



POLICY: Synagis® (palivizumab for intramuscular injection)

APPROVAL DATE: 10/16/2019

OVERVIEW

Synagis is a humanized monoclonal antibody indicated for *prevention* of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients with at least one of the following¹:

- bronchopulmonary dysplasia (BPD) that required medical treatment within the previous 6 months and who are ≤ 24 months of age at the beginning of the RSV season;
- history of premature birth (≤ 35 weeks gestational age) and who are ≤ 6 months of age at the beginning of the RSV season;
- hemodynamically significant congenital heart disease (CHD) who are ≤ 24 months of age at the beginning of the RSV season.

The safety and efficacy of Synagis for the treatment of RSV have not been established.¹ The recommended dose is 15 mg/kg intramuscularly once monthly (every 30 days). 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.

Efficacy

Synagis was licensed by the FDA in June 1998, based largely on data from the IMPact-RSV trial conducted during the 1996-1997 RSV season.^{2,3} IMPact-RSV enrolled children with either prematurity (≤ 35 weeks gestation and ≤ 6 months of age at the time of the study) or chronic lung disease (CLD) and ≤ 24 months of age at the time of the study. The RSV hospitalization rate was 4.8% among patients given Synagis prophylaxis, vs. 10.6% in patients given placebo. Synagis also benefits children with CHD as noted in a randomized, double-blind, placebo-controlled study of Synagis (15 mg/kg) once monthly during RSV season in 1,287 children ≤ 2 years of age with serious CHD.^{2,4} In this study, conducted from 1998 to 2002, RSV hospitalization rates were 5.3% with Synagis and 9.7% with placebo.

More recent literature has emerged to guide appropriate Synagis use.² Mortality from RSV-related hospitalizations has been found to be lower than previously reported. Additionally, reports have described Synagis-resistant RSV isolates from hospitalized patients who received prophylaxis. Therefore, not all infants enrolled in the two randomized trials are included in the current guidance.

Infants with CHD in Second Year of Life

A retrospective analysis of children < 3 years of age in the Tennessee Medicaid program revealed that the RSV hospitalization rate for children with CHD in the second year of life (18.2/1,000) was less than half the hospitalization rate for low-risk infants in the first 5 months after birth (44.1/1,000), a group for whom Synagis prophylaxis is not recommended.² Therefore, prophylaxis is not recommended during the second year of life.

Infants Born Prematurely

The New Vaccine Surveillance Network (NVSN) sponsored by the Centers for Disease Prevention and Control (CDC) was a prospective population-based surveillance program for three geographically diverse locations in the US for young children hospitalized with laboratory-confirmed RSV respiratory illness.² Several studies were published summarizing data from the NVSN. Data revealed that for all preterm infants (< 37 weeks' gestation), the RSV hospitalization rate was 4.6/1,000 children, which was not significantly

different from the hospitalization rate for term infants, which was 5.3/1,000 children. Infants born < 29 weeks' gestation had a higher RSV hospitalization rate (19.3/1,000 children).

Infants with Anatomic Pulmonary Abnormalities or Neuromuscular Disorder

The risk for hospitalization is not well defined in children with neuromuscular disorders that impair the ability to clear secretions from the upper airway because of ineffective cough, recurrent gastroesophageal tract reflux, pulmonary malformations, tracheoesophageal fistula, upper airway conditions, or conditions requiring tracheostomy.² Infants with neuromuscular disease or congenital anomaly that impairs the ability to clear airway secretions from the upper airway because of ineffective cough are known to be at risk for a prolonged hospitalization related to lower respiratory tract infection and, therefore, may be considered for prophylaxis during the first year of life.

Immunocompromised Children

Risk factors for a poor outcome after RSV infection in an immunocompromised patient include age < 2 years, presence of lower respiratory tract symptoms at presentation, corticosteroid therapy, and varying degrees of lymphopenia.²

RSV Seasonality

The CDC National Respiratory and Enteric Virus Surveillance System (NREVSS) provides reports determining RSV seasonality nationally and by region.⁵ For the 2014 to 2017 seasons, median RSV onset occurred mid-October and lasted 31 weeks until early May. The median national peak occurred in early February. Many factors might influence national, regional, and county-level RSV activity, including social and demographic factors, population density, pollution, and climate.

Patterns of weekly RSV circulation in Florida are different from regional and national patterns.⁵ Across the 2014 to 2017 seasons, the median onset for Florida was mid-September and the season continued through mid-April. Despite varying onset and offset dates of the RSV season in different regions of Florida, a maximum of five monthly doses will be adequate for qualifying infants for most RSV seasons in Florida.² Even if the first of five monthly doses is administered in July, protective serum concentrations of Synagis will be present for most infants and young children for at least 6 months and likely into February. More than five monthly doses are not recommended, despite the detection of a small number of cases of RSV infection outside this time window. A small number of sporadic RSV hospitalizations occur before or after the main season in many areas of the US, but maximum benefit from prophylaxis is derived during the peak of the season and not when the incidence of RSV hospitalization is low.

Guidelines

The AAP Policy Statement on the Updated Guidance for Synagis Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for RSV Infection was updated on August 1, 2014.² Additionally, the AAP Red Book was updated in 2018.⁶ Below is a summary of their recommendations.

Groups recommended for a maximum of five monthly doses (5 months):

Infants with CLD

- Prophylaxis may be considered during the RSV season during the first year of life for preterm infants who develop CLD of prematurity defined as < 32 weeks' gestation (\leq 31 weeks, 6 days) AND required > 21% oxygen for at least the first 28 days after birth.
- In the second year of life, prophylaxis is recommended only for infants who satisfy the above definition of CLD AND who continue to require medical support (i.e., chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) during the 6-month period before the start of the second RSV season.

Infants with CHD

- Infants \leq 12 months of age with hemodynamically significant CHD may benefit from prophylaxis with Synagis.
- Infants with CHD who are most likely to benefit from Synagis include: 1) infants with acyanotic heart disease who are receiving medication to control CHF and will require cardiac surgical procedures; and 2) infants with moderate to severe pulmonary hypertension. Decisions regarding prophylaxis with Synagis for infants with cyanotic heart disease may be made in consultation with a pediatric cardiologist.
- The following group of infants are not at increased RSV risk and should generally not receive prophylaxis: 1) infants and children with hemodynamically insignificant heart disease (e.g., secundum atrial septal defect, small ventricular septal defect, pulmonic stenosis, uncomplicated aortic stenosis, mild coarctation of the aorta, and patent ductus arteriosus); 2) infants with lesions adequately corrected by surgery, unless they continue to require heart failure medication; 3) infants with mild cardiomyopathy who are not receiving medical therapy for the condition; and 4) children in their second year of life.
- Following cardiopulmonary bypass or at the conclusion of extracorporeal membrane oxygenation, in children who are receiving Synagis prophylaxis, a postoperative dose (15 mg/kg) should be considered for infants and children $<$ 24 months of age.
- Children $<$ 2 years of age who undergo cardiac transplantation during RSV season may be considered for Synagis prophylaxis.

Preterm infants born before 29 weeks' gestation (\leq 28 weeks, 6 days)

- Synagis prophylaxis may be administered to infants born \leq 28 weeks, 6 days' gestation who are $<$ 12 months at the start of the RSV season. For infants born during the RSV season, fewer than 5 monthly doses will be needed.

Infants with anatomic pulmonary abnormalities or a neuromuscular disease

- Infants with a congenital anomaly or neuromuscular disease that impairs the ability to clear secretions from the upper airway because of ineffective cough may be considered for Synagis prophylaxis during the first year of life.

Immunocompromised children

- Prophylaxis may be considered for children $<$ 24 months of age who are profoundly immunocompromised during the RSV season (e.g., receiving chemotherapy, transplantation).

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Synagis. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Because five monthly doses of Synagis at 15 mg/kg per dose will provide more than 6 months of serum Synagis concentrations for most infants, administration of more than five monthly doses is not recommended within the continental US. Children who qualify for five monthly doses of Synagis should receive the first dose at the time of onset of the RSV season. For qualifying infants born during the RSV

season, fewer than five monthly doses will be needed to provide protection until the RSV season ends in their region (maximum of five monthly doses).

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Synagis for is recommended in those who meet the following criteria:

FDA-Approved Indications

1. Respiratory Syncytial Virus (RSV), Prevention in an Infant with Chronic Lung Disease (CLD).

Approve for a maximum of 5 months if the patient meets one of the following conditions (A or B):

A) Infants \leq 1 year of age at the start of the RSV season must meet the following criteria (i and ii):

- i.** The infant was born at $<$ 32 weeks, 0 days gestation; AND
- ii.** The infant required $>$ 21% oxygen for at least 28 days after birth; OR

B) Infants \leq 2 years of age at the start of the RSV season must meet the following criteria (i, ii, and iii):

- i.** The infant was born at $<$ 32 weeks, 0 days gestation; AND
- ii.** The infant required $>$ 21% oxygen for at least 28 days after birth; AND
- iii.** The child has required medical therapy (i.e., supplemental oxygen, diuretic therapy, or chronic corticosteroid therapy) during the 6 months before the start of the second RSV season.²

Dosing. Approve a dose of 15 mg/kg given intramuscularly once monthly during the RSV season.

2. Respiratory Syncytial Virus (RSV), Prevention in an Infant with Congenital Heart Disease (CHD). Approve for a maximum of 5 months if the patient meets ALL the following criteria (A, B, and C):

A) The infant is \leq 1 year of age at the start of the RSV season;¹ AND

B) The infant meets one of the following conditions (i, ii, iii, or iv) according to the prescribing physician:

- i.** The infant is considered to have hemodynamically significant cyanotic CHD; OR
- ii.** The infant has acyanotic heart disease AND is receiving medication to control heart failure AND will require cardiac surgical procedures; OR
- iii.** The infant has moderate to severe pulmonary hypertension; OR
- iv.** The infant has lesions that have been adequately corrected by surgery AND continues to require medication for congestive heart failure; AND

C) Synagis is prescribed by or in consultation with a cardiologist or intensivist.

Dosing. Approve a dose of 15 mg/kg given intramuscularly once monthly during the RSV season.

3. Respiratory Syncytial Virus (RSV), Prevention in an Infant Born Prematurely. Approve for a maximum of 5 months if the patient meets BOTH the following criteria (A and B):

A) The infant is \leq 12 months of age at the start of the RSV season; AND

B) The infant was born before 29 weeks, 0 days gestation (\leq 28 weeks, 6 days gestation).²

Dosing. Approve a dose of 15 mg/kg given intramuscularly once monthly during the RSV season.

Other Uses with Supportive Evidence

- 4. Respiratory Syncytial Virus (RSV), Prevention in an Infant with Congenital Anatomic Pulmonary Abnormalities or a Neuromuscular Disorder.** Approve for a maximum of 5 months if the patient meets BOTH of the following criteria (A and B):
- A) The infant is ≤ 1 year of age at the start of the RSV season; AND
 - B) According to the prescribing physician, the patient's condition compromises handling of respiratory secretions.

Dosing. Approve a dose of 15 mg/kg given intramuscularly once monthly during the RSV season.

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- 5. Respiratory Syncytial Virus (RSV), Prevention in an Immunocompromised Child.** Approve for a maximum of 5 months if the patient meets ALL of the following criteria (A, B, and C):
- A) The child is < 24 months of age at the start of the RSV season; AND
 - B) Synagis is prescribed by or in consultation with an immunologist or an infectious diseases specialist; AND
 - C) According to the prescribing physician, the child is/will be profoundly immunocompromised during the RSV season (e.g., chemotherapy or transplant).

Dosing. Approve a dose of 15 mg/kg given intramuscularly once monthly during the RSV season.

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- 6. Respiratory Syncytial Virus (RSV), Prevention in a Child with Cardiac Transplant.** Approve for a maximum of 5 months if the patient meets ALL of the following criteria (A, B, and C):
- A) The child is < 2 years of age at the start of the RSV season; AND
 - B) The child has undergone or will undergo cardiac transplantation during the current RSV season; AND
 - C) Synagis is prescribed by or in consultation with a cardiologist, intensivist, or transplant physician.

Note: Children with cardiac transplant may also be immunocompromised. In children who do not meet criteria for cardiac transplant below, please see criterion 5 above (Respiratory Syncytial Virus [RSV], Prevention in an Immunocompromised Child).

Dosing. Approve a dose of 15 mg/kg given intramuscularly once monthly during the RSV season.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Synagis has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

- 1. Respiratory Syncytial Virus (RSV), Prevention in a Patient with Cystic Fibrosis (CF) Who Does Not Meet Any of the Approval Criteria.** The AAP guidelines for RSV note that routine use of Synagis prophylaxis in patients with CF, including neonates diagnosed with CF by newborn screening, is not recommended unless other indications are present.⁶ Available studies indicate the incidence of RSV hospitalization in children with CF is uncommon and unlikely to be different from children without CF.² A Cochrane Review identified one trial (presented in poster/abstract form) eligible for their review of Synagis prophylaxis in children with cystic fibrosis.⁷ In this prospective, double-blind, placebo-controlled, multi-center study, 14.1% vs. 14.9% of Synagis and placebo-treated patients, respectively were hospitalized within the first 6 months, and only one patient in each group was

identified with RSV infection. There were no deaths in either group of patients during the first 6 months follow-up; this outcome was not reported at 12 months follow-up.

2. **Respiratory Syncytial Virus (RSV), Prevention in a Patient with Down Syndrome Who Does Not Meet Any of the Approval Criteria.** Data suggest that children with Down syndrome have a slightly higher hospitalization rate for RSV, but the absolute number of hospitalizations is small, and a number of children with Down syndrome are at increased risk because of other qualifying risk factors (e.g., CHD, abnormalities of the respiratory tract, muscle dystonia).²
3. **Respiratory Syncytial Virus (RSV), Prevention in a Patient with Hematopoietic Stem Cell Transplant (Bone Marrow Transplant [BMT], Peripheral Blood, Placental or Cord Blood) Who Does Not Meet Any of the Approval Criteria.** Phase I studies in a total of 21 patients have evaluated Synagis in BMT patients.⁸ Guidelines (2009) address RSV prevention in patients with hematopoietic stem cell transplant.⁹ Although a definitive, uniformly effective preemptive therapy for RSV infection among hematopoietic stem cell transplant recipients has not been identified, certain other strategies have been proposed, including systemic ribavirin, RSV antibodies (i.e., passive immunization with high RSV-titer intravenous immune globulin [IVIG], RSV immunoglobulin) in combination with aerosolized ribavirin, and RSV monoclonal antibody (e.g., Synagis). No randomized trial has been completed to test the efficacy of these strategies; therefore, no specific recommendation regarding any of these strategies can be given at this time.
4. **Respiratory Syncytial Virus (RSV), Treatment of Disease.** There are limited data investigating Synagis for the treatment of established RSV infections. Passive antibody administration is not effective in treatment of RSV disease and is not approved or recommended for this indication.^{2,6} If any infant or young child receiving monthly Synagis prophylaxis experiences a breakthrough RSV hospitalization, monthly prophylaxis should be discontinued because of the extremely low likelihood of a second RSV hospitalization (< 0.5%).⁶
5. **Wheezing, Prevention in Patients Who Do Not Meet Any of the Approval Criteria.** Prophylaxis with Synagis is not recommended for primary asthma prevention or to reduce subsequent episodes of wheezing.⁶
6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Approval Date
Annual revision	No criteria changes.	09/13/2017
Annual revision	All indications: Added that extended approval is not applicable. Reworded indications where applicable to mirror PA policy. Added policy statement explaining RSV seasonality and removed explanations from individual approval duration criteria. Respiratory Syncytial Virus (RSV), Prevention in an Infant Born Prematurely: Split criteria into A and B to mirror PA policy.	09/26/2018
Annual revision	No criteria changes.	10/16/2019