

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761432Orig1s000**

**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ENFLONZIA safely and effectively. See full prescribing information for ENFLONZIA.

**ENFLONZIA™ (clesrovimab-cfor) injection, for intramuscular use**  
Initial U.S. Approval: 2025

### INDICATIONS AND USAGE

ENFLONZIA is a respiratory syncytial virus (RSV) F protein-directed fusion inhibitor indicated for the prevention of RSV lower respiratory tract disease in neonates and infants who are born during or entering their first RSV season. (1)

### DOSAGE AND ADMINISTRATION

Recommended dosage: 105 mg administered as a single intramuscular (IM) injection. (2.1)

### DOSAGE FORMS AND STRENGTHS

Injection: 105 mg/0.7 mL in a single-dose prefilled syringe. (3)

### CONTRAINDICATIONS

ENFLONZIA is contraindicated in infants with a history of serious hypersensitivity reactions, including anaphylaxis, to any component of ENFLONZIA. (4)

### WARNINGS AND PRECAUTIONS

Hypersensitivity Including Anaphylaxis: Serious hypersensitivity reactions, including anaphylaxis, have been observed with other human immunoglobulin G1 (IgG1) monoclonal antibodies. Initiate appropriate medications and/or supportive care if such reactions occur. (5.1)

### ADVERSE REACTIONS

Most common adverse reactions were injection-site erythema (3.7%), injection-site swelling (2.7%) and rash (2.3%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme LLC at 1-877-888-4231 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### USE IN SPECIFIC POPULATIONS

The safety and effectiveness of ENFLONZIA have not been established in children older than 12 months of age. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2025

## FULL PRESCRIBING INFORMATION: CONTENTS\*

<b>1</b>	<b>INDICATIONS AND USAGE</b>
<b>2</b>	<b>DOSAGE AND ADMINISTRATION</b>
2.1	Recommended Dosage
2.2	Administration Instructions
<b>3</b>	<b>DOSAGE FORMS AND STRENGTHS</b>
<b>4</b>	<b>CONTRAINDICATIONS</b>
<b>5</b>	<b>WARNINGS AND PRECAUTIONS</b>
5.1	Hypersensitivity Including Anaphylaxis
5.2	RSV Diagnostic Test Interference
<b>6</b>	<b>ADVERSE REACTIONS</b>
6.1	Clinical Trials Experience
<b>7</b>	<b>DRUG INTERACTIONS</b>
7.1	Interference with Rapid Antigen Detection RSV Diagnostic Assays
<b>8</b>	<b>USE IN SPECIFIC POPULATIONS</b>
8.1	Pregnancy
8.2	Lactation
8.4	Pediatric Use
<b>10</b>	<b>OVERDOSAGE</b>
<b>11</b>	<b>DESCRIPTION</b>

<b>12</b>	<b>CLINICAL PHARMACOLOGY</b>
12.1	Mechanism of Action
12.2	Pharmacodynamics
12.3	Pharmacokinetics
12.4	Microbiology
12.6	Immunogenicity
<b>13</b>	<b>NONCLINICAL TOXICOLOGY</b>
13.1	Carcinogenesis, Mutagenesis, Impairment of Fertility
<b>14</b>	<b>CLINICAL STUDIES</b>
14.1	Description of Clinical Trials
14.2	Prevention of RSV-Associated Disease in Neonates and Infants (≥29 Weeks Gestational Age) Entering Their First RSV Season (Trial 004)
14.3	Prevention of RSV-Associated Disease in Infants Born at ≤35 Weeks Gestational Age and Infants with CLD of Prematurity or Hemodynamically Significant CHD Entering Their First RSV Season (Trial 007)
<b>16</b>	<b>HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17</b>	<b>PATIENT COUNSELING INFORMATION</b>

\*Sections or subsections omitted from the full prescribing information are not listed

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

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.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Recommended Dosage

The recommended dose for neonates and infants born during or entering their first RSV season is 105 mg administered as a single intramuscular (IM) injection.

For neonates and infants born during the RSV season, administer ENFLONSIA once 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 *Clinical Pharmacology (12.2)*].

#### Infants Undergoing Cardiac Surgery with Cardiopulmonary Bypass

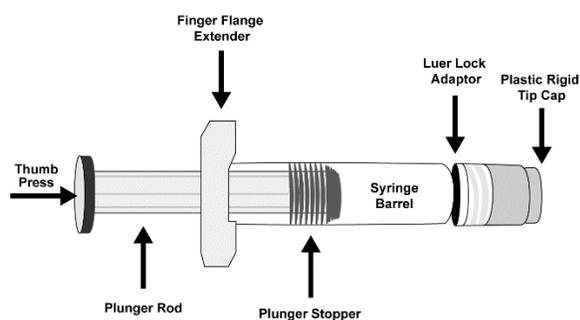
For infants undergoing cardiac surgery with cardiopulmonary bypass during or entering their first RSV season, an additional 105 mg dose administered as an IM injection is recommended as soon as the infant is stable after surgery to ensure adequate clesrovimab-cfor serum levels.

#### 2.2 Administration Instructions

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, whenever solution and container permit. 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 22- to 25-gauge 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.

**Step 4:** Discard syringe into a sharps container.

### **Co-administration with Childhood Vaccines and Immunoglobulin Products**

ENFLONSIA can be given concomitantly with childhood vaccines [see *Clinical Pharmacology (12.3)*]. 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 is no information regarding co-administration of ENFLONSIA with other immunoglobulin products. There are no data regarding substitution of ENFLONSIA for palivizumab once prophylaxis treatment is initiated with palivizumab for the RSV season.

## **3 DOSAGE FORMS AND STRENGTHS**

Injection: 105 mg/0.7 mL clear to slightly opalescent, colorless to slightly yellow solution in a single-dose prefilled syringe.

## **4 CONTRAINDICATIONS**

ENFLONSIA is contraindicated in infants with a history of serious hypersensitivity reactions, including anaphylaxis, to any component of ENFLONSIA [see *Warnings and Precautions (5.1)* and *Description (11)*].

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Hypersensitivity Including Anaphylaxis**

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

### **5.2 RSV Diagnostic Test Interference**

Clesrovimab-cfor may interfere with some immunologically-based RSV diagnostic assays (i.e., rapid antigen tests) as observed in laboratory studies. Confirmation using a reverse transcriptase polymerase chain reaction (RT-PCR) assay is recommended when rapid antigen assay results are negative and clinical observations are consistent with RSV infection [see *Drug Interactions (7.1)*].

## **6 ADVERSE REACTIONS**

### **6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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

#### Neonates and Infants Entering Their First RSV Season (Trial 004)

Trial 004 was a Phase 2b/3, randomized, double-blind placebo-controlled, multisite trial conducted in early and moderate preterm infants ( $\geq 29$  to  $< 35$  weeks gestational age (GA)) and late preterm and full-term infants ( $\geq 35$  weeks GA). Participants were randomized 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 summarizes the adverse reactions in participants who received ENFLONSIA. Most ( $\geq 97\%$ ) of the adverse reactions were toxicity grade 1 (mild) or grade 2 (moderate).

**Table 1: Adverse Reactions Reported at an Incidence Higher Than Placebo (Trial 004)**

Adverse Reaction	ENFLONSIA N=2,412* %	Placebo N=1,202* %
Injection-site erythema <sup>†</sup> (occurring within 5 days post-dose)	3.8	3.3
Injection-site swelling <sup>†</sup> (occurring within 5 days post-dose)	2.7	2.6
Rash <sup>‡</sup> (occurring within 14 days post-dose)	2.3	1.9

\*Sample size reflects the number of participants included in the safety analysis population.

<sup>†</sup>Solicited on Day 1 through Day 5 post-dose using an electronic diary device.

<sup>‡</sup>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 Born at  $\leq 35$  Weeks Gestational Age and Infants with Chronic Lung Disease (CLD) of Prematurity or Hemodynamically Significant Congenital Heart Disease (CHD) Entering Their First RSV Season (Trial 007)

Trial 007 was a Phase 3, randomized, partially-blind, palivizumab-controlled, multisite trial conducted in infants at increased risk of severe RSV disease. Participants were randomized 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 CLD of prematurity or CHD and 270 were early or moderate preterm infants ( $\leq 35$  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 (dose 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 was similar to palivizumab and consistent with the safety profile of ENFLONSIA in infants in Trial 004.

## 7 DRUG INTERACTIONS

### 7.1 Interference with Rapid Antigen Detection RSV Diagnostic Assays

Clesrovimab-cfor may interfere with some immunologically-based RSV diagnostic assays (i.e., rapid antigen tests) as observed in laboratory studies. Confirmation using an RT-PCR assay is recommended when rapid antigen RSV diagnostic assay results are negative and clinical observations are consistent with RSV infection. Clesrovimab-cfor does not interfere with RT-PCR diagnostic assays [see *Warnings and Precautions* (5.2)].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

ENFLONSIA is not indicated for use in females of reproductive potential.

### 8.2 Lactation

ENFLONSIA is not indicated for use in females of reproductive potential.

### 8.4 Pediatric Use

The safety and effectiveness 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 and the information on this use is discussed throughout the labeling.

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

## 10 OVERDOSAGE

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 infant should be monitored for the occurrence of adverse reactions and provided with symptomatic treatment as appropriate.

## 11 DESCRIPTION

Clesrovimab-cfor is a respiratory syncytial virus F protein-directed fusion inhibitor. Clesrovimab-cfor is a fully human immunoglobulin G1 kappa (IgG1 $\kappa$ ) monoclonal antibody produced in recombinant Chinese hamster ovary (CHO) cells. The molecular weight is approximately 149 kDa.

ENFLONSIA (clesrovimab-cfor) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution for intramuscular injection.

Each 0.7 mL contains 105 mg of clesrovimab-cfor, arginine hydrochloride (10.33 mg), histidine (0.55 mg), L-histidine monohydrochloride monohydrate (0.74 mg), polysorbate 80 (0.14 mg), sucrose (35 mg) and water for injection (USP). The pH is 6.0.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

ENFLONSIA is a monoclonal antibody with anti-RSV activity [see *Microbiology* (12.4)].

### 12.2 Pharmacodynamics

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

#### Exposure-Response Relationship

In the Phase 2b/3 trial evaluating the recommended dose of clesrovimab-cfor (a single dose of 105 mg) in healthy preterm and full-term infants (Trial 004), no significant relationship was observed between AUC (from day 1 to day 150) and clinical outcomes (e.g., RSV-associated Medically Attended Lower Respiratory Infection (MALRI)).

### Duration of Protection

Based on clinical trial data, the duration of protection demonstrated by a single dose of ENFLONSIA extends through 5 months [see *Clinical Studies (14.2)*].

## **12.3 Pharmacokinetics**

The PK of clesrovimab-cfor is approximately dose-proportional following a single IM administration of doses ranging from 20 mg to 210 mg in infants. Following IM administration of the 105 mg recommended dose, the geometric mean (% geometric CV) area under the time concentration curve from day 1 to day 150 (AUC<sub>0-150</sub>) is 6,470 mcg×d/mL (22.6%), peak concentration (C<sub>max</sub>) is 120 mcg/mL (25.4%), and the concentration at day 150 (C<sub>150</sub>) is 10.3 mcg/mL (36.6%). In the first RSV season, the clesrovimab-cfor serum exposures were similar in neonates and infants in Trial 004, in preterm neonates and infants born at less than or equal to 35 weeks GA (including less than 29 weeks GA) in Trial 007, and in neonates and infants with CLD or CHD in Trial 007.

### Absorption

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-cfor is 830 mL, for a typical infant weighing 5 kg.

### Elimination

The clesrovimab-cfor 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-cfor is degraded into small peptides by catabolic pathways.

### Specific Populations

No clinically significant differences in the pharmacokinetics of clesrovimab-cfor 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-cfor pharmacokinetics is not expected.

### Drug Interaction Studies

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

### *Clinical Studies*

#### 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.

## **12.4 Microbiology**

### Mechanism of Action

Clesrovimab-cfor is a recombinant human immunoglobulin G1 kappa (IgG1 $\kappa$ ) neutralizing monoclonal antibody with a YTE triple amino acid substitution (M252Y/S254T/T256E) in the Fc region which increases binding to the neonatal Fc receptor leading to an extended serum half-life. Passive immunity is provided by clesrovimab-cfor, which targets the extracellular domain of the RSV fusion (F) protein to prevent fusion of the viral and cellular membranes and viral entry.

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

### Antiviral Activity

A neutralization assay in Hep-2 cells was used to determine clesrovimab-cfor potency against RSV A and RSV B isolates. Clesrovimab-cfor neutralized 47 RSV clinical isolates collected from North America locations between 1987 and 2016, with median  $EC_{50}$  values for RSV A isolates of 25 pM (3.71 ng/mL) (n=24; range of 1.2 to 74 pM [0.18 to 11.11 ng/mL]), and for RSV B isolates of 30 pM (4.48 ng/mL) (n=23; range of 4 to 198 pM [0.59 to 29.65 ng/mL]).

Clesrovimab-cfor also neutralized 12 contemporary isolates isolated from Texas, US, between 2016 and 2021, with a median  $EC_{50}$  value for RSV A isolates of 121 pM (18.02 ng/mL) (n=6; range of 59 to 186 pM [8.79 to 27.74 ng/mL]), and for RSV B isolates of 130 pM (19.41 ng/mL) (n=6; range of 95 to 153 pM [14.22 to 22.92 ng/mL]). The relatively high  $EC_{50}$  values for contemporary isolates compared with historical isolates is thought to be related to assay differences because the values for the control viruses also increased.

### Antiviral Resistance

#### *In Cell Culture*

Clesrovimab-resistant RSV variants were identified after serial passage in cell culture of RSV A or RSV B in the presence of clesrovimab-cfor. Four variants were generated after 6 passages with RSV A, and one variant after 9 passages of RSV B. These variants each had reduced susceptibility to clesrovimab-cfor of >3,800-fold (RSV A) or >360-fold (RSV B) when assessed in cell culture, and harbored the following clesrovimab-cfor binding site substitutions: G446E, S443P+K445N, S443P+G446E, or S443P for the four RSV A variants, respectively, and S443P substitution for the RSV B variant.

#### *In Surveillance Trials*

In sequences reported in the GenBank® database (accessed April 15, 2024), the RSV binding epitope for clesrovimab-cfor was highly conserved (99.8%), with 13 polymorphisms identified at contact residues. Of these polymorphisms, the most common (I432T, 0.04% of sequences) conferred 4-fold (RSV A) or 1.6-fold (RSV B) reductions in susceptibility to clesrovimab-cfor in a cell culture neutralization assay. One polymorphism seen in 3 RSV A sequences, G446E, is a resistance-associated substitution selected in cell culture.

In a global surveillance study conducted between 2019 and 2023 in 8 countries across Northern and Southern Hemispheres, the clesrovimab-cfor binding site was highly conserved (>99%) in 300 RSV A and 255 RSV B sequences in clinical samples collected from individuals of various ages (<1 year to >60 years of age).

#### *In Clinical Trials*

In Trial 004, more substitutions in the clesrovimab-cfor binding site (amino acid positions 426 to 447) were observed at  $\geq 3\%$  variant allele frequency (VAF) in RSV infections of clesrovimab-cfor-treated participants (15/156 [9.6%]) compared with placebo participants (2/150 [1.3%]) from Day 1 through 180 post-dose. The majority of the binding site substitutions affected residue G446 (RSV A: G446E, G446R or G446W; and

RSV B: G446E or G446R), and were seen at >50% VAF in at least one participant each. G446E, G446R, and G446W substitutions are resistance-associated, with G446E and G446W conferring >2,941-fold (RSV A) or >1,299-fold (RSV B) loss of susceptibility to clesrovimab-cfor, and G446R conferring >1,563-fold (RSV A) loss of susceptibility to clesrovimab-cfor (RSV B not assessed). Other binding site substitutions seen in clesrovimab-cfor-treated participants at <10% VAF were RSV B: F435S, S443L, G446V, and V447I (no cell culture neutralization data available).

In Trial 007, RSV infections with binding site substitutions at >50% VAF included RSV A (G446W) and RSV B (G446E and G446R), in clesrovimab-cfor-treated participants.

For Trials 004 and 007, there was no clear association of binding site substitutions seen in RSV infections and RSV-associated Medically Attended Lower Respiratory Infection (MALRI) or hospitalization. However, for substitutions seen at high VAF% from Days 1 to 150 post-dose, one participant in Trial 004 with RSV A G446W substitution had RSV-associated hospitalization, and one participant in Trial 007 with RSV B G446R substitution had RSV-associated severe MALRI and hospitalization.

### Cross-resistance

No cross-resistance was seen for RSV variants harboring palivizumab or nirsevimab resistance-associated substitutions in cell culture neutralization assays. Clesrovimab-cfor did not lose activity against RSV A or RSV B clinical isolates with palivizumab resistance-associated substitution N262Y, or recombinant RSV B with nirsevimab resistance-associated substitutions N208S, I64T+K68E, or I64T+K68E+I206M+Q209R, which were observed in clinical trials of nirsevimab. Not all nirsevimab resistance-associated substitutions have been assessed for cross-resistance with clesrovimab-cfor. Both nirsevimab and palivizumab neutralized RSV A and B variants harboring clesrovimab-cfor resistance-associated substitutions G446E or G446W in cell culture.

## **12.6 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 Trial 004 and Trial 007, after receiving the approved recommended dose in RSV season 1, 6% (120/2112) and 5% (13/291) of participants were ADA-positive on Day 150, respectively; and 12% (124/1033) and 13% (34/261) of participants were ADA-positive through Day 240, respectively.

The impact of ADA on efficacy is unknown due to the low rates of MALRI and ADA. There was no identified impact of ADA on pharmacokinetics, RSV serum neutralizing activity or safety of ENFLONSIA during RSV season 1.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Carcinogenesis, mutagenesis and reproductive toxicity studies have not been performed with ENFLONSIA.

## **14 CLINICAL STUDIES**

### **14.1 Description of Clinical Trials**

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

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

<b>Trial</b>	<b>Study Population</b>	<b>Study Arms*</b>
Trial 004 (NCT04767373)	Infants born at $\geq 29$ weeks GA from birth up to 1 year entering their first RSV season.	ENFLONSIA (N=2,411) Placebo (N=1,203) <sup>†</sup>
Trial 007 (NCT04938830)	Infants born at $\leq 35$ 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 randomized and treated

<sup>†</sup>1 participant was randomized to placebo but received ENFLONSIA

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

#### **14.2 Prevention of RSV-Associated Disease in Neonates and Infants ( $\geq 29$ Weeks GA) Entering Their First RSV Season (Trial 004)**

Trial 004 was a Phase 2b/3, randomized, 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 ( $\geq 29$  to  $< 35$  weeks GA) and late preterm and full-term infants ( $\geq 35$  weeks GA). The trial assessed the efficacy of ENFLONSIA in the prevention of RSV-associated disease across a spectrum of severity. Participants were randomized 2:1 to receive a single 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); 80% were less than 6 months; 16% were greater than or equal to 6 to less than 9 months, 4% were greater than or equal to 9 months of age, and 51% were male. Of these participants, 18% were GA greater than or equal to 29 weeks and less than 35 weeks, and 82% were GA greater than or equal to 35 weeks. The racial distribution was as follows: 45% were White; 27% were Asian; 14% were Black or African American; 12% were Multi-racial and 2% were American Indian or Alaska Native; 28% were of Hispanic or Latino ethnicity.

The primary endpoint was the incidence of RSV-associated Medically Attended Lower Respiratory Infection (MALRI) characterized as cough or difficulty breathing and requiring  $\geq 1$  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 hospitalization through 150 days after dosing was evaluated as a key secondary endpoint. The statistical criterion for success required the lower bound of the 95% CI of efficacy to be greater than 0%. Both efficacy endpoints required an RSV-positive RT-PCR nasopharyngeal (NP) sample.

Table 3 displays efficacy results for the primary and key secondary RSV-associated disease endpoints in preterm and full-term infants from days 1 through 150 post-dose.

**Table 3: Incidence of RSV-Associated Disease in Infants Born at  $\geq 29$  Weeks GA Days 1 Through 150 Post-Dose (Trial 004)**

RSV-Associated Endpoint	ENFLONSIA (n=2,411)		Placebo (n=1,203)		Efficacy* (95% CI) <sup>†</sup>
	Number of cases	Incidence Rate over 5 months	Number of cases	Incidence Rate over 5 months	
MALRI (requiring $\geq 1$ indicator of LRI or severity)	60	0.026	74	0.065	60.5% (44.2, 72.0) <sup>‡</sup>
Hospitalization	9	0.004	28	0.024	84.3% (66.7, 92.6) <sup>‡</sup>

n=Number of participants eligible for inclusion in the full analysis set population.

\*Efficacy for MALRI (requiring  $\geq 1$  indicator of LRI or severity) and hospitalization based on relative risk reduction against placebo adjusted for hemisphere at randomization, gestational age group and age group at randomization.

<sup>†</sup>Estimate and 95% CI of efficacy were estimated from the modified Poisson regression with robust variance method.

<sup>‡</sup>(p<0.001)

### 14.3 Prevention of RSV-Associated Disease in Infants Born at $\leq 35$ Weeks Gestational Age and Infants with CLD of Prematurity or Hemodynamically Significant CHD Entering Their First RSV Season (Trial 007)

Trial 007 is a Phase 3, randomized, 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 ( $\geq 29$  to  $\leq 35$  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 randomized to receive ENFLONSIA or palivizumab by IM injection. Participants randomized to ENFLONSIA received a single 105 mg dose on Day 1 followed by a dose of placebo one month later; 15 mg/kg 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% were less than 6 months; 9% were greater than or equal to 6 to less than 9 months, 2% were greater than or equal to 9 months of age; and 50% were male. Of these participants, 28% had CLD, 11% had CHD, 6% were GA less than 29 weeks with neither CLD nor CHD and 55% were GA greater than or equal to 29 weeks with neither CLD nor CHD. The racial distribution was as follows: 52% were White; 18% were Asian; 15% were Black or African American; 12% were Multi-racial, and 1% were American Indian or Alaska Native; 32% 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 Trial 004 to Trial 007 based on similar pharmacokinetic exposure [see *Clinical Pharmacology (12.3)*]. The incidence rate of RSV-associated MALRI (requiring  $\geq 1$  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=2.9%, 95% CI: 1.5, 5.2). The incidence rate of RSV-associated hospitalization through 150 days after dosing was generally comparable between ENFLONSIA (incidence rate=1.3%, 95% CI: 0.4, 2.9) and palivizumab (incidence rate=1.5%, 95% CI: 0.5, 3.2).

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### How Supplied

ENFLONSIA injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution supplied as follows:

Carton containing one or ten single-dose prefilled type I glass syringe(s) with Luer Lock and plunger stopper. The prefilled syringe is not made with natural rubber latex.

Prefilled syringe	Pack Size	NDC
105 mg/0.7 mL single-dose	Carton of 1	0006-5073-01
105 mg/0.7 mL single-dose	Carton of 10	0006-5073-02

### Storage and Handling

- Store prefilled syringes under refrigeration at 36°F to 46°F (2°C to 8°C).
- Keep the prefilled syringe in the original carton to protect from light until time of use.
- ENFLONSIA may be kept at room temperature between 68°F to 77°F (20°C to 25°C) for a maximum of 48 hours. After removal from the refrigerator, ENFLONSIA must be used within 48 hours or discarded.
- Do not freeze. Do not shake.

## **17 PATIENT COUNSELING INFORMATION**

Advise the child's caregiver to read the FDA-approved patient labeling (Patient Information).

### Hypersensitivity Reactions Including Anaphylaxis

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 infant experiences a hypersensitivity reaction to ENFLONSIA [see *Warnings and Precautions* (5.1)].

### Dosage and Administration

Advise the caregiver that the infant will receive ENFLONSIA by IM injection by a healthcare provider [see *Dosage and Administration* (2.1)].

---

Manufactured by:  
Merck Sharp & Dohme LLC  
Rahway, NJ 07065, USA

U.S. license number 0002

For patent information: [www.msd.com/research/patent](http://www.msd.com/research/patent)

Copyright © 2025 Merck & Co., Inc., Rahway, NJ, USA, and its affiliates.  
All rights reserved.

uspi-mk1654-i-2506r000

**Patient Information**  
**ENFLONSIA™ (en-flahn-see-ah)**  
**(clesrovimab-cfor)**  
**injection, for intramuscular use**

**What is ENFLONSIA?**

ENFLONSIA is a prescription medicine to help prevent lung disease, including severe lung disease, caused by Respiratory Syncytial Virus (RSV) in newborns and babies who are born during or entering their first RSV season.

ENFLONSIA contains antibodies to help prevent RSV disease.

It is not known if ENFLONSIA is safe and effective in children older than 12 months of age.

**Your child should not receive ENFLONSIA if your child has a history of serious allergic reactions to any of the ingredients in ENFLONSIA. See the end of this Patient Information leaflet for a complete list of ingredients in ENFLONSIA.**

**Before your child receives ENFLONSIA, tell their healthcare provider about all of your child's medical conditions, including if your child:**

- is scheduled to have heart surgery during or entering their first RSV season.

**Tell your child's healthcare provider about all the medicines your child takes, including prescription and over-the-counter medicines, vitamins, and herbal supplements.**

**How is ENFLONSIA given?**

- ENFLONSIA is given as an injection, in the thigh muscle, by your child's healthcare provider.
- **Your child should get ENFLONSIA before the start of or during the RSV season.** RSV season is the time of year when RSV infections are most common, usually occurring fall through spring. Your child's healthcare provider can tell you when the RSV season starts in your area.
- **Your child may still get RSV disease after receiving ENFLONSIA.** Talk to your child's healthcare provider about what symptoms to look for.
- If your child has heart surgery, your child's healthcare provider may need to give your child an additional ENFLONSIA injection soon after surgery.
- Your child can get ENFLONSIA at the same time as routine childhood vaccines.

**What are the possible side effects of ENFLONSIA?**

- **Serious allergic reactions have happened with other medicines like ENFLONSIA.** Get medical help right away if your child has any of the following signs or symptoms of a serious allergic reaction, including:
  - swelling of the face, mouth, or tongue
  - difficulty swallowing or breathing
  - unresponsiveness
  - bluish color of skin, lips or under fingernails
  - muscle weakness
  - severe rash, hives or itching

The **most common** side effects of ENFLONSIA are:

- redness and swelling at the site of your child's injection
- rash

These are not all the possible side effects of ENFLONSIA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**General information about the safe and effective use of ENFLONSIA.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or child's healthcare provider for information about ENFLONSIA that is written for health professionals.

**What are the ingredients in ENFLONSIA?**

**Active ingredient:** clesrovimab-cfor

**Inactive ingredients:** arginine hydrochloride, histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, sucrose and water for injection.

Manufactured by: Merck Sharp & Dohme LLC, Rahway, NJ 07065, USA. U.S. License No. 0002

For patent information: [www.msd.com/research/patent](http://www.msd.com/research/patent).

Copyright © 2025 Merck & Co., Inc., Rahway, NJ, USA, and its affiliates.

All rights reserved.

usppi-mk1654-i-2506r000

For more information, go to [www.ENFLONSIA.com](http://www.ENFLONSIA.com) or call 1-877-888-4231.

This Patient Information has been approved by the U.S. Food and Drug Administration

Issued: 06/2025



Each single-dose 0.7 mL prefilled syringe contains: 105 mg of clesrovimab-cfor, arginine hydrochloride (10.33 mg), histidine (0.55 mg), L-histidine monohydrochloride monohydrate (0.74 mg), polysorbate 80 (0.14 mg), sucrose (35 mg), and water for injection, USP. No preservative.



Copyright © 2025 Merck & Co., Inc.  
Rahway, NJ, USA, and its affiliates.  
All rights reserved.



Manufactured by:  
Merck Sharp & Dohme LLC  
Rahway, NJ 07065, USA  
U.S. License No. 0002

Manufactured at:  
Patheon Manufacturing Services LLC  
Greenville, NC 27834, USA

Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. DO NOT FREEZE. Do not shake.  
**Recommended Dosage:** See Prescribing Information.  
Discard syringe after use.  
The prefilled syringe is not made with natural rubber latex.



For Intramuscular Use Only

**ENFLONIA™**  
**(clesrovimab-cfor)**  
**Injection**  
105 mg / 0.7 mL  
Ten 105 mg/0.7 mL  
single-dose prefilled  
syringes



GTIN 00000000000000  
SN  
Exp  
Lot

NDC 0006-5073-02  
Ten 105 mg/0.7 mL single-dose  
prefilled syringes

Encoding area: Space reserved for  
2D Serialization Barcode, Serial  
Number, Expiry and Lot

  
**ENFLONIA™**  
**(clesrovimab-cfor)**  
**Injection**  
**105 mg / 0.7 mL**

**For Intramuscular Use Only**  
This package does not contain needles.  
Must be administered by a healthcare provider.

REFRIGERATE

Rx only



Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. DO NOT FREEZE. Do not shake. Administer at room temperature.

**Recommended Dosage:** See Prescribing Information.

Discard syringe after use.  
The prefilled syringe is not made with natural rubber latex.

XXXXXXXXXX

Manufactured by:  
Merck Sharp & Dohme LLC  
Rahway, NJ 07065, USA  
U.S. License No. 0002

Copyright © 2025 Merck & Co., Inc.  
Rahway, NJ, USA, and its affiliates.  
All rights reserved.

Manufactured at:  
Patheon Manufacturing Services LLC  
Greenville, NC 27834, USA

**ENFLONSIA™**  
**(clesrovimab-cfor)**  
**Injection**  
**105 mg / 0.7 mL**



Each single-dose 0.7 mL prefilled syringe contains: 105 mg of clesrovimab-cfor, arginine hydrochloride (10.33 mg), histidine (0.55 mg), L-histidine monohydrochloride monohydrate (0.74 mg), polysorbate 80 (0.14 mg), sucrose (35 mg), and water for injection, USP. No preservative.

NDC 0006-5073-01  
One 105 mg/0.7 mL single-dose  
prefilled syringe

GTIN 00000000000000  
SN  
EXP  
LOT

Ending area: Space reserved  
for 2D Serialization Barcode,  
serialNumber, ExpiryAndLot

**ENFLONSIA™**  
**(clesrovimab-cfor) Injection**  
**105 mg / 0.7 mL**

**For Intramuscular Use Only**  
This package does not contain a needle.  
Must be administered by a healthcare provider.

REFRIGERATE

Rx Only



NDC 0086-5073-99

One 105 mg/0.7 mL single-dose  
prefilled syringe

**ENFLONSIATM**  
**(clesrovimab-cfor)**  
**Injection**

105 mg / 0.7 mL

For Intramuscular Use Only  
Rx only

Store at 2°C-8°C (36°F-46°F).

Manufactured by: Merck Sharp & Dohme LLC  
U.S. License No. 0002

Lot Exp.

XXXXXXXXXX

2D Barcode Area (box does not print)      Lot and Expiry Area (box does not print)

-----  
**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
-----

/s/  
-----

ADAM I SHERWAT  
06/09/2025 10:46:18 AM