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Respiratory Syncytial Virus (RSV) Immunoprophylaxis

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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For Illinois only: Illinois Public Act 103-0458 [Insurance Code 215 ILCS 5/356z.61] (HB3809 Impaired Children) states all group or individual fully insured PPO, HMO, POS plans amended, delivered, issued, or renewed on or after January 1, 2025 shall provide coverage for therapy, diagnostic testing, and equipment necessary to increase quality of life for children who have been clinically or genetically diagnosed with any disease, syndrome, or disorder that includes low tone neuromuscular impairment, neurological impairment, or cognitive impairment.

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as

safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

NOTE 1: Authorizations shall be limited to the monthly dose(s) necessary to provide prophylaxis through the respiratory syncytial virus (RSV) season offset.

Preterm infants

Monthly administration of immune prophylaxis for RSV with palivizumab (Synagis) during the RSV season **may be considered medically necessary** for infants born before 29 weeks, 0 days' gestation who are younger than 12 months at the start of the RSV season or born during the RSV season.

Preterm infants who develop chronic lung disease (CLD) of prematurity

Monthly administration of immune prophylaxis for RSV with palivizumab (Synagis) during the RSV season **may be considered medically necessary** for preterm infants who are in the first year of life at the start of the RSV season or born during the RSV season and who have chronic lung disease (CLD) of prematurity. CLD of prematurity is defined as infants with gestational age less than 32 weeks, 0 days and a requirement for greater than 21% oxygen for at least the first 28 days after birth.

Monthly administration of immune prophylaxis for RSV with palivizumab (Synagis) during the RSV season **may be considered medically necessary** during the second year of life (i.e., younger than 24 months at the start of the RSV season) for infants who satisfy the definition of CLD of prematurity and who continue to require medical intervention (chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) during the 6-month period before the start of the second RSV season.

Infants with hemodynamically significant congenital heart disease (CHD)

Monthly administration of immune prophylaxis for RSV with palivizumab (Synagis) during the RSV season **may be considered medically necessary** in the following children with hemodynamically significant CHD who are 12 months or younger at the start of the RSV season or born during the RSV season:

- Infants with acyanotic heart disease who are receiving medication to control congestive heart failure; OR
- Infants with moderate to severe pulmonary hypertension; OR
- Infants with cyanotic heart defects (e.g., transposition of the great arteries, Tetralogy of Fallot, etc…) when recommended by a pediatric cardiologist.

Immune prophylaxis for RSV **is considered not medically necessary** for infants with CHD that does not put them at increased risk of RSV, specifically:

1. Hemodynamically insignificant heart disease (e.g., secundum atrial septal defect, small ventricular septal defect, pulmonic stenosis, uncomplicated aortic stenosis, mild coarctation of the aorta, patent ductus arteriosus), OR
2. Lesions adequately corrected by surgery unless the infant continues to require medication for congestive heart failure, OR
3. Mild cardiomyopathy not requiring medical therapy.

Infants who require cardiac transplantation during the RSV season

Monthly administration of immune prophylaxis for RSV with palivizumab (Synagis) during the RSV season **may be considered medically necessary** in children younger than 24 months who undergo cardiac transplantation during the RSV season.

Infants who require cardiopulmonary bypass or extracorporeal membrane oxygenation

Respiratory syncytial virus (RSV) prophylaxis with palivizumab (Synagis) **may be considered medically necessary** for an additional post-operative/post-procedural dose for the following infants and children younger than 24 months during the RSV season who are:

- Receiving prophylaxis and who continue to require prophylaxis after a surgical procedure that involves cardiopulmonary bypass; OR
- At the conclusion of extracorporeal membrane oxygenation.

Infants with anatomic pulmonary abnormalities or neuromuscular disorders

Monthly administration of immune prophylaxis for RSV with palivizumab (Synagis) during the RSV season **may be considered medically necessary** for infants who are younger than 12 months at the start of the RSV season or born during the RSV season and have a neuromuscular disease or congenital anomaly that impairs their ability to clear secretions from the upper airway because of ineffective cough.

Immunocompromised children

Monthly administration of immune prophylaxis for RSV with palivizumab (Synagis) during the RSV season **may be considered medically necessary** for children who are profoundly immunocompromised (e.g., chemotherapy or transplant) and younger than 24 months of age at the start of the RSV season.

Infants with Cystic Fibrosis (CF)

Monthly administration of immune prophylaxis for RSV with palivizumab (Synagis) during the RSV season **may be considered medically necessary** for infants with CF who are in the first year

of life at the start of the RSV season or born during the RSV season and who have clinical evidence of CLD for which they are receiving treatment, and/or nutritional compromise.

Monthly administration of immune prophylaxis for RSV with palivizumab (Synagis) during the RSV season **may be considered medically necessary** during the second year of life (i.e., younger than 24 months at the start of the RSV season) for infants with CF when such infants have manifestations of severe lung disease (previous hospitalization for pulmonary exacerbation in the first year of life or abnormalities on chest radiography or chest computed tomography that persists when stable) or have "weight for length" less than the 10th percentile.

Use of palivizumab (Synagis) after administration of nirsevimab-alip within the same RSV season **is considered experimental, investigational and/or unproven**.

All other indications for immune prophylaxis for RSV (not otherwise addressed) **are considered experimental, investigational and/or unproven,** including but not limited to:

- Children >24 months at the initial request for immunoprophylaxis,
- Adults with any diagnosis,
- Infants and children with Down syndrome unless qualifying heart disease, CLD, airway clearance issues or prematurity (less than 29 weeks, 0 days' gestation) is present,
- Cystic fibrosis (unless meeting criteria listed above),
- Monthly prophylaxis for any child who experiences a breakthrough RSV hospitalization,
- Healthcare-associated RSV disease.

Policy Guidelines

None.

Description

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infections in children. Several factors that put certain children at a higher risk for contracting RSV have been identified: their age (<2 years old), prematurity, chronic lung disease of prematurity (formerly known as bronchopulmonary dysplasia), congenital heart disease, immuno-deficiencies, and multiple congenital anomalies. Immune prophylaxis against RSV is a preventive strategy to reduce the incidence of infection and its associated morbidity, including hospitalization, in high-risk infants.

Background

Respiratory Syncytial Virus Infections

Respiratory syncytial virus (RSV) infections typically occur in the winter months, starting from late mid-October to mid-January and ending anywhere from March until early May. (1) Considerable variation in the timing of community outbreaks is observed from year to year. Historically, the RSV season was defined by consecutive weeks when RSV antigen-based tests

exceeded 10% positivity; however, laboratories have shifted away from antigen-based testing and, since 2014, the majority of tests are determined by polymerase chain reaction (PCR). Annually in the U.S., RSV infection has been associated with an estimated 57,527 hospitalizations and 2.1 million outpatient visits among children less than 5 years of age. (2) While RSV is a near-ubiquitous infection, infants with underlying medical issues, especially a history of prematurity with associated lung problems, are at risk of developing serious complications from bronchiolitis secondary to RSV.

Palivizumab (Synagis®) is a humanized monoclonal antibody, made using recombinant DNA technology, directed against a site on the antigenic site of the F protein of RSV. (3)

Other RSV preventive agents, including vaccines, have been under development. (4) In 2023, the U.S. Food and Drug Administration approved the first 2 RSV vaccines, Arexvy and Abrysvo. (5, 6) Both vaccines are approved for the prevention of lower respiratory tract disease caused by RSV in individuals 60 years of age and older.

This medical policy does not address therapies to treat RSV infection.

Regulatory Status
In 1998, the biologic drug palivizumab (Synagis; MedImmune) was approved for marketing by the U.S. Food and Drug Administration (FDA) through a biologics license application (103770) for use in the prevention of serious lower respiratory tract disease caused by RSV in pediatric patients at a high risk of RSV disease. In 2004, the FDA approved a liquid formulation of Synagis, supplied as a sterile solution ready for injection, thus providing improved convenience for administration. This formulation is used in the physician office or home setting. There are no therapeutic equivalents to this drug.

Rationale

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is

preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

IMMUNE PROPHYLAXIS FOR RESPIRATORY SYNCYTIAL VIRUS

High-Risk Infants

Clinical Context and Therapy Purpose

The purpose of immune prophylaxis in individuals with high-risk indications for respiratory syncytial virus (RSV) in infancy is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is infants with high-risk indications for RSV. Prematurity is one of the most common risk factors for RSV. Chronic lung disease of prematurity (formerly known as bronchopulmonary dysplasia) is a general term for long-term respiratory problems in premature infants. Chronic lung disease results from lung injury to newborns who consequently must use a mechanical ventilator and supplemental oxygen for breathing. With an injury, lung tissues become inflamed, and scarring can result. Causes of lung injury include the following: prematurity, low amounts of surfactant, oxygen use, and mechanical ventilation. Risk factors for developing chronic lung disease include birth at less than 34 weeks of gestation; birth weight less than 2000 grams (4 pounds, 6.5 ounces); hyaline membrane disease; pulmonary interstitial emphysema; patent ductus arteriosus; Caucasian race; male sex; maternal womb infection (chorioamnionitis); and family history of asthma. Clinically significant congenital heart disease is another risk factor for RSV infection in infancy.

Interventions

The therapy being considered is immune prophylaxis for RSV. Currently, palivizumab (Synagis) is approved by the U.S. Food and Drug Administration (FDA) for this indication. Treatment is administered once monthly during RSV season. Monthly prophylaxis should be discontinued if an RSV infection or hospitalization occurs.

Comparators

The comparator is routine care without immune prophylaxis.

Outcomes

The general outcomes of interest are overall survival (OS), symptoms, morbid events, and hospitalizations. The primary outcome of interest is the RSV hospitalization rate. Other outcomes include RSV infection rates and adverse events. Follow-up spans the RSV season.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Homaira et al. (2014) reported on results of a systematic review that included real-world post-licensure studies of RSV prophylaxis. (7) Reviewers included 20 observational studies that generally supported the benefit of RSV prophylaxis in high-risk infants.

A Cochrane review by Andabaka et al. (2013) (8) evaluated 3 pivotal RCTs (N=2831 patients) (9-11) assessing the efficacy of palivizumab in preventing severe RSV infection in high-risk infants. The review reported a reduction in hospitalization rate from 101 to 50 per 1000 (relative risk [RR], 0.49; 95% confidence interval [CI], 0.37 to 0.64).

Another Cochrane review by Garegnani et al. (2021) (12) assessed the effects of palivizumab for preventing severe RSV infection in children through an analysis of 5 RCTs (N=3343 patients). (9-14) All studies were parallel RCTs, evaluating the effects of palivizumab 15 mg/kg every month up to 5 months compared to placebo or no intervention in an outpatient setting, although a single study also included hospitalized infants. Results revealed that palivizumab reduced hospitalization due to RSV infection at 2 years follow-up (RR, 0.44; 95% CI, 0.30 to 0.64; high certainty evidence); however, palivizumab resulted in little to no effect on mortality at 2 years (RR, 0.69; 95% CI, 0.42 to 1.15; moderate certainty evidence) or adverse events at 150 days follow-up (RR, 1.09; 95% CI, 0.85 to 1.39; moderate certainty evidence). Palivizumab treatment also resulted in a slight reduction in respiratory-related illness hospitalization and a large reduction in RSV infections.

Randomized Controlled Trials

Several RCTs have demonstrated the success of immune prophylaxis of RSV. Among them, Tavsu et al. (2014) reported on a small RCT that evaluated developmental and growth outcomes for infants born at less than 32 weeks of gestation treated with palivizumab prophylaxis. (13) The trial randomized 83 infants with an indication for palivizumab prophylaxis but without chronic lung disease (infants born at 28 weeks of gestation who were <12 months old and those born at 29 to 32 weeks of gestation who were <6 months old at the beginning of RSV season) to palivizumab prophylaxis (n=41) or no therapy (n=42) over 2 RSV seasons. Subjects in the palivizumab group had significantly lower rates of RSV-related lower respiratory tract infection and hospitalizations than the control group during the first year of prophylaxis (infection, 23.1% vs. 53.7%, p=.005; hospitalizations, 0% vs. 24.4%; p=.001, respectively), with similar differences in the second year of prophylaxis. However, anthropometric indices and

results on the Guide for Monitoring Child Development (a developmental assessment tool) at 18 months corrected for age did not differ significantly between groups.

Blanken et al. (2013) reported on the findings of the multicenter, double-blind, randomized, placebo-controlled MAKI trial that allocated 429 otherwise healthy preterm infants born at a gestational age of 33 to 35 weeks to monthly palivizumab (n=214) or placebo (n=215) during RSV season. (14) This trial was not included in the previously described 2013 Cochrane review. The prespecified primary outcome was the total number of parent-reported wheezing days in the first year of life. Premature infants treated with palivizumab had a significant 61% (95% CI, 56% to 65%) relative decrease in the total number of wheezing days during the first year of life. Moreover, the effect of RSV prevention on the number of wheezing days persisted in the post-prophylaxis period (i.e., starting at 2 months after the last injection), for a relative reduction of 73% (95% CI, 66% to 80%). Additionally, palivizumab treatment reduced hospitalizations related to RSV infection (12.6% in the RSV prevention group vs. 21.9% in the placebo group; p=.04).

Feltes et al. (2003) reported on the results of a double-blind RCT that randomized 1287 children with hemodynamically significant congenital heart disease. (9) Those receiving palivizumab had a 45% relative reduction in hospitalizations for RSV. Hospitalizations for RSV occurred in 5.3% (34/639) of the palivizumab group and in 9.7% (63/648) of the no prophylaxis group.

The IMpact-RSV Study (1998) reported on the results of a double-blind RCT that randomized 1502 premature children (≤35 weeks) or children with bronchopulmonary dysplasia during the 1996 to 1997 RSV season to palivizumab or placebo. (10) The primary endpoint was hospitalization with confirmed RSV infection. Palivizumab resulted in a 55% reduction in RSV hospital admission (4.8% [48/1002] in the palivizumab group vs. 10.6% [53/500] in the no prophylaxis group). Similar reductions in other measures of RSV severity in breakthrough infections also were reported.

Nonrandomized Studies

Multiple nonrandomized studies have assessed the efficacy of palivizumab in preventing severe RSV infection in high-risk infants. For example, Farber et al. (2016) published results of a claims analysis that revealed healthy preterm infants (born at 29 to 36 weeks of gestation treated with at least 1 dose of palivizumab during their first RSV season occurring in 2012, 2013, or 2014) had only a minor absolute difference in RSV hospitalization rates (3.1%) compared with infants not treated with palivizumab (5.0%; p=.04). (15) However, the small absolute reduction in the rate of RSV-related hospitalizations favoring palivizumab was offset by increased hospitalizations for bronchiolitis without RSV diagnosis (3.3% vs. 1.9%, p=.05).

Ozyurt et al. (2015) reported on the results of a case-control study, although the methods used were more consistent with a retrospective cohort study, that showed lower respiratory tract infection-related hospitalizations were less frequent in the palivizumab prophylaxis group (RR, 0.75; p<.001) compared with those who did not receive palivizumab prophylaxis. (16) Cohen et al. (2008) reported a cumulative incidence of RSV hospitalization of 1.9% among patients with congenital heart disease who received prophylaxis. (17)

Section Summary: High-Risk Infants

Systematic reviews of RCTs have demonstrated the effectiveness of palivizumab prophylaxis in reducing the risk of RSV-related infection and hospitalizations in infants at high risk for RSV-related infection due to prematurity, chronic lung disease of prematurity, and congenital heart disease.

Cystic Fibrosis

Clinical Context and Therapy Purpose

The purpose of immune prophylaxis in infants with cystic fibrosis (CF) without other risk factors for RSV is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is infants with CF without other risk factors for RSV.

Interventions

The therapy being considered is immune prophylaxis for RSV. Currently, palivizumab (Synagis) is approved by the FDA for this indication. Treatment is administered once monthly for a maximum of 5 doses, during RSV season. In the U.S., RSV season typically has a median onset of mid-October and lasts until potentially early May. Monthly prophylaxis should be discontinued if an RSV infection or hospitalization occurs.

Comparators

The comparator is routine care without immune prophylaxis.

Outcomes

The general outcomes of interest are OS, symptoms, morbid events, and hospitalizations. The primary outcome of interest is the RSV hospitalization rate. Other outcomes include RSV infection rates and adverse events. Follow-up spans the RSV season.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Sánchez-Solis et al. (2015) published a meta-analysis of palivizumab prophylaxis for RSV infection in CF patients. (18) Literature was searched through December 2012 and 4 prospective and retrospective observational studies, a questionnaire, and a randomized trial included in a prior Cochrane review were selected (N=617 patients). Historical controls and nonprophylaxed cohorts from 3 other studies were also included. In separate random-effects meta-analyses, weighted mean hospitalization rates were 0.018 (95% CI, 0.007 to 0.048) for 354 palivizumab-treated patients and 0.126 (95% CI, 0.086 to 0.182) for 463 controls, a statistically significant difference (p<.001). However, in a meta-analysis of the 3 studies that included treated and untreated patients (i.e., contemporaneous controls), the between-group difference was not statistically significant (weighted mean hospitalization rate, 0.024 [95% CI, 0.005 to 0.098] for palivizumab-treated patients vs. 0.093 [95% CI, 0.037 to 0.218] for controls; p=.115).

Robinson et al. (2010) published a Cochrane review (updated in 2013, 2014, and 2016), which assessed the use of palivizumab in children with CF based on a literature search through May 2016. (19-22) Reviewers identified a single RCT that randomized 186 infants (<2 years old) with CF to palivizumab (n=92) or placebo (n=94). One member of each group was hospitalized for RSV within the 6-month follow-up. The incidence of adverse events was relatively high in both groups, with serious adverse events not differing significantly between the palivizumab (20.2%) and placebo (17.3%) groups. Robinson et al. noted that it was not possible to draw conclusions on the safety and tolerability of RSV immune prophylaxis in CF. Although the review reported similar incidences of adverse events, it did not specify how adverse events were classified, and no clinically meaningful outcome differences were noted at 6-month follow-up. Reviewers called for additional randomized studies to establish the safety and efficacy of immune prophylaxis in children with CF.

Registry Studies

Groves et al. (2016) reported on a retrospective review of a CF registry of 92 children treated from 1997 to 2007, comparing outcomes of those treated before and after palivizumab prophylaxis became routine in 2002. (23) In addition to the study's primary objective (RSV-related hospitalization rates in pre- and post-2002 cohorts), the authors reported on lung function, growth parameters, and bacterial colonization in both cohorts at age 6. Forty-five patients were born after 2002, and all received palivizumab in their first year of life before RSV season. The overall rate of RSV-related hospitalizations was 13%. The risk of RSV infection among palivizumab nonrecipients was approximately 5 times that for palivizumab recipients (RR, 4.78; 95% CI, 1.1 to 20.7).

Section Summary: Cystic Fibrosis

Some evidence, summarized in systematic reviews, has demonstrated reductions in hospitalization rates in palivizumab-treated patients with CF when historical controls were involved in the analysis. However, analyses limited to studies that used contemporaneous controls have not demonstrated reductions in hospitalization rates. In the single RCT, event rates were low and did not differ statistically between palivizumab and placebo. Rates of adverse events were high in both groups, making it difficult to draw conclusions about the net benefit of palivizumab. A more recent nonrandomized study using noncontemporaneous

controls found a reduced likelihood of RSV infections in palivizumab-treated compared with palivizumab-untreated patients. Additional studies are needed to establish the benefit of palivizumab in patients with CF.

Infants with Immunodeficiencies

Clinical Context and Therapy Purpose

The purpose of immune prophylaxis in infants with immunodeficiency syndromes without other risk factors for RSV is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is infants with immunodeficiencies without other risk factors for RSV.

Interventions

The therapy being considered is immune prophylaxis for RSV. Currently, palivizumab (Synagis) is approved by the FDA for this indication. Treatment is administered once monthly during RSV season. Monthly prophylaxis should be discontinued if an RSV infection or hospitalization occurs.

Comparators

The comparator is routine care without immune prophylaxis.

Outcomes

The general outcomes of interest are OS, symptoms, morbid events, and hospitalizations. The primary outcome of interest is the RSV hospitalization rate. Other outcomes include RSV infection rates and adverse events. Follow-up spans the RSV season.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

The use of palivizumab in children with primary immunodeficiency syndrome has not been formally evaluated in clinical trials or in nonrandomized comparative studies. Lanari et al. (2014) published a literature review on RSV infection in infants with primary immunodeficiency disorders and speculated that the absence of RCTs assessing palivizumab prophylaxis in

immunocompromised infants was attributable to "the low incidence of these disorders and the ethical controversies surrounding them." (24) In the absence of empirical data to support the use of palivizumab prophylaxis in immunocompromised infants, reviewers cited findings of a consensus panel of pediatric pulmonologists, as reported by Gaboli et al. (2014), who would consider off-label use of palivizumab in primary immunodeficiencies. (25) This recommendation was based on a case report by Manzoni et al. (2007) who discussed 2 infants with primary immunodeficiencies and 2 infants with acquired immunodeficiencies in whom palivizumab was used with good compliance and efficacy. (26)

Section Summary: Infants with Immunodeficiencies

A relatively small body of literature has evaluated the use of palivizumab for RSV immunoprophylaxis in patients with primary or acquired immunodeficiency. Comparative evidence of efficacy is lacking.

Down Syndrome

Clinical Context and Therapy Purpose

The purpose of immune prophylaxis in infants with Down Syndrome without other risk factors for RSV is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant populations of interest is infants with Down syndrome without other risk factors for RSV.

Interventions

The therapy being considered is immune prophylaxis for RSV. Currently, palivizumab (Synagis) is approved by the U.S. Food and Drug Administration (FDA) for this indication. Treatment is administered once monthly during RSV season. Monthly prophylaxis should be discontinued if an RSV infection or hospitalization occurs.

Comparators

The comparator is routine care without immune prophylaxis.

Outcomes

The general outcomes of interest are OS, symptoms, morbid events, and hospitalization. The primary outcome of interest is the RSV hospitalization rate. Other outcomes include RSV infection rates and adverse events. Follow-up spans the RSV season.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.

- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Prospective Cohort Study

Yi et al. (2014) reported on a prospective cohort study that compared RSV infection and related hospitalization in a cohort of children younger than 2 years of age with Down syndrome who received palivizumab during the RSV season between 2005 and 2012 (n=532) with a previously published, similarly untreated Down syndrome birth cohort (n=233). (27) Overall, 31 (9.9%) children were hospitalized for RSV (23 untreated, 8 treated). The adjusted risk of RSV-related hospitalizations was higher in untreated subjects than in palivizumab recipients (incidence rate ratio, 3.63; 95% CI, 1.52 to 8.67). The adjusted risk of hospitalization for all respiratory tract infections (147 events; 73 untreated vs. 74 treated) was similar (incidence rate ratio untreated vs. palivizumab, 1.11; 95% CI, 0.80 to 1.55). Use of a noncontemporaneous control from another country introduced potential bias due to different indications for hospitalization and different environmental factors that could have affected the severity of RSV infection. Therefore, these study design limitations preclude the interpretation of the study results.

Section Summary: Down Syndrome

One prospective cohort study, which used nonconcurrent controls, has reported reductions in RSV-related hospitalization risk in palivizumab-treated patients with Down syndrome. However, study methodology limited the conclusions that could be drawn.

Summary of Evidence

For individuals with high-risk indications for respiratory syncytial virus (RSV) in infancy who receive immune prophylaxis for RSV, the evidence includes several systematic reviews of randomized controlled trials (RCTs). Relevant outcomes are overall survival (OS), symptoms, morbid events, and hospitalizations. Evidence from systematic reviews of RCTs has demonstrated that RSV prophylaxis with palivizumab is associated with reductions in RSV-related hospitalizations and length of intensive care unit stays. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with cystic fibrosis (CF) without other risk factors for RSV in infancy who receive immune prophylaxis for RSV, the evidence includes an RCT, several prospective and retrospective cohort studies, and systematic reviews. Relevant outcomes are OS, symptoms, morbid events, and hospitalizations. Although some studies have demonstrated reductions in hospitalizations in palivizumab-treated patients, studies that used contemporaneous controls did not. In the available RCT, rates of adverse events were high in both the palivizumab and the placebo groups, making it difficult to draw conclusions about the net benefit of palivizumab. A more recent nonrandomized study using noncontemporaneous controls found fewer RSV infections in palivizumab-treated patients with CF. Additional studies are needed. The evidence

is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with immunodeficiencies without other risk factors for RSV in infancy who receive immune prophylaxis for RSV, the evidence includes case series. Relevant outcomes are OS, symptoms, morbid events, and hospitalizations. Descriptive findings from a consensus panel and case reports of 2 infants with primary immunodeficiencies and 2 infants with acquired immunodeficiencies in whom palivizumab was used with good compliance and efficacy have been reported in the literature. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with Down syndrome without other risk factors for RSV in infancy who receive immune prophylaxis for RSV, the evidence includes a prospective cohort study. Relevant outcomes are OS, symptoms, morbid events, and hospitalizations. The available cohort study reported reduced rates of RSV-related hospitalization in treated patients but had methodologic limitations, including the use of a noncontemporaneous comparative cohort from a different country; such limitations introduce uncertainty into any conclusions that can be made. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

American Academy of Pediatrics

In 2014, the American Academy of Pediatrics (AAP) updated its guidelines on the use of palivizumab in high-risk infants. (28) In 2019, the AAP reviewed the guidelines and concluded that its recommendations should remain unchanged (Table 1). (29)

Table 1. Guidelines on Use of Palivizumab Prophylaxis for Infants

Recommendations for Using Palivizumab Prophylaxis
Prophylaxis recommended
• Infants born before 29 weeks, 0 days gestation, during first year of life
• Infants born before 32 weeks, 0 days of gestation with chronic lung disease of prematurity, during first year of life
• Children in the second year of life who require 28 or more days of supplemental oxygen and continue to require medical intervention during respiratory syncytial virus season
Prophylaxis may be considered
• Infants with hemodynamically significant heart failure, during first year of life
• Infants with a pulmonary abnormality or neuromuscular disease that impairs ability to clear secretions from lower airways, during first year of life
• Children younger than 24 months who are profoundly immunocompromised during respiratory syncytial virus season
Prophylaxis not recommended
• Healthy infants born at or after 29 weeks, 0 days of gestation

- There is insufficient evidence for children with cystic fibrosis or Down syndrome without other risk factors

In 2014, the AAP also published guidelines on the diagnosis, management, and prevention of bronchiolitis (updating 2006 guidelines), and made the following recommendations about the use of palivizumab for RSV prevention (Table 2). (30)

Table 2. Guidelines on the Diagnosis, Management, and Prevention of Bronchiolitis

Recommendation	QOE	SOR
"Clinicians should not administer palivizumab to otherwise healthy infants with a gestational age of 29 weeks, 0 days or greater."	B	Strong
"Clinicians should administer palivizumab during the first year of life to infants with hemodynamically significant heart disease or chronic lung disease of prematurity defined as preterm infants <32 weeks 0 days' gestation who require >21% oxygen for at least the first 28 days of life."	B	Moderate
"Clinicians should administer a maximum 5 monthly doses (15 mg/kg/dose) of palivizumab during the respiratory syncytial virus season to infants who qualify for palivizumab in the first year of life."	B	Moderate

QOE: quality of evidence; SOR: strength of recommendation.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in June 2023 did not identify any ongoing or unpublished trials that would likely influence this policy.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	90378
HCPCS Codes	S9562

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
01/01/2025	Document updated with literature review. Minor editorial refinements made to Coverage without change to intent. Added/updated references 3, 5 and 6.
12/01/2023	Reviewed. No changes.
09/15/2023	Document updated. The following change was made to Coverage: Added "Use of palivizumab (Synagis) after administration of nirsevimab-alip within the same RSV season is considered experimental, investigational and/or unproven."
11/15/2022	Document updated with literature review. The following significant changes were made to Coverage: 1) Added "NOTE 1: Authorizations shall be limited to the monthly dose(s) necessary to provide prophylaxis through the respiratory syncytial virus (RSV) season offset."; 2) Modified conditional criteria for infants with hemodynamically significant congenital heart disease; 3) Modified conditional criteria for immunocompromised children; 4) Modified conditional criteria for infants with cystic fibrosis; and 5) Removed "Patients undergoing stem cell transplantation" from experimental, investigational and/or unproven list. Added reference 11.
12/01/2021	Reviewed. No changes.
05/01/2021	Document updated with literature review. The following change was made to Coverage: Added "to a maximum of five monthly doses" to criteria under section on infants with anatomic pulmonary abnormalities or neuromuscular disorders. Added/updated the following references: 1, 2, 10, 13, 20, 22-24, 26, and 27; others removed.
04/01/2019	Reviewed. No changes.
01/15/2018	Document updated with literature review. The following change was made to Coverage: The phrase "as defined in this policy" was replaced with "for which they are receiving treatment" in the following statement: Respiratory syncytial virus (RSV) prophylaxis with palivizumab (Synagis) may be considered medically necessary**,** to a maximum of five monthly doses, for infants with CF who are younger than 12 months at the start of the RSV season and who have clinical evidence of CLD for which they are receiving treatment.
09/01/2017	Reviewed. No changes.
12/01/2016	Document updated with literature review. Coverage unchanged.
10/15/2015	Reviewed. No changes.

12/15/2014	Document updated with literature review. Coverage for indications and risk factors has changed. Respiratory syncytial virus (RSV) prophylaxis with palivizumab (Synagis) may be considered medically necessary when stated criteria are met.
01/01/2013	Document updated with literature review. Coverage unchanged.
08/15/2011	Coverage revised. The following was removed from the coverage criteria addressing infants who have congenital abnormalities of the airway OR a neuromuscular condition that compromises handling of respiratory secretions: “born on or before 34 weeks, 6 days gestation”.
08/15/2010	Policy updated without literature review. The following was changed: criteria for medically necessary for 28 wks 6 days gestation infants who are under 12 months at initiation for therapy.
10/01/2009	Revised, updated policy with literature review. Indications, dose limitations, and risk factors have changed
05/15/2008	CPT/HCPCS code(s) updated
02/15/2008	Coverage Revised
02/01/2008	Revised/Updated Entire Document
10/01/2004	New Medical Document