1 mL presentation as required.

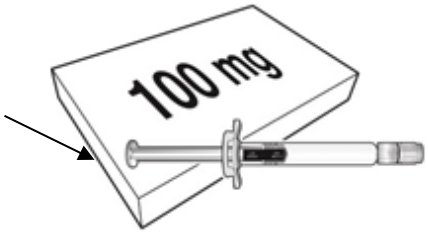
BEYFORTUS 50 mg in 0.5 mL
prefilled syringe with a purple plunger rod.

Purple



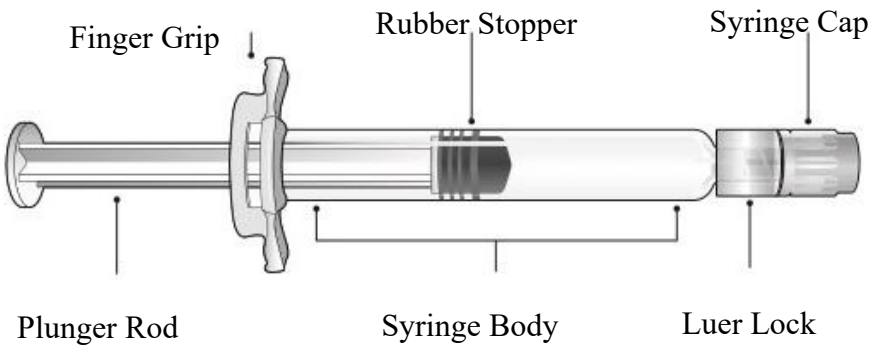
BEYFORTUS 100 mg in 1 mL
prefilled syringe with a light blue plunger rod.

Light Blue



Refer to Figure 1 for prefilled 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 prefilled syringe by gently twisting the needle clockwise onto the prefilled 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 BEYFORTUS prefilled 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.

Step 5 Dispose of the used syringe immediately (see Section 6.6 Special precautions for disposal).

If two injections are required, repeat steps 1-5 in a different injection site.

4.3 CONTRAINDICATIONS

Individuals with a history of severe hypersensitivity reactions, including anaphylaxis, to the active substances or to any of the excipients listed in Section 6.1 List of excipients and Section 4.4 Special warnings and precautions for use.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity including anaphylaxis

Serious hypersensitivity reactions have been reported following BEYFORTUS administration. These reactions included urticaria, dyspnoea, 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 reaction occur, immediately discontinue administration and initiate appropriate medicinal products and/or supportive therapy.

Inform the patient's caregiver of the signs and symptoms of potential hypersensitivity reactions, and advise the caregiver to seek medical attention immediately if the child experiences a hypersensitivity reaction to BEYFORTUS.

Use in individuals with clinically significant bleeding disorders

As with any other IM injections, BEYFORTUS should be given with caution to individuals with thrombocytopenia, any coagulation disorder or to individuals on anticoagulation therapy.

Use in individuals with protein-losing conditions

In some individuals with protein-losing conditions, an increased clearance of nirsevimab was observed in clinical trials (see Section 5.2 Pharmacokinetic properties). Nirsevimab may not provide the same level of protection in individuals with significant protein loss.

Use in hepatic impairment

See Section 5.2 Pharmacokinetic properties.

Use in renal impairment

See Section 5.2 Pharmacokinetic properties.

Use in the elderly

No data available.

Paediatric use

The safety and effectiveness of BEYFORTUS have not been established in children older than 24 months of age. No data are available.

Effects on laboratory tests

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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been conducted. Monoclonal antibodies do not typically have significant drug-drug interaction potential, as they do not directly affect cytochrome P450 enzymes and are not substrates of hepatic or renal transporters.

Nirsevimab-mediated drug-drug interactions are unlikely as the target of nirsevimab is an exogenous virus.

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 6.2 Incompatibilities). When administered concomitantly with injectable vaccines, they should be given with separate syringes and at different injection sites.

Co-administration with immunoglobulin products

There is no information regarding co-administration of BEYFORTUS with other immunoglobulin products. Palivizumab should not be administered to infants who have already received BEYFORTUS in the same season. There are no data regarding substitution of BEYFORTUS for palivizumab once prophylaxis treatment is initiated with palivizumab for the RSV season. BEYFORTUS may be administered prior to or during the second RSV season to children up to 24 months of age who remain vulnerable to severe RSV disease, and who received palivizumab in their first RSV season.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

BEYFORTUS is only indicated for children under 2 years of age. No human or animal data are available for possible effects on fertility.

Use in pregnancy (Category B2)

BEYFORTUS is only indicated for children under 2 years of age. No human or animal data are available to assess the associated risks in pregnancy. BEYFORTUS is not indicated for use in females of reproductive potential.

Use in lactation

BEYFORTUS is only indicated for children under 2 years of age. No human or animal data are available to assess the impact of nirsevimab on milk production, its presence in breast milk, or its effects on the breastfed infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Not applicable.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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. The following CIOMS frequencies of occurrence of adverse reactions are defined as are used, when applicable: very common (≥10%); common (≥1 and <10%); uncommon (≥0.1 and 1%); rare (≥0.01 and 0.1%); very rare (<0.01%) and not known (cannot be estimated from available data).

Clinical trials experience

Overall, 2,966 term and preterm infants (Gestational Age [GA] ≥29 weeks) received nirsevimab in two placebo-controlled clinical trials (D5290C00003 and MELODY).

Table 2 presents the adverse reactions of the pooled analysis from D5290C00003 and MELODY (All subjects).

Table 2 - Adverse reactions – pooled analysis D5290C00003 and MELODY (All subjects)

Frequency	MedDRA System Organ Class	Event
Uncommon	Skin and subcutaneous tissue disorders	Rash [a]
	General disorders and administration site conditions	Injection site reaction [b]
		Pyrexia [c]

a. Rash was defined by the following grouped preferred terms: rash, rash maculo-papular, rash macular, occurring within 14 days post dose.
b. 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, occurring within 7 days post dose.
c. Pyrexia occurring within 7 days post dose.

Infants at higher risk and children vulnerable to severe RSV disease

Safety was 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 CLD, or CHD entering their first RSV season, who received nirsevimab (614) or palivizumab (304). The safety profile of nirsevimab in infants who received nirsevimab in their first RSV season was comparable to the palivizumab comparator and consistent with the safety profile of nirsevimab in term and preterm infants GA ≥29 weeks (D5290C00003 and MELODY).

Safety was evaluated in MEDLEY in 220 children with CLD or CHD who received nirsevimab or palivizumab in their first RSV season and went on to receive nirsevimab entering their second RSV season. The safety profile of nirsevimab in children who received nirsevimab in their first and second RSV season (180) was comparable to that in children who received palivizumab in their first RSV season and then nirsevimab in their second RSV season (40). The safety profile of nirsevimab in these children from both arms was consistent with the safety profile of nirsevimab in term and preterm infants GA ≥29 weeks (D5290C00003 and MELODY) and comparable to children who received palivizumab for both RSV seasons.

Safety was also evaluated in MUSIC, an open label, uncontrolled, single dose trial in 100 immunocompromised infants and children ≤24 months, who received nirsevimab in their first or second RSV season. This included subjects with at least one of the following conditions: immunodeficiency (combined, antibody, or other aetiology) (33); systemic high-dose corticosteroid

therapy (29); organ or bone marrow transplantation (16); receiving immunosuppressive chemotherapy (20); other immunosuppressive therapy (15), and HIV infection (8). The safety profile of nirsevimab administered in the first or second RSV season was consistent with that expected for a population of immunocompromised children and with the safety profile of nirsevimab in term and preterm infants GA ≥29 weeks (D5290C00003 and MELODY).

Term and Preterm Infants entering their first RSV season

Safety of BEYFORTUS 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 (4,016) or no intervention (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).

Post-marketing experience

The following adverse reactions have been identified during post approval use of BEYFORTUS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Not known: hypersensitivity reactions (see Section 4.4 Special warnings and precautions for use).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is very limited experience of overdose with nirsevimab.

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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 KD = 0.12 nM and KD = 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.

The potential for rapid protection was evaluated in a cotton rat model of RSV infection using a non-YTE version of nirsevimab (IG7). Intramuscular administration 1 day prior to inoculation with RSV A or B provided complete protection from viral replication in the upper and lower respiratory tracts.

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 EC50 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 as compared to reference). 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 surveillance trials

In prospective, observational, global molecular epidemiology studies (OUTSMART-RSV and INFORM-RSV) genetic diversity of RSV F protein sequences has remained low (most amino acids in both RSV A and RSV B >99% conserved) and prevalence of variants harbouring nirsevimab resistance-associated substitutions has been rare (<1%). Since 2015, most amino acid residues in the nirsevimab binding site have remained highly conserved (>99%) at all positions in RSV A and 22 of the 25 positions in RSV B. Co-occurring mutations I206M:Q209R in the binding site that have become prevalent in RSV B since 2017 retain full susceptibility to nirsevimab (I206M:Q209R,

0.23-fold change). The S211N substitution which has expanded in prevalence also retains susceptibility to nirsevimab, both individually (1.2-fold change) and as co-occurring substitutions (I206M:Q209R:S211N, 0.5-fold change).

In clinical trials

In MELODY, MEDLEY, MUSIC and subjects who received the recommended dose of 50 mg nirsevimab if <5 Kg weight in D5290C00003, no subject with medically attended RSV lower respiratory tract infection (MA RSV LRTI) or any RSV case definition had an RSV isolate containing a nirsevimab resistance-associated substitution in any treatment group.

In D5290C00003 (subjects who received a single dose of 50 mg nirsevimab), 2 of 40 subjects with RSV infections corresponding to any case definition had a variant containing nirsevimab resistance-associated substitutions. RSV B variants occurred in two subjects receiving below the recommended nirsevimab dose and harboured I64T:K68E:I206M:Q209R co-occurring substitutions or the N208S substitution that showed reduced susceptibility to nirsevimab (IC50 >ULOQ). Resistance associated substitutions were not identified as major variants in any sampling timepoints in MELODY, MEDLEY or MUSIC studies, including post day 361 when nirsevimab titres have waned.

Minimal data are available that show that variants resistant to nirsevimab could have cross-resistance to other monoclonal antibodies targeting the F protein of RSV; palivizumab retained full neutralisation potency against resistant associated substitutions identified in D5290C00003. Nirsevimab retained activity against recombinant RSV harbouring palivizumab resistance-associated substitutions identified in molecular epidemiology studies and in neutralisation escape variants of palivizumab.

Pharmacokinetic/pharmacodynamic relationship(s)

In D5290C00003 and MELODY (Primary cohort) a positive correlation was observed between a serum AUC (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 IM dose for infants in their first RSV season and a 200 mg IM dose for children entering their second RSV season was selected on the basis of these results.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralising antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and the paediatric population studied. For these reasons, comparison of the incidence of antibodies to nirsevimab to other products may be misleading.

In D5290C00003 and MELODY anti-nirsevimab antibodies were detected in 148/2493 (5.9%) infants who received a single dose of nirsevimab at the recommended dosing regimen during the 361 days post dosing period, and 110/2404 (4.6%) tested positive for anti-drug antibodies (ADA) against the YTE domain. In MELODY 26/1877 (1.4%) of subjects tested positive for nirsevimab neutralising antibodies. For subjects receiving a single dose of nirsevimab in their first RSV season in MEDLEY, anti-nirsevimab antibodies were detected in 32/587 (5.5%) of infants during the 361 days post dosing period. Nirsevimab neutralising antibodies were detected in 2/564 (0.4%) of infants and 29/564 (5.1%) of infants tested positive for ADA against the YTE domain. Of 180

subjects who received nirsevimab in two consecutive RSV seasons, 8 subjects (4.4%) and 13 (7.2%) became ADA positive for the first time in the first and second RSV season respectively. Only one subject was ADA positive in both RSV seasons. In the second RSV season, 8 subjects had anti-YTE ADA and one of the subjects also had neutralising antibodies. For subjects receiving nirsevimab in their first or second RSV season in MUSIC, anti-nirsevimab antibodies were detected in 11/97 (11.3%) of children during the 361 days post dosing period. Nirsevimab neutralising antibodies were detected in 1/97 (1.0%) of children and 11/97 (11.3%) of children tested positive for ADA against the YTE domain.

The development of ADA against nirsevimab appears to have no clinically relevant effect on its clearance (up to 5 months), efficacy or safety.

Clinical trials

The efficacy and safety of BEYFORTUS were evaluated in two randomised, double-blind, placebo-controlled multicentre trials (D5290C00003 and MELODY) for the prevention of MA RSV LRTI in term and preterm infants (GA ≥29 weeks) entering their first RSV season. Safety and pharmacokinetics (PK) of BEYFORTUS were also evaluated in a randomised, double-blind, palivizumab-controlled multicentre trial (MEDLEY) in infants at higher risk for severe RSV disease, including extremely preterm infants (GA <29 weeks) and infants with CLD of prematurity, or haemodynamically significant CHD, entering their first RSV season, and children with CLD or CHD entering their second RSV season.

Table 3 - Trials Conducted with BEYFORTUS for the Prevention of MA RSV LRTI

Trial	Population	Study Arms
D5290C00003 NCT02878330	Infants born at ≥29 to <35 weeks GA entering their first RSV season	BEYFORTUS (N=969)* **Placebo (N=484)**
D5290C00004 MELODY NCT03979313	Infants born at ≥35 weeks GA entering their first RSV season	**Primary Cohort†:** BEYFORTUS (N=994) Placebo (N=496) **Safety Cohort‡:** BEYFORTUS (N=1,015) Placebo (N=507)
D5290C00005 MEDLEY NCT03959488	Infants born at <35 weeks GA and infants born with CLD or CHD entering their first RSV season Infants with CLD or CHD only entering their second RSV season	**RSV Season One:** BEYFORTUS (N=616) Palivizumab (N=304) **RSV Season Two:** BEYFORTUS (N=220) Palivizumab (N=42)

GA gestational age; CLD chronic lung disease; CHD hemodynamically significant chronic heart disease

* All subjects in D5290C00003 were included in the efficacy analysis. All subjects in D5290C00003 received 50 mg of BEYFORTUS IM injections regardless of body weight. The recommended BEYFORTUS dose in neonates and infants born during or entering their first RSV season is single IM 50 mg and 100 mg dose for those who weigh <5 kg and ≥5 kg, respectively (see Section 4.2).

† The primary efficacy analysis for MELODY is based on subjects from the Primary Cohort. For MELODY safety population see Section 4.8.

‡ MELODY safety analysis included both Primary and Safety Cohorts (see Section 4.8).

Safety and PK of BEYFORTUS were also evaluated in an open-label, uncontrolled, single dose multicentre trial (MUSIC) in immunocompromised children ≤24 months of age.

Efficacy and safety of BEYFORTUS 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 for palivizumab).

Key demographics and baseline characteristics for MELODY, D5290C00003, and MEDLEY are summarised in Table 4 and Table 5. Across MELODY, D5290C00003 and MEDLEY, demographic and baseline characteristics were similar between the nirsevimab and comparator groups and the study populations were representative of the intended target population of all infants in their first RSV season and children who remain vulnerable to severe RSV disease in their second RSV season, including extremely preterm infants, and infants and children up to 24 months of age with CLD or CHD.

Table 4 - Select Demographic and Baseline Characteristics – MELODY (Primary Cohort), MELODY (All Subjects), D5290C00003 (Recommended Dose), D5290C00003

Statistic	Term and late preterm infants born ≥35 wGA		Very and moderately preterm infants born ≥29 to <35 wGA	
	MELODY (Primary Cohort)[b]	MELODY (All Subjects)	D5290C00003 (Recommended Dose)[c]	D5290C00003
	Total (N = 1490)	Total (N = 3012)	Total (N = 860)	Total (N = 1453)
Race, n (%) [a]				
American Indian or Alaska Native	83 (5.6)	144 (4.8)	0	1 (0.1)
Asian	54 (3.6)	159 (5.3)	9 (1.0)	15 (1.0)
Black or African American	422 (28.4)	437 (14.5)	160 (18.6)	256 (17.6)
Native Hawaiian or other Pacific Islander	11 (0.7)	23 (0.8)	9 (1.0)	11 (0.8)
White	796 (53.5)	1593 (52.9)	601 (70.0)	1048 (72.2)
Weight group on Day 1, n (%)				
<2.5 kg	37 (2.5)	73 (2.4)	246 (28.6)	246 (17.0)
<5 kg	595 (40.0)	1192 (39.6)	860 (100.0)	860 (59.5)
≥5 kg	893 (60.0)	1817 (60.4)	0	585 (40.9)
Gestational age group, n (%)				
<29 weeks	NA	NA	NA	NA
≥29 to <32 weeks	NA	NA	189 (22.2)	294 (20.3)
≥32 to <35 weeks	NA	NA	664 (77.8)	1152 (79.7)
≥35 weeks to <37 weeks	208 (14.0)	361 (12.0)	NA	NA
≥37 weeks	1280 (86.0)	2649 (88.0)	NA	NA

a Each race category counts subjects who selected only that category.

b MELODY (Primary Cohort): All randomized subjects through 510 days post dose (DCO 09 August 2021)

c D5290C00003 (Recommended Dose): All randomized subjects who received the recommended dose of nirsevimab (i.e., excluding subjects weighting ≥5 kg at the time of dosing)

Table 5 - Select Demographic and Baseline Characteristics – MEDLEY (RSV Season 1) and MEDLEY (RSV Season 2)

	Infants and Children at higher risk for severe RSV disease	
	MEDLEY RSV Season 1	MEDLEY RSV Season 2 (CHD/CLD)
Statistic	**Total (N = 925)**	**Total (N = 262)**
Race, n (%) [a]		
American Indian or Alaska Native	16 (1.7)	0 (0.0)
Asian	50 (5.4)	15 (5.7)
Black or African American	88 (9.5)	12 (4.6)
Native Hawaiian or other Pacific Islander	5 (0.5)	1 (0.4)
White	732 (79.2)	225 (85.9)
Weight group on Day 1, n (%)		
<5 kg	518 (56.5)	NE
≥5 kg	399 (43.5)	NE
<7 kg	NE	6 (2.3)
<10 kg	NE	147 (56.1)
Gestational age group, n (%)		
<29 weeks	200 (21.6)	103 (39.3)
≥29 to <32 weeks	199 (21.5)	43 (16.4)
≥32 to <35 weeks	388 (41.9)	36 (13.7)
≥35 weeks	138 (14.9)	80 (30.5)
CLD/CHD Status, n (%)		
CLD	217 (23.5)	189 (72.1)
CHD	104 (11.2)	81 (30.9)

a Each race category counts subjects who selected only that category.
NE = not evaluated; RSV = respiratory syncytial virus

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 1453 very and moderately preterm infants (GA ≥29 to <35 weeks) entering their first RSV season (2:1) to receive a single IM dose of 50 mg BEYFORTUS 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; and 59.5% weighed <5 Kg. The median age was 2.80 months (range: 0.1 to 11.9 months); 53.2% were ≤3.0 months; 32.6% were >3.0 to ≤6.0 months, and 14.2% were >6.0 months of age.

MELODY (Primary cohort) randomised a total of 1490 term and late preterm infants (GA ≥35 weeks) entering their first RSV season (2:1) to receive a single IM dose of BEYFORTUS (50 mg BEYFORTUS if <5 Kg weight or 100 mg BEYFORTUS 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; and 40.0% weighed <5 Kg. The median age was 2.60 months (range: 0.03 to 11.10 months); 57.9% were ≤3.0 months; 32.1% were >3.0 to ≤6.0 months and 10.0% were >6.0 months of age. MELODY continued to enrol infants following the primary analysis, and overall, 3012 infants (All

subjects) were randomised to receive BEYFORTUS (2009) or placebo (1003). At randomisation, 12.0% were GA ≥35 to <37 weeks; 88.0% were GA ≥37 weeks; 52.3% were male; 52.9% were White; 14.5% were of African origin; 5.3% were Asian; and 39.6% weighed <5 Kg. The median age was 2.53 months (range: 0.00 to 14.00 months); 59.0% were ≤3.0 months; 31.8% were >3.0 to ≤6.0 months, and 9.1% were >6.0 months of age.

Demographic and baseline characteristics were comparable between the BEYFORTUS 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). BEYFORTUS demonstrated efficacy in both individual trials in term and preterm infants (GA ≥29 weeks) entering their first RSV season (Table 6).

Table 6 - Efficacy in term and preterm infants against MA RSV LRTI through 150 days post dose - D5290C00003 and MELODY (Primary cohort)

Group	Treatment	N	Incidence % (n)	Efficacy[a] (95% CI)
Very and moderately preterm GA ≥29 to <35 weeks (D5290C00003)	BEYFORTUS	969	2.6 (25)	70.1% (52.3, 81.2) p<0.0001
	Placebo	484	9.5 (46)	
Term and late preterm GA ≥35 weeks (MELODY)	BEYFORTUS	994	1.2 (12)	74.5% (49.6, 87.1) p<0.0001
	Placebo	496	5.0 (25)	

a. Based on relative risk reduction versus placebo. Prespecified 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 incidence of hospitalisation in infants with MA RSV LRTI and very severe MA RSV LRTI were evaluated. 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 defined as MA RSV LRTI with hospitalisation and requirement for supplemental oxygen or intravenous (IV) fluids. The efficacy of BEYFORTUS in D5290C00003 and MELODY (All subjects) in term and preterm infants (GA ≥29 weeks) entering their first RSV season against MA RSV LRTI with hospitalisation and very severe MA RSV LRTI are shown in Table 7.

Table 7 - Efficacy in term and preterm infants against MA RSV LRTI with hospitalisation and very severe MA RSV LRTI through 150 days post dose, D5290C00003 and MELODY (All subjects).

Group	Treatment	N	Incidence % (n)	Efficacy[a] (95% CI)
Efficacy in infants against MA RSV LRTI with hospitalisation through 150 days post dose				
Very and moderately preterm GA ≥29 to <35 weeks (D5290C00003)	BEYFORTUS	969	0.8 (8)	78.4% (51.9, 90.3)b
	Placebo	484	4.1 (20)	

Group	Treatment	N	Incidence % (n)	Efficacy[a] (95% CI)
Term and late preterm GA ≥35 weeks, MELODY (all subjects)	BEYFORTUS	2009	0.4 (9)	76.8% (49.4, 89.4)c
	Placebo	1003	2.0 (20)	
Efficacy in infants against very severe MA RSV LRTI through 150 days post dose				
Very and moderately preterm GA ≥29 to <35 weeks (D5290C00003)	BEYFORTUS	969	0.4 (4)	87.5% (62.9, 95.8)d
	Placebo	484	3.3 (16)	
Term and late preterm GA ≥35 weeks, MELODY (all subjects)	BEYFORTUS	2009	0.3 (7)	78.6% (48.8, 91.0)d
	Placebo	1003	1.7 (17)	

a. Based on relative risk reduction versus placebo
b. Prespecified multiplicity controlled p-value <0.001.
c. Prespecified after primary cohort results had been revealed, not multiplicity controlled.
d. Not multiplicity controlled.

In infants in D5290C00003 who received the recommended dose (50 mg if body weight <5 Kg at time of dosing), the efficacy of BEYFORTUS against MA RSV LRTI, MA RSV LRTI with hospitalisation, and very severe MA RSV LRTI in very and moderately preterm infants (GA ≥29 to <35 weeks) was 86.2% (95% CI 68.0, 94.0), 86.5% (95% CI 53.5, 96.1) and 100.0% (95% CI 79.7, not evaluated), respectively.

A pooled analysis of D5290C00003 (recommended dose) and MELODY (Primary cohort) was specified after data on D5290C00003 had been revealed. Efficacy of BEYFORTUS against MA RSV LRTI, MA RSV LRTI with hospitalisation, and very severe MA RSV LRTI through 150 days post dose was 79.5% (95% CI 65.9, 87.7), 77.3% (95% CI 50.3, 89.7) and 86.0% (95% CI 62.5, 94.8), respectively.

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 BEYFORTUS vs placebo.

Efficacy against MA RSV LRTI in infants and children vulnerable to severe RSV disease (MEDLEY and MUSIC)

MEDLEY randomised a total of 925 infants at higher risk for severe RSV disease including infants with CLD or CHD and preterm infants GA <35 weeks, entering their first RSV season. Infants received a single IM dose (2:1) of BEYFORTUS (50 mg BEYFORTUS if <5 Kg weight or 100 mg BEYFORTUS if ≥5 Kg weight at the time of dosing), followed by 4 once-monthly IM doses of placebo, or 5 once-monthly IM 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 23.5% had CLD; 11.2% had CHD; 53.5% were male; 79.2% were White; 9.5% were of African origin; 5.4% were Asian; and 56.5% weighed <5 Kg. The median age was 3.46 months (range: 0.07 to 12.25 months); 45.2% were ≤3.0 months; 33.6% were >3.0 months to ≤6.0 months and 21.2% were >6.0 months of age.

Children at higher risk with CLD or CHD ≤24 months of age continued in the trial for a second RSV season. Subjects who received BEYFORTUS during their first RSV season received a second single dose of 200 mg BEYFORTUS entering their second RSV season (180) followed by 4 once-monthly IM doses of placebo. Subjects who received palivizumab during their first RSV season were re-randomised 1:1 to either the BEYFORTUS or the palivizumab group entering their

second RSV season. Subjects in the BEYFORTUS group (40) received a single fixed dose of 200 mg followed by 4 once-monthly IM doses of placebo. Subjects in the palivizumab group (42) received 5 once-monthly IM doses of 15 mg/Kg palivizumab. Of these children 72.1% had CLD, 30.9% had CHD; 57.6% were male; 85.9% were White; 4.6% were of African origin; 5.7% were Asian; and 2.3% weighed <7 Kg. Demographic and baseline characteristics were comparable between the BEYFORTUS/BEYFORTUS, palivizumab/BEYFORTUS and palivizumab/palivizumab groups.

The efficacy of BEYFORTUS in infants at higher risk for severe RSV disease, including extremely preterm infants (GA <29 weeks) and infants with CLD or CHD, and in children with CLD or CHD ≤24 months of age entering their second RSV season is established by extrapolation from the efficacy of BEYFORTUS in D5290C00003 and MELODY based on PK exposure. In MEDLEY, 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. There were no cases of MA RSV LRTI through 150 days in the second RSV season.

In MUSIC, the efficacy of BEYFORTUS in immunocompromised infants and children ≤24 months entering their first or second RSV season, who received the recommended dose of BEYFORTUS is established by extrapolation from the efficacy of BEYFORTUS in D5290C00003 and MELODY based on PK exposure. There were no cases of MA RSV LRTI through 150 days post dose.

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

HARMONIE randomised a total of 8,058 term and preterm infants (GA ≥29) born during or entering their first RSV season to receive a single IM dose of BEYFORTUS (50 mg if <5 kg weight or 100 mg if ≥5 kg weight at the time of dosing). 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 RSV 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 10 of 4,037 infants in the nirsevimab group (incidence rate = 0.001) and in 60 of 4021 infants in the no intervention group (incidence rate = 0.008), corresponding to a superior efficacy of 83.2% (95% CI, 67.8 to 92.0; p<0.0001) in preventing RSV LRTI hospitalisations.

The Primary Analysis was conducted to evaluate the efficacy of nirsevimab under real world conditions. Following the Primary Analysis, the First Year Analysis was conducted to evaluate efficacy against RSV LRTI hospitalisation at 150 and 180 days post-dosing.

Efficacy endpoints through 150 days post-dosing/randomisation

RSV LRTI hospitalisations occurred in 12 of 4,038 infants in the nirsevimab group (incidence rate = 0.001) and in 67 of 4,019 infants in the no intervention group (incidence rate = 0.003) through 150 days post-dosing/randomisation, corresponding to an efficacy of 82.4% (95% CI, 67.3 to 91.4).

Efficacy endpoints through 180 days post-dosing/randomisation

The efficacy of nirsevimab observed in the primary analysis was sustained and consistent through 180 days. RSV LRTI hospitalisations occurred in 12 of 4,038 infants in the nirsevimab group (incidence rate = 0.001) and in 68 of 4,019 infants in the no intervention group (incidence rate = 0.003) through 180 days post-dosing/randomisation, corresponding to an efficacy of 82.7% (95% CI, 67.8 to 91.5).

Duration of protection

The minimum duration of protection offered by a single dose of nirsevimab is at least 5 to 6 months based on clinical and PK data.

5.2 PHARMACOKINETIC PROPERTIES

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

Absorption

The estimated absorption half-life following IM administration was 1.7 days, and the estimated absolute bioavailability was 84% based on population PK analysis. The median time to maximum concentration was 6 days (range 1 to 28 days).

Distribution

Based on population PK analysis, the estimated central and peripheral volume of distribution of nirsevimab were 216 mL and 261 mL, respectively, for an infant weighing 5 Kg.

Metabolism

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

Excretion

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.

Based on population PK analysis, the estimated clearance of nirsevimab was 3.42 mL/day for an infant weighing 5 Kg and the terminal half-life was approximately 71 days.

Special populations

Race and ethnicity

Based on population PK analysis there was no clinically relevant effect of race and ethnicity on the PK of nirsevimab.

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 and children who remain vulnerable to severe RSV disease

There was no significant influence of CLD or CHD on the PK of nirsevimab based on population PK analysis. Serum concentrations at day 151 in MEDLEY were comparable to those in MELODY.

In infants born extremely preterm (GA <29 weeks) entering their first RSV season and children with CLD or CHD entering their first or second RSV season (MEDLEY), the pre-defined acceptance criteria for extrapolation were met; >80% of infants/children achieved nirsevimab exposures associated with RSV protection following a single dose.

In MUSIC, 75% (72/96) of immunocompromised infants/children entering their first or second RSV season achieved nirsevimab exposures associated with RSV protection. When excluding 14 children with protein-losing conditions as evidenced by increased clearance of nirsevimab, 87% (71/82) achieved nirsevimab exposures associated with RSV protection.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Nirsevimab is a monoclonal antibody, as such genotoxicity studies have not been conducted. As a large protein molecule, nirsevimab is not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity

No carcinogenicity studies have been conducted because nirsevimab binds a viral-specific target that is not expressed in nonclinical models or in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

BEYFORTUS solution for injection contains the excipients histidine, histidine hydrochloride monohydrate, arginine hydrochloride, sucrose, polysorbate 80 and water for injections.

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (Refrigerate. Do not freeze).

BEYFORTUS may be kept at room temperature (Store below 25°C) when protected from light for a maximum of 48 hours. After removal from the refrigerator, BEYFORTUS must be used within 48 hours or discarded.

Keep the prefilled syringe in the outer carton in order to protect from light.

Do not shake or expose to heat.

6.5 NATURE AND CONTENTS OF CONTAINER

Siliconised Luer lock Type I glass prefilled syringe with a FluroTec-coated plunger stopper.

Each prefilled syringe contains 0.5 mL or 1 mL solution.

Pack size: 1 or 5 single use prefilled syringe(s)* without needles.

*not all pack sizes may be available in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Dispose of the used syringe immediately, together with the needle, in a sharps disposal container.

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

General structure

Nirsevimab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. The Fc region of nirsevimab has been engineered with a triple amino acid substitution (YTE) to extend serum half-life.

CAS number

1989556-22-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

sanofi-aventis australia pty ltd
International Tower 3, Level 23
300 Barangaroo Avenue
Sydney NSW 2000
Freecall: 1800 818 806
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9 DATE OF FIRST APPROVAL

24 November 23

10 DATE OF REVISION

20 August 2026

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
6.4	Revision of storage conditions and shelf life