▼ 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
ENFLONSIA® (clesrovimab) Solution for Injection

1 NAME OF THE MEDICINE

Clesrovimab

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.7 mL dose contains 105 mg of clesrovimab.

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

3 PHARMACEUTICAL FORM

ENFLONSIA is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution for intramuscular injection available in a 0.7 mL single dose prefilled syringe.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ENFLONSIA is indicated for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in neonates and infants who are born during or entering their first RSV season.

ENFLONSIA should be used in accordance with official recommendations.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

Neonates and Infants: First RSV Season

The recommended dose is 105 mg administered as a 0.7 mL single intramuscular (IM) injection.

For neonates and infants born during the RSV season, administer ENFLONSIA starting from birth. For infants born outside the RSV season, administer ENFLONSIA once prior to the start of their first RSV season considering the duration of protection provided by ENFLONSIA [See Section 5.1 PHARMACODYNAMIC PROPERTIES – Duration of Protection].

Dosing in infants with a body weight between 0.5 kg and 1.1 kg is based on extrapolation; no clinical data are available. Exposure in infants < 1.1 kg is anticipated to yield higher exposures than in those weighing more. The benefits and risks of clesrovimab in infants < 1.1 kg should be carefully considered.

There are limited clinical data available in extremely preterm infants (gestational age (GA) < 29

weeks) who are of chronological age less than 8 weeks. No clinical data are available in infants with a postmenstrual age (GA plus chronological age) of less than 32 weeks [See Section 5.1 PHARMACODYNAMIC PROPERTIES].

Infants Undergoing Cardiac Surgery with Cardiopulmonary Bypass

For infants undergoing cardiac surgery with cardiopulmonary bypass during the first RSV season, an additional 105 mg dose is recommended as soon as the infant is stable after surgery to ensure adequate clesrovimab serum levels.

Method of Administration

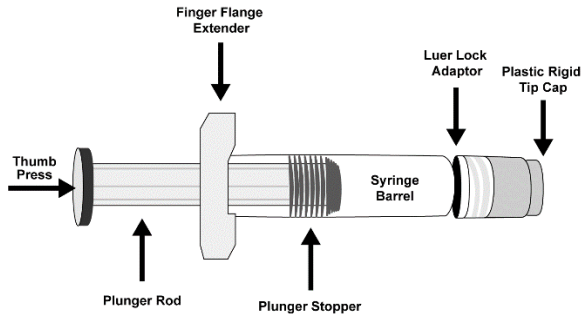
For intramuscular use only.

Instructions For Use

ENFLONSIA must be administered by a healthcare provider.

Before injection, remove ENFLONSIA from the refrigerator and allow the prefilled syringe to come to room temperature for approximately 15 minutes. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. ENFLONSIA is a clear to slightly opalescent, colorless to slightly yellow solution. This product should not be used if particulate matter or discoloration is found. Do not use if the prefilled syringe has been dropped or damaged, the security seal on the carton has been broken, or the expiration date has passed. Refer to Figure 1 for prefilled syringe components.

Figure 1: Prefilled Syringe Components



Step 1: Hold the syringe barrel in one hand and unscrew the tip cap by twisting it counter clockwise with the other hand. Do not remove the Luer Lock adaptor and the finger flange extender.

Step 2: Attach a sterile Luer Lock needle by twisting in a clockwise direction until the needle fits securely on the syringe. Due to the viscosity of the product, use a 25 gauge or larger needle.

Step 3: Inject the entire contents of the ENFLONSIA prefilled syringe intramuscularly, in the anterolateral aspect of the thigh. ENFLONSIA should not be injected in the gluteal area or areas where there may be a major nerve trunk and/or blood vessel.

Co-administration with Childhood Vaccines and Immunoglobulin Products

ENFLONSIA can be given concomitantly with childhood vaccines [see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS]. When ENFLONSIA is administered concomitantly with injectable vaccines, it should be given

using a separate syringe and at a different injection site. Do not mix ENFLONSIA with any vaccines or medications in the same syringe or vial.

There are no data regarding substitution of ENFLONSIA for palivizumab once prophylaxis treatment is initiated with palivizumab for the RSV season.

There are no data regarding interchangeability of ENFLONSIA with nirsevimab once prophylaxis is initiated with nirsevimab for the RSV season.

4.3 CONTRAINDICATIONS

ENFLONSIA is contraindicated in infants with a history of serious hypersensitivity reactions, including anaphylaxis, to any component of ENFLONSIA [see Sections 2 QUALITATIVE AND QUANTITATIVE COMPOSITION, 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 6.1 LIST OF EXCIPIENTS].

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity Including Anaphylaxis

Serious hypersensitivity reactions, including anaphylaxis, have been observed with other human immunoglobulin G1 (IgG1) monoclonal antibodies. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, initiate appropriate medications and/or supportive therapy.

Use in Individuals with Clinically Significant Bleeding

As with any intramuscular injection, ENFLONSIA should be given with caution to individuals with clinically significant bleeding disorders, thrombocytopenia, any coagulation disorder or to individuals on anticoagulation therapy because bleeding or bruising may occur following an intramuscular administration in these individuals.

Use in the Elderly

ENFLONSIA is not indicated for use in adult populations.

Paediatric Use

The safety and efficacy of ENFLONSIA have been established for the prevention of RSV lower respiratory tract disease in neonates and infants born during or entering their first RSV season.

Use of ENFLONSIA for this indication is supported by evidence from adequate and well-controlled studies in neonates and infants from birth up to 12 months of age [see Sections 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and 5.1 PHARMACODYNAMIC PROPERTIES.

The safety and efficacy of ENFLONSIA have not yet been established in children older than 12 months of age.

Effects on laboratory tests

Interference with RT-PCR or Rapid Antigen Detection RSV Diagnostic Assays

Clesrovimab 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 0, I, II, III, or V on the RSV fusion (F) protein. For rapid antigen detection RSV diagnostic assay results which are negative when clinical observations are consistent with

RSV infection, it is recommended to confirm using an RT-PCR-based assay.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Since clesrovimab is eliminated by catabolism, no metabolic drug-drug interactions are expected. However, no formal drug interaction studies have been performed with ENFLONSIA.

Concomitant Administration with Vaccines

Since ENFLONSIA 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.

In clinical trials, when ENFLONSIA was given concomitantly with routine childhood vaccines, the safety profile of the co-administered regimen was generally comparable to the safety profile when ENFLONSIA and childhood vaccines were administered alone.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

ENFLONSIA is not indicated for use in individuals of child-bearing age.

Reproductive toxicity studies have not been performed with ENFLONSIA.

Use in Pregnancy

ENFLONSIA is not indicated for use in females of child-bearing age.

Developmental toxicity studies have not been performed with ENFLONSIA.

Use in Lactation

ENFLONSIA is not indicated for use in females of child-bearing age.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Not relevant.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials Experience

The safety of ENFLONSIA was evaluated in 2,858 infants who received ENFLONSIA in Phase 2b/3 and Phase 3 clinical trials (Protocol 004 and Protocol 007).

<u>Neonates and Infants Entering Their First RSV Season (Protocol 004)</u>

Protocol 004 was a Phase 2b/3, randomised, double-blind, placebo-controlled, multi-site trial conducted in early and moderate preterm infants (≥29 to <35 weeks gestational age (GA)) and late preterm and full-term infants (≥35 weeks GA). Participants were randomised 2:1 and received a single 105 mg dose of ENFLONSIA (N=2,412, including 422 early and moderate preterm infants) or saline placebo (N=1,202, including 209 early and moderate preterm infants) by IM injection. Participants were monitored for 30 minutes post-dose. Safety was assessed using an electronic diary device from Days 1 through 42 post-dose. Participants were monitored for serious adverse events (SAEs) through the duration of their participation for up to 365 days post-dose. A subset of participants was monitored for SAEs for up to 515 days post-dose.

Table 1 summarises the adverse reactions in participants who received ENFLONSIA. Most (>96%) of the adverse reactions were toxicity grade 1 (mild) or grade 2 (moderate).

Table 1: Adverse Reactions Reported at an Incidence Greater Than or Equal to Placebo (Protocol 004)

Adverse Reaction	ENFLONSIA N=2,409* %	Placebo N=1,202* %
Injection-site erythema† (occurring within 5 days post-dose)	4.4	3.6
Injection-site swelling† (occurring within 5 days post-dose)	3.2	3.2
Rash‡ (occurring within 14 days post-dose)	2.3	1.9

*Sample size reflects the number of participants included in the safety analysis population.
†Solicited on Day 1 through Day 5 post-dose using an electronic diary device.
‡Defined by the following grouped preferred terms: rash, rash erythematous, rash macular, rash papular, rash maculo-papular, rash vesicular, rash exfoliative, dermatitis allergic, drug eruption and toxic skin eruption.

Infants at Increased Risk of Severe RSV Disease Entering Their First RSV Season (Protocol 007)

Protocol 007 was a Phase 3, randomised, partially-blind, palivizumab-controlled, multi-site trial conducted in infants at increased risk of severe RSV disease. Participants were randomised and received a single 105 mg dose of ENFLONSIA (N=446) followed by a dose of placebo one month later or 3 to 5 monthly doses of 15 mg/kg palivizumab (N=450) by IM injection. Of the 446 participants who received ENFLONSIA, 176 had chronic lung disease (CLD) of prematurity or hemodynamically significant congenital heart disease (CHD), and 270 were early or moderate preterm infants (≤35 weeks GA) without CLD of prematurity or CHD. Participants were monitored for 30 minutes post-dose. Safety was assessed using an electronic diary device from Day 1 through 14 days post-dose 2 and 14 days after each subsequent dose. Participants were monitored for serious adverse events in the first RSV season for up to 365 days.

The safety profile of ENFLONSIA in infants at increased risk of severe RSV disease entering their first season is generally comparable to palivizumab and consistent with the safety profile of ENFLONSIA in infants in Protocol 004.

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 http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is limited experience of overdose with ENFLONSIA. There is no specific treatment for an overdose with ENFLONSIA. 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 Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Clesrovimab is a fully human immunoglobulin G1 kappa (IgG1κ) neutralising monoclonal antibody with a triple amino acid substitution (YTE) in the Fc region which increases binding to the neonatal Fc receptor leading to an extended serum half-life. Clesrovimab provides passive immunity by targeting the RSV outer membrane fusion (F) protein to prevent viral entry into cells.

Clesrovimab binds to a conserved epitope on antigenic site IV on the fusion F protein. Clesrovimab binds to RSV pre-fusion F glycoprotein and post-fusion F glycoprotein with equilibrium dissociation constant values (K_D) of 71 pM and 480 pM, respectively.

Pharmacodynamics

RSV serum neutralising antibody titer correlates with clesrovimab serum concentration. Following IM administration of clesrovimab in infants, the RSV neutralising antibody titers in serum were estimated to be approximately 7 times higher than baseline at 4 hours after clesrovimab dosing, and maximum titers were estimated to be approximately 78 times higher than baseline at approximately 7 days, for a typical infant weighing 5 kg.

Duration of Protection

Based on clinical data from Protocol 004, the duration of protection offered by a single dose of ENFLONSIA extend through 6 months but the observation is limited by a low event incidence that occurred after 5 months post-dose [see Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical Trials].

Clinical Trials

Description of Clinical Trials

The efficacy and safety of ENFLONSIA were evaluated in preterm and full-term infants in the trials summarised in Table 2.

Table 2: Trials Conducted with ENFLONSIA for the Prevention of Medically Attended RSV Lower Respiratory Tract Disease

Trial	Study Population	Study Arms*
Protocol 004 (NCT04767373)	Infants ≥29 weeks GA from birth up to 1 year entering their first RSV season.	ENFLONSIA (N=2,411) Placebo (N=1,203)†
Protocol 007 (NCT04938830)	Infants ≤35 weeks GA or infants with CLD of prematurity or hemodynamically significant CHD from birth up to 1 year entering their first RSV season.	ENFLONSIA (N=446) Palivizumab (N=450)

*Participants randomised and treated.

†1 participant was randomised to receive placebo but received ENFLONSIA.

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

Efficacy Against RSV-associated MALRI, Hospitalisation and Severe MALRI in Neonates and Infants Entering Their First RSV Season (Protocol 004)

Protocol 004 was a Phase 2b/3, randomised, double-blind, placebo-controlled, multi-site trial conducted in 22 countries from the Northern and Southern Hemispheres to evaluate the efficacy of ENFLONSIA in early and moderate preterm infants (≥29 to <35 weeks GA) and late preterm and full-term infants (≥35 weeks GA). The study assessed the efficacy of ENFLONSIA in the prevention of RSV-associated disease across a spectrum of severity. Participants were randomised 2:1 to receive a 105 mg dose of ENFLONSIA or saline placebo by IM injection.

Among participants who received ENFLONSIA or saline placebo, the median age of infants was 3.1 months (range: 0 to 12 months); 79.9% were less than 6 months; 15.9% were greater than or equal to 6 to less than 9 months; 4.2% were greater than or equal to 9 months of age; and 51.1% were male. Of these participants, 17.5% were GA greater than or equal to 29 weeks and less than 35 weeks and 82.5% were GA greater than or equal to 35 weeks. The racial distribution was as follows: 45.2% were White; 26.6% were Asian; 13.8% were Black or African American; 12.2% were Multi-racial and 1.9% were American Indian or Alaska Native; 28.1% were of Hispanic or Latino ethnicity.

The primary endpoint was the incidence of RSV-associated Medically Attended Lower Respiratory Infection (MALRI) characterised as cough or difficulty breathing and requiring ≥1 indicator of LRI (wheezing, rales/crackles) or severity (chest wall in-drawing/retractions, hypoxemia, tachypnea, dehydration due to respiratory symptoms) through 150 days after dosing. Medically Attended (MA) includes all healthcare provider visits in settings such as outpatient clinic, clinical study site, emergency department, urgent care center, and/or hospital. The statistical criterion for success required the lower bound of the 95% CI of efficacy to be greater than 25%.

RSV-associated hospitalisation through 150 days after dosing and RSV-associated MALRI through 180 days after dosing were also evaluated as secondary endpoints. For RSV-associated hospitalisation through 150 days, the statistical criterion for success required the lower bound of the 95% CI of efficacy to be greater than 0%.

RSV-associated severe MALRI, a pre-specified exploratory endpoint, characterised by 1) cough or difficulty breathing and 2) severe hypoxemia or the need for supplemental oxygen or mechanical ventilatory support, was evaluated through 150 days after dosing. Efficacy for all endpoints through 180 days after dosing was also a pre-specified exploratory analysis.

All efficacy endpoints evaluated required an RSV-positive RT-PCR nasopharyngeal (NP) sample.

Table 3 displays the efficacy results for RSV-associated disease endpoints, in order of increasing severity, in preterm and full-term infants from days 1 through 150 post-dose.

Table 3: Incidence of RSV-Associated Disease in Preterm and Full-Term Infants Days 1 through 150 Post-Dose (Protocol 004)

RSV-Associated Endpoint	ENFLONSIA (n=2,398)		Placebo (n=1,201)		Efficacy (95% CI)* (p-value)
	Number of cases	Incidence Rate over 5 months	Number of cases	Incidence Rate over 5 months	
MALRI (requiring ≥1 indicator of LRI or severity)†	60	0.026	74	0.065	60.4% (44.1, 71.9) (p <0.001)
Hospitalisation‡	9	0.004	28	0.024	84.2% (66.6, 92.6) (p <0.001)
Severe MALRI§	2	0.001	12	0.01	91.7% (62.9, 98.1)

n=Number of participants eligible for inclusion in the full analysis set population.
*Estimate and 95% CI of efficacy were estimated from the modified Poisson regression with robust variance method.
†A post-hoc analysis evaluated RSV-associated MALRI requiring ≥2 indicators of LRI/severity (at least 1 indicator of LRI, including rhonchi, and at least 1 indicator of severity) and an RSV-positive RT-PCR NP sample. The estimated efficacy was 88.0% (95% CI: 76.1, 94.0).
‡An exploratory analysis evaluated RSV-associated LRI hospitalisation characterised by cough or difficulty breathing and requiring ≥1 indicator of LRI or severity in a hospitalised infant with an RSV-positive RT-PCR NP sample. The estimated efficacy was 90.9% (95% CI: 76.2, 96.5).
§Exploratory efficacy endpoint.

Subgroup analyses of both RSV-associated MALRI and hospitalisation by gestational age, chronological age, body weight, sex, race, and region showed results consistent with the overall population.

When analysed through 180 days after dosing, the efficacy estimate for RSV-associated MALRI (requiring ≥1 indicator of LRI or severity) was 59.5% (95% CI: 43.3, 71.1). Efficacy for all endpoints was maintained through 180 days after dosing.

In the second season (Days 365 through 515 after dosing), the incidence rates of RSV-associated MALRI (requiring ≥1 indicator of LRI or severity) and RSV-associated hospitalisation were generally comparable between recipients of ENFLONSIA or placebo.

Efficacy Against RSV-Associated MALRI and Hospitalisation in Infants at Increased Risk of Severe RSV Disease Entering Their First RSV Season (Protocol 007)

Protocol 007 is a Phase 3, randomised, partially-blind, palivizumab-controlled, multi-site trial conducted in 27 countries from the Northern and Southern Hemispheres to evaluate the efficacy of ENFLONSIA in early (<29 weeks GA) or moderate preterm infants (≥29 to ≤35 weeks GA), and infants with chronic lung disease of prematurity or congenital heart disease of any GA, who are at increased risk for severe RSV disease. Participants were randomised to receive ENFLONSIA or palivizumab by IM injection. Participants randomised to ENFLONSIA received a single 105 mg dose on Day 1 followed by a dose of placebo one month later; palivizumab was administered on Day 1 and every month thereafter for a total of 3 to 5 doses.

Among participants who received ENFLONSIA or palivizumab, the median age of infants was 2.5 months (range: 0 to 12 months); 89.2% were less than 6 months; 9.4% were greater than or equal to 6 to less than 9 months; 1.5% were greater than or equal to 9 months of age; and 49.8% were male. Of these participants, 27.9% had CLD, 11.3% had CHD, 5.6% were GA less than 29 weeks with neither CLD nor CHD and 55.2% were GA greater than or equal to 29 weeks with neither CLD nor CHD. The racial distribution was as follows: 52.2% were White; 18.1% were Asian; 15.4% were Black or African American; 12.2% were Multi-racial, and 1.3% were American Indian or Alaska Native; 31.7% were of Hispanic or Latino ethnicity.

The efficacy of ENFLONSIA in infants at increased risk for severe RSV disease, including preterm infants and infants with chronic lung disease of prematurity or congenital heart disease, was established by extrapolation of efficacy of ENFLONSIA from Protocol 004 to Protocol 007 based on similar pharmacokinetic exposure [See Section 5.2 PHARMACOKINETIC PROPERTIES]. In Protocol 007, the incidence rate of RSV-associated MALRI (requiring ≥1 indicator of LRI or severity) through 150 days after dosing was generally comparable between ENFLONSIA (incidence rate=3.6%, 95% CI: 2.0, 6.0) and palivizumab (incidence rate=3.0%, 95% CI: 1.6, 5.3). The incidence rate of RSV-associated hospitalisation through 150 days after dosing was generally comparable between ENFLONSIA (incidence rate=1.3%, 95% CI: 0.4, 3.0) and palivizumab (incidence rate=1.5%, 95% CI: 0.6, 3.3).

Immunogenicity

The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies.

In Protocol 004 and Protocol 007, 12.0% (124/1033) and 13.0% (34/261) of participants were ADA-positive through Day 240, respectively.

There was no identified impact of ADA on pharmacokinetics, RSV serum neutralising activity, efficacy, or safety of ENFLONSIA during RSV season 1.

Microbiology

Antiviral Activity

An *in vitro* infection neutralisation assay was used to determine clesrovimab potency against RSV strains A and B using HEp-2 cells. In the laboratory, clesrovimab neutralised RSV strain A and B with an IC50 ± SD of 6.0 ± 4.3 and 3.0 ± 2.0 ng/mL, respectively. Clesrovimab was assessed for its ability to neutralise 47 RSV clinical isolates using a similar *in vitro* assay, with IC50 values ranging from 0.18 ng/mL to 11.11 ng/mL for RSV A and 0.58 ng/mL to 29.65 ng/mL for RSV B. The clinical isolate panel consisted of a broad range of clinical RSV isolated between years 1987 and 2016. Recent clinical isolates (RSV A and RSV B) from 2016 through 2021 were equipotently neutralised by clesrovimab as compared to the reference RSV strains.

Antiviral Resistance

In Cell Culture

Monoclonal antibody-resistant viral mutants (MARMs) were identified after serial infection in cell culture of RSV A or RSV B. Four RSV strain A MARMs for clesrovimab were generated after 6 rounds of serial infection. The 4 MARM viruses were subjected to an additional 3 rounds of serial infection prior to being processed for characterisation. The four RSV A MARMs were sequenced and found to have mutations located in the binding epitope region reported for

clesrovimab, G446E, S443P and K445N, S443P and G446E, or S443P. An *in vitro* assay confirmed that clesrovimab was not able to neutralise the 4 MARMs. One RSV B MARM was identified after 9 rounds of serial infection. The RSV B MARM was found to have a mutation located in the binding epitope region reported for clesrovimab, S443P.

In Surveillance Trials

In sequences reported in the GenBank database, the RSV binding epitope for clesrovimab was highly conserved (99.8%). Thirteen (13) clesrovimab epitope variants were identified, including 1 variant, I432T, identified in 5 RSV A and 1 RSV B samples (0.04%). This variant was shown to reduce clesrovimab neutralising activities by 4 times (RSV A) and 1.6 times (RSV B). The I432T variant demonstrated reduced fitness as compared to the wild-type virus. Two RSV A MARMs were identified with a mutation at position 446 (G446E). This mutation was found in 3 GenBank variant RSV A F sequences (0.02%) in the database. The *in vitro* data for the RSV A MARM virus with the G446E mutation suggest reduced viral fitness compared to wild-type RSV strain A and are less likely to dominate in circulation in subsequent seasons compared to wild-type.

In a global surveillance study conducted between 2019 and 2023 in 8 countries, which included both the Northern and Southern Hemispheres, the clesrovimab binding site was highly conserved (100%). There were 652 RSV-positive clinical samples collected from individuals of various ages. Of these, the 555 RSV-positive sequenced clinical samples consisted of 300 RSV A (54%) and 255 RSV B (46%). There were no sequence variants identified in the clesrovimab binding site.

In Clinical Trials

Resistance substitutions were not associated with the development of RSV-associated disease in Protocol 004 and Protocol 007. Viral phenotypic testing of RSV-positive nasal swabs demonstrated that the majority of the clesrovimab binding site (IV) substitutions affected residue G446, resulting in the following substitutions: G446E, G446R or G446W (RSV A) and G446E or G446R (RSV B). The G446E substitution was previously found in the GenBank database and RSV MARM study. In Protocol 004, there were no cases of RSV-associated MALRI and 1 case of RSV-associated hospitalisation (RSV A) associated with the G446W substitution. In Protocol 007, 1 case of RSV-associated MALRI (RSV A) and 1 case of RSV-associated severe MALRI (RSV B) in ENFLONSIA participants within 2 weeks of dosing carried the G446R substitution. Overall, the G446 substitutions were rare in Protocol 004 and Protocol 007.

Cross-Resistance

Clesrovimab neutralised both palivizumab- and nirsevimab-resistant isolates. Clesrovimab was 5.2 times and 1.7 times more potent on the N262Y RSV A and RSV B palivizumab-resistant clinical isolate strains, as compared to RSV A and B reference strains, respectively. Nirsevimab-resistant mutants of RSV B strains (N208S, I64T+K68E, I64T+K68E+I206M+Q209R) observed in the clinic were equipotently neutralised by clesrovimab as compared to RSV B wild-type control virus. The potency against L204S+I206M+Q209R+S211N RSV B mutant was undeterminable due to insufficient growth of the virus.

5.2 PHARMACOKINETIC PROPERTIES

General Introduction

The PK of clesrovimab is approximately dose-proportional following a single IM administration of doses ranging from 20 mg to 210 mg in infants. Following the recommended dose in the first RSV season, the clesrovimab serum exposures were similar in neonates and infants in Protocol 004, in preterm neonates and infants born at less than or equal to 35 weeks GA (including less than 29 weeks GA) in Protocol 007, and in neonates and infants with CLD or CHD in Protocol 007.

Absorption

The estimated clesrovimab absolute bioavailability is 77.8% and the median time to maximum concentration is 6.5 days (5.9, 7.4, which are the 2.5 and 97.5 percentiles, respectively).

Distribution

The estimated apparent volume of distribution for clesrovimab is 830 mL, for a typical infant weighing 5 kg.

Clesrovimab was readily detected in the nasal mucosa of sampled adult participants. The concentration of clesrovimab measured in the epithelial lining fluid of the nasal mucosa was 1.4% to 3.3% of the concentration measured in the serum.

Elimination

The clesrovimab terminal half-life is approximately 44.0 days and the estimated apparent clearance is 19.7 mL/day for a typical infant weighing 5 kg.

Metabolism

Clesrovimab is expected to be degraded into small peptides and amino acids by catabolic pathways.

Special Populations

No clinically significant differences in the pharmacokinetics of clesrovimab were observed based on race or vulnerability to severe RSV disease (i.e., CLD, CHD, or GA <29 weeks). An effect of renal or hepatic impairment on clesrovimab pharmacokinetics is not expected.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Genotoxicity studies have not been performed with ENFLONSIA.

Carcinogenicity

Carcinogenicity studies have not been performed with ENFLONSIA.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

sucrose
arginine hydrochloride
histidine hydrochloride monohydrate
histidine
polysorbate 80
water for injections

6.2 INCOMPATIBILITIES

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

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 refrigerated at 2°C to 8°C.
Do not freeze.
Do not shake.

Keep the prefilled syringe in the original carton to protect from light until time of use.
ENFLONSIA may be kept at room temperature between 20°C to 25°C (68°F to 77°F) for a maximum of 48 hours. After removal from the refrigerator, ENFLONSIA must be used within 48 hours or discarded.

6.5 NATURE AND CONTENTS OF CONTAINER

ENFLONSIA is a solution for injection available in 0.7 mL single-dose pre-filled syringes (Type I glass) in packs of 1 and 10.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemistry

ENFLONSIA (clesrovimab) is a respiratory syncytial virus F protein-directed fusion inhibitor. Clesrovimab is a fully human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody produced in recombinant Chinese hamster ovary (CHO) cells. The molecular weight is approximately 149 kDa.

CAS number

2429913-18-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
Level 1, Building A, 26 Talavera Road
Macquarie Park NSW 2113

http://www.msd-australia.com.au
Tel (+61) 02 8988 8000

9 DATE OF FIRST APPROVAL

24 March 2026

10 DATE OF REVISION

NA

Summary Table of Changes

Section changed	Summary of new information
All	New PI

CCDS-MK1654-I-102024
RCN: 000027481-AU

CCDS-MK1654-I-122025
RCN: 000028784-AU