



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

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Subject **Palivizumab (Synagis®)**

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INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), 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 participant'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 participant's benefit plan document **always supercedes** 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 group 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. Proprietary information of CIGNA. Copyright ©2010 CIGNA

Coverage Policy

CIGNA covers palivizumab (Synagis®) as medically necessary for the prevention of lower respiratory tract infection with Respiratory Syncytial Virus (RSV) for **ANY** of the following indications as outlined for the specific duration specified:

1. **Chronic Lung Disease (CLD)** - infant or child ≤ 24 months old at the start of RSV season, with Chronic Lung Disease (i.e., bronchopulmonary dysplasia) requiring medical care (i.e., supplemental oxygen, bronchodilator, diuretic, or corticosteroid therapy) for CLD within 6 months of the anticipated start of RSV season** for up to 5 consecutive monthly doses.
2. **Prematurity**
 - Infant born at ≤ 28 weeks of gestation if < 12 months of age at the start of RSV season** for up to 5 consecutive monthly doses.
 - Infant born at 29–32 weeks of gestation if < 6 months of age at the start of the RSV season** for up to 5 consecutive monthly doses.
 - Infant born at 32–35 weeks of gestation if the infant is born within the 3 months before the onset of RSV season** or during the RSV season for either up to 3 consecutive monthly doses or until age 3 months (whichever comes first) AND with at least ONE of the following risk factors
 - sibling living in the household who is less than 5 years of age
 - child-care attendance

3. **Congenital Heart Disease (CHD)** - infant or child with hemodynamically significant congenital heart disease \leq 24 months of age at the start of RSV season for up to 5 consecutive monthly doses during RSV season** **AND** any of the following:
 - Ongoing treatment of congestive heart failure
 - Moderate-to-severe pulmonary hypertension
 - Cyanotic congenital heart disease (CHD)
4. **Severe immunodeficiency** - infant or child with a severe immunodeficiency (e.g., severe combined immunodeficiency or severe acquired immunodeficiency syndrome) \leq 24 months of age at the start of the RSV season** for up to 5 consecutive monthly doses.
5. **Congenital Abnormalities of the Airway or Neuromuscular disease (e.g. Cerebral Palsy, Muscular Dystrophy, neurological diseases of the brain and spinal cord like Tay Sachs, Spinal Muscular Atrophy)** - infant or child born before 35 weeks gestation with a congenital abnormality of the airway or a neuromuscular disease that compromises the handling of respiratory secretions and \leq 12 months of age at the start of RSV season** for up to 5 consecutive monthly doses.

****For most of the United States, RSV season begins in November and ends in March. In communities where there is elevated RSV viral isolation reported by either the CDC or local public health authorities, RSV season may begin earlier. Communities in the southern United States tend to experience the earliest onset of RSV activity. For southeast Florida (Miami-Dade County), RSV season typically begins July 1st and lasts until January 1st. For north central and southwest Florida, RSV season typically begins September 15th and lasts until March 15th. However, the duration of the Synagis season remains 5 consecutive months for all geographic areas in the United States.**

CIGNA does not cover palivizumab (Synagis[®]) for any the following indications because it is considered experimental, investigational or unproven (this list may not be all-inclusive):

- Prophylaxis of RSV in an infant or child with hemodynamically insignificant heart disease (e.g., atrial septal defect, small ventricular septal defect, pulmonic stenosis, uncomplicated aortic stenosis, mild coarctation of the aorta and patent ductus arteriosus)
- Prophylaxis of RSV in an infant with surgically-corrected congenital heart disease unless there is a continuing need for medical treatment of congestive heart failure
- Prophylaxis of RSV in an infant or child with mild cardiomyopathy not requiring medical treatment
- Prophylaxis for RSV in an immunocompromised individual older than 24 months
- Treatment of RSV disease

When covered and medically necessary, the dosage, frequency, site of administration, and duration of therapy should be reasonable, clinically appropriate, and supported by evidence-based literature.

FDA Approved Indication

Palivizumab 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 (\leq 35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD).

FDA Recommended Dosing

The recommended dose of palivizumab is 15 mg/kg of body Weight, administered by intramuscular injection. Patients, including those who develop an RSV infection, should continue to receive monthly doses throughout the RSV season. The first dose should be administered prior to commencement of 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.

Drug Availability

Synagis is supplied in single-dose vials at the concentration of 100 mg/mL for 1M injection in 1) 50 mg vial containing 50 mg Synagis in 0.5 mL, and 2) 100 mg vial containing 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. In pediatric patients less than 24 months of age, the mean half-life is 20 days.

Guidelines

In 2003, the American Academy of Pediatrics Committee on Infectious Diseases (AAP) stated that palivizumab should be administered approximately once per month (e.g., every 30 days), beginning just before onset of the RSV season, which typically occurs in November. In July 2009, major changes to the recommendations from the 2003 AAP statement were released. Following are the summary of the major changes to the 2003 AAP recommendations:

1. Recommendations for initiation and termination of prophylaxis are modified to reflect current CDC descriptions of RSV seasonality in different geographic locations within the United States.
2. The recommendations remain unchanged for infants with congenital heart disease, chronic lung disease of prematurity and birth before 32 weeks' gestation.
3. Regardless of the month when the first dose is administered, the recommendation for a maximum number of 5 doses for all geographic areas is emphasized for infants with hemodynamically significant congenital heart disease, chronic lung disease of prematurity or birth before 32 weeks' gestation and for a maximum number of 3 doses for infants with a gestational age of 32 to 35 weeks without hemodynamically significant congenital heart disease or chronic lung disease.
4. Risk factors for severe RSV lower respiratory tract disease among infants born between 32 to 35 weeks' gestation have been modified to include only:
 - a. Infant attends child care
 - b. Siblings living in the household are less than 5 years of age
5. Infants 32 to 35 weeks' gestation age who are born within the 3 months before the onset of RSV season and throughout the RSV season will qualify for prophylaxis if they have at least one risk factor. Earlier recommendations required 2 of 5 risk factors.
6. Infants who qualify for prophylaxis in the 32 to 35 weeks' gestation age group should receive prophylaxis only until they reach 90 days of age or a maximum of 3 doses (whichever comes first). This is a change from the previous recommendation for 5 months of prophylaxis.
7. The AAP's definition of gestational age is used throughout the updated statement (For example, 32 to 35 weeks' gestation is defined as 32 weeks, 0 days through 34 weeks, 6 days).

According to AAP regarding the initiation and termination of immunoprophylaxis (Table 1), peak RSV activity normally occurs between November and March in the temperate climates of North America. In the same community, significant variation has been reported in timing of community outbreaks of RSV disease from year to year and between communities in the same year, even in the same region. These variations occur within the overall pattern of RSV outbreaks, usually beginning in November or December, peaking in January or February, and ending by the end of March or sometime in April. However, the communities in the southern United States, particularly some communities in the state of Florida, tend to experience the earliest onset of RSV activity. Data from the Centers for Disease Control and Prevention (CDC) have identified variations in the onset and offset of the RSV season in the state of Florida that should affect the timing of palivizumab administration. Northwest Florida has an onset in mid-November, which is consistent with other areas of the United States. In north central and southwest Florida, the onset of RSV season typically is late September to early October. The RSV season in southeast Florida (Miami-Dade County) typically has its onset in July. Despite varied onsets, the RSV season is of equal duration in the different regions of Florida. RSV regional trends are posted on the CDC National Respiratory and Enteric Virus Surveillance System (NREVSS) website based on the weekly laboratory test result data collected on a voluntary basis in each region.

Tabel 1: Palivizumab Prophylaxis for Infants and Young Children

Geographic Location	Earliest Date for Initiation of Five (5) Monthly Doses
Southeast Florida	July 1
North central and southwest Florida	September 15
Most other areas of United States	November 1

Infants and children who qualify for palivizumab prophylaxis for the entire RSV season (infants and children with chronic lung disease of prematurity or congenital heart disease or preterm infants born before 32 weeks' gestation) should receive palivizumab only during the five months following the onset of RSV season in their region (maximum of 5 doses), which should provide coverage during the peak of the season, when prophylaxis is most effective. In general, the initiation of immunoprophylaxis in November and continuation for a total of 5 monthly doses will provide protection into April and is recommended for most areas of the United States. If prophylaxis is initiated in October, the fifth and final dose should be administered in February. (Table 2)

Table 2: Maximum Number of Monthly Doses of Palivizumab for Respiratory Syncytial Virus Prophylaxis

Infants Eligible for a Maximum of 5 Doses	Infants Eligible for a Maximum of 3 Doses
Infants younger than 24 months of age with chronic lung disease and requiring medical therapy	Preterm infants with gestational age of 32 weeks, 0 days to 34 weeks, 6 days with at least 1 risk factor and born 3 months before or during RSV season
Infants younger than 24 months of age and requiring medical therapy for congenital heart disease	
Preterm infants born at 31 weeks, 6 days of gestation or less	
Certain infants with neuromuscular disease or congenital abnormalities of the airways	

To date limited studies show that some patients with cystic fibrosis may be at increased risk of RSV infection. It is not clear if RSV infection exacerbates the chronic lung disease of cystic fibrosis. In addition, insufficient data exist to determine the effectiveness of palivizumab use in this patient population. Currently routine prophylaxis in patients with cystic fibrosis is not recommended. According to 2009 recommendation, the following groups of infants are not at increased risk of RSV and generally should not receive immunoprophylaxis: Infants and children with hemodynamically insignificant heart disease (eg, secundum atrial septal defect, small ventricular septal defect, pulmonic stenosis, uncomplicated aortic stenosis, mild coarctation of the aorta, and patent ductus arteriosus), infants with lesions adequately corrected by surgery, unless they continue to require medication for congestive heart failure, and infants with mild cardiomyopathy who are not receiving medical therapy for the condition. Additionally, the use of Synagis for prophylaxis for RSV in immunocompromised individual older than 24 months or for treatment of RSV disease is not recommended.

Clinical Efficacy

The safety and efficacy of palivizumab were assessed in two randomized, double-blind, placebo-controlled trials of prophylaxis against RSV infection in pediatric patients at high risk of an RSV-related hospitalization. Trial 1 was conducted during a single RSV season and studied a total of 1502 patients = 24 months of age with bronchopulmonary dysplasia (BPD) or infants with premature birth (approximately 35 weeks gestation) who were approximately six months of age at study entry. Trial 2 was conducted over four consecutive seasons among a total of 1287 patients who were 24 months of age with hemodynamically significant congenital heart disease. In both trials, participants received 15 mg/kg palivizumab or an equivalent volume of placebo IM monthly for five injections and were followed for 150 days from randomization. In Trial 1, the reduction of RSV

hospitalization was observed both in patients with BPD (34/266 [12.8%] placebo vs. 39/496 [7.9%] palivizumab), and in premature infants without BPD (19/234 [8.1%] placebo vs. 9/506 [1.8%] palivizumab). In Trial 2, reductions were observed in acyanotic (36/305 [11.8%] placebo versus 15/300 [5.0%] palivizumab and cyanotic children (27/343 [7.9%] placebo versus 19/339 [5.6%] palivizumab). Overall, palivizumab reduces RSV hospitalizations and total hospitalizations, but has no effect on overall mortality, intensive care unit (ICU) admission, or need for mechanical ventilation.

Meissner et al. (2004) reviewed the evidence supporting the AAP position that five monthly doses of palivizumab will provide effective protection during the RSV season, even with variations in the onset and end of the season. The recommendation for five monthly doses of palivizumab was derived from the IMpact-RSV trial, involving children with hemodynamically significant congenital heart disease. Results showed that five monthly doses of palivizumab resulted in serum concentrations 30 µg/mL for > 20 weeks in almost all subjects. A serum palivizumab concentration 30 µg/mL is the proposed serologic correlate of protection, derived from the cotton rat model, in which this concentration results in a decrease in pulmonary RSV replication by > 100-fold. One month after the fourth monthly dose of palivizumab, the mean serum trough concentration was 72 µg/mL among subjects in the IMpact-RSV trial, indicating that the trough serum level > 30 days after the fifth dose will be > 30 µg/mL for most children. Thus for most infants, five monthly doses of palivizumab will provide substantially > 20 weeks of serum antibody levels, which should be protective and cover most of the RSV season even with variation in season onset and end.

Adverse Reactions

Adverse events with palivizumab therapy are generally mild and similar to placebo. The adverse reactions most commonly observed in palivizumab-treated patients were upper respiratory tract infection, otitis media, fever, rhinitis, rash, diarrhea, cough, vomiting, gastroenteritis, and wheezing. The most serious adverse reactions occurring with palivizumab treatment are anaphylaxis and other acute hypersensitivity reactions. Palivizumab does not interfere with childhood vaccination schedules.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT®* Codes	Description
90378	Respiratory syncytial virus immune globulin (RSV_IGIM) for intramuscular use, 50 mg each.

ICD-9-CM Diagnosis Codes	Description
042	Human immunodeficiency virus (HIV) disease
279.2	Combined Immunity deficiency
330.1	Cerebral lipidosis
358.0-358.9	Myoneural disorders
359.0-359.1	Muscular dystrophy
416.0	Primary pulmonary hypertension
428.0	Congestive heart failure unspecified
746.00- 746.89	Congenital heart disease
748.0-748.9	Congenital anomalies of respiratory system
765.21	Weeks of gestation; less than 24 weeks of gestation
765.22	Weeks of gestation; 24 completed weeks of gestation
765.23	Weeks of gestation; 25-26 completed weeks of gestation
765.24	Weeks of gestation; 27-28 completed weeks of gestation
765.25	Weeks of gestation; 29-30 weeks of gestation

765.26	Weeks of gestation; 31-32 weeks of gestation
765.27	Weeks of gestation; 33-34 weeks of gestation
770.7	Chronic respiratory disease arising in the perinatal period
V04.82	Need for prophylactic vaccination and inoculation, Respiratory syncytial virus (RSV)

Experimental/Investigational/Unproven/Not Covered when used as prophylaxis of RSV for the following conditions:

ICD-9-CM Diagnosis Codes	Description
277.00-277.09	Cystic fibrosis
425.0-425.9	Cardiomyopathies
746.02	Stenosis of pulmonary valve, congenital
747.0	Patent ductus arteriosus
747.10-747.11	Coarctation of aorta
747.3	Congenital anomaly of pulmonary artery

Experimental/Investigational/Unproven/Not Covered when used for the treatment of RSV disease:

ICD-9-CM Diagnosis Codes	Description
079.6	Respiratory syncytial virus (RSV)

***Current Procedural Terminology (CPT®) ©2010 American Medical Association: Chicago, IL.**

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Policy History

<u>Pre-Merger Organizations</u>	<u>Last Review Date</u>	<u>Policy Number</u>	<u>Title</u>
CIGNA HealthCare Great-West Healthcare	10/15/2008	5012	Palivizumab (Synagis®)

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA’s subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.