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PALIVIZUMAB (Synagis®) Preauthorization Criteria for Approval

Medications and Dosage Forms Included in Criteria

Generic Name	Brand Name	Dosage Form(s)
Palivizumab	Synagis®	Intramuscular Injection

FDA Approved Indications

Palivizumab (Synagis®) is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease. Safety and efficacy were established in infants with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (≤ 35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD).¹

Description

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory infections in children. Those at highest risk of serious RSV illness include those less than 2 years old with prematurity, chronic lung disease (CLD, formerly known as bronchopulmonary dysplasia), congenital heart disease (CHD), certain congenital abnormalities, and certain immunodeficiencies. Infections typically occur in the winter months, starting from October to December and ending from March to May. Annually in the United States, RSV is responsible for 57,000 pediatric hospitalizations and 500 deaths.

Since 1993, immune prophylaxis has been available with the use of intravenous immunoglobulin (IVIg) prepared from donors screened for high titers of RSV neutralizing antibody (RSV-IVIg or RespiGam®). In 1998, the U.S. Food and Drug Administration (FDA) approved palivizumab (Synagis), a humanized RSV monoclonal antibody that can be administered intramuscularly. RespiGam is no longer available. Individuals who meet criteria for palivizumab receive monthly injections during the course of their approval which begins at the start of the RSV season.

Criteria

1. Does the infant or child have an immune deficiency diagnosis?
If yes, approve Synagis for RSV prophylaxis for 5 monthly doses (through March 31).
If no, continue 2.
2. Does the infant or child, aged 24 months old or less on November 1, have a diagnosis of hemodynamically significant congenital heart disease (CHD) and require medical therapy?
If yes, approve Synagis for RSV prophylaxis for 5 monthly doses (through March 31).
If no, continue to 3.
3. Does the infant or child have a diagnosis of chronic lung disease (CLD)?
If yes, continue to 4.
If no, continue to 5.

4. Is the infant or child 24 months old or less on November 1 and has required medical therapy (supplemental oxygen, bronchodilator, diuretic, or chronic corticosteroid therapy) within six months prior to the start of the RSV season?
If yes, approve Synagis for RSV prophylaxis for 5 monthly doses (through March 31).
If no, do not approve.
5. Is the infant or child less than 12 months old on November 1, born at less than 35 weeks gestation, and diagnosed with congenital abnormalities of the airways or neuromuscular disease?
If yes, approve Synagis for RSV prophylaxis for 5 monthly doses (through March 31).
If no, continue to 6.
6. Is the infant or child at increased risk for RSV infection defined by the following age criteria?
 - a. Gestational age is 28 weeks or less and patient age is 12 months or less on November 1.
 - b. Gestational age is less than 32 weeks but greater than or equal to 29 weeks and the patient age is 6 months or less at the start of the RSV season
 - c. Gestational age is less than 35 weeks (34 weeks, 6 days) but greater than or equal to 32 weeks, 0 days and the patient age is 6 months or less at the start of the RSV seasonIf a or b, approve Synagis for RSV prophylaxis for 5 monthly doses through March 31.
If c, continue to 7.
7. Does one or more of the following risk factors apply to the infant or child?
 - a. child care attendance
 - b. sibling(s) younger than 5 years of ageIf yes, approve Synagis for RSV prophylaxis for a maximum of 3 monthly doses up to 3 months of age or through March 31 (whichever comes first).
If no, do not approve.

Rationale

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory infections in infants and children. In children less than 5 years old, RSV is responsible for approximately 57,527 hospitalizations (1 of every 334 hospitalizations in this age group)² and 500 deaths annually.³ Children at increased risk for serious RSV infections and increased morbidity and mortality are those with chronic lung disease (CLD), congenital heart disease (CHD), history of prematurity, and immunocompromised patients.^{1,4} Prophylaxis is important in these individuals during the RSV season.

The IMpact-RSV trial was the first to examine the correlation between use of palivizumab in high risk infants and RSV hospitalization rates.⁵ The study recruited over 1500 children with either bronchopulmonary dysplasia (BPD; now known as CLD) or a history of premature birth. Palivizumab resulted in a fifty-five percent reduction in RSV hospitalization compared to placebo (4.8% vs. 10.6%, $P < 0.001$). Another trial was conducted to evaluate the efficacy of palivizumab in preventing RSV hospitalizations among children with hemodynamically significant CHD.⁶ This study recruited 1287 children and resulted in a forty-five percent reduction in RSV hospitalization compared to placebo (5.3% vs 9.7%, $P = 0.003$).⁶ The hospitalization rates in these clinical trials have been substantiated in an outcomes study that investigated hospitalization rates outside of a clinical trial environment.⁷ Hospitalization rates for infants with CLD and CHD were 5.8% and 4.3%, respectively.⁷ Palivizumab has not been evaluated in randomized clinical trials for use in immunocompromised (e.g., severe combined immunodeficiency or severe acquired immunodeficiency syndrome) patients.⁴ Recommendations can not be made in this patient population, however, these patients may benefit from prophylaxis⁴ and may be approved for palivizumab.

The objective of the preauthorization (PA) criteria for palivizumab is to enable patients prescribed palivizumab who meet specific utilization requirements. These requirements are based on package labeling as approved by the FDA, clinical trials published in peer-reviewed medical literature, and recommendations for appropriate RSV prophylaxis published by the American Academy of Pediatrics (AAP).⁴ The FDA approved the use of palivizumab in 1998 to be administered as prophylaxis against serious lower respiratory tract disease caused by RSV in high risk pediatric patients.¹ In 2009, the AAP

released an updated policy statement providing recommendations for the appropriate use of palivizumab. Those patients at high risk for serious RSV infection are: children less than 24 months old with hemodynamically significant cyanotic or acyanotic congenital heart disease (CHD), children with chronic lung disease (CLD) less than 24 months old who require medical therapy (supplemental oxygen, chronic corticosteroid therapy, bronchodilator, or diuretics) for CLD within 6 months of the start of the RSV season, infants less than 12 months old with congenital abnormalities of the airways or neuromuscular disease that compromises handling of respiratory tract secretions, infants born at 28 weeks gestation or earlier (\leq 28 weeks, 6 days) who are 12 months of age or less at the start of the RSV season, infants born less than 32 weeks (31 weeks, 6 days) gestation but greater than 28 weeks gestation who are less than 6 months old at the beginning of RSV season (*born May 1 or later*), and infants born at 32 to less than 35 weeks gestation (32 weeks, 0 days through 34 weeks, 6 days) with one or more specific risk factors (child care attendance or sibling(s) younger than 5 years of age) who are less than 3 months old at the start of the RSV season (*born August 1 or later*).⁴

The use of palivizumab for RSV prophylaxis in patients with CHD should be decided upon the degree of physiologic cardiovascular compromise.⁴ Children with CHD most likely to benefit from palivizumab are those children less than 24 months of age who have at least one of the following conditions: congestive heart failure that requires medication, moderate to severe pulmonary hypertension, or cyanotic heart disease.⁴ Children who still need prophylaxis and meet these requirements can also receive an additional postoperative dose if undergoing a surgical procedure that requires cardiopulmonary bypass.⁴ Infants not at an increased risk of a serious RSV illness are individuals with hemodynamically insignificant heart disease (e.g., patent ductus arteriosus, mild coarctation of the aorta, secundum atrial septal defect, small ventricular septal defect, pulmonic stenosis, and uncomplicated aortic stenosis), surgically corrected lesions no longer requiring use of medications to control congestive heart failure, and mild cardiomyopathy not requiring medical therapy.⁴

The AAP policy statement has stated that economic analyses on the use of palivizumab for prophylaxis of serious RSV illness is not cost-effective if all "at-risk" patients receive palivizumab.⁴ These analyses and palivizumab clinical trials have not shown that palivizumab decreases the rate of mortality; only a decrease in the rate of hospitalization.^{4,6,8-10} The cost difference, or absence of health care savings, between health care services used in those cohorts receiving or not receiving palivizumab is due to the high cost of treatment.⁹ There is mixed evidence that serious RSV infections in infancy have an effect on children's risk for asthma¹⁰⁻¹³ allergies¹¹⁻¹³, or recurrent wheezing^{14,15} later in life.

The AAP guidelines currently recommend a maximum of up to five monthly doses of palivizumab starting just prior to the RSV season and continuing until the end of the season for those infants with CHD, CLD, congenital abnormalities of the airways, neuromuscular disease, and premature birth before 32 weeks gestation.⁴ This guideline is based upon the outcome of two pivotal trials on the use of palivizumab in high risk children that five monthly injections provided mean serum palivizumab concentrations greater than or equal to 30 micrograms per milliliter.⁵⁻⁶ This serum concentration has been shown to decrease RSV replication and is considered protective.⁵ The five monthly injections schedule should provide greater than 20 weeks of protection which should cover the majority of the RSV season even with variability in the severity, peak, duration, onset, and conclusion of the season.^{4,16} For those infants born 32 weeks to less than 35 weeks gestation with one of two risk factors, the AAP guidelines recommend prophylaxis with 3 monthly injections of palivizumab up to 3 months of age (whichever comes first).⁴ This recommendation is provided by the literature that these infants have the greatest risk for RSV hospitalization in the first 3 months of life.⁴

The recommended dose of palivizumab is 15mg/kg of body weight administered intramuscularly.^{1,4} The first dose should be given prior to the start of the RSV season and the last dose administered at the end of the season.⁴ Based on geographic location, the earliest date for initiation of prophylaxis is November 1.⁴ Based on the AAP recommendations for RSV season onset and maximum monthly dosage limits, the preauthorization criteria will approve palivizumab therapy for the dosage maximums explained previously through March 31st of the current RSV season.

RespiGam® (RSV-IVIG): On October 1, 2003, MedImmune and Massachusetts Public Health & Biologics Laboratory (MPHBL), the manufacturers of RespiGam, announced that production of RespiGam would be discontinued. As of March 15, 2004, all current inventory levels of RespiGam had been depleted and no product is available for sale from MedImmune or MPHBL.

References

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Billing/Coding

CODES	NUMBER	DESCRIPTION
CPT	90378	Respiratory syncytial virus immune globulin (RSV-IgIM), for intramuscular use, 50mg, each
HCPCS	C9003	Palivizumab-RSV-IgM, per 50mg
GPI	19502060002020	Synagis 50mg, 0.5mL
	19502060002020	Synagis 100mg, 1.0mL

Type of Service	Prescription Drug	
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Place of Service	Outpatient	
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Update Information

Date	Action	Reason
07/01/08	Replace PA criteria	New PA criteria
09/24/09	Updated criteria	New AAP guidelines effective for the 2009-2010 RSV season. Criteria updated to reflect new guidelines for infants born 32 to less than 35 weeks gestation along with requirement of only 2 risk factors. Infants with congenital abnormalities of the airways and severe neuromuscular disease are independent risk factors.

Preauthorization Criteria History

05/22/08	Reviewed by QMC
07/01/08	Preauthorization criteria original effective date
05/28/09	Annual review - Reviewed and approved by QMC – No updates
09/24/09	Updated criteria – Reviewed and approved by QMC
Sept. 2010	Next Review