ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Enflonsia 105 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 105 mg of clesrovimab in 0.7 mL.

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

Excipient with known effect

This medicinal product contains 0.14 mg of polysorbate 80 in each 105 mg (0.7 mL) dose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

Clear to slightly opalescent, colourless to slightly yellow solution, with a pH of 5.5 – 6.5, and an osmolality of 320 – 420 mOsm/kg.

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 during their first RSV season.

Enflonsia should be used in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Neonates and infants: first RSV season
The recommended dose is 105 mg administered as a single 0.7 mL intramuscular (IM) injection.

For neonates and infants born during the RSV season, Enflonsia should be administered starting from birth. For infants born outside the RSV season, it should be administered once prior to the start of their first RSV season (see section 5.1).

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).

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

Children from 1 to 18 years of age
The safety and efficacy of clesrovimab in children aged 1 to 18 years have not yet been established. No data are available.

Method of administration

Enflonsia is for intramuscular use only.

The medicinal product should be administered intramuscularly by a healthcare professional, in the anterolateral aspect of the thigh. It should not be injected in the gluteal area or areas where there may be a major nerve trunk and/or blood vessel.

For instructions on handling of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 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

If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, appropriate treatment and/or supportive therapy should be initiated.

Individuals with thrombocytopenia and coagulation disorders

As with any other intramuscular injections, clesrovimab should be given with caution to infants with thrombocytopenia or any coagulation disorder, because bleeding or bruising may occur following an intramuscular administration in these individuals.

Excipients with known effect

This medicinal product contains 0.14 mg of polysorbate 80 per dose. Polysorbates may cause allergic reactions.

4.5 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 clesrovimab is an exogenous virus.

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.

Concomitant administration with childhood vaccines

Since clesrovimab 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 studies, when clesrovimab was given concomitantly with routine childhood vaccines, the safety profile of the co-administered regimen was similar to the safety profile when clesrovimab and childhood vaccines were administered alone. Clesrovimab can be given concomitantly with childhood vaccines.

When clesrovimab is administered concomitantly with injectable vaccines, it should be given using a separate syringe and at a different injection-site. It should not be mixed with any vaccines or medications in the same syringe or vial (see section 6.2).

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

4.6 Fertility, pregnancy and lactation

Not relevant.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions were injection-site pain (6.5%), injection-site erythema (4.4%), injection-site swelling (3.2%) and rash (2.3%). Most (> 96%) of the adverse reactions were mild or moderate.

Tabulated list of adverse reactions

Safety was evaluated in 2 854 infants who received clesrovimab in phase 2b/3 and phase 3 clinical studies (Study 004 and Study 007, respectively) (see section 5.1).

Table 1 presents the adverse reactions reported in 2 409 preterm and full-term infants (GA ≥ 29 weeks) who received clesrovimab.

Adverse reactions reported with clesrovimab are listed by MedDRA system organ class and in decreasing order of frequency. Frequencies 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), and very rare (< 1/10 000) and not known (cannot be estimated from available data).

Table 1: Adverse reactions

System organ class	Adverse reaction	Frequency
Skin and subcutaneous tissue disorders	Rash*	Common
	Urticaria	Uncommon
General disorders and administration site conditions	Injection-site pain†	Common
	Injection-site erythema†	Common
	Injection-site swelling†	Common

*Rash was defined by the following grouped preferred terms occurring within 14 days post-dose: rash, rash erythematous, rash papular, rash maculo-papular, rash vesicular, dermatitis allergic, and drug eruption
†Solicited on Day 1 through Day 5 post-dose

The safety profile of clesrovimab in 445 infants at increased risk of severe RSV disease entering their first season (Study 007, see section 5.1) was similar to palivizumab (450 infants) and consistent with the safety profile of clesrovimab in infants in Study 004.

Serious adverse events reported in early preterm infants GA < 29 weeks were similar in number and pattern between recipients of clesrovimab (21/97 participants) and palivizumab (31/108 participants).

Subgroup analyses by age groups at randomisation (< 3 months; ≥ 3 to ≤ 6 months and > 6 months) in Study 004 and Study 007 showed similar safety results in the clesrovimab and control arms (see section 5.1) across the age-groups in each study.

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 listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immune sera and immunoglobulins, antiviral monoclonal antibodies, ATC code: J06BD10

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.

RSV A and B isolates were equipotently neutralised by clesrovimab *in vitro*.

Pharmacodynamic effects

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. Clesrovimab neutralises the virus without the requirement of Fc effector function.

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 4 RSV A MARMs were sequenced and found to have substitutions 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 substitution located in the binding epitope region reported for clesrovimab, S443P.

In surveillance studies
In sequences reported in the GenBank database, the RSV binding epitope for clesrovimab was highly conserved (99.8%). Thirteen 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 substitution at position 446 (G446E). This substitution 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 substitution 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 studies
Resistance substitutions were not associated with the development of RSV-associated disease in Study 004 and Study 007. Viral genotypic 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 Study 004, there was 1 case of RSV-associated hospitalisation (RSV A) with the G446W substitution. There were no cases of RSV-associated medically attended lower respiratory infection (MALRI) associated with any G446 substitution. In Study 007, 1 case of RSV-associated MALRI (RSV A) and 1 case of RSV-associated severe MALRI (RSV B) in clesrovimab participants within 2 weeks of dosing carried the G446R substitution. No G446 substitutions were found in the placebo or palivizumab treatment arm.

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.

Immunogenicity
In Study 004 and Study 007, 12.0% (124/1033) and 13.0% (34/261) of participants who received clesrovimab were anti-drug antibodies (ADA)-positive through Day 240, respectively.

There was no identified impact of ADA on pharmacokinetics, RSV serum neutralising activity, or safety of clesrovimab during RSV season 1. The impact of ADA on efficacy could not be established.

Clinical efficacy

The efficacy and safety of clesrovimab were evaluated in preterm and full-term infants in the clinical studies 004 and 007.

Efficacy against RSV-associated MALRI, hospitalisation, and severe MALRI in neonates and infants entering their first RSV season (Study 004)
Study 004 was a Phase 2b/3, randomised, double-blind placebo-controlled, multicentre study conducted in 22 countries from the Northern and Southern hemispheres to evaluate the efficacy of clesrovimab in healthy early and moderate preterm infants (≥ 29 to < 35 weeks GA) and late preterm and full-term infants (≥ 35 weeks GA). Participants were randomised 2:1 to receive a 105 mg dose of clesrovimab (n=2 412, including 422 early and moderate preterm infants) or saline placebo (n=1 202, including 209 early and moderate preterm infants) by intramuscular injection.

Among participants who received clesrovimab or saline placebo, the median age of infants was 3.1 months (range: 0 to 12 months); 14.9% were ≤ 1 month of age; 34.5% were > 1 to ≤ 3 months; 30.6% were > 3 to ≤ 6 months; 20.1% were > 6 months; and 51.1% were male. Of these participants, 17.5% were GA ≥ 29 to < 35 weeks and 82.5% were GA ≥ 35 weeks. The median body weight was 5.8 kg (range: 1.6 to 11.9 kg). 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 MALRI characterised as cough or difficulty breathing and requiring ≥ 1 indicator of LRI (wheezing, rales/crackles) or severity (chest wall in-drawing/retractions, hypoxemia, tachypnoea, dehydration due to respiratory symptoms) through 150 days after dosing. Medically Attended (MA) includes all healthcare professional visits in settings such as outpatient clinic, clinical study site, emergency department, urgent care centre, 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. RSV-associated hospitalisation was defined as hospitalisation for respiratory symptoms with a positive test for RSV. 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.

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

Table 2 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 2: Incidence of RSV-associated disease in preterm and full-term infants Days 1 through 150 Post-dose (Study 004)

RSV-Associated Endpoint	Clesrovimab (n=2 398)		Placebo (n=1 201)		Efficacy (95% CI)*
	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)†
Hospitalisation‡	9	0.004	28	0.024	84.2% (66.6, 92.6)†
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.
* Based on relative risk reduction vs placebo. Estimate and 95% CI of efficacy were estimated from the modified Poisson regression with robust variance method.
†Pre-specified multiplicity controlled; p-value < 0.001
‡An exploratory analysis evaluated RSV-associated LRI hospitalisation characterised by cough or difficulty breathing and requiring ≥1 indicator of LRI or severity in hospitalised infants with an RSV positive RT PCR NP sample (5 cases/2398 in the clesrovimab arm and 27 cases/1201 in the placebo arm; endpoint not multiplicity controlled). The estimated efficacy was 90.9% (95% CI: 76.2, 96.5).
§Exploratory efficacy endpoint, not multiplicity controlled.

Subgroup analyses of the primary efficacy endpoint of RSV-associated MALRI 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).

The incidence rates of RSV-associated MALRI (requiring ≥ 1 indicator of LRI or severity) in the second season in the absence of additional prophylaxis (Days 365 through 515 post-dose) were similar between recipients of clesrovimab (53 events/1008 participants, incidence = 0.055 over 5 months) and placebo (26 events/501 participants, incidence = 0.054 over 5 months).

Efficacy against RSV-associated MALRI and hospitalisation in infants at increased risk of severe RSV disease entering their first RSV season (Study 007)
Study 007 is a phase 3, randomised, partially blind, palivizumab controlled, multicentre study conducted in 27 countries from the Northern and Southern hemispheres to evaluate the safety, efficacy and pharmacokinetics of clesrovimab 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 entering in their first RSV season. Participants were randomised to receive clesrovimab (n=446, including 176 infants with chronic lung disease (CLD) of prematurity or haemodynamically significant congenital heart disease (CHD) and 270 early or moderate preterm infants (≤ 35 weeks GA) without CLD of prematurity or CHD), or palivizumab (n=450, including 175 infants with CLD of prematurity or CHD and 275 early or moderate preterm infants (≤ 35 weeks GA) without CLD of prematurity or CHD) by intramuscular injection. Participants randomised to clesrovimab 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 of 15 mg/kg.

Among participants who received clesrovimab or palivizumab, the median age of infants was 2.5 months (range: 0 to 12 months); 14.3% were ≤ 1 month of age; 44.3% were > 1 to ≤ 3 months; 30.6% were > 3 to ≤ 6 months; 10.8% were > 6 months; 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 median body weight was 3.3 kg (range: 1.1 to 9.6 kg). 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 clesrovimab in infants at increased risk for severe RSV disease was established by extrapolation of efficacy of clesrovimab from Study 004 to Study 007 based on pharmacokinetic exposure (see section 5.2). In Study 007, the incidence rate of RSV-associated MALRI (requiring ≥ 1 indicator of LRI or severity) through 150 days after dosing was 3.6% (95% CI: 2.0, 6.0; 14 cases/443 in analysis set) in the clesrovimab arm and 3.0% (95% CI: 1.6, 5.3; 12 cases/437 in the analysis set) in the palivizumab arm. The incidence rate of RSV-associated hospitalisation through 150 days after dosing was 1.3% (95% CI: 0.4, 3.0; 5 cases/443 in analysis set) in the clesrovimab arm and 1.5% (95% CI: 0.6, 3.3; 6 cases/437 in analysis set) in the palivizumab arm.

Duration of protection
Based on clinical efficacy data from Study 004, the duration of protection offered by a single dose of clesrovimab could extend through 6 months but the observation is limited by a low event incidence that occurred after 5 months post-dose.

5.2 Pharmacokinetic properties

The pharmacokinetic (PK) of clesrovimab is approximately dose-proportional following a single intramuscular administration of doses ranging from 20 mg to 210 mg in infants.

Absorption

The estimated clesrovimab absolute bioavailability is 77.8% and the median (range) time to maximum concentration is 6.5 (4.7, 11.0) days.

Distribution

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

Biotransformation

Clesrovimab is degraded into small peptides by catabolic pathways.

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. Consistent with other monoclonal antibodies, clesrovimab clearance is lower in younger infants and/or infants with lower body weight.

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). No clinical studies have been conducted to investigate the effect of renal or hepatic impairment. An effect of renal or hepatic impairment on clesrovimab pharmacokinetics is not expected.

Pharmacokinetic/pharmacodynamic relationships

RSV serum neutralising antibody (SNA) titre correlates with clesrovimab serum concentration. Following intramuscular administration of clesrovimab in infants, the RSV neutralising antibody titres in serum were estimated to be approximately 7 times higher than baseline at 4 hours after clesrovimab injection, and maximum titres were reached by Day 7, for a typical infant weighing 5 kg. At days 150 and 180 post administration of clesrovimab, the RSV neutralising antibody titres in serum were estimated to be approximately 11 times and 7 times higher than baseline.

Due to flat exposure efficacy relationship over the range of exposures studied in Study 004, no exposure or SNA titre threshold could be identified to confer protection against RSV disease.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine hydrochloride monohydrate
Arginine hydrochloride
Sucrose
Polysorbate 80 (E433)
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

30 months
Enflonsia may be kept at room temperature (20 °C - 25 °C) for a maximum 48 hours. After removal from the refrigerator, it must be used within 48 hours or discarded.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.
Do not shake.

6.5 Nature and contents of container

0.7 mL solution in pre-filled syringe (Type I glass) with a plunger stopper and a tip cap with or without needles.

Enflonsia is available in the following pack sizes:
- 1 pre-filled syringe
- 1 pre-filled syringe + 1 needle
- 1 pre-filled syringe + 2 needles
- 10 pre-filled syringes
- 10 pre-filled syringes + 10 needles

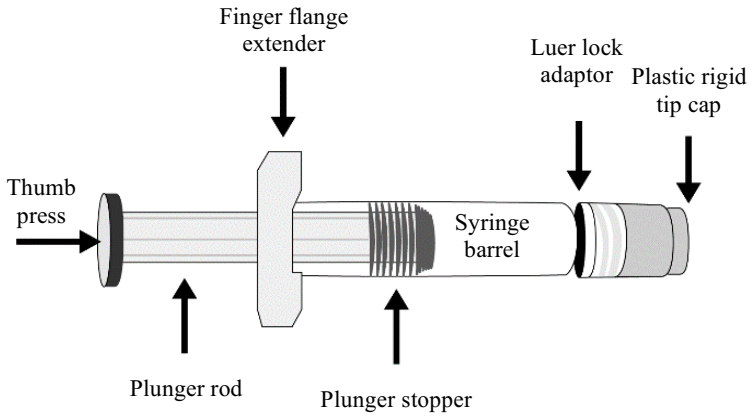
- 10 pre-filled syringes + 20 needles
- Multipacks containing 50 (5 packs of 10) pre-filled syringes

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before injection, remove the carton from the refrigerator and allow the pre-filled syringe to come to room temperature for approximately 15 minutes. Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. It should not be used if particulate matter or discolouration is found. Do not use Enflonsia if the pre-filled syringe has been dropped or damaged, the security seal on the carton has been broken, or the expiry date has passed. Refer to Figure 1 for pre-filled syringe components.

Figure 1: Pre-filled 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. If not provided, due to the viscosity of the product, use a 25 gauge or larger needle.

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

Enflonsia is for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1984/001
EU/1/25/1984/002
EU/1/25/1984/003
EU/1/25/1984/004
EU/1/25/1984/005
EU/1/25/1984/006
EU/1/25/1984/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Lonza Biologics Inc.
101 International Drive
Portsmouth, NH 03801
United States

Name and address of the manufacturer responsible for batch release

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Enflonsia 105 mg solution for injection in pre-filled syringe
clesrovimab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 105 mg of clesrovimab in 0.7 mL.

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe
1 pre-filled syringe + 1 needle
1 pre-filled syringe + 2 needles
10 pre-filled syringes
10 pre-filled syringes + 10 needles
10 pre-filled syringes + 20 needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the syringe in the outer carton in order to protect from light.
Do not shake.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBERS

EU/1/25/1984/001 - 1 pre-filled syringe
EU/1/25/1984/002 - 1 pre-filled syringe + 1 needle
EU/1/25/1984/003 - 1 pre-filled syringe + 2 needles
EU/1/25/1984/004 - 10 pre-filled syringes
EU/1/25/1984/005 - 10 pre-filled syringes + 10 needles
EU/1/25/1984/006 - 10 pre-filled syringes + 20 needles

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Enflonsia 105 mg solution for injection in pre-filled syringe
clesrovimab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 105 mg of clesrovimab in 0.7 mL.

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
Multipack:
50 (5 packs of 10) pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.
Do not shake.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1984/007 - multipack containing 50 (5 packs of 10) pre-filled syringes

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Enflonsia 105 mg solution for injection in pre-filled syringe
clesrovimab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 105 mg of clesrovimab in 0.7 mL.

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
10 pre-filled syringes
Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze
Keep the pre-filled syringe in the outer carton in order to protect from light.
Do not shake.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1984/007 - 10 pre-filled syringes

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Enflonsia 105 mg injection
clesrovimab
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.7 mL

6. OTHER

MSD

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Enflonsia 105 mg solution for injection in pre-filled syringe
clesrovimab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child is given this medicine because it contains important information for you and your child.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor, pharmacist or nurse.
- If your child gets any side effects, talk to your child's doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Enflonsia is and what it is used for

Enflonsia contains the active substance clesrovimab. This is an antibody (a protein that the body uses to fight harmful germs) that helps prevent lung disease caused by *respiratory syncytial virus* (RSV) disease.

It is given to newborns and babies up to 12 months of age who are born during or entering their first RSV season.

RSV season is the time of year when RSV infections are most common, usually occurring autumn through spring of the next year.

RSV is a common respiratory virus that usually causes symptoms similar to the common cold but can also affect the lungs. Signs of RSV infection may include a runny nose, trouble feeding, difficulty breathing, coughing, sneezing, wheezing (whistling sound during breathing) or fever.

Anyone can become infected by RSV. Almost all children get an RSV infection by the time they are 2 years old. While most recover quickly, RSV can cause severe illness including inflammation of the small airways in the lung (bronchiolitis) and infection of the lungs (pneumonia) that may lead to hospitalisation and even death. Children at greatest risk include newborns and babies up to 12 months of age, especially those 6 months and younger, or with medical vulnerabilities, for example being born too soon or with heart or lung problems.

2. What you need to know before your child is given Enflonsia

Do not give Enflonsia
Your child must not be given Enflonsia if they are allergic to clesrovimab or any of the other ingredients of this medicine (listed in section 6).

Tell your child's doctor, pharmacist or nurse about any medical conditions or allergies your child has or had.

Warnings and precautions
Serious allergic reactions may happen with Enflonsia. Tell your child's doctor or seek medical care right away if your child has any of the following signs and symptoms of a serious allergic reaction, which may include:

- swelling of the face, mouth, or tongue
- difficulty swallowing or breathing
- unresponsiveness
- blue tint to the colour of skin, lips or under fingernails
- muscle weakness
- severe rash, hives or itching

Talk to your child's healthcare professional before your child is given Enflonsia if they have any bleeding problems, bruises easily, or are taking medicines to prevent blood clots.

Children and adolescents
Do not give this medicine to children between the age of 1 and 18 years of age. This is because it has not yet been studied in this group.

Other medicines and Enflonsia
Tell your child's doctor or pharmacist if your child is taking, has recently taken or might take any other medicines.

Enflonsia may be given at the same time as vaccines that are part of the national immunisation programme.

Enflonsia contains polysorbate 80
This medicine contains 0.14 mg of polysorbate 80 per dose. Polysorbates may cause allergic reactions. Tell your doctor if your child has any known allergies.

3. How and when Enflonsia is given

Enflonsia is given by a healthcare professional as an injection in the muscle. It is usually given in the thigh.

The recommended dose is 105 mg given as a single injection. This is given before the start of or during the RSV season.

Your child's healthcare professional can tell you when the RSV season starts in your area.

If your child is scheduled to have surgery for certain types of heart disease, your child's healthcare professional may need to give your child an additional injection of Enflonsia after surgery.

Your child may still get RSV disease after receiving this medicine. Talk to your child's healthcare professional about what signs to look for.

If you have any further questions on the use of this medicine, ask your child's doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your child's doctor, pharmacist or nurse if your child has any of the following side effects:

Common (may affect up to 1 in 10 children)
- pain, redness (erythema), or swelling where your child got the injection
- rash

Uncommon (may affect up to 1 in 100 children)
- red, itchy swollen bumps on the skin; also called hives

Reporting of side effects
If your child gets any side effects, talk to your child's doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Enflonsia

Your child's doctor, pharmacist or nurse is responsible for storing this medicine and disposing of any unused product correctly. The following information is intended for healthcare professionals.

Keep this medicine out of reach of children.

Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C). Do not freeze. After removal from the refrigerator, the medicine must be used within 48 hours or discarded.

Keep the pre-filled syringe in the outer carton in order to protect from light.
Do not shake.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What Enflonsia contains
- The active substance is clesrovimab. One pre-filled syringe of 0.7 mL contains 105 mg of clesrovimab.
- The other ingredients are histidine, histidine hydrochloride monohydrate, arginine hydrochloride, sucrose, polysorbate 80 (E433) (see section 2 "Enflonsia contains polysorbate 80") and water for injections.

What Enflonsia looks like and contents of the pack
Enflonsia is a clear to slightly opalescent, colourless to slightly yellow solution for injection.

Enflonsia is available in the following pack sizes:
- 1 pre-filled syringe
- 1 pre-filled syringe + 1 needle
- 1 pre-filled syringe + 2 needles
- 10 pre-filled syringes
- 10 pre-filled syringes + 10 needles
- 10 pre-filled syringes + 20 needles
- Multipacks comprising 5 cartons, each containing 10 pre-filled syringes.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Merck Sharp & Dohme B.V., Waarderweg 39, 2031 BN Haarlem, The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

- Before injection, remove the carton from the refrigerator and allow the pre-filled syringe to come to room temperature for approximately 15 minutes.
- Visually inspect the medicinal product for particulate matter and discolouration. The medicinal product is a clear to slightly opalescent, colourless to slightly yellow solution. It should not be used if particulate matter or discolouration is found.
- Do not use Enflonsia if the pre-filled syringe has been dropped or damaged, the security seal on the carton has been broken, or the expiry date has passed.
- Hold the syringe barrel in one hand to unscrew the tip cap by twisting it counter-clockwise with the other hand. Do not remove the Luer lock adaptor or the finger flange extender.
- Attach a sterile Luer lock needle by twisting in a clockwise direction until the needle fits securely on the pre-filled syringe. If not provided, due to the viscosity of the medicinal product, use a 25 gauge or larger needle.

- Inject the entire contents of the pre-filled syringe intramuscularly in the anterolateral aspect of the thigh. The medicinal product should not be injected in the gluteal area or areas where there may be a major nerve trunk and/or blood vessel.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

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