

# Comprehensive Review Of ENFLONIA For Prevention Of Respiratory Syncytial Virus Infection In Infants

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## ABSTRACT

ENFLONIA (clesrovimab-cfor) is a long-acting monoclonal antibody developed for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in neonates and infants entering their first RSV season. RSV is a major cause of bronchiolitis, pneumonia, hospitalization, and severe respiratory illness in young infants, particularly in preterm babies and those with underlying cardiac or pulmonary disease. ENFLONIA provides passive immunity by specifically targeting the RSV fusion (F) protein and preventing viral entry into host cells. Due to its extended half-life, a single intramuscular dose of 105 mg provides protection for approximately five months, covering an entire RSV season. Unlike vaccines, ENFLONIA directly supplies protective antibodies without stimulating active immune responses. Clinical studies demonstrated significant efficacy in reducing RSV-associated medically attended lower respiratory infections (MALRI) and RSV-related hospitalizations in both preterm and full-term infants. In Trial 004, ENFLONIA reduced RSV-associated MALRI by 60.5% and hospitalization by 84.3% compared with placebo. In high-risk infants included in Trial 007, efficacy and safety were comparable to Palivizumab<sup>1</sup>. The safety profile of ENFLONIA was generally favorable, with most adverse reactions being mild to moderate, including injection-site erythema, swelling, and rash. Serious hypersensitivity reactions, including anaphylaxis, are rare but important precautions. ENFLONIA may be administered concomitantly with routine childhood vaccines using separate syringes and injection sites. Overall, ENFLONIA represents an important advancement in RSV prevention by offering long-acting passive protection with a single-dose regimen for infants during their first RSV season.

**Keywords:** bronchiolitis, hospitalization, injection-site, Respiratory Syncytial Virus Infection.

## INTRODUCTION

ENFLONIA is a long-acting monoclonal antibody indicated for the prevention of Respiratory Syncytial Virus Infection in neonates and infants during their first RSV season. Respiratory syncytial virus (RSV) is a common viral infection that can cause serious lower respiratory tract illness, especially in young infants and newborns. ENFLONIA provides passive immunity by supplying antibodies that help protect infants against RSV infection. It is administered as a single intramuscular injection and is intended for use in infants born during or entering their first RSV season, including those undergoing cardiac surgery with cardiopulmonary bypass who may require an additional dose<sup>2</sup>.

ENFLONIA provides passive immunity by targeting the RSV fusion (F) protein, thereby preventing viral fusion and entry into host cells. Unlike traditional vaccines, it does not stimulate active immune

responses but directly supplies protective antibodies with prolonged activity due to its extended half-life. A single intramuscular dose of 105 mg provides protection for approximately five months, covering a typical RSV season. Clinical trials have demonstrated that ENFLONIA effectively reduces RSV-associated medically attended lower respiratory infections and hospitalizations in both preterm and fullterm infants. The safety profile was generally favorable, with most adverse reactions being mild to moderate, including injection-site erythema, swelling, and rash. Serious hypersensitivity reactions, including anaphylaxis, are rare but remain important precautions.

ENFLONIA may be administered concomitantly with routine childhood vaccines using separate syringes and different injection sites. It is supplied as a preservative-free, single-dose prefilled syringe

**Relevant conflicts of interest/financial disclosures:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

containing 105 mg/0.7 mL solution for intramuscular administration by a healthcare professional.

## 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.

Infants Undergoing Cardiac Surgery with Cardiopulmonary Bypass<sup>3</sup>.

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 only by a qualified healthcare provider. Before administration, the prefilled syringe should be removed from refrigeration and allowed to reach room temperature for approximately 15 minutes.

Remove the prefilled syringe from the refrigerator and allow it to reach room temperature for about 15 minutes.

Inspect the solution for discoloration or particles. Do not use if damaged or expired.

#### Steps for administration:

1. Hold the syringe barrel firmly in one hand and remove the tip cap by twisting it counterclockwise

with the other hand. The Luer Lock adaptor and finger flange extender should not be removed.

2. Attach a sterile Luer Lock needle by twisting it clockwise until securely fitted onto the syringe.

3. Administer the entire contents of the prefilled syringe as an intramuscular injection into the anterolateral aspect of the thigh.

The injection should not be given in the gluteal region or in areas containing major nerves or blood vessels.

4. After administration, dispose of the used syringe immediately into an approved sharps disposal container<sup>4</sup>.

### Co-administration with Vaccines and Immunoglobulin Products:

ENFLONSIA may be administered together with routine childhood vaccines. When given concomitantly with injectable vaccines, separate syringes and different injection sites should be used. ENFLONSIA should not be mixed with vaccines or other medications in the same syringe or vial.

There is currently no available information regarding the co-administration of ENFLONSIA with other immunoglobulin products. In addition, there are no data supporting substitution of Palivizumab with ENFLONSIA after RSV prophylaxis with palivizumab has already been initiated during 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<sup>5-6</sup>.

## 5. WARNING AND PRECAUTIONS:

### 1. Hypersensitivity Including Anaphylaxis:

ENFLONSIA may cause serious hypersensitivity reactions, including anaphylaxis, similar to other

human IgG1 monoclonal antibodies. If symptoms such as difficulty breathing, swelling, rash, or severe allergic reactions occur, appropriate medical treatment and supportive care should be initiated immediately.

## 2. RSV Diagnostic Test Interference:

Clesrovimab-cfor may interfere with some immunologically based RSV diagnostic tests, particularly rapid antigen assays. If rapid antigen test results are negative but clinical symptoms strongly suggest Respiratory Syncytial Virus Infection, confirmation with an RTPCR assay is recommended.

## 6. ADVERSE REACTIONS:

ENFLONSIA was evaluated in Phase 2b/3 and Phase 3 clinical trials involving infants, including preterm infants and infants at high risk for severe RSV disease. In Trial 004, 2,412 infants received a single 105 mg intramuscular dose of ENFLONSIA and 1,202 infants received placebo. Participants were monitored for immediate reactions, adverse events, and serious adverse events for up to one year or longer.

Most adverse reactions ( $\geq 97\%$ ) were mild to moderate in severity<sup>8</sup>.

The most common adverse reactions reported slightly more frequently than placebo were:

- Injection-site redness (**3.8%**).
- Injection-site swelling (**2.7%**).
- Rash (**2.3%**).

In Trial 007, ENFLONSIA was studied in infants at increased risk of severe RSV disease, including infants born at  $\leq 35$  weeks gestational age and infants with chronic lung disease (CLD) of prematurity or congenital heart disease (CHD). The safety profile of ENFLONSIA was similar to palivizumab and consistent with results observed in

Trial 004.

## 7. DRUG INTERACTIONS:

Clesrovimab-cfor may interfere with some immunologically-based rapid antigen tests used for diagnosing Respiratory Syncytial Virus Infection.

Laboratory studies showed that the drug can affect the accuracy of certain rapid RSV antigen assays, potentially causing false-negative results even when RSV infection is present. Therefore, if a rapid antigen test result is negative but the infant's clinical symptoms and findings are consistent with RSV infection, confirmation with an RT-PCR assay is recommended. RT-PCR testing is not affected by clesrovimab-cfor and remains reliable for RSV diagnosis<sup>9</sup>.

## 8. USE IN SPECIFIC POPULATION:

### 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.

### 8.3 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 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<sup>10</sup>.

## 9. OVER DOSE:

There is limited experience with overdose of ENFLONSIA. No specific antidote or treatment is available for overdose.

If overdose occurs, the infant should be monitored for adverse reactions and given supportive and symptomatic treatment as needed.

## 10. DESCRIPTION:

ENFLONSIA (clesrovimab-cfor) is a respiratory syncytial virus (RSV) 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. Its molecular weight is approximately 149 kDa.

ENFLONSIA injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution intended for intramuscular injection.

### Composition

Each 0.7 mL contains:

- Clesrovimab-cfor — 105 mg
- Arginine hydrochloride — 10.33 mg
- Histidine — 0.55 mg
- L-histidine monohydrochloride monohydrate — 0.74 mg
- Polysorbate 80 — 0.14 mg
- Sucrose — 35 mg
- Water for Injection (USP) The solution has a pH of 6.0.

## 11. CLINICAL PHARMACOLOGY:

### 11.1 Mechanism of action

ENFLONSIA is a monoclonal antibody with anti-RSV activity.

### 11.2 Pharmacodynamics

- RSV antibody levels increase after intramuscular administration.
- Antibody titers are about 7 times above baseline within 4 hours.
- Maximum antibody levels are reached by Day 7.
- A single dose provides protection for up to 5 months<sup>11</sup>.

### 11.3 Pharmacokinetics

#### Absorption

Median time to peak concentration: 6.5 days

#### Distribution

Volume of distribution: 830 mL in a typical 5 kg infant

### Metabolism

Broken down into small peptides through catabolic pathways

### Elimination

Half-life: approximately 44 days Clearance: 19.7 mL/day.

### 11.4 Microbiology

#### Mechanism of action

ENFLONSIA contains clesrovimab-cfor, a monoclonal antibody that provides passive immunity against Respiratory Syncytial Virus Infection.

- Targets the RSV fusion (F) protein
- Prevents viral entry into cells
- Engineered with YTE modification for longer half-life

#### Antiviral activity

- Historical RSV Isolates (1987–2016)
    - RSV A: median EC50 = 25 pM
    - RSV B: median EC50 = 30 pM
  - Contemporary RSV Isolates (2016–2021)
    - RSV A: median EC50 = 121 pM
    - RSV B: median EC50 = 130 pM
- Antiviral resistance** Cell Culture Resistance

#### Mutations RSV A

- G446E
- S443P + K445N
- S443P + G446E
- S443P **RSV B** ● S443P

Resistance caused major reductions in susceptibility to clesrovimab-cfor. **Surveillance findings**

- Binding site highly conserved (>99%)
- Most common mutation: I432T
- Resistance-associated mutation identified: G446E

### Clinical trial findings Trail 004

Binding-site substitutions occurred more often in treated participants:

- Treated: 9.6%
- Placebo: 1.3% Common mutations:
- RSV A: G446E, G446R, G446W
- RSV B: G446E, G446R<sup>12</sup>.

### Trail 007

Detected mutations:

- RSV A: G446W • RSV B: G446E, G446R

Some participants with these mutations experienced RSV hospitalization or severe MALRI.

### Cross resistance

Palivizumab and Nirsevimab remained active against clesrovimab-cfor-resistant variants. Clesrovimab-cfor also retained activity against several palladium- and nirsevimab-resistant RSV variants.

## 12. NON CLINIICAL TOXICOLOGY

### Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis, mutagenesis and reproductive toxicity studies have not been performed with ENFLONSIA<sup>13</sup>.

## 13. CLINICAL STUDIES

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

### Trials Conducted with ENFLONSIA for the Prevention of Medically Attended RSV Lower Respiratory tract diseases.

Trails	Study population	Arms
Trial 004	Infants born at $\geq 29$ weeks ENFLONSIA (N=2,411). GA from birth up to 1 year entering their first RSV season.	Placebo (n=1203)
Trail 007	Infants born at $\leq 35$ weeks GA, ENFLONSIA (N=446) or infants with CLD of prematurity hemodynamically significant CHD from birth up to 1 year entering their first RSV season.	Palivizumab (N=450)

### Trail 004:

- Phase 2b/3 randomized, double-blind, placebo-controlled study.
- Included infants born at  $\geq 29$  weeks gestational age entering first RSV season.
- Participants received single IM dose of ENFLONSIA or placebo.
- Primary endpoint: prevention of RSV-associated medically attended lower respiratory infection (MALRI) within 150 days.

### Results:

- MALRI reduced by 60.5% compared with placebo.
- RSV hospitalization reduced by 84.3% compared with placebo.

### Trail 007:

- Phase 3 randomized, palivizumab-controlled study.
- Included high-risk infants:
  - $\leq 35$  weeks gestational age
  - Chronic lung disease (CLD)
  - Congenital heart disease (CHD)

**Results;**

ENFLONSIA showed efficacy comparable to Palivizumab.

RSV-associated MALRI and hospitalization rates were similar between both groups.

**How supplied:**

ENFLONSIA injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution.

**Available package :**

**14. HOW SUPPLIED/STORAGE AND HANDLING**

Strength	Pack size	NDC
105 mg/0.7 mL 0006-507301 single-dose prefilled syringe	Corton 1 of 1	0006-5073-01
105 mg/0.7 mL single-dose prefilled syringe	Corton of 10.	0006-5073-02

- Supplied in single-dose prefilled type I glass syringes with Luer Lock and plunger stopper.
- Prefilled syringe is not made with natural rubber latex<sup>14</sup>.

**Storage and handling:**

- Store refrigerated at 2°C to 8°C (36°F to 46°F).
- Keep in original carton to protect from light.
- May be kept at room temperature 20°C to 25°C (68°F to 77°F) for up to 48 hours.
- Use within 48 hours after removal from refrigerator or discard. • Do not freeze. • Do not shake.

**15. 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<sup>15</sup>.

**Dosage and administration:**

Advise the caregiver that the infant will receive ENFLONSIA by IM injection by a healthcare provider.

**CONCLUSION**

ENFLONSIA is an important advancement in the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in neonates and infants entering their first RSV season. By providing long-acting passive immunity through targeted inhibition of the RSV fusion (F) protein, ENFLONSIA offers effective seasonal protection with a single intramuscular dose.

Clinical studies demonstrated significant reductions in RSV-associated medically attended lower respiratory infections and hospitalizations in both preterm and full-term infants, including those at high risk for severe RSV disease. The safety profile was generally favorable, with most adverse reactions being mild to moderate and serious hypersensitivity reactions occurring rarely.

Its convenient single-dose regimen, prolonged duration of protection, and compatibility with routine childhood immunizations make ENFLONSIA a valuable option for RSV prophylaxis in infants. Overall, ENFLONSIA represents a promising



strategy for reducing the burden of RSV related morbidity and hospitalization during early infancy.

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**HOW TO CITE:** M. Prasada Rao\*, Y. Narasimha Rao, S. Rajini, B. Sri Vasu Naik, Comprehensive Review Of ENFLONSIA For Prevention Of Respiratory Syncytial Virus Infection In Infants, *Int. J. Sci. R. Tech.*, 2026, 3 (5), 897-903. <https://doi.org/10.5281/zenodo.20395434>