Drug and Biologic Coverage Policy

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Coverage Policy Number 5012

Palivizumab

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Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

Palivizumab (Synagis®) is considered medically necessary for the prevention of lower respiratory tract infection with respiratory syncytial virus (RSV) for up to 5 consecutive monthly doses during RSV season for ANY of the following indications when additional condition specific criteria are met as outlined below:**

- **Prematurity**
- **Chronic Lung Disease (CLD)**
- **Congenital Heart Disease (CHD)**
- **Cardiac Transplantation**
- **Congenital Abnormalities of the Airway or Neuromuscular Disease**
- **Cystic Fibrosis**
- **Severe Immunodeficiency**
- **Alaska Native or American Indian Infant**

I. **Prematurity** when BOTH of the following criteria are met:
- Infant less than 12 months of age at the start of RSV season
- Infant born before 29 weeks, 0 days' gestation

II. **Chronic Lung Disease (CLD)** when ONE of the following criteria are met:
- Infant less than 12 months of age at the start of RSV season and BOTH of the following:
  - CLD of prematurity (born before 32 weeks, 0 days' gestation)
  - Supplemental oxygen required for at least the first 28 days after birth
- Child 12-24 months of age at the start of RSV season and ALL of the following:
  - CLD of prematurity (born before 32 weeks, 0 days' gestation)
  - Supplemental oxygen required for at least the first 28 days after birth
  - Medical support (chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) continues to be required during the 6 month period prior to the start of the RSV season

III. **Congenital Heart Disease (CHD)** when BOTH of the following criteria are met:
- Infant less than 12 months of age at the start of RSV season
- Hemodynamically significant CHD and ONE of the following:
  - Acyanotic CHD receiving treatment for congestive heart failure (CHF) and will require cardiac surgical procedures
  - Cyanotic CHD and prescribed by, or in consultation with, a pediatric cardiologist
  - Moderate-to-severe pulmonary hypertension

IV. **Cardiac Transplantation** when BOTH of the following criteria are met:
- Infant or child less than 24 months of age
- Undergoing cardiac transplantation during the RSV season

V. **Congenital Abnormalities of the Airway or Neuromuscular Disease** when BOTH of the following criteria are met:
- Infant less than 12 months of age at the start of RSV season
- Congenital abnormality of the airway or a neuromuscular disease (for example, cerebral palsy, muscular dystrophy, neurological diseases of the brain and spinal cord [Tay Sachs, spinal muscular dystrophy]) that compromises the handling of respiratory secretions

VI. **Cystic Fibrosis** when ONE of the following criteria are met:
- Infant less than 12 months of age at the start of RSV season with EITHER of the following:
  - Clinical evidence of CLD of prematurity (born before 32 weeks, 0 days' gestation) and supplemental oxygen required for at least the first 28 days after birth
  - Nutritional compromise as evidenced by weight for length less than the 10th percentile on a pediatric growth chart
- Child 12-24 months of age at the start of RSV season with EITHER of the following:
  - Manifestations of severe lung disease (history of hospitalization for pulmonary exacerbation, abnormal chest x-ray or chest computed tomography [CT] SCAN)
  - Nutritional compromise as evidenced by weight for length less than the 10th percentile on a pediatric growth chart

VII. **Severe Immunodeficiency** when BOTH of the following criteria are met:
- Infant or child less than 24 months of age
- Severe immunodeficiency (for example, severe combined immunodeficiency or severe acquired immunodeficiency syndrome) during the RSV season

VIII. **Alaska Native or American Indian Infant** (Navajo, White Mountain Apache) for an infant less than 12 months of age at the start of RSV season.

An additional dose of palivizumab following cardiac bypass or extra-corporeal membrane oxygenation for infants and children less than 24 months of age who are receiving RSV prophylaxis and will continue to require prophylaxis following surgery is covered.

****When medically necessary, Synagis is approved for the duration of RSV season which begins in November and ends in March for most areas of the United States. In regions where elevated RSV**

isolation is documented by either surveillance data from the Centers for Disease Control (CDC) and Prevention or local public health authorities, early starts may be approved based on results of local RSV activity; however, the total number of Synagis doses is limited to a maximum of 5 consecutive months.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Palivizumab (Synagis) is considered experimental, investigational or unproven for ANY other use including the following:

- RSV prophylaxis in an inpatient setting
- RSV prophylaxis in cystic fibrosis or down syndrome in an infant or child not otherwise meeting the above medical necessity criteria
- RSV prophylaxis in an infant or child with hemodynamically insignificant heart disease (for example, atrial septal defect, small ventricular septal defect, pulmonic stenosis, uncomplicated aortic stenosis, mild coarctation of the aorta and patent ductus arteriosus)
- RSV prophylaxis in an infant or child with mild cardiomyopathy not requiring medical treatment
- RSV prophylaxis for children in the second year of life not otherwise meeting the above criteria
- RSV prophylaxis continuation for an infant or child after breakthrough RSV infection
- Treatment of RSV disease

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

FDA Approved Indications

FDA Approved Indication

Synagis is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients:

- with a history of premature birth (less than or equal to 35 weeks gestational age) and who are 6 months of age or younger at the beginning of RSV season,
- with bronchopulmonary dysplasia (BPD) that required medical treatment within the previous 6 months and who are 24 months of age or younger at the beginning of RSV season,
- with hemodynamically significant congenital heart disease (CHD) and who are 24 months of age or younger at the beginning of RSV season.

Limitations of Use:
The safety and efficacy of Synagis have not been established for treatment of RSV disease.

Recommended Dosing

FDA Recommended Dosing

The recommended dose of Synagis is 15 mg per kg of body weight given monthly by intramuscular injection. The first dose of Synagis should be administered prior to commencement of the RSV season and the remaining doses should be administered monthly throughout the RSV season. Children who develop an RSV infection should continue to receive monthly doses throughout the RSV season. In the northern hemisphere, the RSV season typically commences in November and lasts through April, but it may begin earlier or persist later in certain communities.

Synagis serum levels are decreased after cardio-pulmonary bypass. Children undergoing cardio-pulmonary bypass should receive an additional dose of Synagis as soon as possible after the cardio-pulmonary bypass procedure (even if sooner than a month from the previous dose). Thereafter, doses should be administered monthly as scheduled.

The efficacy of Synagis at doses less than 15 mg per kg, or of dosing less frequently than monthly throughout the RSV season, has not been established.

Drug Availability
Synagis is supplied in single-dose, liquid solution vials containing 50 mg Synagis in 0.5 mL, and 100 mg Synagis in 1 mL.

General Background

Pharmacology
Palivizumab is a humanized monoclonal antibody that is produced by recombinant deoxyribonucleic acid (DNA) technology. It selectively binds to RSV antigens to prevent viral replication. Administration of palivizumab results in a reduction in pulmonary RSV titer. The pharmacokinetics of palivizumab is similar to those of human immunoglobulin G (IgG). Its activity against RSV titers is 50 to 100 times more than RSV-IGIV in in-vitro models. (McEvoy, 2017)

Professional Societies/Organizations
The American Academy of Pediatrics (AAP) 2014 recommendations for respiratory syncytial virus (RSV) include the following populations:

Population	Gestational Age Born	Age	Additional Characteristics or Information
Preterm Infants without Chronic Lung Disease or Prematurity or Congenital Heart Disease	Before 29 weeks, 0 days	Younger than 12 months	Not recommended in the second year of life on the basis of prematurity alone
Preterm Infants with Chronic Lung Disease	Before 32 weeks, 0 days	First year of life	AND required >21% oxygen for at least the first 28 days after birth
Preterm Infants with Chronic Lung Disease	Before 32 weeks, 0 days	Second year of life	Required >21% oxygen for at least the first 28 days after birth AND continue to require medical support (i.e., chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) during the 6 months prior to the start of the second RSV season
Infants with Hemodynamically Significant Congenital Heart Disease	n/a	12 months or younger	One of the following groups: • Acyanotic heart disease 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)
Children undergoing cardiac transplantation during RSV season	n/a	Younger than 2 years	
Children with anatomic pulmonary abnormalities or neuromuscular disorder	n/a	First year of life	

Immunocompromised children	n/a	Younger than 24 months	

(AAP, 2014)

The AAP recommends against routine prophylaxis for children with Down syndrome; infants and children with hemodynamically insignificant heart disease; infants with lesions adequately corrected by surgery unless requiring medication for congestive heart failure; and infants with mild cardiomyopathy not receiving medical therapy. Routine prophylaxis of cystic fibrosis patients during the first year of life is not recommended, unless other factors exist (i.e. evidence of CLD, nutritional compromise). A post-operative dose of palivizumab should be considered following cardiac bypass or extra-corporeal membrane oxygenation for infants and children less than 24 months of age who are receiving RSV prophylaxis and will continue to require prophylaxis. (AAP, 2014) In addition, the AAP recommends discontinuing monthly palivizumab prophylaxis in an infant or child who experiences a breakthrough RSV hospitalization. The AAP also does not recommend administration of more than 5 monthly doses within the continental United States. For most areas of the United States, the first dose should be given in November and continued for a total of 5 monthly doses, which will provide protection through April. Data from the Florida Department of Health should be utilized to determine timing of the first dose of palivizumab for the different regions in Florida. Data from the state of Alaska can assist with determining the start and end of RSV season in Alaska. (AAP, 2014)

The AAP recognizes there is a lack of data specifically supporting the use of Synagis in an inpatient setting to prevent RSV outbreaks, and states that rigorous infection-control procedures are the foundation for decreasing the incidence of RSV in the hospitalized infant. For infants who qualify for RSV prophylaxis, discharge planning might include first dose injection 48 to 72 hours prior to discharge. (AAP, 2014)

The AAP also notes that there may be broader use of palivizumab due to the burden of RSV disease and costs associated with transport in Alaska Native populations and also in selected other American Indian populations (i.e., Navajo, White Mountain Apache). (AAP, 2014)

The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative

No recommendations are available for the prevention of respiratory syncytial virus (RSV) in pediatric individuals.

Centers for Medicare & Medicaid Services - National Coverage Determinations (NCDs)

There are no CMS National Coverage Determinations for the prevention of respiratory syncytial virus (RSV) in pediatric individuals.

Clinical Efficacy

The safety and efficacy of Synagis were assessed in two randomized, double-blind, placebo-controlled trials of prophylaxis against RSV infection in children at high risk of an RSV-related hospitalization. Trial 1 was conducted during a single RSV season and studied a total of 1502 children less than or equal to 24 months of age with BPD or infants with premature birth (less than or equal to 35 weeks gestation) who were less than or equal to 6 months of age at study entry. (IMpact-RSV Study Group, 1998) Trial 2 was conducted over four consecutive seasons among a total of 1287 children less than or equal to 24 months of age with hemodynamically significant congenital heart disease. (Feltes, 2003) In both trials participants received 15 mg per kg Synagis or an equivalent volume of placebo via intramuscular injection monthly for five injections and were followed for 150 days from randomization. In Trial 1, 99% of all subjects completed the study and 93% completed all five injections. (IMpact-RSV Study Group, 1998) In Trial 2, 96% of all subjects completed the study and 92% completed all five injections. (Feltes, 2003)

In Trial 1, the reduction of RSV hospitalization was observed both in children with BPD (34/266 [12.8%] placebo versus 39/496 [7.9%] Synagis) and in premature infants without BPD (19/234 [8.1%] placebo versus 9/506 [1.8%] Synagis). (IMpact-RSV Study Group, 1998) In Trial 2, reductions were observed in acyanotic (36/305 [11.8%] placebo versus 15/300 [5.0%] Synagis) and cyanotic children (27/343 [7.9%] placebo versus 19/339 [5.6%] Synagis). (Feltes, 2003) The clinical studies do not suggest that RSV infection was less severe among children hospitalized with RSV infection who received Synagis for RSV prophylaxis compared to those who received placebo.

Experimental, Investigational, Unproven Uses

There is insufficient evidence in the peer-reviewed published scientific literature to support the safety and efficacy of Synagis used as prophylaxis or treatment of RSV infection in immunocompromised adults.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
90378	Respiratory syncytial virus, monoclonal antibody, recombinant, for intramuscular use, 50 mg, each

***Current Procedural Terminology (CPT®) ©2017 American Medical Association: Chicago, IL.**

References

1. American Academy of Pediatrics Committee on Infectious Diseases and Bronchiolitis Guidelines Committee. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics; originally published online July 28, 2014; DOI: 10.1542/peds.2014-1665. Accessed 6/27/2019.
2. Centers for Disease Control and Prevention (CDC), National Respiratory and Enteric Virus Surveillance System (NREVSS) - RSV regional trends. Available at: http://www.cdc.gov/surveillance/nrevss/rsv/region.html.
3. Feltes TF, Cabalka AK, Meissner HC, et al. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. J Pediatr 2003; 143 (4): 532-40.
4. McEvoy GK, Pharm.D., ed. 2019. AHFS Drug Information® - 59th Ed. Bethesda, MD. American Society of Health-System Pharmacists.
5. The IMpact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. Pediatrics 1998; 102 (3 Pt 1): 531–7.
6. Synagis (palivizumab) injection, for intramuscular use [product information]. Gaithersburg, MD: MedImmune, LLC. May 2017.