Clinical Policy: Palivizumab (Synagis)

Reference Number: PA.CP.PHAR.16
Effective Date: 01/2018
Last Review Date: 04/2023 Revision Log

Description
Palivizumab (Synagis®) is a recombinant humanized monoclonal antibody with anti-respiratory syncytial virus (RSV).

FDA Approved Indication(s)
Synagis is indicated for the prevention of serious lower respiratory tract disease caused by RSV in pediatric patients:

- With a history of premature birth (less than or equal to 35 weeks gestational age) and who are 6 months of age or younger at the beginning of RSV season;
- With bronchopulmonary dysplasia (BPD) that required medical treatment within the previous 6 months and who are 24 months of age or younger at the beginning of RSV season;
- With hemodynamically significant congenital heart disease and who are 24 months of age or younger at the beginning of RSV season.

Limitation(s) of use: The safety and efficacy of Synagis have not been established for treatment of RSV disease.

Policy/Criteria
It is the policy of PA Health & Wellness that Synagis is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Preterm Infant (must meet all)**:**

1. Diagnosis of preterm infant with gestational age < 29 weeks;
2. Age at onset of RSV season < 12 months;
3. Request is for RSV prophylaxis;
4. Medical justification supports requests for RSV beyond September through May (*see Appendix D*);
5. Member has not been hospitalized with RSV disease during the current RSV season;
6. Dose does not exceed 15 mg/kg once a month by intramuscular (IM) administration (*see Appendix E for dose rounding guidelines*).

Approval duration: up to 5 doses per RSV season * *Overlap of two seasons due to elevated interseasonal RSV activity does not preclude a member from receiving more than 5 consecutive doses, so long as doses are limited to 5 per season*

B. Chronic Lung Disease of Prematurity (must meet all):

1. Diagnosis of chronic lung disease (CLD) of prematurity (i.e., bronchopulmonary dysplasia) defined as both of the following (a or b):
   a. Gestational age < 32 weeks;
   b. Requirement for > 21% oxygen for ≥ 28 days after birth;
2. Age at onset of RSV season (a or b):

a. Age < 12 months;
b. Age ≥ 12 months to < 24 months and continues to require supplemental oxygen, chronic systemic corticosteroid therapy, bronchodilator therapy, or diuretic therapy within 6 months of the start of the RSV season;

3. Request is for RSV prophylaxis;
4. Medical justification supports requests for RSV beyond September through May (*see Appendix D*);
5. Member has not been hospitalized with RSV disease during the current RSV season;
6. Dose does not exceed 15 mg/kg once a month by IM administration (*see Appendix E for dose rounding guidelines*).

Approval duration: up to 5 doses per RSV season* *Overlap of two seasons due to elevated interseasonal RSV activity does not preclude a member from receiving more than 5 consecutive doses, so long as doses are limited to 5 per season*

C. Congenital Heart Disease (must meet all)**:**

1. Age and diagnosis at onset of RSV season (a or b):
   a. Age < 12 months and either (i or ii);
      i. Diagnosis of acyanotic heart disease and either (a or b):
         a) Receiving medication to control congestive heart failure AND will require a cardiac surgical procedure;
         b) Diagnosis of moderate to severe pulmonary hypertension;
      ii. Diagnosis of a cyanotic heart defect and RSV prophylaxis is recommended by a pediatric cardiologist;
   b. Age < 24 months and undergoing cardiac transplantation or cardio-pulmonary bypass during the current RSV season;
2. Request is for RSV prophylaxis;
3. Medical justification supports requests for RSV beyond September through May (see Appendix D);
4. Member has not been hospitalized with RSV disease during the current RSV season;
5. Dose does not exceed 15 mg/kg once a month by IM administration (*see Appendix E for dose rounding guidelines*).

Approval duration: up to 5 doses per RSV season *(6 doses if cardio-pulmonary bypass)** *Overlap of two seasons due to elevated interseasonal RSV activity does not preclude a member from receiving more than 5 consecutive doses, so long as doses are limited to 5 per season*

D. Anatomic Pulmonary Abnormalities, Neuromuscular Disorders, Infants Profoundly Immunocompromised (must meet all)**:**

1. Age and diagnosis at onset of RSV season (a or b):
   a. Age < 12 months and diagnosis of an anatomic pulmonary abnormality or neuromuscular disorder that impairs the ability to clear secretions from the upper airway (e.g., due to ineffective cough);
   b. Age < 24 months and will be profoundly immunocompromised during the RSV season (e.g., due to solid organ or hematopoietic stem cell transplantation, chemotherapy, severe combined immunodeficiency, chronic granulomatous disease);
2. Request is for RSV prophylaxis;

3. Medical justification supports requests for RSV beyond September through May (see Appendix D);
4. Member has not been hospitalized with RSV disease during the current RSV season;
5. Dose does not exceed 15 mg/kg once a month by IM administration (*see Appendix E for dose rounding guidelines*).

Approval duration: up to 5 doses per RSV season * *Overlap of two seasons due to elevated interseasonal RSV activity does not preclude a member from receiving more than 5 consecutive doses, so long as doses are limited to 5 per season*

E. Cystic Fibrosis (off-label) (must meet all)**:**

1. Diagnosis of cystic fibrosis and one of the following (a or b);
   a. Clinical evidence of nutritional compromise;
   b. Diagnosis of CLD of prematurity defined as both of the following (i or ii):
      i. Gestational age < 32 weeks;
      ii. Requirement for > 21% oxygen for ≥ 28 days after birth;
2. Age at onset of RSV season (a or b):
   a. Age < 12 months;
   b. Age < 24 months and (i or ii):
      i. Manifestations of severe lung disease (e.g., previous hospitalization for pulmonary exacerbation in the first year of life or abnormalities on chest radiography or chest computed tomography that persist when stable);
      ii. Weight for length < 10th percentile;
3. Request is for RSV prophylaxis;
4. Medical justification supports requests for RSV beyond September through May (*see Appendix D*);
5. Member has not been hospitalized with RSV disease during the current RSV season;
6. Dose does not exceed 15 mg/kg once a month by IM administration (*see Appendix E for dose rounding guidelines*).

Approval duration: up to 5 doses per RSV season* *Overlap of two seasons due to elevated interseasonal RSV activity does not preclude a member from receiving more than 5 consecutive doses, so long as doses are limited to 5 per season*

F. Alaska Native and Other American Indian Infants (off-label) (must meet all):

1. Medical director consultation is required for requests relating to Alaska native and other American Indian infants that fall outside the criteria outlined above;
2. Alaska native infants: Eligibility for prophylaxis may differ from the remainder of the U.S. on the basis of epidemiology of RSV in Alaska, particularly in remote regions where the burden of RSV disease is significantly greater than in the general U.S. population,
3. Other American Indian infants: Limited information is available concerning the burden of RSV disease among American Indian populations. However, special consideration may be prudent for Navajo and White Mountain Apache infants in the first year of life.
4. Request is for RSV prophylaxis;
5. Medical justification supports requests for RSV beyond September through May (see Appendix D);
6. Member has not been hospitalized with RSV disease during the current RSV season;

7. Dose does not exceed 15 mg/kg once a month by IM administration (*see Appendix E for dose rounding guidelines*).

Approval duration: up to 5 doses per RSV season* *Overlap of two seasons due to elevated interseasonal RSV activity does not preclude a member from receiving more than 5 consecutive doses, so long as doses are limited to 5 per season*

G. Other diagnoses/indications: Refer to PA.CP.PMN.53.

II. Continued Approval

A. All Indications in Section I (must meet all)**:**

1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
2. Request is for RSV prophylaxis;
3. Member will not reach 24 months of age at the start of RSV season;
4. Medical justification supports requests for RSV beyond September through May (*see Appendix D*);
5. Member has not received 5 doses of Synagis in the current RSV season *(6 doses if cardio-pulmonary bypass)*;
6. Member has not been hospitalized with RSV disease during the current RSV season;
7. If request is for a dose increase, new dose does not exceed 15 mg/kg once a month by IM administration (*see Appendix E for dose rounding guidelines*).

Approval duration: up to 5 doses per RSV season *(6 doses if cardio-pulmonary bypass)* ** Overlap of two seasons due to elevated interseasonal RSV activity does not preclude a member from receiving more than 5 consecutive doses, so long as doses are limited to 5 per season*

B. Other diagnoses/indications (1 or 2)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies; or
2. Refer to PA.CP.PMN.53.

III. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

BPD: bronchopulmonary dysplasia
CLD: chronic lung disease of prematurity
FDA: Food and Drug Administration
HHS: Health and Human Services
RSV: respiratory syncytial virus

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

- *Contraindication(s): previous significant hypersensitivity reaction to Synagis*
- *Boxed warning(s): none reported*

Appendix D: RSV Seasonal Durations across the United States - Initiation and Termination of RSV Prophylaxis

- Historical 2014-2017 CDC data from the 10 U.S. Department of Health and Human Services (HHS) regions, with the exception of Florida, shows RSV seasons commencing as early as September in some regions and ending as late as May in others.[2-3]
- Because 5 monthly Synagis doses at 15 mg/kg/dose will provide more than 6 months of serum palivizumab concentrations above the threshold for protection for most infants, administration of more than 5 monthly doses is not recommended within the continental U.S. Children who qualify for Synagis prophylaxis should receive the first dose at the onset of the RSV season. For qualifying infants born during the RSV season, fewer than 5 Synagis doses will be needed to provide protection until the RSV season ends in their region. A small number of sporadic RSV hospitalizations will occur before or after the main season in many areas of the U.S., but the greatest benefit from prophylaxis is derived during peak season and not when the incidence of RSV hospitalization is low.[4-7]
- Data from the Florida Department of Health (http://www.floridahealth.gov/diseases-and-conditions/respiratory-syncytial-virus/) may be used to determine the appropriate timing of Synagis prophylaxis across Florida's regions where RSV seasons may begin at different times throughout the year. However, despite Florida's variable region-specific RSV seasons, a maximum of 5 monthly Synagis doses should be adequate.[4-7]
- The Centers for Disease Control and Prevention (CDC) is issuing this health advisory to notify clinicians and caregivers about increased interseasonal respiratory syncytial virus (RSV) activity across parts of the Southern United States. Compared with previous years, RSV activity remained relatively low from May 2020 to March 2021. However, since late March, CDC has observed an increase in RSV detections reported to the National Respiratory and Enteric Virus Surveillance System (NREVSS). CDC noted increases in laboratory detections and in the percentages of positive detections for both antigen and PCR testing in parts of HHS Region 4 (Alabama, Florida, Georgia, Kentucky, Mississippi, North Carolina, South Carolina, and Tennessee) and Region 6 (Arkansas, Louisiana, New Mexico, Oklahoma, and Texas). Due to limited testing outside of the typical RSV season, data are limited in some jurisdictions and may be incomplete for the most recent weeks. Since this elevated interseasonal activity is a deviation in the typical circulation patterns for RSV, at this time it is not possible to anticipate the likely spread, peak, or duration of activity with any certainty.
- Traditionally, the RSV season was defined by consecutive weeks when RSV antigen-based tests exceeded 10% positivity; however, since 2008, laboratories have shifted away from antigen-based RSV testing, and since 2014 the majority of tests and RSV detections among consistently reporting laboratories are determined by polymerase chain reaction (PCR). The method that consistently captured the highest percentage of PCR detections for retrospectively characterizing RSV seasons was determined to be the retrospective slope 10 (RS10) method. This method uses a centered 5-week moving average of RSV detections normalized to a season peak of 1,000 detections. The season onset was defined as the second of 2 consecutive weeks when the slope, or normalized 5-week moving average of RSV detections between subsequent weeks, exceeded 10. The season offset was the last week when the standardized (normalized) detections exceeded the standardized detections at onset. The peak was the week with the most standardized detections. The season duration was the inclusive weeks between onset and offset. The RS10 method captures a high proportion of RSV PCR detections for retrospectively

determining RSV seasonality, but cannot be used to determine seasonal onset and offset in real time, and can only be employed after the season ends. Alternative statistical methods, including the tenfold baseline or 3% threshold methods might be used to determine seasonality in real time or near real time.

- The American Academy of Pediatrics (AAP) updated guidance for the 2021-2022 RSV season states the following:
    - For the current (2021-2022) fall and winter season, the AAP recommends beginning administration of palivizumab prophylaxis in all regions of the country at the usual time, regardless of whether an area experienced unusual interseasonal RSV activity. Initiating palivizumab prophylaxis to eligible infants similar to a typical winter season is consistent with AAP policy. The 2021-22 winter RSV season is considered a new season, rather than a continuation of the interseason spread in the spring and summer of 2021.
    - These considerations could reasonably lead to providing more than five consecutive doses of palivizumab to eligible children in some regions and less than five doses in other areas in the current fall and winter season. Although there is a paucity of data on the provision of more than 5 consecutive doses, there is no evidence of increased frequency or severity of adverse events with later doses in a 5-dose series nor with doses beyond 5 doses in the few published data.5,6,7,8 Given this information, together with the known efficacy and recent unpredictable epidemiology, the AAP recommends programmatic consideration of providing more than five consecutive doses from the atypical interseason period through the 2021-2022 winter season.
- The updated guidance provided by the AAP for the 2022-2023 RSV seasons states because of the continued variability in RSV circulation, the AAP continues to support the use of palivizumab in eligible patients in any region experiencing rates of RSV activity at any time in 2022 similar to a typical fall-winter season. The AAP continues to recommend programmatic consideration of providing more than 5 consecutive doses of palivizumab depending on the duration of the current RSV surge in a given region of the country.

Appendix E: Dose Rounding Guidelines

Weight-based Dose Range	Vial Quantity Recommendation
≤ 52.49 mg	1 vial of 50 mg/0.5 mL
52.5 mg – 104.99 mg	1 vial of 100 mg/1 mL
105 mg – 157.49 mg	1 vial of 50 mg/0.5 mL and 1 vial of 100 mg/1 mL
157.5 mg – 209.99 mg	2 vials of 100 mg/1 mL
210 mg – 262.49 mg	1 vial of 50 mg/0.5 mL and 2 vials of 100 mg/1 mL
262.5 mg – 314.99 mg	3 vials of 100 mg/1 mL

IV. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
RSV prophylaxis in pediatric patients	15 mg/kg IM once a month	15 mg/kg/month; up to 5 doses per RSV season (1 extra dose if cardio-pulmonary bypass)

V. Product Availability

Single-dose vials: 50 mg/0.5 mL, 100 mg/1 mL

VI. References

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8. Errata: RSV Policy Statement: Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. American Academy of Pediatrics. *Pediatrics.* December 2014; 134(6): 1221.
9. Robbie, G, Zhao, L, Mondick, J, et al. Population Pharmacokinetics of Palivizumab, a Humanized Anti-Respiratory Syncytial Virus Monoclonal Antibody in Adults and Children. Antimicrobial Agents and Chemotherapy. Sept 2012; 56(9): 4927-4936.

10. CDC Health Alert Network: Increased Interseasonal Respiratory Syncytial Virus (RSV) Activity in Parts of the Southern United States. June 10, 2021. Available at: https://emergency.cdc.gov/han/2021/han00443.asp.
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12. Updated guidance: Use of Palivizumab Prophylaxis to Prevent Hospitalization From Severe Respiratory Syncytial Virus Infection During the 2022-2023 RSV Season. American Academy of Pediatrics. Pediatrics. November 17, 2022. Available at: https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/interim-guidance-for-use-of-palivizumab-prophylaxis-to-prevent-hospitalization/. Accessed January 25, 2023.

Reviews, Revisions, and Approvals	Date	Approval Date
2Q 2018 annual review: references reviewed and updated.	02.13.18	04.18
2Q 2019 annual review: RSV seasonal patterns are updated in Appendix D per the CDC and state health departments to indicate a season onset as early as September extending to as late as May.	04.17.19	
2Q 2020 annual review: change made to clarify preterm/gestational age requirement in Section I.A.: diagnosis of preterm birth is updated to indicate diagnosis of preterm infant; defined as gestational age < 29 weeks is updated to indicate with gestational age < 29 weeks; added appendix E: dose rounding guidelines; added reference to appendix E within criteria; references reviewed and updated.	04/2020	
2Q 2021 annual review: Seasonal coverage criteria are added to all indications; related AAP/CDC guidance is added to Appendix D; per prescribing information, added requirement for continued therapy that member will not reach 24 months of age at the start of RSV season; references reviewed and updated.	04/2021	
2Q 2022 annual review: Appendix D updated to include American Academy of Pediatrics (AAP) updated guidance for the 2021-2022 RSV season; references reviewed and updated.	04/2022	
2Q 2023 annual review: for CLD added bronchodilator therapy as an additional option to confirm appropriateness of therapy in the second year of life per AAP guidance; references reviewed and updated.	04/2023	