Monoclonal Antibodies for Prevention of Respiratory Syncytial Virus (RSV)

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the Monoclonal Antibodies for Prevention of Respiratory Syncytial Virus (RSV) drug policy is to ensure appropriate selection of patients for therapy with Synagis® (palivizumab) and appropriate dosing/quantities for Synagis (palivizumab) based on product labeling, clinical guidelines, The Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) recommendations, and clinical studies.

Synagis is a recombinant humanized monoclonal antibody which exhibits neutralizing and fusion-inhibitory activity against respiratory syncytial virus (RSV). Synagis is approved by the Food and Drug Administration (FDA) for the prevention of serious lower respiratory tract disease caused by RSV in pediatric patients considered to be high risk for developing complications from RSV disease. Safety and efficacy were established in infants with bronchopulmonary dysplasia ([BPD], now more commonly referred to as chronic lung disease of prematurity [CLD]), infants with a history of premature birth, and children with hemodynamically significant congenital heart disease (CHD). The primary benefit of immunoprophylaxis with Synagis is a reduction in RSV related hospitalizations; no prospective, randomized controlled trials have demonstrated a significant reduction in mortality or long-term respiratory outcomes. The safety and efficacy of Synagis have not been established for the treatment of RSV disease.

Beyfortus® is a monoclonal antibody with activity against RSV indicated for the prevention of RSV lower respiratory tract disease in neonates and infants born during or entering their first RSV season and children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. Additionally, Beyfortus was unanimously recommended by the CDC's Advisory Committee on Immunization

Practices (ACIP) for infants aged <8 months born during or entering their first RSV season and for children aged 8 to 19 months who are at increased risk of severe RSV disease and are entering their second RSV season.

Coverage of Beyfortus (nirsevimab) is provided without prior authorization for members 24 months and younger, including additional doses required for members undergoing cardiac surgery with cardiopulmonary bypass during their first or second RSV season.

Enflonsia™ is a monoclonal antidbody indicated for the prevention of RSV lower respiratory tract diseas in neonates and infants who are born during or entering their first RSV season. ACIP voted to recommend Enflonsia for infants aged <8 months of age born during or entering their first RSV season. The recommendation was adopted by the CDC Director as an official recommendation of the CDC.

Coverage of Enflonsia (clesrovimab) is provided without prior authorization for members 12 months and younger.

Note: The safety and efficacy of Synagis has not been evaluated in patients who have already received a dose of Beyfortus (nirsevimab) or Enflonsia (clesrovimab) during the RSV season. The safety and efficacy of Synagis, Beyfortus, or Enflonsia have not been evaluated in infants who have already received prevention of RSV from birth through 6 months of age due to the active immunization of pregnant individuals with a dose of Abrysvo® (respiratory syncytial virus vaccine [recombinant]; RSVpreF) at 32 through 36 weeks' gestational age.

POLICY

***Beyfortus (nirsevimab) and Enflonsia (clesrovimab)** DO NOT require review based on product labeling, clinical guidelines, the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) recommendations, and clinical studies.

Criteria for Initial Approval

I. Synagis (palivizumab) may be considered **medically necessary** for use as immunoprophylaxis for RSV in infants who were born at less than 29 weeks' gestation (28 weeks, 6 days and earlier) **AND** who are younger than 12 months of age at the onset of RSV season

   Approval will be for a **maximum of 5 doses.**

II. Synagis (palivizumab) may be considered **medically necessary** for use as immunoprophylaxis for RSV in preterm infants and children born before 32 weeks gestation (31 weeks, 6 days and earlier) with chronic lung disease of prematurity (CLD) defined as a greater than 21% oxygen requirement for at least 28 days after birth when the following criteria are met:

- The patient is younger than 12 months of age at the onset of RSV season
  OR
- The patient is younger than 24 months of age at the start of RSV season **AND** has continued to require medical therapy (i.e., supplemental oxygen, diuretic therapy, chronic corticosteroid therapy) during the 6-month period prior to the start of the RSV season

  Approval will be for a **maximum of 5 doses.**

III. Synagis (palivizumab) may be considered **medically necessary** for use as immunoprophylaxis for RSV in infants and children with congenital heart disease (CHD) who are less than 12 months of age at the onset of RSV season when the following criteria are met:

- The patient has a diagnosis of hemodynamically significant congenital heart disease (CHD) including **ONE** of the following:
  - Acyanotic heart disease for which the patient is receiving medication to control congestive heart failure **AND** will require cardiac surgical procedures
  - Moderate to severe pulmonary hypertension
  - Cyanotic heart disease in consultation with a pediatric cardiologist

Approval will be for a **maximum of 5 doses.***

***For children with heart disease meeting the above criteria, an additional postoperative dose of palivizumab may be considered **medically necessary** following cardiopulmonary bypass or the conclusion of extracorporeal membrane oxygenation.

IV. Synagis (palivizumab) may be considered **medically necessary** for use as immunoprophylaxis for RSV in infants and children younger than 24 months of age at the onset of RSV season that have undergone cardiac transplantation during RSV season.

Approval will be for a **maximum of 5 doses.**

V. Synagis (palivizumab) may be considered **medically necessary** for use as immunoprophylaxis for RSV in infants with congenital abnormalities of the airways or neuromuscular condition that compromises the handling of secretions when the patient is younger than 12 months of age at the onset of RSV season.

Approval will be for a **maximum of 5 doses**

VI. Synagis (palivizumab) may be considered **medically necessary** for use as immunoprophylaxis for RSV in infants and children younger than 24 months of age who are profoundly immunocompromised (e.g., including those who have undergone solid organ transplant, undergoing hematopoietic stem cell transplant, receiving chemotherapy) during the RSV season.

Approval will be for a **maximum of 5 doses.**

VII. Synagis (palivizumab) may be considered **medically necessary** for use as immunoprophylaxis for RSV in infants and children with a diagnosis of cystic fibrosis and meet the following criteria:
- The patient is less than 12 months of age at the onset of RSV season and have **ONE** of the following:
  - Clinical evidence of CLD
  - Nutritional compromise

OR
- The patient is less than 24 months of age at the onset of RSV season and have **ONE** of the following:
  - Manifestations of severe lung disease defined as a previous hospitalization for pulmonary exacerbation in the first year of life or an abnormal chest radiography or chest computed tomography that persists when stable
  - Weight for length less than 10^{th} percentile

Approval will be for a **maximum of 5 doses.**

VIII. Synagis is considered **not medically necessary** for patients who do not meet the criteria set forth above.

Other
For all indications: the patient cannot use Synagis (palivizumab) concomitantly with either Beyfortus (nirsevimab) or Enflonsia (clesroimab) during the same RSV season.

For all off-season Synagis requests, authorization of 1 dose per request, up to a maximum of 5 doses per RSV season, may be granted if the RSV activity for the requested region is ≥ 3% (with real-time polymerase chain reaction (PCR) test) within 2 weeks of the intended dose according to the CDC National Respiratory and Enteric Virus Surveillance System (NREVSS). The local health department or the CDC NREVSS will be consulted to assess the RSV activity for that region or state (http://www.cdc.gov/surveillance/nrevss/rsv/index.html). Initial Criteria for Approval criteria and Quantity/Dosing limits will apply.

Wellmark RSV Season for 2025-2026 will be November 1, 2025 to April 30, 2026. For the current 2025-2026 fall and winter season, the American Academy of Pediatrics (AAP) supports initiating the standard palivizumab regimen (five consecutive monthly doses) for eligible infants in regions of the United States with interseasonal rates of RSV activity similar to those in a typical fall-winter season. During the COVID-19 pandemic, RSV did not follow its typical seasonality of late fall through spring, leading the AAP to support use of the monoclonal antibody at other times of the year if activity is comparable to a regular season. Currently, virus activity varies by region. Please note, any doses received prior to November 1st will not count towards the 2025-2026 season's 5 dose total.

Dosage and Administration
Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. Synagis should be administered intramuscularly at a dose of 15 mg/kg once per month beginning prior to the onset of the RSV season, which typically occurs in November. Because 5 monthly doses of Synagis will provide more than 6 months of serum Synagis concentrations above the desired serum concentration for most infants, administration of more than 5 monthly doses is not recommended within the continental United States.

Quantity Limits Apply:
Synagis (palivizumab) 5 doses per RSV season

CLINICAL RATIONALE

Each year in the United States an estimated 58,000 to 80,000 infants and susceptible toddlers are hospitalized for RSV related illness and 100 to 300 deaths are attributed to RSV. Hospitalization rates are highest in the first year of life. In addition to hospitalizations, RSV illness results in a significant number of both emergency department and pediatric office visits.

While most children will have been exposed to RSV by the time they reach two years of age, the illness generally manifests as an upper respiratory infection and rarely poses significant harm. Children born premature and those with specific medical conditions have been identified as being most vulnerable to severe RSV infection, which can require hospitalization. Although severe disease occurs more frequently among high risk infants and toddlers, the majority of RSV-related hospitalizations and deaths occur in children without an underlying high-risk condition.

RSV treatment primarily involves supportive measures. In the United States, Synagis (palivizumab), Beyfortus (nirsevimab), and Enflonsia (clesrovimab) are available as immunoprophylaxis. In studies, palivizumab has been shown to reduce hospitalization rates in high-risk patient populations. According to the two large randomized controlled trials, for which palivizumab approval is based, palivizumab

demonstrated a reduction in hospitalization rates by ~50 percent, which was associated with numbers needed to treat (NNT) of 16 (for those born premature), 20 (for those with chronic lung disease of prematurity or CLD), and 23 (for those with hemodynamically significant congenital heart disease or CHD). There is no evidence palivizumab affects mortality associated with RSV infection. Given the high cost of immunoprophylaxis with palivizumab, identifying those most likely to benefit and timing the administration to align with the RSV season is critical to ensure its most cost-effective use. The American Academy of Pediatrics (AAP) has established recommendations for palivizumab, defining those most likely to benefit based on the available evidence; their recommendations serve as the foundation for this drug policy. In July 2014 the AAP released updated guidance that was considerably more restrictive in nature. The Academy makes clear their recommendations were not based on cost, but instead "driven by the ***limited clinical benefit*** derived from palivizumab prophylaxis". In September 2017, the Committee on Infectious Diseases and the Subcommittee on Bronchiolitis reviewed new data and reaffirmed the 2014 AAP recommendations. The 2014 AAP recommendations were reaffirmed again in 2019. In 2024, the AAP provided guidance that Beyfortus is the recommended product for RSV disease protection due to its efficacy, duration of action, and dosing regimen. In cases where Beyfortus is not available or feasible for administration, Synagis should be considered in the interim.

In most areas of the United States, the usual time for the beginning of the RSV outbreaks occurs in November/December, peaking in January/February, with outbreaks ending in March/April. RSV season may commence earlier or persist later in certain communities. Variations in the timing and intensity of RSV from season to season and among different communities may arise from several factors including weather conditions that affect virus virility, and population factors such as population density and immunity, which may affect the likelihood of transmission.

Regardless of the month when the first dose is administered, the AAP guidelines make clear the recommendation for a maximum of 5 doses for the entire RSV season. Results from clinical trials indicate that 5 monthly doses provide more than 6 months of protective serum antibody concentration, which provides adequate coverage for an RSV season. Specifically, the AAP states the following: "For qualifying infants who require 5 doses, a dose beginning in November and continuation for a total of 5 monthly doses will provide protection for most infants **through April** and is recommended for most areas of the United States." Administration of more than 5 monthly doses is **NOT** recommended within the continental United States.

Due to the small probability of a second RSV hospitalization occurring in the same season (<0.5%), immunoprophylaxis with Synagis should be discontinued in any infant or child who experiences a breakthrough RSV hospitalization.

Beyfortus (nirsevimab) is approved as a single dose, intramuscular injection for prevention of RSV lower respiratory tract disease in neonates and infants born during or entering their first RSV season, and pediatric patients up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. Enflonsia (clesrovimab) is approved as a single dose, intramuscular injection for prevention of RSV lower respiratory tract disease in neonates and infants who are born during or entering their first RSV season. The safety and efficacy of Synagis has not been evaluated in patients who have already received a dose of Beyfortus (nirsevimab) or Enflonsia (clesrovimab) during the RSV season. Due to a lack of evidence supporting combination use, the administration of both Synagis and either Beyfortus or Enflonsia within the same RSV season is restricted. The CDC's Advisory Committee on Immunization Practices (ACIP) unanimously recommended Beyfortus for infants aged <8 months born during or entering their first RSV season and for children aged 8 to 19 months who are at increased risk of severe RSV disease and entering their second RSV season for the prevention of RSV lower respiratory tract disease. Similarly, the CDC's ACIP recommended Enflonsia for infants aged <8 months born during or entering their first RSV

season who are not protected by maternal vaccination. Patients meeting ACIP recommendations DO NOT require review and coverage is provided without prior authorization.

The AAP, in conjunction with ACIP, provided recommendations for the use of Beyfortus and Enflonsia highlighting the need for equitable access. The AAP states when Beyfortus is administered, the patient should not receive Synagis later in the same season. In situations where Synagis is administered initially in the season with fewer than five dose administered, the provider should complete RSV prophylaxis by administering a single dose of Beyfortus or Enflonsia (if entering the first RSV season). For children eligible for RSV prophylaxis in season two, the AAP recommends Beyfortus regardless of which product was administered the previous season, but only recommends Enflonsia for the first RSV season in alignment with the FDA approved indication. The recommendations also suggest administration of Beyfortus or Enflonsia within the first week of life when the infant is born shortly before or during the RSV season, ideally during their birth hospitalization. The AAP states that Beyfortus should be administered to infants <8 months and eligible infants and children 8 months through 19 months shortly before the start of the RSV season. Similarly, the AAP states that Enflonsia should be administered to infants <8 months and eligible infants entering their first RSV season. In accordance with CDC's best practices, the concomitant administration of Beyfortus or Enflonsia with age-appropriate childhood vaccines is recommended.

Abrysvo (respiratory syncytial virus [RSV] vaccine) is approved as a single dose, intramuscular injection for active immunization of pregnant individuals at 32 to 36 weeks' gestational age for prevention of lower respiratory tract disease (LRTD) and severe LRTD caused by RSV in infants from birth through 6 months of age. The CDC's Advisory Committee on Immunization Practices (ACIP) recommends Abrysvo for pregnant individuals at 32 to 36 weeks' gestational age, seasonally, from September through January. ACIP also provided guidance that the routine use of Beyfortus or Enflonsia in combination with Abrysvo is not cost-effective for most infants. The administration of Beyfortus, Enflonsia, or Synagis in infants born to women who received a maternal dose of Abrysvo has not been studied at this time.

A practice advisory published by the American College of Obstetrics and Gynecologists (ACOG) recommends a single dose of Abrysvo to pregnant individuals between 32 and 36 weeks of gestation, using seasonal administration. ACOG reiterates that most newborns and infants will not need both maternal vaccination and monoclonal antibody administration. An exception may be made when infants are born at less than 34 weeks or prior to the 14 days from maternal vaccination for transplacental transfer of maternal antibodies to take place. Additional considerations should be made for pregnant persons who may not mount and adequate immune response, may have conditions inhibiting transplacental antibody transfer, or for infants who undergo cardiopulmonary bypass after birth. Providers should use clinical judgement in these rare scenarios. Maternal RSV vaccine may be administered in conjunction with all other vaccines routinely recommended during pregnancy.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- 90378 Respiratory syncytial virus, monoclonal antibody, recombinant, for intramuscular use, 50 mg, each
- 90380 Beyfortus (respiratory syncytial virus, monoclonal antibody) Injection, 0.5 mL
- 90381 Beyfortus (respiratory syncytial virus, monoclonal antibody) Injection, 1 mL
- 90382 Enflonsia (respiratory syncytial virus, monoclonal antibody) Injection, 0.7 mL
- S9562 Home injectable therapy, palivizumab, including administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

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POLICY HISTORY

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