BACKGROUND

Synagis is a humanized monoclonal antibody (IgG1K) that has neutralizing and fusion-inhibitory activity against respiratory syncytial virus (RSV). It is approved by the Food and Drug Administration (FDA) for the prevention of serious lower respiratory tract disease caused by RSV in pediatric patients at high risk of RSV disease.¹ 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). No additional placebo-controlled trials regarding the efficacy of Synagis in any other subgroup have been published.²

The American Academy of Pediatrics (AAP) revised their policy statement and modified their recommendations for use of Synagis for prevention of RSV infections in 2014.² A maximum of 5 monthly doses for all geographic locations is recommended regardless of the month when prophylaxis is started for CHD, chronic lung disease of prematurity (CLD), and premature infants/children born before 29 weeks’ 0 days gestation. In the updated recommendations the only group of children who qualify for Synagis prophylaxis in the second year of life are those born < 32 weeks, 0 days gestation who required at least 28 days of oxygen after birth and who continue to require supplemental oxygen, chronic systemic corticosteroid therapy, or bronchodilator therapy within 6 months of the start of the second RSV season.

The Centers for Disease Control and Prevention (CDC) published a report on RSV activity in the US from July 2011 through January 2013.³ For the 2011/2012 seasons, the onset ranged from early March to early May in all 10 Department of Health and Human Services (DHHS) regions, excluding Florida. Florida is reported separately because it has an earlier season onset and longer duration than the rest of the country. Nationally, RSV onset occurred the week ending November 19, 2011, and lasted 21 weeks until the week ending April 7, 2012 (20 weeks in duration). In Florida, the RSV season onset was August 13, 2011 and the season offset was March 3, 2011 (30 weeks in duration).

Synagis is available as preservative-free liquid in single-dose vials containing 50 mg in 0.5 mL or 100 mg in 1 mL.¹ Synagis is given by intramuscular (IM) injection preferably in the anterolateral aspect of the thigh. The gluteal muscle should not be used routinely as an injection site because of the risk of damage to the sciatic nerve. The dose per month is 15 mg per kg. If the injection volume is over 1 mL, the dose should be divided.

REQUIRED REVIEW AND APPROVALS

Prior authorization by the Community Health Plan of Washington (CHPW) Medical Director or his/her designee is required.

This service also requires a referral to CHPW’s Case Management department for evaluation of care coordination and support potentially required by high risk infants and their families.
All approvals for initial therapy are provided for the initial approval duration noted below.

In Washington State (and the Pacific Northwest not including Alaska), peak RSV activity typically occurs between November and April. The duration of RSV season is 5 months.

**INDICATIONS/Criteria**

Coverage of Synagis for prevention of respiratory syncytial virus (RSV) is recommended in those who meet one of the following criteria:

**Food and Drug Administration (FDA)-Approved Indications**

<table>
<thead>
<tr>
<th>I.</th>
<th>Prevention of RSV Infection in an Infant With Chronic Lung Disease (CLD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria:</td>
<td></td>
</tr>
<tr>
<td><strong>A.</strong></td>
<td>The patient must meet the one of the following conditions (a OR b):</td>
</tr>
<tr>
<td>a.</td>
<td>Infant ≤ 1 year of age at the start of the RSV season.</td>
</tr>
<tr>
<td>i.</td>
<td>The infant was born at &lt; 32 weeks, 0 days gestation; AND</td>
</tr>
<tr>
<td>ii.</td>
<td>The infant required &gt; 21% oxygen for at least 28 days after birth.</td>
</tr>
<tr>
<td>OR</td>
<td>b. Infant ≤ 2 years of age at the start of the RSV season.</td>
</tr>
<tr>
<td>i.</td>
<td>The infant was born at &lt; 32 weeks, 0 days gestation; AND</td>
</tr>
<tr>
<td>ii.</td>
<td>The infant required &gt; 21% oxygen for at least 28 days after birth; AND</td>
</tr>
<tr>
<td>iii.</td>
<td>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</td>
</tr>
</tbody>
</table>

Synagis is indicated for the prevention of RSV infections in high-risk pediatric patients which includes infants with BPD.¹ The AAP guidelines (2014) recommend that prophylaxis be considered during the RSV season during the first year of life for preterm infants who develop CLD of prematurity defined as gestational age < 32 weeks, 0 days and have a requirement for > 21% oxygen for at least the first 28 days after birth.² During the second year of life, consideration of Synagis is recommended only for infants who satisfy the definition of CLD detailed above and continue to require medical support (chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) during the 6-month period before the start of the second RSV season. For infants with CLD who do not continue to require medical support in the second year of life, prophylaxis is not recommended. Most children who are hospitalized with RSV are ≤ 1 year of age and < 20% of all pediatric RSV hospitalizations occur during the second year of life.² Regardless of the presence of absence of comorbidities, RSV hospitalization rates decline during the second RSV season for all children.

**B. Dosing in Infants with CLD.** Dosing must meet the following:  
15 mg per kg once monthly given IM during the RSV season.¹
The FDA-approved dose is 15 mg per kg once monthly during the RSV season.

C. Initial Approval/Extended Approval.

Approve a maximum of 5 months during the RSV season (lasting November through March in most areas). [Example: If the child meets criteria in November, approve for 5 months; if patient meets criteria in December, approve for 4 months etc. The RSV season in some areas of the US commences earlier than November, such as in Florida, where the onset may be as early as July. The RSV season is of the same duration (5 months) for Florida therefore, if a patient is eligible in July, approve 5 months; if a patient is eligible in August, approve 4 months, etc.]

D. Duration of Therapy in Infants with CLD: Up to 5 months.

II. Prevention of RSV Infection in an Infant with Congenital Heart Disease (CHD)

Criteria:

A. The patient must meet the following criteria (a, b, AND c):
   a. The infant is ≤ 1 year of age at the start of the RSV season; 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;
      ii. The infant has acyanotic heart disease AND is receiving medication control heart failure AND will require cardiac surgical procedures;
      iii. The infant has moderate to severe pulmonary hypertension;
      iv. The infant has lesions that have been adequately corrected by surgery AND continues to require medication for congestive heart failure; AND
   v. Synagis is prescribed by or in consultation with a cardiologist or intensivist

Synagis is indicated for the prevention of RSV infections in high-risk pediatric patients which includes children with hemodynamically significant CHD. AAP recommends use of prophylactic Synagis in children ≤ 1 year of age with hemodynamically significant CHD. Children with hemodynamically significant CHD who are most likely to benefit from immunoprophylaxis include infants with cyanotic heart disease who are receiving medication to control congestive heart failure and will require cardiac surgical procedures and infants with moderate to severe pulmonary hypertension. Decision regarding prophylaxis for infants with cyanotic heart defects in the first year of life may be made in consultation with a pediatric cardiologist. The following groups of infants are not at increased risk for RSV infection and generally should not receive immunoprophylaxis: 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 medication for congestive heart failure, 3) Infants with mild cardiomyopathy who are not receiving medical therapy for the condition, and 4) Children in the second year of life. A retrospective analysis of children aged < 3 years 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. Therefore, prophylaxis is not recommended during the second year of life.

B. **Dosing in Infants with CHD:** *Dosing must meet the following:* 15 mg per kg once monthly given IM during the RSV season.¹

The FDA-approved dose is 15 mg per kg once monthly during the RSV season.

C. **Initial Approval/Extended Approval.**

Approve a maximum of 5 months during the RSV season (lasting November through March in most areas).²⁻³ [Example: If the child meets criteria in November, approve for 5 months; if patient meets criteria in December, approve for 4 months etc.] The RSV season in some areas of the US commences earlier than November, such as in Florida, where the onset may be as early as July.

D. **Duration of Therapy in Infants with CHD:** Up to 5 months.

E. **Labs/Diagnostics:** None required.

---

### III. Prevention of RSV in an Infant Born Prematurely

**Criteria**

A. ***The patient must meet the following criterion***

i. The infant is ≤ 12 months of age at the start of the RSV season and was born before 29 weeks, 0 days gestation (≤ 28 weeks, 6 days gestation).²

Synagis is FDA-approved for the prevention of RSV infections in high-risk pediatric patients which includes infants born prematurely.¹ Available data for infants born at 29 weeks, 0 days gestation or later do not identify clear gestational age cutoff for which the benefits of prophylaxis with Synagis are clear.² For this reason, infants born at 29 weeks, 0 days gestation or later are not universally recommended to receive Synagis unless they meet other conditions of coverage (e.g., CHD or CLD). Synagis is not recommended in the second year of life on the basis of prematurity alone. There are some experts who believe on the basis of the data quantifying a small increase in the risk of hospitalization, even for infants born earlier than 29 weeks, 0 days gestation, Synagis prophylaxis is not justified.

B. **Dosing in an Infant Born Prematurely.** *Dosing must meet the following:* 15 mg per kg once monthly given IM during the RSV season.¹

The FDA-approved dose is 15 mg per kg once monthly during the RSV season.

C. **Initial Approval/Extended Approval.**

Prevention of RSV in a child ≤ 12 months of age and born at 28 weeks 6 days gestation or earlier: Approve a maximum of 5 months during the RSV season (lasting November through March in most areas).²⁻³ [Example: If the child meets criteria in November, approve for 5 months; if patient meets criteria in December, approve for 4 months etc.]. The RSV season in some areas of the US commences earlier than...
CLINICAL COVERAGE CRITERIA

November, such as in Florida, where the onset may be as early as July. Note: For children born during the RSV season, fewer than 5 monthly doses will be needed.

D. Duration of Therapy in an Infant Born Prematurely.
Prevention of RSV in a child ≤ 12 months of age and born at 28 weeks 6 days gestation or earlier: up to 5 months.

E. Labs/Diagnostics. None required.

Other Uses with Supportive Evidence:

IV. Prevention of RSV in an Infant with Congenital Anatomic Pulmonary Abnormalities or a Neuromuscular Disorder

Criteria
A. The patient must meet the following criteria (a AND b):
   i. Infant is ≤ 1 year of age at the start of the RSV season;
   ii. According to the prescribing physician, the patient’s condition compromises handling of respiratory secretions.

In the professional opinion of specialized physicians reviewing the data, children ≤ 1 year of age with an underlying condition that predisposes to respiratory complications are considered high-risk in the clinical practice setting and should receive Synagis.

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.

B. Dosing in an Infant with Congenital Anatomic Pulmonary Abnormalities or a Neuromuscular Disorder. Dosing must meet the following: 15 mg per kg once monthly given IM during the RSV season.1

The FDA-approved dose is 15 mg per kg once monthly during the RSV season.

C. Initial Approval/Extended Approval.
Approve a maximum of 5 months during the RSV season (lasting November through March in most areas).23 [Example: If the child meets criteria in November, approve for 5 months; if patient meets criteria in December, approve for 4 months etc.]. The RSV season in some areas of the US commences earlier than November, such as in Florida, where the onset may be as early as July.

D. Duration of Therapy in an Infant with Congenital Anatomic Pulmonary Abnormalities or a Neuromuscular Disorder. Up to 5 months.

UM117CCC_Palivizumab (Synagis®)
E. Labs/Diagnostics. None required.

V. Prevention of RSV in an Immunocompromised Child

Criteria
A. *The patient must meet the following criteria (a, b, AND c):*
   i. The child is < 24 months of age at the start of the RSV season; AND
   ii. Synagis is prescribed by or in consultation with an immunologist or an infectious diseases specialist; AND
   iii. According to the prescribing physician, the child is/will be profoundly immunocompromised during the RSV season (e.g., chemotherapy or transplant).

In the professional opinion of specialist physicians reviewing the data, we have adopted this criterion.

Guidelines note that that there are no population-based data on the incidence of RSV hospitalization in children who undergo solid organ transplantation. Severe and even fatal disease attributed to RSV is recognized in children receiving chemotherapy because of other conditions, but the efficacy of prophylaxis in this cohort is not known. Prophylaxis may be considered for children < 24 months of age who are profoundly immunocompromised during the RSV season.

B. Dosing in an Immunocompromised Child. *Dosing must meet the following:* 15 mg per kg once monthly given IM during the RSV season.

The FDA-approved dose is 15 mg per kg once monthly during the RSV season.

C. Initial Approval/Extended Approval.
Approve a maximum of 5 months during the RSV season (lasting November through March in most areas). [Example: If the child meets criteria in November, approve for 5 months; if patient meets criteria in December, approve for 4 months etc.]. The RSV season in some areas of the US commences earlier than November, such as in Florida, where the onset may be as early as July.

D. Duration of Therapy in Severely Immunocompromised Children: Up to 5 months.

E. Labs/Diagnostics: None required.

VI. Prevention of RSV in a Child with Cardiac Transplant.

Criteria
A. *The patient must meet the following criteria (a, b, AND c):*
   i. The child is < 2 years of age at the start of the RSV season; AND
   ii. The child has undergone or will undergo cardiac transplantation during the current RSV season; AND
   iii. 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 (Prevention of RSV in an Immunocompromised Child).

The AAP guidelines note that in children < 2 years of age who undergo cardiac transplantation during the RSV season may be considered for Synagis prophylaxis.²

B. Dosing in a Child with Cardiac Transplant. **Dosing must meet the following:** 15 mg per kg once monthly given IM during the RSV season.

The FDA-approved dose is 15 mg per kg once monthly during the RSV season.

C. Initial Approval/Extended Approval. Approve a maximum of 5 months during the RSV season (lasting November through March in most areas).² [Example: If the child meets criteria in November, approve for 5 months; if patient meets criteria in December, approve for 4 months etc.]. The RSV season in some areas of the US commences earlier than November, such as in Florida, where the onset may be as early as July.

D. Duration of Therapy in a Child with Cardiac Transplant. Up to 5 months.

E. Labs/Diagnostics. None required.

**Waste Management for All Indications**
The dose is 15 mg per kg with the dose being adjusted each month as the child’s weight changes. The dose should be calculated and the number of vials needed assessed.

**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. **Treatment of RSV Disease.** There are limited data investigating Synagis for the treatment of established RSV infections.¹²⁴ Passive antibody administration is not effective in treatment of RSV disease and is not approved or recommended for this indication.² 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%).

2. **Prevention of RSV 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 Above.** Phase I studies in a total of 21 patients have evaluated Synagis in BMT patients.⁵ Guidelines (2009) cosponsored by the Center for International Blood and Marrow Transplant Research (CIBMTR), National Marrow Donor Program (NMDP), European Blood and Marrow Transplant Group (EBMT), American Society for Blood and Marrow Transplant (ASBMT), Canadian Blood and Marrow Transplant
Group (CBMTG), Infectious Diseases Society of America (IDSA), Society for Healthcare Epidemiology of America (SHEA), Association of Medical Microbiology and Infectious Diseases (AMMI), the CDC, and the Health Resources and Services Administration address RSV prevention in patients with hematopoietic stem cell transplant. These guidelines state preemptive aerosolized ribavirin is recommended by some for patients with RSV upper respiratory infection (URI), especially those with lymphopenia (during the first 3 months after hematopoietic stem cell transplant), and preexisting obstructive lung disease (late after hematopoietic stem cell transplant). The recommendation is based on retrospective studies as well as a prospective trial with inadequate accrual. 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 (mAb [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.

3. Prevention of RSV in a Patient with Cystic Fibrosis (CF) Who Does Not Meet Any of the Approval Criteria Above. The AAP guidelines for RSV (2014) 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. An infant with CF with clinical evidence of CLD and/or nutritional compromise in the first year of life may be considered for infants with 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 persist when stable) or weight for length less than the 10th percentile. A Cochrane Review identified one trial (presented in poster/abstract form) eligible for their review of Synagis prophylaxis in children with cystic fibrosis. 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. The authors calculated a risk ratio (RR) and found no significant difference between the two groups (RR 1.02; 95% confidence interval [CI]: 0.06, 16.09). There were no deaths in either group of participants during the first 6 months of follow-up; this outcome was not reported at 12 months follow-up.

4. Prevention of RSV in a Patient with Down Syndrome Who Does Not Meet Any of the Approval Criteria Above. Limited data suggest a slight increase in RSV hospitalization rates among children with Down syndrome. However, data are insufficient to justify a recommendation for routine use of prophylaxis in children with Down syndrome unless qualifying heart disease, CLD, airway clearance issues, or prematurity is present. Multiple logistic-regression analyses of data from a 4-year population-based prospective study revealed of the evaluated risk factors (male gender, child care attendance, smoke exposure, lack of breastfeeding, and other children in the house), only preterm birth and young chronologic age independently correlated with more severe RSV disease after adjusting for other covariates. In the professional opinion of specialized physicians reviewing the data, we have adopted this criterion.

5. Wheezing, Prevention in Patients Who Do Not Meet Any of the Approval Criteria Above. Prophylaxis with Synagis is not recommended for primary asthma prevention or to reduce subsequent episodes of
wheezing. In the professional opinion of specialized physicians reviewing the data, we have adopted this criterion.

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

SPECIAL CONSIDERATIONS

None.

LIMITATIONS/EXCLUSIONS

Please refer to a product line’s certificate of coverage for benefit limitations and exclusions for these services:

<table>
<thead>
<tr>
<th>PRODUCT LINE</th>
<th>LINK TO CERTIFICATE OF COVERAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>WASHINGTON HEALTH PROGRAM</td>
<td><a href="http://chpw.org/our-plans/apple-health/">http://chpw.org/our-plans/apple-health/</a></td>
</tr>
</tbody>
</table>

CITATIONS & REFERENCES

<table>
<thead>
<tr>
<th>CFR</th>
<th>WAC</th>
<th>RCW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contract Citation</td>
<td>WAH</td>
<td><a href="http://chpw.org/our-plans/apple-health/">http://chpw.org/our-plans/apple-health/</a></td>
</tr>
<tr>
<td></td>
<td>FIMC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HBE</td>
<td></td>
</tr>
</tbody>
</table>

Other Requirements

NCQA Elements

References

2. Infectious Diseases and Bronchiolitis Guidelines Committee. Updated
**Clinical Coverage Criteria**

|---|---|

**Other References Utilized**

**Clinical Coverage Criteria**

**REVISION HISTORY**

<table>
<thead>
<tr>
<th>Revision Date</th>
<th>Revision Description</th>
<th>Revision Made By</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/03/2014</td>
<td>Original</td>
<td>Kate Brostoff</td>
</tr>
<tr>
<td>11/10/2014</td>
<td>Approval</td>
<td>MMLT</td>
</tr>
<tr>
<td>10/29/2015</td>
<td>Updated to reflect American Academy of Pediatrics (AAP) policy revised in 2014.</td>
<td>Kelly Force; Kate Brostoff, MD</td>
</tr>
<tr>
<td>02/01/2016</td>
<td>Renumbered from UM235 to UM117</td>
<td>Compliance</td>
</tr>
<tr>
<td>02/02/2016</td>
<td>Approval</td>
<td>MMLT</td>
</tr>
<tr>
<td>04/10/2017</td>
<td>Updated format and references, reviewed content for accuracy and no updates made</td>
<td>Sophia Yun, PharmD</td>
</tr>
<tr>
<td>04/18/2017</td>
<td>Approval</td>
<td>MMLT</td>
</tr>
</tbody>
</table>