

[DATE]

[HCP First and last name, Title]

[HCP Practice name]

[HCP Address]

[HCP City, State, ZIP]

Dear [HCP First and last name, Title]:

The attached template is offered as a resource a healthcare provider could use when responding to a request from a patient's health benefits company to provide a letter of medical necessity for administering Synagis[®] (palivizumab). **Attachments to be included with the letter of medical necessity are [original claim form, copy of denial or explanation of benefits, and any other additional supporting documents].** A copy of the full prescribing information for Synagis is attached for your reference. If you need additional references, please contact our medical affairs department at 1-877-MEDI-411 (1-877-633-4411).

Use of the attached letter does not guarantee that the insurance company will provide reimbursement for Synagis, and is not intended to be a substitute for or an influence on the independent medical judgment of the physician.

Important Safety Information

Synagis is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in children at high risk of RSV disease. Safety and efficacy were established in children with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (≤ 35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD). The recommended dose of Synagis is 15 mg/kg of body weight given monthly by intramuscular injection. 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. Children who develop an RSV infection should continue to receive monthly doses throughout the RSV season.

The efficacy of Synagis at doses less than 15 mg/kg, or of dosing less frequently than monthly throughout the RSV season, has not been established.

Synagis is contraindicated in children who have had a previous significant hypersensitivity reaction to Synagis. Cases of anaphylaxis and anaphylactic shock, including fatal cases, have been reported following initial exposure or re-exposure to Synagis. Other acute hypersensitivity reactions, which may be severe, have also been reported on initial exposure or re-exposure to Synagis. The relationship between these reactions and the development of antibodies to Synagis is unknown. If a significant hypersensitivity reaction occurs with Synagis, its use should be permanently discontinued. If a mild hypersensitivity reaction occurs, clinical judgment should be used regarding cautious re-administration of Synagis. As with any intramuscular injection, Synagis should be given with caution to children with thrombocytopenia or any coagulation disorder. Palivizumab may interfere with immunological-based RSV diagnostic tests, such as some antigen detection-based assays.

Adverse reactions occurring greater than or equal to 10% and at least 1% more frequently than placebo are fever and rash. In post-marketing reports, cases of severe thrombocytopenia (platelet count $< 50,000$ /microliter) and injection site reactions have been reported.

Please see accompanying full Prescribing Information for Synagis, including Patient Information.

Sincerely,

The MedImmune Access 360 Team

CONFIDENTIALITY NOTE

The documents accompanying this telecopy transmission contain confidential or privileged information. The information is intended to be for the use of the individual or entity named on this transmission sheet. If you are not the intended recipient, be aware that any disclosure, copying, distribution or use of the contents of this telecopied information is prohibited. If you have received this telecopy in error, please notify us by telephone immediately so that we can arrange for the retrieval of the original document at no cost to your office. Thank you for your assistance.

#14332A-81502

[Date]

[Contact - usually the medical director]

[Title]

[Name of Health Insurance Company]

[Address]

[City, State, ZIP Code]

Insured: [Name]

Policy Number: [Number]

Group Number: [Number]

Dear [Name of Contact]:

I am writing on behalf of my patient, [name of patient], to request that [name of health insurance company] approve coverage for Synagis[®] (palivizumab) to help prevent severe RSV disease. This letter documents the medical necessity for this therapy and provides information about the patient's medical history and treatment.

Patient history and diagnosis

[Name of patient] is a [age], [male/female] with a diagnosis of [diagnosis] as of [date] and has received medical treatment of [list medications/procedures associated with the treatment of hemodynamically significant congenital heart disease (CHD) that the patient has received and the date they were last received].

[Provide a brief description of the patient's medical condition here]

[Include a short summary of the patient's medical history.]

[Explain why the patient is at high risk for being hospitalized for severe RSV Disease.]

[Describe the potential consequences of the child contracting RSV and/or enduring a RSV hospitalization.]

[Attach a supporting letter of medical necessity from the cardiologist, if possible]

Synagis prophylaxis for severe RSV disease

Major risk categories for development of severe RSV disease are most closely related to history of pre-existing chronic lung disease of prematurity (CLDP, also known as bronchopulmonary dysplasia [BPD]) (Boyce 2000, Groothuis 1988), hemodynamically significant congenital heart disease (CHD) (Boyce 2000, MacDonald 1982), and preterm birth (Hall 2009). In the CHD population, the risk for RSV-related hospitalization in the first year of life is second only to infants with BPD with an adjusted incidence rate ratio of 10.7 (95% CI: 8.4-13.6) vs. 2.8 (95% CI: 2.3-3.3), respectively (Boyce 2000). Several reports confirm the high morbidity rate of severe RSV infection in children with CHD (Altman 2000, Moler 1992, Navas 1992, Anderson 1990, MacDonald 1982).

Synagis is approved by the FDA for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease. The safety and efficacy in CHD was established in the Synagis Cardiac Study which was a randomized double-blind placebo controlled study conducted over four consecutive seasons and included 1,287 children less \leq 24 months of age with hemodynamically significant congenital heart disease (Feltz 2003). Participants received 15 mg/kg palivizumab or an equivalent volume of placebo via intramuscular injection monthly for five injections and were followed for 150 days from randomization. Statistically significant reduction in the rate of RSV-related hospitalization were observed in acyanotic, 11.8% (36/305) with placebo versus 5.0% (15/300) with palivizumab, and in cyanotic children, 7.9% (27/343) with placebo versus 5.6% (19/339) with palivizumab. The clinical studies do not suggest that RSV infection was less severe among children hospitalized with RSV infection who received palivizumab for RSV prophylaxis compared to those who received placebo.

The AAP-COVID 2012 Red Book recommendations for prevention of severe RSV disease includes a recommendation for prophylaxis for high-risk children including, "Children who are 24 months of age or younger with hemodynamically significant cyanotic or acyanotic CHD may benefit from palivizumab prophylaxis. Decisions regarding prophylaxis with palivizumab in children with CHD should be made on the basis of the degree of physiologic cardiovascular compromise. Children younger than 24 months of age with CHD who are most likely to benefit from immunoprophylaxis include: infants who are receiving medication to control congestive heart failure; infants with moderate to severe pulmonary hypertension; and infants with cyanotic heart disease."

Based on the above information, therapy with Synagis is medically necessary for this patient. Thank you for your prompt attention to this matter.

If you have any further questions, please feel free to contact me at [physician telephone number, including area code] to discuss. Thank you in advance for your immediate attention to this request and assisting me in providing the required care for this baby in order to keep them as healthy as possible.

Sincerely,

[Physician's Name]

[Physician's Practice Name]

References

- AAP (American Academy of Pediatrics). Respiratory Syncytial Virus. In: Pickering LK, ed. RED BOOK: 2012 (29 Edition). Report of the Committee on Infectious Diseases. Elk Grove Village, IL: American Academy of Pediatrics; pp 609-618.
- Altman CA, et al. Respiratory syncytial virus in patients with congenital heart disease: A contemporary look at epidemiology and success of preoperative screening. *Pediatr Cardiol.* 2000; 21:433-438.
- Anderson LJ, et al. Association between respiratory syncytial virus outbreaks and lower respiratory tract deaths of infants and young children. *J Infect Dis.* 1990;161:640-646.
- Boyce TG, et al. Rates of hospitalization for respiratory syncytial virus infection among children in Medicaid. *J Pediatr.* 2000;137:865-870.
- Feltes TF, et al (Cardiac Synagis Study Group). Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. *J Pediatr.* 2003;143:532-540.
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- Hall CB, et al. The burden of respiratory syncytial virus infection in young children. *N Engl J Med.* 2009;360:588-598.
- MacDonald NE, et al. Respiratory syncytial viral infection in infants with congenital heart disease. *N Engl J Med.* 1982;307:397-400.
- Moler FW, et al. Respiratory syncytial virus morbidity and mortality estimates in congenital heart disease patients: a recent experience. *Crit Care Med.* 1992;20: 1406-1413.
- Navas L, et al. Improved outcome of respiratory syncytial virus infection in a high-risk hospitalized population of Canadian children. Pediatric Investigators Collaborative Network on Infections in Canada. *J Pediatr.* 1992;121:348-354.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SYNAGIS safely and effectively. See full prescribing information for SYNAGIS.

SYNAGIS® (palivizumab) injection for intramuscular use
Initial U.S. Approval: 1998

INDICATIONS AND USAGE

Synagis is a respiratory syncytial virus (RSV) F protein inhibitor monoclonal antibody indicated for the prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease.

- Safety and efficacy were established in children with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (less than or equal to 35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD).
- The safety and efficacy of Synagis have not been established for treatment of RSV disease. (1)

DOSAGE AND ADMINISTRATION

15 mg per kg of body weight, administered intramuscularly prior to commencement of the RSV season and remaining doses administered monthly throughout the RSV season. (2.1)

Children undergoing cardio-pulmonary bypass should receive an additional dose of Synagis as soon as possible after the cardio-pulmonary bypass procedure (even if sooner than a month from the previous dose). Thereafter, doses should be administered monthly as scheduled. (2.1, 12.3)

DOSAGE FORMS AND STRENGTHS

Single-dose liquid solution vials: 50 mg per 0.5 mL and 100 mg per 1 mL. (3)

FULL PRESCRIBING INFORMATION: CONTENTS*

- 1 INDICATIONS AND USAGE
- 2 DOSAGE AND ADMINISTRATION
 - 2.1 Dosing Information
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- 3 DOSAGE FORMS AND STRENGTHS
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- 5 WARNINGS AND PRECAUTIONS
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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Synagis is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in children at high risk of RSV disease.

The following points should be considered when prescribing Synagis:

- Safety and efficacy were established in children with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (less than or equal to 35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD) [see *Clinical Studies* (14)].
- The safety and efficacy of Synagis have not been established for treatment of RSV disease.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of Synagis is 15 mg per kg of body weight given monthly by intramuscular injection. 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. Children who develop an RSV infection should continue to receive monthly doses throughout the RSV season. In the northern hemisphere, the RSV season typically commences in November and lasts through April, but it may begin earlier or persist later in certain communities.

Synagis serum levels are decreased after cardio-pulmonary bypass [see *Clinical Pharmacology* (12.3)]. Children undergoing cardio-pulmonary bypass should receive an additional dose of Synagis as soon as possible after the cardio-pulmonary bypass procedure (even if sooner than a month from the previous dose). Thereafter, doses should be administered monthly as scheduled.

The efficacy of Synagis at doses less than 15 mg per kg, or of dosing less frequently than monthly throughout the RSV season, has not been established.

2.2 Administration Instructions

- **DO NOT DILUTE THE PRODUCT.**
- **DO NOT SHAKE OR VIGOROUSLY AGITATE THE VIAL.**
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials exhibiting particulate matter or discoloration.

CONTRAINDICATIONS

Previous significant hypersensitivity reaction to Synagis. (4)

WARNINGS AND PRECAUTIONS

- Anaphylaxis and anaphylactic shock (including fatal cases), and other severe acute hypersensitivity reactions have been reported. Permanently discontinue Synagis and administer appropriate medications if such reactions occur. (5.1)
- As with any intramuscular injection, Synagis should be given with caution to children with thrombocytopenia or any coagulation disorder. (5.2)
- Palivizumab may interfere with immunological-based RSV diagnostic tests such as some antigen detection-based assays. (5.3, 12.4)

ADVERSE REACTIONS

Adverse reactions occurring greater than or equal to 10% and at least 1% more frequently than placebo are fever and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact MedImmune at 1-877-633-4411 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Safety and effectiveness in children greater than 24 months of age at the start of dosing have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 3/2014

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*Sections or subsections omitted from the full prescribing information are not listed.

- Using aseptic techniques, attach a sterile needle to a sterile syringe. Remove the flip top from the Synagis vial and wipe the rubber stopper with a disinfectant (e.g., 70% isopropyl alcohol). Insert the needle into the vial and withdraw into the syringe an appropriate volume of solution. Administer immediately after drawing the dose into the syringe.
- Synagis should be administered in a dose of 15 mg per kg intramuscularly using aseptic technique, 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 (volume of injection in mL) per month = patient weight (kg) x 15 mg per kg ÷ 100 mg per mL of Synagis. Injection volumes over 1 mL should be given as a divided dose.
- Synagis is supplied as a single-dose vial and does not contain preservatives. Do not re-enter the vial after withdrawal of drug; discard unused portion. Only administer one dose per vial.
- Use sterile disposable syringes and needles. To prevent the transmission of hepatitis viruses or other infectious agents from one person to another, DO NOT reuse syringes and needles.

3 DOSAGE FORMS AND STRENGTHS

Single-dose liquid solution vials: 50 mg per 0.5 mL and 100 mg per 1 mL.

4 CONTRAINDICATIONS

Synagis is contraindicated in children who have had a previous significant hypersensitivity reaction to Synagis [see *Warnings and Precautions* (5.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Cases of anaphylaxis and anaphylactic shock, including fatal cases, have been reported following initial exposure or re-exposure to Synagis. Other acute hypersensitivity reactions, which may be severe, have also been reported on initial exposure or re-exposure to Synagis. Signs and symptoms may include urticaria, pruritus, angioedema, dyspnea, respiratory failure, cyanosis, hypotonia, hypotension, and unresponsiveness. The relationship between these reactions and the development of antibodies to Synagis is unknown. If a significant hypersensitivity reaction occurs with Synagis, its use should be permanently discontinued. **If anaphylaxis or other significant hypersensitivity reaction occurs, administer appropriate medications (e.g., epinephrine) and provide supportive care as required.** If a mild hypersensitivity reaction occurs, clinical judgment should be used regarding cautious readministration of Synagis.

5.2 Coagulation Disorders

Synagis is for intramuscular use only. As with any intramuscular injection, Synagis should be given with caution to children with thrombocytopenia or any coagulation disorder.

5.3 RSV Diagnostic Test Interference

Palivizumab may interfere with immunological-based RSV diagnostic tests such as some antigen detection-based assays. In addition, palivizumab inhibits virus replication in cell culture, and therefore may also interfere with viral culture assays. Palivizumab does not interfere with reverse transcriptase-polymerase chain reaction based assays. Assay interference could lead to false-negative RSV diagnostic test results. Therefore, diagnostic test results, when obtained, should be used in conjunction with clinical findings to guide medical decisions [see *Microbiology* (12.4)].

5.4 Treatment of RSV Disease

The safety and efficacy of Synagis have not been established for treatment of RSV disease.

5.5 Proper Administration

The single-dose vial of Synagis does not contain a preservative. Administration of Synagis should occur immediately after dose withdrawal from the vial. The vial should not be re-entered. Discard any unused portion.

6 ADVERSE REACTIONS

The most serious adverse reactions occurring with Synagis are anaphylaxis and other acute hypersensitivity reactions [see *Warnings and Precautions* (5.1)].

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to Synagis (n=1639) compared with placebo (n=1143) in children 3 days to 24.1 months of age at high risk of RSV-related hospitalization in two clinical trials. Trial 1 was conducted during a single RSV season and studied a total of 1502 children less than or equal to 24 months of age with BPD or infants with premature birth (less than or equal to 35 weeks gestation) who were less than or equal to 6 months of age at study entry. Trial 2 was conducted over four consecutive seasons among a total of 1287 children less than or equal to 24 months of age with hemodynamically significant congenital heart disease.

In Trials 1 and 2 combined, fever and rash were each reported more frequently among Synagis than placebo recipients, 27% versus 25%, and 12% versus 10%, respectively. Adverse reactions observed in the 153-patient crossover study comparing the liquid and lyophilized formulations were comparable for the two formulations, and were similar to those observed with Synagis in Trials 1 and 2.

Immunogenicity

In Trial 1, the incidence of anti-palivizumab antibody following the fourth injection was 1.1% in the placebo group and 0.7% in the Synagis group. In children receiving Synagis for a second season, one of the fifty-six children had transient, low titer reactivity. This reactivity was not associated with adverse events or alteration in serum concentrations. Immunogenicity was not assessed in Trial 2.

A trial of high-risk preterm children less than or equal to 24 months of age was conducted to evaluate the immunogenicity of the lyophilized formulation of Synagis (used in Trials 1 and 2 above) and the liquid formulation of Synagis. Three hundred seventy-nine children contributed to the 4 to 6 months post-final dose analysis. The rate of anti-palivizumab antibodies at this time point was low in both formulation groups (anti-palivizumab antibodies were not detected in any subject in the liquid formulation group and were detected in one subject in the lyophilized group (0.5%), with an overall rate of 0.3% for both treatment groups combined).

These data reflect the percentage of children whose test results were considered positive for antibodies to palivizumab in an enzyme-linked immunosorbent assay (ELISA) and are highly dependent on the sensitivity and specificity of the assay.

The ELISA has substantial limitations in detecting anti-palivizumab antibodies in the presence of palivizumab. Immunogenicity samples tested with the ELISA assay likely contained palivizumab at levels that may interfere with the detection of anti-palivizumab antibodies.

An electrochemical luminescence (ECL) based immunogenicity assay, with a higher tolerance for palivizumab presence compared to the ELISA, was used to evaluate the presence of anti-palivizumab antibodies in subject samples from two additional clinical trials. The rates of anti-palivizumab antibody positive results in these trials were 1.1% and 1.5%.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Synagis. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: severe thrombocytopenia (platelet count less than 50,000 per microliter)

General Disorders and Administration Site Conditions: injection site reactions

Limited information from post-marketing reports suggests that, within a single RSV season, adverse events after a sixth or greater dose of Synagis are similar in character and frequency to those after the initial five doses.

7 DRUG INTERACTIONS

No formal drug-drug interaction studies were conducted. In Trial 1, the proportions of children in the placebo and Synagis groups who received routine childhood vaccines, influenza vaccine, bronchodilators, or corticosteroids were similar and no incremental increase in adverse reactions was observed among children receiving these agents.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Synagis is not indicated for adult usage. It is not known whether Synagis can cause fetal harm or could affect reproductive capacity when administered to a pregnant woman.

Animal Data

Animal reproduction studies have not been conducted.

8.4 Pediatric Use

The safety and effectiveness of Synagis in children greater than 24 months of age at the start of dosing have not been established.

10 OVERDOSAGE

Overdoses with doses up to 85 mg per kg have been reported in clinical studies and post-marketing experience with Synagis, and in some cases, adverse reactions were reported. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

11 DESCRIPTION

Palivizumab is a humanized monoclonal antibody (IgG1 κ) produced by recombinant DNA technology, directed to an epitope in the A antigenic site of the F protein of RSV. Palivizumab is a composite of human (95%) and murine (5%) antibody sequences. The human heavy chain sequence was derived from the constant domains of human IgG1 and the variable framework regions of the V_H genes Cor and Cess. The human light chain sequence was derived from the constant domain of C κ and the variable framework regions of the V_L gene K104 with J κ -4. The murine sequences were derived from a murine monoclonal antibody, Mab 1129, in a process that involved the grafting of the murine complementarity determining regions into the human antibody frameworks. Palivizumab is composed of two heavy chains and two light chains and has a molecular weight of approximately 148,000 Daltons.

Synagis is supplied as a sterile, preservative-free liquid solution at 100 mg per mL to be administered by intramuscular injection. Thimerosal or other mercury-containing salts are not used in the production of Synagis. The solution has a pH of 6.0 and should appear clear or slightly opalescent.

Each 100 mg single-dose vial of Synagis liquid solution contains 100 mg of palivizumab and also contains chloride (0.5 mg), glycine (0.1 mg), and histidine (3.9 mg), in a volume of 1 mL. Each 50 mg single-dose vial of Synagis liquid solution contains 50 mg of palivizumab and also contains chloride (0.2 mg), glycine (0.06 mg), and histidine (1.9 mg), in a volume of 0.5 mL.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Palivizumab is a recombinant humanized monoclonal antibody with anti-RSV activity [see *Microbiology* (12.4)].

12.3 Pharmacokinetics

In children less than or equal to 24 months of age without congenital heart disease (CHD), the mean half-life of palivizumab was 20 days and monthly intramuscular doses of 15 mg per kg achieved mean \pm SD 30 day trough serum drug concentrations of 37 \pm 21 mcg per mL after the first injection, 57 \pm 41 mcg per mL after the second injection, 68 \pm 51 mcg per mL after the third injection, and 72 \pm 50 mcg per mL after the fourth injection. Trough concentrations following the first and fourth Synagis dose were similar in children with CHD and in non-cardiac patients. In children given Synagis for a second season, the mean \pm SD serum concentrations following the first and fourth injections were 61 \pm 17 mcg per mL and 86 \pm 31 mcg per mL, respectively.

In 139 children less than or equal to 24 months of age with hemodynamically significant CHD who received Synagis and underwent cardio-pulmonary bypass for open-heart surgery, the mean \pm SD serum palivizumab concentration was 98 \pm 52 mcg per mL before bypass and declined to 41 \pm 33 mcg per mL after bypass, a reduction of 58% [see *Dosage and Administration* (2.1)]. The clinical significance of this reduction is unknown.

Specific studies were not conducted to evaluate the effects of demographic parameters on palivizumab systemic exposure. However, no effects of gender, age, body weight, or race on palivizumab serum trough concentrations were observed in a clinical study with 639 children with CHD (less than or equal to 24 months of age) receiving five monthly intramuscular injections of 15 mg per kg of Synagis.

The pharmacokinetics and safety of Synagis liquid solution and Synagis lyophilized formulation administered via intramuscular injection at 15 mg per kg were studied in a cross-over trial of 153 infants less than or equal to 6 months of age with a history of prematurity. The results of this trial indicated that the trough serum concentrations of palivizumab were comparable between the liquid solution and the lyophilized formulation, which was the formulation used in the clinical studies. A population pharmacokinetic analysis was performed across 22 studies in 1800 patients (1684 pediatric and 116 adult patients) to characterize palivizumab pharmacokinetics and inter-subject variability in serum concentrations. Palivizumab pharmacokinetics was described by a two-compartment linear model with an elimination half-life of 24.5 days in pediatric patients. Clearance of palivizumab in a typical pediatric patient (body weight 4.5 kg) less than or equal to 24 months of age without CHD was estimated to be 11 mL per day with a bioavailability of 70% following intramuscular administration. The inter-patient variability in drug clearance was 48.7% (CV%). Covariate analysis did not identify any factors that could account for the inter-patient variability in order to predict serum concentrations a priori in an individual patient.

12.4 Microbiology

Mechanism of Action

Palivizumab, a recombinant humanized monoclonal antibody which provides passive immunity against RSV, acts by binding the RSV envelope fusion protein (RSV F) on the surface of the virus and blocking a critical step in the membrane fusion process. Palivizumab also prevents cell-to-cell fusion of RSV-infected cells.

Antiviral Activity

The antiviral activity of palivizumab was assessed in a microneutralization assay in which increasing concentrations of antibody were incubated with RSV prior to addition of the human epithelial cells HEP-2. After incubation for 4-5 days, RSV antigen was measured in an ELISA assay. The neutralization titer (50% effective concentration [EC₅₀]) is expressed as the antibody concentration required to reduce detection of RSV antigen by 50% compared with untreated virus-infected cells. Palivizumab exhibited median EC₅₀ values of 0.65 mcg per mL (mean 0.75 ± 0.53 mcg per mL; n=69, range 0.07-2.89 mcg per mL) and 0.28 mcg per mL (mean 0.35 ± 0.23 mcg per mL; n=35, range 0.03-0.88 mcg per mL) against clinical RSV A and RSV B isolates, respectively. The majority of clinical RSV isolates tested (n=96) were collected from subjects across the United States (CA, CO, CT, IL, MA, NC, NY, PA, RI, TN, TX, VA), with the remainder from Japan (n=1), Australia (n=5) and Israel (n=2). These isolates encoded the most common RSV F sequence polymorphisms found among clinical isolates worldwide.

Palivizumab serum concentrations of greater than or equal to 40 mcg per mL have been shown to reduce pulmonary RSV replication in the cotton rat model of RSV infection by 100-fold.

Resistance

Palivizumab binds a highly conserved region on the extracellular domain of mature RSV F, referred to as antigenic site II or site A, which encompasses amino acids 262 to 275. All RSV mutants that exhibit resistance to palivizumab have been shown to contain amino acid changes in this region on the F protein.

F protein sequence variations within antigenic site A: Amino acid substitutions in antigenic site A selected either in cell culture, in animal models, or in human subjects that resulted in palivizumab resistance were N262D, N268I, K272E/M/N/Q/T, and S275F/L. RSV variants expressing the K272N substitution in F protein showed a 5164 ± 1731-fold decrease in susceptibility (i.e., fold increase in EC₅₀ value) when compared to the wild-type RSV, while variants containing the N262D, S275F/L, or K272E/M/N/Q/T substitutions showed a greater than 25,000-fold decrease in susceptibility to palivizumab. The N268I substitution conferred partial resistance to palivizumab; however, fold changes in susceptibility were not quantified for this mutant. Studies carried out to investigate the mechanism of virus escape from palivizumab showed a correlation between antibody binding and virus neutralization. RSV with substitutions in antigenic site A that were resistant to neutralization by palivizumab did not bind to palivizumab.

At least one of the palivizumab resistance-associated substitutions, N262D, K272E/Q, or S275F/L was identified in 8 of 126 clinical RSV (59 RSV A and 67 RSV B) isolates from subjects who failed immunoprophylaxis, resulting in a combined resistance-associated mutation frequency of 6.3%. A review of clinical findings revealed no association between antigenic A site sequence changes and RSV disease severity among children receiving palivizumab immunoprophylaxis who develop RSV lower respiratory tract disease.

Analysis of 254 clinical RSV isolates (145 RSV A and 109 RSV B) collected from immunoprophylaxis-naïve subjects revealed palivizumab resistance-associated substitutions in 2 (1 with N262D and 1 with S275F), resulting in a resistance-associated mutation frequency of 0.79%.

F protein sequence variations outside antigenic site A: In addition to the sequence variations in antigenic site A known to confer palivizumab resistance, F protein substitutions T100A, G139S, N165D/V406I; T326A, V450A in RSV A, and T74I, A147V, I206L, S285G, V450I, T455I in RSV B were identified in viruses isolated from failures of immunoprophylaxis. These substitutions were not identified in RSV F sequences derived from 254 clinical isolates from immunoprophylaxis-naïve subjects and thus are considered treatment-associated and non-polymorphic. Recombinant RSV B encoding the S285G substitution exhibited palivizumab sensitivity (EC₅₀ value = 0.39 ± 0.02 mcg per mL) similar to recombinant wild-type RSV B (EC₅₀ value = 0.17 ± 0.02 mcg per mL).

Palivizumab susceptibility of RSV encoding common F protein sequence polymorphisms located proximal to antigenic site A was evaluated. Recombinant RSV A encoding N276S (EC₅₀ value = 0.72 ± 0.07 mcg per mL), and recombinant RSV B with S276N (EC₅₀ value = 0.42 ± 0.04 mcg per mL), exhibited sensitivities comparable to the corresponding recombinant wild-type RSV A (EC₅₀ value = 0.63 ± 0.22 mcg per mL) and RSV B (EC₅₀ value = 0.23 ± 0.07 mcg per mL). Likewise, RSV B clinical isolates containing the polymorphic variation V278A were at least as sensitive to neutralization by palivizumab (EC₅₀ range 0.08-0.45 mcg per mL) as laboratory strains of wild-type RSV B (EC₅₀ value = 0.54 ± 0.08 mcg per mL). No known polymorphic or non-polymorphic sequence variations outside the antigenic site A on RSV F have been demonstrated to render RSV resistant to neutralization by palivizumab.

Interference of RSV Diagnostic Assays by Palivizumab

Interference with immunologically-based RSV diagnostic assays by palivizumab has been observed in laboratory studies. Rapid chromatographic/enzyme immunoassays (CIA/EIA), immunofluorescence assays (IFA), and direct immunofluorescence assays (DFA) using monoclonal antibodies targeting RSV F protein may be inhibited. Therefore, caution should be used in interpreting negative immunological assay results when clinical observations are consistent with RSV infection. A reverse transcriptase-polymerase chain reaction (RT-PCR) assay, which is not inhibited by palivizumab, may prove useful for laboratory confirmation of RSV infection [see *Warnings and Precautions* (5.3)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis, mutagenesis, and reproductive toxicity studies have not been performed.

14 CLINICAL STUDIES

The safety and efficacy of Synagis were assessed in two randomized, double-blind, placebo-controlled trials of prophylaxis against RSV infection in children at high risk of an RSV-related hospitalization. Trial 1 was conducted during a single RSV season and studied a total of 1502 children less than or equal to 24 months of age with BPD or infants with premature birth (less than or equal to 35 weeks gestation) who were less than or equal to 6 months of age at study entry. Trial 2 was conducted over four consecutive seasons among a total of 1287 children less than or equal to 24 months of age with hemodynamically significant congenital heart disease. In both trials participants received 15 mg per kg Synagis or an equivalent volume of placebo via intramuscular injection monthly for five injections and were followed for 150 days from randomization. In Trial 1, 99% of all subjects completed the study and 93% completed all five injections. In Trial 2, 96% of all subjects completed the study and 92% completed all five injections. The incidence of RSV hospitalization is shown in Table 1. The results were shown to be statistically significant using Fisher's exact test.

Table 1: Incidence of RSV Hospitalization by Treatment Group

Trial		Placebo	Synagis	Difference Between Groups	Relative Reduction
Trial 1 Impact-RSV	N	500	1002		
	Hospitalization	53 (10.6%)	48 (4.8%)	5.8%	55%
Trial 2 CHD	N	648	639		
	Hospitalization	63 (9.7%)	34 (5.3%)	4.4%	45%

In Trial 1, the reduction of RSV hospitalization was observed both in children with BPD (34/266 [12.8%] placebo versus 39/496 [7.9%] Synagis) and in premature infants without BPD (19/234 [8.1%] placebo versus 9/506 [1.8%] Synagis). In Trial 2, reductions were observed in acyanotic (36/305 [11.8%] placebo versus 15/300 [5.0%] Synagis) and cyanotic children (27/343 [7.9%] placebo versus 19/339 [5.6%] Synagis).

The clinical studies do not suggest that RSV infection was less severe among children hospitalized with RSV infection who received Synagis for RSV prophylaxis compared to those who received placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

Synagis is supplied in single-dose vials as a preservative-free, sterile liquid solution at 100 mg per mL for intramuscular injection.

50 mg vial NDC 60574-4114-1

The 50 mg vial contains 50 mg Synagis in 0.5 mL.

100 mg vial NDC 60574-4113-1

The 100 mg vial contains 100 mg Synagis in 1 mL.

The rubber stopper used for sealing vials of Synagis is not made with natural rubber latex.

Storage

Upon receipt and until use, Synagis should be stored between 2°C and 8°C (36°F and 46°F) in its original container. DO NOT freeze. DO NOT use beyond the expiration date.

17 PATIENT COUNSELING INFORMATION

o **“Advise the patient to read the FDA-approved patient labeling (Patient Information)”**

The healthcare provider should discuss the potential benefits and risks of Synagis with the parents or guardians of Synagis recipients. Parents or guardians should be informed of the possible side effects of Synagis and of the signs and symptoms of potential allergic reactions and should be advised of the appropriate actions. Parents or guardians should understand the dosing schedule and the importance of compliance with the full course of therapy.

Synagis® is a registered trademark of MedImmune, LLC.



Manufactured by:

MedImmune, LLC
Gaithersburg, MD 20878
U.S. License No. 1799
1-877-633-4411

RAL-SYNNV17
Component No.: 26920A

PATIENT INFORMATION
SYNAGIS® (Sĭ-nă-jĭs)
(palivizumab)
Injection

Read this Patient Information before your child starts receiving SYNAGIS and before each injection. The information may have changed. This leaflet does not take the place of talking with your child's healthcare provider about your child's condition or treatment.

What is SYNAGIS?

SYNAGIS is a prescription medication that is used to help prevent a serious lung disease caused by Respiratory Syncytial Virus (RSV). Your child is prescribed SYNAGIS because he or she is at high risk for severe lung disease from RSV.

SYNAGIS contains man-made, disease-fighting proteins called antibodies. These antibodies help prevent RSV disease. Children at high risk for severe RSV disease often do not have enough of their own antibodies. SYNAGIS is used in certain groups of children to help prevent severe RSV disease by increasing protective RSV antibodies.

SYNAGIS is not used to treat the symptoms of RSV disease once a child already has it. It is only used to prevent RSV disease.

SYNAGIS is not for adults or for children older than 24 months of age at the start of dosing.

Who should not receive SYNAGIS?

Your child should not receive SYNAGIS if they have ever had a severe allergic reaction to it. Signs and symptoms of a severe allergic reaction could include:

- severe rash, hives, or itching skin
- swelling of the lips, tongue, or face
- closing of the throat, difficulty swallowing
- difficult, rapid, or irregular breathing
- bluish color of skin, lips, or under fingernails
- muscle weakness or floppiness
- a drop in blood pressure
- unresponsiveness

What should I tell my child's healthcare provider before my child receives SYNAGIS?

Tell your child's healthcare provider about:

- **any reactions** you believe your child has ever had to SYNAGIS.
- **any bleeding or bruising problems.** SYNAGIS is given by injection. If your child has a problem with bleeding or bruises easily, an injection could cause a problem.
- **any other medical problems.**

Tell your child's healthcare provider about all the medicines your child takes, including prescription and non-prescription medicines, vitamins, and herbal supplements. Especially tell your child's healthcare provider if your child takes a blood thinner medicine.

How is SYNAGIS given?

- SYNAGIS is given as a monthly injection, usually in the thigh (leg) muscle, by your child's healthcare provider. Your child's healthcare provider will prescribe the amount of SYNAGIS that is right for your child (based on their weight).
- Your child's healthcare provider will give you detailed instructions on when SYNAGIS will be given.
 - "RSV season" is a term used to describe the time of year when RSV infections most commonly occur (usually fall through spring in most parts of the country). During this time, when RSV is most active, your child will need to receive SYNAGIS shots. Your child's healthcare provider can tell you when the RSV season starts in your area.
 - Your child should receive their **first SYNAGIS shot before the RSV season starts** to help protect them before RSV becomes active. If the season has already started, your child should receive their first SYNAGIS shot as soon as possible to help protect them when exposure to the virus is more likely.

- **SYNAGIS is needed every 28-30 days during the RSV season.** Each dose of SYNAGIS helps protect your child from severe RSV disease for about a month. **Keep all appointments with your child's healthcare provider.**

- **If your child misses an injection, talk to your healthcare provider and schedule another injection as soon as possible.**
- Your child may still get severe RSV disease after receiving SYNAGIS; talk to your child's healthcare provider about what symptoms to look for. If your child has an RSV infection, they should continue to get their scheduled SYNAGIS injections to help prevent severe disease from new RSV infections.
- If your child has certain types of heart disease and has corrective surgery, your healthcare provider may need to give your child an additional SYNAGIS injection soon after surgery.

What are the possible side effects of SYNAGIS?

Synagis may cause serious side effects including:

- Severe allergic reactions (may occur after any dose of SYNAGIS). Such reactions may be life-threatening or cause death.
 - See "Who should not take SYNAGIS?" for a list of signs and symptoms.
- Unusual bruising or groups of tiny red spots on the skin.

Call your child's healthcare provider or get medical help right away if your child has any of the serious side effects listed above after any dose of SYNAGIS.

Common side effects of SYNAGIS include:

- fever
- rash

Other possible side effects include skin reactions around the area where the shot was given (like redness, swelling, warmth, or discomfort).

These are not all the possible side effects of SYNAGIS. Tell your child's healthcare provider about any side effect that bothers your child or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to MedImmune at 1-877-633-4411.

General Information about SYNAGIS

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets.

This leaflet summarizes important information about SYNAGIS. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about SYNAGIS that is written for health professionals.

For more information, go to www.synagis.com or call 1-877-633-4411.

What are the ingredients in SYNAGIS?

Active Ingredient: palivizumab

Inactive Ingredients: chloride, glycine, and histidine

What is RSV?

Respiratory Syncytial Virus (RSV) is a common virus that is easily spread from person to person. RSV infects nearly all children by their second birthday. In most children, RSV infection is usually no worse than a bad cold. For some children, RSV infection can cause serious lung disease (like pneumonia and bronchiolitis) or breathing problems, and affected children may need to be admitted to the hospital or need emergency care.

Children who are more likely to get severe RSV disease (high-risk children) include babies born prematurely (35 weeks or less) or babies born with certain heart or lung problems.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Synagis® is a registered trademark of MedImmune, LLC.



Manufactured by: MedImmune, LLC

Gaithersburg, MD 20878

Issued March 2014

[DATE]

[HCP First and last name, Title]

[HCP Practice name]

[HCP Address]

[HCP City, State, ZIP]

Dear [HCP First and last name, Title]:

The attached template is offered as a resource a healthcare provider could use when responding to a request from a patient's health benefits company to provide a letter of medical necessity for administering Synagis[®] (palivizumab). **Attachments to be included with the letter of medical necessity are [original claim form, copy of denial or explanation of benefits, and any other additional supporting documents].** A copy of the full prescribing information for Synagis is attached for your reference. If you need additional references, please contact our medical affairs department at 1-877-MEDI-411 (1-877-633-4411).

Use of the attached letter does not guarantee that the insurance company will provide reimbursement for Synagis, and is not intended to be a substitute for or an influence on the independent medical judgment of the physician.

Important Safety Information

Synagis is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in children at high risk of RSV disease. Safety and efficacy were established in children with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (≤ 35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD). The recommended dose of Synagis is 15 mg/kg of body weight given monthly by intramuscular injection. 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. Children who develop an RSV infection should continue to receive monthly doses throughout the RSV season.

The efficacy of Synagis at doses less than 15 mg/kg, or of dosing less frequently than monthly throughout the RSV season, has not been established.

Synagis is contraindicated in children who have had a previous significant hypersensitivity reaction to Synagis. Cases of anaphylaxis and anaphylactic shock, including fatal cases, have been reported following initial exposure or re-exposure to Synagis. Other acute hypersensitivity reactions, which may be severe, have also been reported on initial exposure or re-exposure to Synagis. The relationship between these reactions and the development of antibodies to Synagis is unknown. If a significant hypersensitivity reaction occurs with Synagis, its use should be permanently discontinued. If a mild hypersensitivity reaction occurs, clinical judgment should be used regarding cautious re-administration of Synagis. As with any intramuscular injection, Synagis should be given with caution to children with thrombocytopenia or any coagulation disorder. Palivizumab may interfere with immunological-based RSV diagnostic tests, such as some antigen detection-based assays.

Adverse reactions occurring greater than or equal to 10% and at least 1% more frequently than placebo are fever and rash. In post-marketing reports, cases of severe thrombocytopenia (platelet count $< 50,000$ /microliter) and injection site reactions have been reported.

Please see accompanying full Prescribing Information for Synagis, including Patient Information.

Sincerely,

The MedImmune Access 360 Team

CONFIDENTIALITY NOTE

The documents accompanying this telecopy transmission contain confidential or privileged information. The information is intended to be for the use of the individual or entity named on this transmission sheet. If you are not the intended recipient, be aware that any disclosure, copying, distribution or use of the contents of this telecopied information is prohibited. If you have received this telecopy in error, please notify us by telephone immediately so that we can arrange for the retrieval of the original document at no cost to your office. Thank you for your assistance.

#14237A-81005

[Date]

[Contact - usually the medical director]

[Title]

[Name of Health Insurance Company]

[Address]

[City, State, ZIP Code]

Insured: [Name]

Policy Number: [Number]

Group Number: [Number]

Dear [Name of Contact]:

I am writing on behalf of my patient, [name of patient], to request that [name of health insurance company] approve coverage for Synagis® (palivizumab) to prevent severe RSV disease. This letter documents the medical necessity for this therapy and provides information about the patient's medical history and treatment.

Patient history and diagnosis

[Name of patient] is a [age], [male/female] with a diagnosis of [diagnosis] as of [date] and has received medical treatment of [list medications/procedures associated with the treatment of chronic lung disease of prematurity (CLDP) or bronchopulmonary dysplasia (BPD) that the patient has received and the date they were last received].

[Provide a brief description of the patient's medical condition here]

[Include a short summary of the patient's medical history.]

[Explain why the patient is at high risk for being hospitalized for severe RSV Disease.]

[Describe the potential consequences of the child contracting RSV and/or enduring a RSV hospitalization.]

[Attach a supporting letter of medical necessity from the pulmonologist, if possible]

Synagis prophylaxis for severe RSV disease

Major risk categories for development of severe RSV disease are most closely related to history of pre-existing chronic lung disease of prematurity (CLDP, also known as bronchopulmonary dysplasia [BPD]) (Boyce 2000, Groothuis 1988), hemodynamically significant congenital heart disease (CHD) (Boyce 2000, MacDonald 1982), and preterm birth (Hall 2009). Bronchopulmonary dysplasia (BPD) is a form of chronic lung disease (CLD) that most often occurs in premature infants and is referred to as chronic lung disease of prematurity (CLDP). CLDP is often used synonymously with BPD and accounts for the majority of cases of BPD in the United States (Baraldi 2007). Up to 30% of infants born with BPD will likely require hospitalization related to RSV infection during their first 2 years of life (Boyce 2000, Chye 1995, Groothuis 1988). BPD is defined as oxygen dependency for at least 28 postnatal days (Jobe 2002; Baraldi 2007). Although rare, BPD may occur in full-term infants who suffered pulmonary damage due to for example: pneumonia or sepsis; aspiration syndrome; persistent pulmonary hypertension of the newborn; pulmonary hypoplasia; diaphragmatic hernia; congenital heart disease (Baraldi 2007).

Synagis is approved by the FDA for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease. Safety and efficacy were established in children with BPD in a randomized, double-blind placebo controlled clinical trial during a single RSV season and included a total of 1,502 patients who were ≤ 24 months of age with bronchopulmonary dysplasia (BPD) or infants with premature birth (≤ 35 weeks gestation) who were ≤ 6 months of age at study entry (Connor 1998). Participants received 15 mg/kg Synagis or an equivalent volume of placebo IM monthly for five injections and were followed for 150 days from randomization. The rate of RSV-related hospitalization was significantly reduced in patients with BPD, 12.8% (34/266) with placebo vs. 7.9% (39/496) with Synagis, and in premature infants without BPD, 8.1% (19/234) with placebo vs. 1.8% (9/506) with Synagis.

Based on the above information, therapy with Synagis is medically necessary for this patient. Thank you for your prompt attention to this matter.

If you have any further questions, please feel free to contact me at [physician telephone number, including area code] to discuss. Thank you in advance for your immediate attention to this request and assisting me in providing the required care for this baby in order to keep them as healthy as possible.

Sincerely,

[Physician's Name]

[Physician's Practice Name]

#14237A-81304

References

Boyce TG, et al. Rates of hospitalization for respiratory syncytial virus infection among children in Medicaid. *J Pediatr*. 2000;137:865-870.

Baraldi E, Philipponne M. Chronic lung disease after premature birth. *N Engl J Med*. 2007;347(19):1946-1955.

Chye JK, Gray PH. Rehospitalization and growth of infants with bronchopulmonary dysplasia: a matched control study. *J Paediatr Child Health Care*. 1995; 31:105-111.

Connor EM and the IMPact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics*. 1998;102:531-537.

Groothuis JR, et al. Respiratory syncytial virus infection in children with bronchopulmonary dysplasia. *Pediatrics*. 1988;82:199-203.

Hall CB, et al. The burden of respiratory syncytial virus infection in young children. *N Engl J Med*. 2009;360:588-598.

Jobe AH. The new bronchopulmonary dysplasia. *Curr Opin Pediatr*. 2011;23:167-172.

MacDonald NE, et al. Respiratory syncytial viral infection in infants with congenital heart disease. *N Engl J Med*. 1982;307:397-400.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SYNAGIS safely and effectively. See full prescribing information for SYNAGIS.

SYNAGIS® (palivizumab) injection for intramuscular use
Initial U.S. Approval: 1998

INDICATIONS AND USAGE

Synagis is a respiratory syncytial virus (RSV) F protein inhibitor monoclonal antibody indicated for the prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease.

- Safety and efficacy were established in children with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (less than or equal to 35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD).
- The safety and efficacy of Synagis have not been established for treatment of RSV disease. (1)

DOSAGE AND ADMINISTRATION

15 mg per kg of body weight, administered intramuscularly prior to commencement of the RSV season and remaining doses administered monthly throughout the RSV season. (2.1)

Children undergoing cardio-pulmonary bypass should receive an additional dose of Synagis as soon as possible after the cardio-pulmonary bypass procedure (even if sooner than a month from the previous dose). Thereafter, doses should be administered monthly as scheduled. (2.1, 12.3)

DOSAGE FORMS AND STRENGTHS

Single-dose liquid solution vials: 50 mg per 0.5 mL and 100 mg per 1 mL. (3)

FULL PRESCRIBING INFORMATION: CONTENTS*

- 1 INDICATIONS AND USAGE
- 2 DOSAGE AND ADMINISTRATION
 - 2.1 Dosing Information
 - 2.2 Administration Instructions
- 3 DOSAGE FORMS AND STRENGTHS
- 4 CONTRAINDICATIONS
- 5 WARNINGS AND PRECAUTIONS
 - 5.1 Hypersensitivity Reactions
 - 5.2 Coagulation Disorders
 - 5.3 RSV Diagnostic Test Interference
 - 5.4 Treatment of RSV Disease
 - 5.5 Proper Administration
- 6 ADVERSE REACTIONS
 - 6.1 Clinical Studies Experience
 - 6.2 Postmarketing Experience

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Synagis is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in children at high risk of RSV disease.

The following points should be considered when prescribing Synagis:

- Safety and efficacy were established in children with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (less than or equal to 35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD) [see *Clinical Studies* (14)].
- The safety and efficacy of Synagis have not been established for treatment of RSV disease.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of Synagis is 15 mg per kg of body weight given monthly by intramuscular injection. 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. Children who develop an RSV infection should continue to receive monthly doses throughout the RSV season. In the northern hemisphere, the RSV season typically commences in November and lasts through April, but it may begin earlier or persist later in certain communities.

Synagis serum levels are decreased after cardio-pulmonary bypass [see *Clinical Pharmacology* (12.3)]. Children undergoing cardio-pulmonary bypass should receive an additional dose of Synagis as soon as possible after the cardio-pulmonary bypass procedure (even if sooner than a month from the previous dose). Thereafter, doses should be administered monthly as scheduled.

The efficacy of Synagis at doses less than 15 mg per kg, or of dosing less frequently than monthly throughout the RSV season, has not been established.

2.2 Administration Instructions

- **DO NOT DILUTE THE PRODUCT.**
- **DO NOT SHAKE OR VIGOROUSLY AGITATE THE VIAL.**
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials exhibiting particulate matter or discoloration.

CONTRAINDICATIONS

Previous significant hypersensitivity reaction to Synagis. (4)

WARNINGS AND PRECAUTIONS

- Anaphylaxis and anaphylactic shock (including fatal cases), and other severe acute hypersensitivity reactions have been reported. Permanently discontinue Synagis and administer appropriate medications if such reactions occur. (5.1)
- As with any intramuscular injection, Synagis should be given with caution to children with thrombocytopenia or any coagulation disorder. (5.2)
- Palivizumab may interfere with immunological-based RSV diagnostic tests such as some antigen detection-based assays. (5.3, 12.4)

ADVERSE REACTIONS

Adverse reactions occurring greater than or equal to 10% and at least 1% more frequently than placebo are fever and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact MedImmune at 1-877-633-4411 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Safety and effectiveness in children greater than 24 months of age at the start of dosing have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 3/2014

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.4 Pediatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics
- 12.4 Microbiology

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

- Using aseptic techniques, attach a sterile needle to a sterile syringe. Remove the flip top from the Synagis vial and wipe the rubber stopper with a disinfectant (e.g., 70% isopropyl alcohol). Insert the needle into the vial and withdraw into the syringe an appropriate volume of solution. Administer immediately after drawing the dose into the syringe.
- Synagis should be administered in a dose of 15 mg per kg intramuscularly using aseptic technique, 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 (volume of injection in mL) per month = patient weight (kg) x 15 mg per kg ÷ 100 mg per mL of Synagis. Injection volumes over 1 mL should be given as a divided dose.
- Synagis is supplied as a single-dose vial and does not contain preservatives. Do not re-enter the vial after withdrawal of drug; discard unused portion. Only administer one dose per vial.
- Use sterile disposable syringes and needles. To prevent the transmission of hepatitis viruses or other infectious agents from one person to another, DO NOT reuse syringes and needles.

3 DOSAGE FORMS AND STRENGTHS

Single-dose liquid solution vials: 50 mg per 0.5 mL and 100 mg per 1 mL.

4 CONTRAINDICATIONS

Synagis is contraindicated in children who have had a previous significant hypersensitivity reaction to Synagis [see *Warnings and Precautions* (5.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Cases of anaphylaxis and anaphylactic shock, including fatal cases, have been reported following initial exposure or re-exposure to Synagis. Other acute hypersensitivity reactions, which may be severe, have also been reported on initial exposure or re-exposure to Synagis. Signs and symptoms may include urticaria, pruritus, angioedema, dyspnea, respiratory failure, cyanosis, hypotonia, hypotension, and unresponsiveness. The relationship between these reactions and the development of antibodies to Synagis is unknown. If a significant hypersensitivity reaction occurs with Synagis, its use should be permanently discontinued. **If anaphylaxis or other significant hypersensitivity reaction occurs, administer appropriate medications (e.g., epinephrine) and provide supportive care as required.** If a mild hypersensitivity reaction occurs, clinical judgment should be used regarding cautious readministration of Synagis.

5.2 Coagulation Disorders

Synagis is for intramuscular use only. As with any intramuscular injection, Synagis should be given with caution to children with thrombocytopenia or any coagulation disorder.

5.3 RSV Diagnostic Test Interference

Palivizumab may interfere with immunological-based RSV diagnostic tests such as some antigen detection-based assays. In addition, palivizumab inhibits virus replication in cell culture, and therefore may also interfere with viral culture assays. Palivizumab does not interfere with reverse transcriptase-polymerase chain reaction based assays. Assay interference could lead to false-negative RSV diagnostic test results. Therefore, diagnostic test results, when obtained, should be used in conjunction with clinical findings to guide medical decisions [see *Microbiology* (12.4)].

5.4 Treatment of RSV Disease

The safety and efficacy of Synagis have not been established for treatment of RSV disease.

5.5 Proper Administration

The single-dose vial of Synagis does not contain a preservative. Administration of Synagis should occur immediately after dose withdrawal from the vial. The vial should not be re-entered. Discard any unused portion.

6 ADVERSE REACTIONS

The most serious adverse reactions occurring with Synagis are anaphylaxis and other acute hypersensitivity reactions [see *Warnings and Precautions* (5.1)].

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to Synagis (n=1639) compared with placebo (n=1143) in children 3 days to 24.1 months of age at high risk of RSV-related hospitalization in two clinical trials. Trial 1 was conducted during a single RSV season and studied a total of 1502 children less than or equal to 24 months of age with BPD or infants with premature birth (less than or equal to 35 weeks gestation) who were less than or equal to 6 months of age at study entry. Trial 2 was conducted over four consecutive seasons among a total of 1287 children less than or equal to 24 months of age with hemodynamically significant congenital heart disease.

In Trials 1 and 2 combined, fever and rash were each reported more frequently among Synagis than placebo recipients, 27% versus 25%, and 12% versus 10%, respectively. Adverse reactions observed in the 153-patient crossover study comparing the liquid and lyophilized formulations were comparable for the two formulations, and were similar to those observed with Synagis in Trials 1 and 2.

Immunogenicity

In Trial 1, the incidence of anti-palivizumab antibody following the fourth injection was 1.1% in the placebo group and 0.7% in the Synagis group. In children receiving Synagis for a second season, one of the fifty-six children had transient, low titer reactivity. This reactivity was not associated with adverse events or alteration in serum concentrations. Immunogenicity was not assessed in Trial 2.

A trial of high-risk preterm children less than or equal to 24 months of age was conducted to evaluate the immunogenicity of the lyophilized formulation of Synagis (used in Trials 1 and 2 above) and the liquid formulation of Synagis. Three hundred seventy-nine children contributed to the 4 to 6 months post-final dose analysis. The rate of anti-palivizumab antibodies at this time point was low in both formulation groups (anti-palivizumab antibodies were not detected in any subject in the liquid formulation group and were detected in one subject in the lyophilized group (0.5%), with an overall rate of 0.3% for both treatment groups combined).

These data reflect the percentage of children whose test results were considered positive for antibodies to palivizumab in an enzyme-linked immunosorbent assay (ELISA) and are highly dependent on the sensitivity and specificity of the assay.

The ELISA has substantial limitations in detecting anti-palivizumab antibodies in the presence of palivizumab. Immunogenicity samples tested with the ELISA assay likely contained palivizumab at levels that may interfere with the detection of anti-palivizumab antibodies.

An electrochemical luminescence (ECL) based immunogenicity assay, with a higher tolerance for palivizumab presence compared to the ELISA, was used to evaluate the presence of anti-palivizumab antibodies in subject samples from two additional clinical trials. The rates of anti-palivizumab antibody positive results in these trials were 1.1% and 1.5%.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Synagis. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: severe thrombocytopenia (platelet count less than 50,000 per microliter)

General Disorders and Administration Site Conditions: injection site reactions

Limited information from post-marketing reports suggests that, within a single RSV season, adverse events after a sixth or greater dose of Synagis are similar in character and frequency to those after the initial five doses.

7 DRUG INTERACTIONS

No formal drug-drug interaction studies were conducted. In Trial 1, the proportions of children in the placebo and Synagis groups who received routine childhood vaccines, influenza vaccine, bronchodilators, or corticosteroids were similar and no incremental increase in adverse reactions was observed among children receiving these agents.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Synagis is not indicated for adult usage. It is not known whether Synagis can cause fetal harm or could affect reproductive capacity when administered to a pregnant woman.

Animal Data

Animal reproduction studies have not been conducted.

8.4 Pediatric Use

The safety and effectiveness of Synagis in children greater than 24 months of age at the start of dosing have not been established.

10 OVERDOSAGE

Overdoses with doses up to 85 mg per kg have been reported in clinical studies and post-marketing experience with Synagis, and in some cases, adverse reactions were reported. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

11 DESCRIPTION

Palivizumab is a humanized monoclonal antibody (IgG1 κ) produced by recombinant DNA technology, directed to an epitope in the A antigenic site of the F protein of RSV. Palivizumab is a composite of human (95%) and murine (5%) antibody sequences. The human heavy chain sequence was derived from the constant domains of human IgG1 and the variable framework regions of the V_H genes Cor and Cess. The human light chain sequence was derived from the constant domain of C κ and the variable framework regions of the V_L gene K104 with J κ -4. The murine sequences were derived from a murine monoclonal antibody, Mab 1129, in a process that involved the grafting of the murine complementarity determining regions into the human antibody frameworks. Palivizumab is composed of two heavy chains and two light chains and has a molecular weight of approximately 148,000 Daltons.

Synagis is supplied as a sterile, preservative-free liquid solution at 100 mg per mL to be administered by intramuscular injection. Thimerosal or other mercury-containing salts are not used in the production of Synagis. The solution has a pH of 6.0 and should appear clear or slightly opalescent.

Each 100 mg single-dose vial of Synagis liquid solution contains 100 mg of palivizumab and also contains chloride (0.5 mg), glycine (0.1 mg), and histidine (3.9 mg), in a volume of 1 mL. Each 50 mg single-dose vial of Synagis liquid solution contains 50 mg of palivizumab and also contains chloride (0.2 mg), glycine (0.06 mg), and histidine (1.9 mg), in a volume of 0.5 mL.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Palivizumab is a recombinant humanized monoclonal antibody with anti-RSV activity [see *Microbiology* (12.4)].

12.3 Pharmacokinetics

In children less than or equal to 24 months of age without congenital heart disease (CHD), the mean half-life of palivizumab was 20 days and monthly intramuscular doses of 15 mg per kg achieved mean \pm SD 30 day trough serum drug concentrations of 37 \pm 21 mcg per mL after the first injection, 57 \pm 41 mcg per mL after the second injection, 68 \pm 51 mcg per mL after the third injection, and 72 \pm 50 mcg per mL after the fourth injection. Trough concentrations following the first and fourth Synagis dose were similar in children with CHD and in non-cardiac patients. In children given Synagis for a second season, the mean \pm SD serum concentrations following the first and fourth injections were 61 \pm 17 mcg per mL and 86 \pm 31 mcg per mL, respectively.

In 139 children less than or equal to 24 months of age with hemodynamically significant CHD who received Synagis and underwent cardio-pulmonary bypass for open-heart surgery, the mean \pm SD serum palivizumab concentration was 98 \pm 52 mcg per mL before bypass and declined to 41 \pm 33 mcg per mL after bypass, a reduction of 58% [see *Dosage and Administration* (2.1)]. The clinical significance of this reduction is unknown.

Specific studies were not conducted to evaluate the effects of demographic parameters on palivizumab systemic exposure. However, no effects of gender, age, body weight, or race on palivizumab serum trough concentrations were observed in a clinical study with 639 children with CHD (less than or equal to 24 months of age) receiving five monthly intramuscular injections of 15 mg per kg of Synagis.

The pharmacokinetics and safety of Synagis liquid solution and Synagis lyophilized formulation administered via intramuscular injection at 15 mg per kg were studied in a cross-over trial of 153 infants less than or equal to 6 months of age with a history of prematurity. The results of this trial indicated that the trough serum concentrations of palivizumab were comparable between the liquid solution and the lyophilized formulation, which was the formulation used in the clinical studies. A population pharmacokinetic analysis was performed across 22 studies in 1800 patients (1684 pediatric and 116 adult patients) to characterize palivizumab pharmacokinetics and inter-subject variability in serum concentrations. Palivizumab pharmacokinetics was described by a two-compartment linear model with an elimination half-life of 24.5 days in pediatric patients. Clearance of palivizumab in a typical pediatric patient (body weight 4.5 kg) less than or equal to 24 months of age without CHD was estimated to be 11 mL per day with a bioavailability of 70% following intramuscular administration. The inter-patient variability in drug clearance was 48.7% (CV%). Covariate analysis did not identify any factors that could account for the inter-patient variability in order to predict serum concentrations a priori in an individual patient.

12.4 Microbiology

Mechanism of Action

Palivizumab, a recombinant humanized monoclonal antibody which provides passive immunity against RSV, acts by binding the RSV envelope fusion protein (RSV F) on the surface of the virus and blocking a critical step in the membrane fusion process. Palivizumab also prevents cell-to-cell fusion of RSV-infected cells.

Antiviral Activity

The antiviral activity of palivizumab was assessed in a microneutralization assay in which increasing concentrations of antibody were incubated with RSV prior to addition of the human epithelial cells HEP-2. After incubation for 4-5 days, RSV antigen was measured in an ELISA assay. The neutralization titer (50% effective concentration [EC₅₀]) is expressed as the antibody concentration required to reduce detection of RSV antigen by 50% compared with untreated virus-infected cells. Palivizumab exhibited median EC₅₀ values of 0.65 mcg per mL (mean 0.75 ± 0.53 mcg per mL; n=69, range 0.07-2.89 mcg per mL) and 0.28 mcg per mL (mean 0.35 ± 0.23 mcg per mL; n=35, range 0.03-0.88 mcg per mL) against clinical RSV A and RSV B isolates, respectively. The majority of clinical RSV isolates tested (n=96) were collected from subjects across the United States (CA, CO, CT, IL, MA, NC, NY, PA, RI, TN, TX, VA), with the remainder from Japan (n=1), Australia (n=5) and Israel (n=2). These isolates encoded the most common RSV F sequence polymorphisms found among clinical isolates worldwide.

Palivizumab serum concentrations of greater than or equal to 40 mcg per mL have been shown to reduce pulmonary RSV replication in the cotton rat model of RSV infection by 100-fold.

Resistance

Palivizumab binds a highly conserved region on the extracellular domain of mature RSV F, referred to as antigenic site II or site A, which encompasses amino acids 262 to 275. All RSV mutants that exhibit resistance to palivizumab have been shown to contain amino acid changes in this region on the F protein.

F protein sequence variations within antigenic site A: Amino acid substitutions in antigenic site A selected either in cell culture, in animal models, or in human subjects that resulted in palivizumab resistance were N262D, N268I, K272E/M/N/Q/T, and S275F/L. RSV variants expressing the K272N substitution in F protein showed a 5164 ± 1731-fold decrease in susceptibility (i.e., fold increase in EC₅₀ value) when compared to the wild-type RSV, while variants containing the N262D, S275F/L, or K272E/M/N/Q/T substitutions showed a greater than 25,000-fold decrease in susceptibility to palivizumab. The N268I substitution conferred partial resistance to palivizumab; however, fold changes in susceptibility were not quantified for this mutant. Studies carried out to investigate the mechanism of virus escape from palivizumab showed a correlation between antibody binding and virus neutralization. RSV with substitutions in antigenic site A that were resistant to neutralization by palivizumab did not bind to palivizumab.

At least one of the palivizumab resistance-associated substitutions, N262D, K272E/Q, or S275F/L was identified in 8 of 126 clinical RSV (59 RSV A and 67 RSV B) isolates from subjects who failed immunoprophylaxis, resulting in a combined resistance-associated mutation frequency of 6.3%. A review of clinical findings revealed no association between antigenic A site sequence changes and RSV disease severity among children receiving palivizumab immunoprophylaxis who develop RSV lower respiratory tract disease.

Analysis of 254 clinical RSV isolates (145 RSV A and 109 RSV B) collected from immunoprophylaxis-naïve subjects revealed palivizumab resistance-associated substitutions in 2 (1 with N262D and 1 with S275F), resulting in a resistance-associated mutation frequency of 0.79%.

F protein sequence variations outside antigenic site A: In addition to the sequence variations in antigenic site A known to confer palivizumab resistance, F protein substitutions T100A, G139S, N165D/V406I; T326A, V450A in RSV A, and T74I, A147V, I206L, S285G, V450I, T455I in RSV B were identified in viruses isolated from failures of immunoprophylaxis. These substitutions were not identified in RSV F sequences derived from 254 clinical isolates from immunoprophylaxis-naïve subjects and thus are considered treatment-associated and non-polymorphic. Recombinant RSV B encoding the S285G substitution exhibited palivizumab sensitivity (EC₅₀ value = 0.39 ± 0.02 mcg per mL) similar to recombinant wild-type RSV B (EC₅₀ value = 0.17 ± 0.02 mcg per mL).

Palivizumab susceptibility of RSV encoding common F protein sequence polymorphisms located proximal to antigenic site A was evaluated. Recombinant RSV A encoding N276S (EC₅₀ value = 0.72 ± 0.07 mcg per mL), and recombinant RSV B with S276N (EC₅₀ value = 0.42 ± 0.04 mcg per mL), exhibited sensitivities comparable to the corresponding recombinant wild-type RSV A (EC₅₀ value = 0.63 ± 0.22 mcg per mL) and RSV B (EC₅₀ value = 0.23 ± 0.07 mcg per mL). Likewise, RSV B clinical isolates containing the polymorphic variation V278A were at least as sensitive to neutralization by palivizumab (EC₅₀ range 0.08-0.45 mcg per mL) as laboratory strains of wild-type RSV B (EC₅₀ value = 0.54 ± 0.08 mcg per mL). No known polymorphic or non-polymorphic sequence variations outside the antigenic site A on RSV F have been demonstrated to render RSV resistant to neutralization by palivizumab.

Interference of RSV Diagnostic Assays by Palivizumab

Interference with immunologically-based RSV diagnostic assays by palivizumab has been observed in laboratory studies. Rapid chromatographic/enzyme immunoassays (CIA/EIA), immunofluorescence assays (IFA), and direct immunofluorescence assays (DFA) using monoclonal antibodies targeting RSV F protein may be inhibited. Therefore, caution should be used in interpreting negative immunological assay results when clinical observations are consistent with RSV infection. A reverse transcriptase-polymerase chain reaction (RT-PCR) assay, which is not inhibited by palivizumab, may prove useful for laboratory confirmation of RSV infection [see *Warnings and Precautions* (5.3)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis, mutagenesis, and reproductive toxicity studies have not been performed.

14 CLINICAL STUDIES

The safety and efficacy of Synagis were assessed in two randomized, double-blind, placebo-controlled trials of prophylaxis against RSV infection in children at high risk of an RSV-related hospitalization. Trial 1 was conducted during a single RSV season and studied a total of 1502 children less than or equal to 24 months of age with BPD or infants with premature birth (less than or equal to 35 weeks gestation) who were less than or equal to 6 months of age at study entry. Trial 2 was conducted over four consecutive seasons among a total of 1287 children less than or equal to 24 months of age with hemodynamically significant congenital heart disease. In both trials participants received 15 mg per kg Synagis or an equivalent volume of placebo via intramuscular injection monthly for five injections and were followed for 150 days from randomization. In Trial 1, 99% of all subjects completed the study and 93% completed all five injections. In Trial 2, 96% of all subjects completed the study and 92% completed all five injections. The incidence of RSV hospitalization is shown in Table 1. The results were shown to be statistically significant using Fisher's exact test.

Table 1: Incidence of RSV Hospitalization by Treatment Group

Trial		Placebo	Synagis	Difference Between Groups	Relative Reduction
Trial 1 Impact-RSV	N	500	1002		
	Hospitalization	53 (10.6%)	48 (4.8%)	5.8%	55%
Trial 2 CHD	N	648	639		
	Hospitalization	63 (9.7%)	34 (5.3%)	4.4%	45%

In Trial 1, the reduction of RSV hospitalization was observed both in children with BPD (34/266 [12.8%] placebo versus 39/496 [7.9%] Synagis) and in premature infants without BPD (19/234 [8.1%] placebo versus 9/506 [1.8%] Synagis). In Trial 2, reductions were observed in acyanotic (36/305 [11.8%] placebo versus 15/300 [5.0%] Synagis) and cyanotic children (27/343 [7.9%] placebo versus 19/339 [5.6%] Synagis).

The clinical studies do not suggest that RSV infection was less severe among children hospitalized with RSV infection who received Synagis for RSV prophylaxis compared to those who received placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

Synagis is supplied in single-dose vials as a preservative-free, sterile liquid solution at 100 mg per mL for intramuscular injection.

50 mg vial NDC 60574-4114-1

The 50 mg vial contains 50 mg Synagis in 0.5 mL.

100 mg vial NDC 60574-4113-1

The 100 mg vial contains 100 mg Synagis in 1 mL.

The rubber stopper used for sealing vials of Synagis is not made with natural rubber latex.

Storage

Upon receipt and until use, Synagis should be stored between 2°C and 8°C (36°F and 46°F) in its original container. DO NOT freeze. DO NOT use beyond the expiration date.

17 PATIENT COUNSELING INFORMATION

o **“Advise the patient to read the FDA-approved patient labeling (Patient Information)”**

The healthcare provider should discuss the potential benefits and risks of Synagis with the parents or guardians of Synagis recipients. Parents or guardians should be informed of the possible side effects of Synagis and of the signs and symptoms of potential allergic reactions and should be advised of the appropriate actions. Parents or guardians should understand the dosing schedule and the importance of compliance with the full course of therapy.

Synagis® is a registered trademark of MedImmune, LLC.



Manufactured by:

MedImmune, LLC
Gaithersburg, MD 20878
U.S. License No. 1799
1-877-633-4411

RAL-SYNV17
Component No.: 26920A

PATIENT INFORMATION
SYNAGIS® (Sĭ-nă-jĭs)
(palivizumab)
Injection

Read this Patient Information before your child starts receiving SYNAGIS and before each injection. The information may have changed. This leaflet does not take the place of talking with your child's healthcare provider about your child's condition or treatment.

What is SYNAGIS?

SYNAGIS is a prescription medication that is used to help prevent a serious lung disease caused by Respiratory Syncytial Virus (RSV). Your child is prescribed SYNAGIS because he or she is at high risk for severe lung disease from RSV.

SYNAGIS contains man-made, disease-fighting proteins called antibodies. These antibodies help prevent RSV disease. Children at high risk for severe RSV disease often do not have enough of their own antibodies. SYNAGIS is used in certain groups of children to help prevent severe RSV disease by increasing protective RSV antibodies.

SYNAGIS is not used to treat the symptoms of RSV disease once a child already has it. It is only used to prevent RSV disease.

SYNAGIS is not for adults or for children older than 24 months of age at the start of dosing.

Who should not receive SYNAGIS?

Your child should not receive SYNAGIS if they have ever had a severe allergic reaction to it. Signs and symptoms of a severe allergic reaction could include:

- severe rash, hives, or itching skin
- swelling of the lips, tongue, or face
- closing of the throat, difficulty swallowing
- difficult, rapid, or irregular breathing
- bluish color of skin, lips, or under fingernails
- muscle weakness or floppiness
- a drop in blood pressure
- unresponsiveness

What should I tell my child's healthcare provider before my child receives SYNAGIS?

Tell your child's healthcare provider about:

- **any reactions** you believe your child has ever had to SYNAGIS.
- **any bleeding or bruising problems.** SYNAGIS is given by injection. If your child has a problem with bleeding or bruises easily, an injection could cause a problem.
- **any other medical problems.**

Tell your child's healthcare provider about all the medicines your child takes, including prescription and non-prescription medicines, vitamins, and herbal supplements. Especially tell your child's healthcare provider if your child takes a blood thinner medicine.

How is SYNAGIS given?

- SYNAGIS is given as a monthly injection, usually in the thigh (leg) muscle, by your child's healthcare provider. Your child's healthcare provider will prescribe the amount of SYNAGIS that is right for your child (based on their weight).
- Your child's healthcare provider will give you detailed instructions on when SYNAGIS will be given.
 - "RSV season" is a term used to describe the time of year when RSV infections most commonly occur (usually fall through spring in most parts of the country). During this time, when RSV is most active, your child will need to receive SYNAGIS shots. Your child's healthcare provider can tell you when the RSV season starts in your area.
 - Your child should receive their **first SYNAGIS shot before the RSV season starts** to help protect them before RSV becomes active. If the season has already started, your child should receive their first SYNAGIS shot as soon as possible to help protect them when exposure to the virus is more likely.

- **SYNAGIS is needed every 28-30 days during the RSV season.** Each dose of SYNAGIS helps protect your child from severe RSV disease for about a month. **Keep all appointments with your child's healthcare provider.**

- **If your child misses an injection, talk to your healthcare provider and schedule another injection as soon as possible.**
- Your child may still get severe RSV disease after receiving SYNAGIS; talk to your child's healthcare provider about what symptoms to look for. If your child has an RSV infection, they should continue to get their scheduled SYNAGIS injections to help prevent severe disease from new RSV infections.
- If your child has certain types of heart disease and has corrective surgery, your healthcare provider may need to give your child an additional SYNAGIS injection soon after surgery.

What are the possible side effects of SYNAGIS?

Synagis may cause serious side effects including:

- Severe allergic reactions (may occur after any dose of SYNAGIS). Such reactions may be life-threatening or cause death.
 - See "Who should not take SYNAGIS?" for a list of signs and symptoms.
- Unusual bruising or groups of tiny red spots on the skin.

Call your child's healthcare provider or get medical help right away if your child has any of the serious side effects listed above after any dose of SYNAGIS.

Common side effects of SYNAGIS include:

- fever
- rash

Other possible side effects include skin reactions around the area where the shot was given (like redness, swelling, warmth, or discomfort).

These are not all the possible side effects of SYNAGIS. Tell your child's healthcare provider about any side effect that bothers your child or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to MedImmune at 1-877-633-4411.

General Information about SYNAGIS

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets.

This leaflet summarizes important information about SYNAGIS. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about SYNAGIS that is written for health professionals.

For more information, go to www.synagis.com or call 1-877-633-4411.

What are the ingredients in SYNAGIS?

Active Ingredient: palivizumab

Inactive Ingredients: chloride, glycine, and histidine

What is RSV?

Respiratory Syncytial Virus (RSV) is a common virus that is easily spread from person to person. RSV infects nearly all children by their second birthday. In most children, RSV infection is usually no worse than a bad cold. For some children, RSV infection can cause serious lung disease (like pneumonia and bronchiolitis) or breathing problems, and affected children may need to be admitted to the hospital or need emergency care.

Children who are more likely to get severe RSV disease (high-risk children) include babies born prematurely (35 weeks or less) or babies born with certain heart or lung problems.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Synagis® is a registered trademark of MedImmune, LLC.



Manufactured by: MedImmune, LLC

Gaithersburg, MD 20878

Issued March 2014

[DATE]

[HCP First and last name, Title]

[HCP Practice name]

[HCP Address]

[HCP City, State, ZIP]

Dear [HCP First and last name, Title]:

The attached template is offered as a resource a healthcare provider could use when responding to a request from a patient's health benefits company to provide a letter of medical necessity for administering Synagis® (palivizumab). **Attachments to be included with the letter of medical necessity are [original claim form, copy of denial or explanation of benefits, and any other additional supporting documents].** A copy of the full prescribing information for Synagis is attached for your reference. If you need additional references, please contact our medical affairs department at 1-877-MEDI-411 (1-877-633-4411).

Use of the attached letter does not guarantee that the insurance company will provide reimbursement for Synagis, and is not intended to be a substitute for or an influence on the independent medical judgment of the physician.

Important Safety Information

Synagis is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in children at high risk of RSV disease. Safety and efficacy were established in children with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (≤ 35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD). The recommended dose of Synagis is 15 mg/kg of body weight given monthly by intramuscular injection. 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. Children who develop an RSV infection should continue to receive monthly doses throughout the RSV season.

The efficacy of Synagis at doses less than 15 mg/kg, or of dosing less frequently than monthly throughout the RSV season, has not been established.

Synagis is contraindicated in children who have had a previous significant hypersensitivity reaction to Synagis. Cases of anaphylaxis and anaphylactic shock, including fatal cases, have been reported following initial exposure or re-exposure to Synagis. Other acute hypersensitivity reactions, which may be severe, have also been reported on initial exposure or re-exposure to Synagis. The relationship between these reactions and the development of antibodies to Synagis is unknown. If a significant hypersensitivity reaction occurs with Synagis, its use should be permanently discontinued. If a mild hypersensitivity reaction occurs, clinical judgment should be used regarding cautious re-administration of Synagis. As with any intramuscular injection, Synagis should be given with caution to children with thrombocytopenia or any coagulation disorder. Palivizumab may interfere with immunological-based RSV diagnostic tests, such as some antigen detection-based assays.

Adverse reactions occurring greater than or equal to 10% and at least 1% more frequently than placebo are fever and rash. In post-marketing reports, cases of severe thrombocytopenia (platelet count $< 50,000/\text{microliter}$) and injection site reactions have been reported.

Please see accompanying full Prescribing Information for Synagis, including Patient Information.

Sincerely,

The MedImmune Access 360 Team

CONFIDENTIALITY NOTE

The documents accompanying this telecopy transmission contain confidential or privileged information.

The information is intended to be for the use of the individual or entity named on this transmission sheet. If you are not the intended recipient, be aware that any disclosure, copying, distribution or use of the contents of this telecopied information is prohibited. If you have received this telecopy in error, please notify us by telephone immediately so that we can arrange for the retrieval of the original document at no cost to your office.

Thank you for your assistance.

#14333A-80905

[Date]

[Contact - usually the medical director]

[Title]

[Name of Health Insurance Company]

[Address]

[City, State, ZIP Code]

Insured: [Name]

Policy Number: [Number]

Group Number: [Number]

Dear [Name of Contact]:

I am writing on behalf of my patient, [name of patient], to request that [name of health insurance company] approve coverage for Synagis® (palivizumab) to help prevent severe RSV disease. This letter documents the medical necessity for this therapy and provides information about the patient's medical history and treatment.

Patient History and Diagnosis

[Name of patient] is a [male/female] baby who was born prematurely at [Gestational age] weeks gestation. [Name of patient] is now [chronological age] and has risk factors that increase [his/her] chances of contracting RSV. These risk factors include [list risk factors]. This baby has received [number of doses] doses of Synagis and the last one was given on [date of last dose received]. RSV activity is currently at [number] % positive in [state] where the child resides, indicating that RSV is widespread and prophylaxis should continue.

Treatment Information

I am requesting Synagis for this patient based on evidence-based medicine noted in the package insert of the drug, which states that Synagis should be given 15mg/kg of body weight, IM, prior to the commencement of the RSV season and administered monthly throughout the season. This seasonality is captured by the CDC in their surveillance of RSV virology. I have included a copy of the RSV virology data for my state as reported by the CDC.

The Impact-RSV trial found the mean half-life of palivizumab was 20 days and a wide variety of serum trough levels in the subjects studied (Connor 1998). Serum trough drug concentration levels of palivizumab were found to be 37 ± 21 mcg/mL (mean \pm SD) after the first dose, 57 ± 41 mcg/mL after the second dose and 68 ± 51 mcg/mL after the third dose, and 72 ± 50 mcg/mL after the fourth injection. However, there was significant variation in trough levels as indicated by the large standard deviations notes with 68% of the infants falling between 22 and 122 mcg/mL immediately before the fifth dose, as well as some children with undetectable levels. Further, 30 days after the 4th injection, 25% of the patients (223 out of 892) had trough serum levels at or less than 42 mcg/mL (Synagis BLA 1998). It is also important to note that these trough levels in the study were measured in highly compliant subjects, whose dosing regimen was strictly adhered to, which is not always the case in real life situations. Given the serum half-life and high level of patient-to-patient variability (as discussed above), the existing pharmacokinetic data and clinical trial evidence does not support increasing the dose interval beyond 30 days for any patient regardless of the number of consecutive monthly doses of palivizumab administered.

According to data available from the CDC, which I have included, RSV is widespread in my area therefore I am recommending extending Synagis monthly dosing until the RSV virology is less than 10% positive for two consecutive weeks. Given this data, I believe it is medically appropriate and necessary to continue to provide RSV prophylaxis to this child, who has been previously approved by [insert Payer name] for Synagis. The above data demonstrates that unless prophylaxis is continued, children are at high risk for severe RSV disease when RSV virology is widespread in the community. Also the guidance provided by the American Academy of Pediatrics (AAP) states that healthcare providers should base their dosing decisions on the level of RSV activity in their area and their clinical judgment.

Thank you for assisting me in my continued effort to protect this baby from RSV and the complications associated with this disease.

If you have any further questions, please feel free to contact me at [physician telephone number, including area code] to discuss. Thank you in advance for your immediate attention to this request.

Sincerely,

[Physician's Name]

[Physician's Practice Name]

Reference

Synagis® [package insert]. Gaithersburg, MD: MedImmune, LLC.

Connor EM and the IMPact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics*. 1998;102:531-537.

Synagis Biologics License Application - U.S. Food and Drug Administration. Palivizumab Product Approval Information - Licensing Action.. Clinical Review. Approved June 19, 1998. Available at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm093366.htm>. (Accessed August 20, 2012)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SYNAGIS safely and effectively. See full prescribing information for SYNAGIS.

SYNAGIS® (palivizumab) injection for intramuscular use
Initial U.S. Approval: 1998

INDICATIONS AND USAGE

Synagis is a respiratory syncytial virus (RSV) F protein inhibitor monoclonal antibody indicated for the prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease.

- Safety and efficacy were established in children with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (less than or equal to 35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD).
- The safety and efficacy of Synagis have not been established for treatment of RSV disease. (1)

DOSAGE AND ADMINISTRATION

15 mg per kg of body weight, administered intramuscularly prior to commencement of the RSV season and remaining doses administered monthly throughout the RSV season. (2.1)

Children undergoing cardio-pulmonary bypass should receive an additional dose of Synagis as soon as possible after the cardio-pulmonary bypass procedure (even if sooner than a month from the previous dose). Thereafter, doses should be administered monthly as scheduled. (2.1, 12.3)

DOSAGE FORMS AND STRENGTHS

Single-dose liquid solution vials: 50 mg per 0.5 mL and 100 mg per 1 mL. (3)

FULL PRESCRIBING INFORMATION: CONTENTS*

- 1 INDICATIONS AND USAGE
- 2 DOSAGE AND ADMINISTRATION
 - 2.1 Dosing Information
 - 2.2 Administration Instructions
- 3 DOSAGE FORMS AND STRENGTHS
- 4 CONTRAINDICATIONS
- 5 WARNINGS AND PRECAUTIONS
 - 5.1 Hypersensitivity Reactions
 - 5.2 Coagulation Disorders
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 - 5.4 Treatment of RSV Disease
 - 5.5 Proper Administration
- 6 ADVERSE REACTIONS
 - 6.1 Clinical Studies Experience
 - 6.2 Postmarketing Experience

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Synagis is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in children at high risk of RSV disease.

The following points should be considered when prescribing Synagis:

- Safety and efficacy were established in children with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (less than or equal to 35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD) [see *Clinical Studies* (14)].
- The safety and efficacy of Synagis have not been established for treatment of RSV disease.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of Synagis is 15 mg per kg of body weight given monthly by intramuscular injection. 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. Children who develop an RSV infection should continue to receive monthly doses throughout the RSV season. In the northern hemisphere, the RSV season typically commences in November and lasts through April, but it may begin earlier or persist later in certain communities.

Synagis serum levels are decreased after cardio-pulmonary bypass [see *Clinical Pharmacology* (12.3)]. Children undergoing cardio-pulmonary bypass should receive an additional dose of Synagis as soon as possible after the cardio-pulmonary bypass procedure (even if sooner than a month from the previous dose). Thereafter, doses should be administered monthly as scheduled.

The efficacy of Synagis at doses less than 15 mg per kg, or of dosing less frequently than monthly throughout the RSV season, has not been established.

2.2 Administration Instructions

- **DO NOT DILUTE THE PRODUCT.**
- **DO NOT SHAKE OR VIGOROUSLY AGITATE THE VIAL.**
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials exhibiting particulate matter or discoloration.

CONTRAINDICATIONS

Previous significant hypersensitivity reaction to Synagis. (4)

WARNINGS AND PRECAUTIONS

- Anaphylaxis and anaphylactic shock (including fatal cases), and other severe acute hypersensitivity reactions have been reported. Permanently discontinue Synagis and administer appropriate medications if such reactions occur. (5.1)
- As with any intramuscular injection, Synagis should be given with caution to children with thrombocytopenia or any coagulation disorder. (5.2)
- Palivizumab may interfere with immunological-based RSV diagnostic tests such as some antigen detection-based assays. (5.3, 12.4)

ADVERSE REACTIONS

Adverse reactions occurring greater than or equal to 10% and at least 1% more frequently than placebo are fever and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact MedImmune at 1-877-633-4411 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Safety and effectiveness in children greater than 24 months of age at the start of dosing have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 3/2014

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
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10 OVERDOSAGE

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*Sections or subsections omitted from the full prescribing information are not listed.

- Using aseptic techniques, attach a sterile needle to a sterile syringe. Remove the flip top from the Synagis vial and wipe the rubber stopper with a disinfectant (e.g., 70% isopropyl alcohol). Insert the needle into the vial and withdraw into the syringe an appropriate volume of solution. Administer immediately after drawing the dose into the syringe.
- Synagis should be administered in a dose of 15 mg per kg intramuscularly using aseptic technique, 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 (volume of injection in mL) per month = patient weight (kg) x 15 mg per kg ÷ 100 mg per mL of Synagis. Injection volumes over 1 mL should be given as a divided dose.
- Synagis is supplied as a single-dose vial and does not contain preservatives. Do not re-enter the vial after withdrawal of drug; discard unused portion. Only administer one dose per vial.
- Use sterile disposable syringes and needles. To prevent the transmission of hepatitis viruses or other infectious agents from one person to another, DO NOT reuse syringes and needles.

3 DOSAGE FORMS AND STRENGTHS

Single-dose liquid solution vials: 50 mg per 0.5 mL and 100 mg per 1 mL.

4 CONTRAINDICATIONS

Synagis is contraindicated in children who have had a previous significant hypersensitivity reaction to Synagis [see *Warnings and Precautions* (5.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Cases of anaphylaxis and anaphylactic shock, including fatal cases, have been reported following initial exposure or re-exposure to Synagis. Other acute hypersensitivity reactions, which may be severe, have also been reported on initial exposure or re-exposure to Synagis. Signs and symptoms may include urticaria, pruritus, angioedema, dyspnea, respiratory failure, cyanosis, hypotonia, hypotension, and unresponsiveness. The relationship between these reactions and the development of antibodies to Synagis is unknown. If a significant hypersensitivity reaction occurs with Synagis, its use should be permanently discontinued. **If anaphylaxis or other significant hypersensitivity reaction occurs, administer appropriate medications (e.g., epinephrine) and provide supportive care as required.** If a mild hypersensitivity reaction occurs, clinical judgment should be used regarding cautious readministration of Synagis.

5.2 Coagulation Disorders

Synagis is for intramuscular use only. As with any intramuscular injection, Synagis should be given with caution to children with thrombocytopenia or any coagulation disorder.

5.3 RSV Diagnostic Test Interference

Palivizumab may interfere with immunological-based RSV diagnostic tests such as some antigen detection-based assays. In addition, palivizumab inhibits virus replication in cell culture, and therefore may also interfere with viral culture assays. Palivizumab does not interfere with reverse transcriptase-polymerase chain reaction based assays. Assay interference could lead to false-negative RSV diagnostic test results. Therefore, diagnostic test results, when obtained, should be used in conjunction with clinical findings to guide medical decisions [see *Microbiology* (12.4)].

5.4 Treatment of RSV Disease

The safety and efficacy of Synagis have not been established for treatment of RSV disease.

5.5 Proper Administration

The single-dose vial of Synagis does not contain a preservative. Administration of Synagis should occur immediately after dose withdrawal from the vial. The vial should not be re-entered. Discard any unused portion.

6 ADVERSE REACTIONS

The most serious adverse reactions occurring with Synagis are anaphylaxis and other acute hypersensitivity reactions [see *Warnings and Precautions* (5.1)].

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to Synagis (n=1639) compared with placebo (n=1143) in children 3 days to 24.1 months of age at high risk of RSV-related hospitalization in two clinical trials. Trial 1 was conducted during a single RSV season and studied a total of 1502 children less than or equal to 24 months of age with BPD or infants with premature birth (less than or equal to 35 weeks gestation) who were less than or equal to 6 months of age at study entry. Trial 2 was conducted over four consecutive seasons among a total of 1287 children less than or equal to 24 months of age with hemodynamically significant congenital heart disease.

In Trials 1 and 2 combined, fever and rash were each reported more frequently among Synagis than placebo recipients, 27% versus 25%, and 12% versus 10%, respectively. Adverse reactions observed in the 153-patient crossover study comparing the liquid and lyophilized formulations were comparable for the two formulations, and were similar to those observed with Synagis in Trials 1 and 2.

Immunogenicity

In Trial 1, the incidence of anti-palivizumab antibody following the fourth injection was 1.1% in the placebo group and 0.7% in the Synagis group. In children receiving Synagis for a second season, one of the fifty-six children had transient, low titer reactivity. This reactivity was not associated with adverse events or alteration in serum concentrations. Immunogenicity was not assessed in Trial 2.

A trial of high-risk preterm children less than or equal to 24 months of age was conducted to evaluate the immunogenicity of the lyophilized formulation of Synagis (used in Trials 1 and 2 above) and the liquid formulation of Synagis. Three hundred seventy-nine children contributed to the 4 to 6 months post-final dose analysis. The rate of anti-palivizumab antibodies at this time point was low in both formulation groups (anti-palivizumab antibodies were not detected in any subject in the liquid formulation group and were detected in one subject in the lyophilized group (0.5%), with an overall rate of 0.3% for both treatment groups combined).

These data reflect the percentage of children whose test results were considered positive for antibodies to palivizumab in an enzyme-linked immunosorbent assay (ELISA) and are highly dependent on the sensitivity and specificity of the assay.

The ELISA has substantial limitations in detecting anti-palivizumab antibodies in the presence of palivizumab. Immunogenicity samples tested with the ELISA assay likely contained palivizumab at levels that may interfere with the detection of anti-palivizumab antibodies.

An electrochemical luminescence (ECL) based immunogenicity assay, with a higher tolerance for palivizumab presence compared to the ELISA, was used to evaluate the presence of anti-palivizumab antibodies in subject samples from two additional clinical trials. The rates of anti-palivizumab antibody positive results in these trials were 1.1% and 1.5%.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Synagis. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: severe thrombocytopenia (platelet count less than 50,000 per microliter)

General Disorders and Administration Site Conditions: injection site reactions

Limited information from post-marketing reports suggests that, within a single RSV season, adverse events after a sixth or greater dose of Synagis are similar in character and frequency to those after the initial five doses.

7 DRUG INTERACTIONS

No formal drug-drug interaction studies were conducted. In Trial 1, the proportions of children in the placebo and Synagis groups who received routine childhood vaccines, influenza vaccine, bronchodilators, or corticosteroids were similar and no incremental increase in adverse reactions was observed among children receiving these agents.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Synagis is not indicated for adult usage. It is not known whether Synagis can cause fetal harm or could affect reproductive capacity when administered to a pregnant woman.

Animal Data

Animal reproduction studies have not been conducted.

8.4 Pediatric Use

The safety and effectiveness of Synagis in children greater than 24 months of age at the start of dosing have not been established.

10 OVERDOSAGE

Overdoses with doses up to 85 mg per kg have been reported in clinical studies and post-marketing experience with Synagis, and in some cases, adverse reactions were reported. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

11 DESCRIPTION

Palivizumab is a humanized monoclonal antibody (IgG1 κ) produced by recombinant DNA technology, directed to an epitope in the A antigenic site of the F protein of RSV. Palivizumab is a composite of human (95%) and murine (5%) antibody sequences. The human heavy chain sequence was derived from the constant domains of human IgG1 and the variable framework regions of the V_H genes Cor and Cess. The human light chain sequence was derived from the constant domain of C κ and the variable framework regions of the V_L gene K104 with J κ -4. The murine sequences were derived from a murine monoclonal antibody, Mab 1129, in a process that involved the grafting of the murine complementarity determining regions into the human antibody frameworks. Palivizumab is composed of two heavy chains and two light chains and has a molecular weight of approximately 148,000 Daltons.

Synagis is supplied as a sterile, preservative-free liquid solution at 100 mg per mL to be administered by intramuscular injection. Thimerosal or other mercury-containing salts are not used in the production of Synagis. The solution has a pH of 6.0 and should appear clear or slightly opalescent.

Each 100 mg single-dose vial of Synagis liquid solution contains 100 mg of palivizumab and also contains chloride (0.5 mg), glycine (0.1 mg), and histidine (3.9 mg), in a volume of 1 mL. Each 50 mg single-dose vial of Synagis liquid solution contains 50 mg of palivizumab and also contains chloride (0.2 mg), glycine (0.06 mg), and histidine (1.9 mg), in a volume of 0.5 mL.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Palivizumab is a recombinant humanized monoclonal antibody with anti-RSV activity [see *Microbiology* (12.4)].

12.3 Pharmacokinetics

In children less than or equal to 24 months of age without congenital heart disease (CHD), the mean half-life of palivizumab was 20 days and monthly intramuscular doses of 15 mg per kg achieved mean \pm SD 30 day trough serum drug concentrations of 37 \pm 21 mcg per mL after the first injection, 57 \pm 41 mcg per mL after the second injection, 68 \pm 51 mcg per mL after the third injection, and 72 \pm 50 mcg per mL after the fourth injection. Trough concentrations following the first and fourth Synagis dose were similar in children with CHD and in non-cardiac patients. In children given Synagis for a second season, the mean \pm SD serum concentrations following the first and fourth injections were 61 \pm 17 mcg per mL and 86 \pm 31 mcg per mL, respectively.

In 139 children less than or equal to 24 months of age with hemodynamically significant CHD who received Synagis and underwent cardio-pulmonary bypass for open-heart surgery, the mean \pm SD serum palivizumab concentration was 98 \pm 52 mcg per mL before bypass and declined to 41 \pm 33 mcg per mL after bypass, a reduction of 58% [see *Dosage and Administration* (2.1)]. The clinical significance of this reduction is unknown.

Specific studies were not conducted to evaluate the effects of demographic parameters on palivizumab systemic exposure. However, no effects of gender, age, body weight, or race on palivizumab serum trough concentrations were observed in a clinical study with 639 children with CHD (less than or equal to 24 months of age) receiving five monthly intramuscular injections of 15 mg per kg of Synagis.

The pharmacokinetics and safety of Synagis liquid solution and Synagis lyophilized formulation administered via intramuscular injection at 15 mg per kg were studied in a cross-over trial of 153 infants less than or equal to 6 months of age with a history of prematurity. The results of this trial indicated that the trough serum concentrations of palivizumab were comparable between the liquid solution and the lyophilized formulation, which was the formulation used in the clinical studies. A population pharmacokinetic analysis was performed across 22 studies in 1800 patients (1684 pediatric and 116 adult patients) to characterize palivizumab pharmacokinetics and inter-subject variability in serum concentrations. Palivizumab pharmacokinetics was described by a two-compartment linear model with an elimination half-life of 24.5 days in pediatric patients. Clearance of palivizumab in a typical pediatric patient (body weight 4.5 kg) less than or equal to 24 months of age without CHD was estimated to be 11 mL per day with a bioavailability of 70% following intramuscular administration. The inter-patient variability in drug clearance was 48.7% (CV%). Covariate analysis did not identify any factors that could account for the inter-patient variability in order to predict serum concentrations a priori in an individual patient.

12.4 Microbiology

Mechanism of Action

Palivizumab, a recombinant humanized monoclonal antibody which provides passive immunity against RSV, acts by binding the RSV envelope fusion protein (RSV F) on the surface of the virus and blocking a critical step in the membrane fusion process. Palivizumab also prevents cell-to-cell fusion of RSV-infected cells.

Antiviral Activity

The antiviral activity of palivizumab was assessed in a microneutralization assay in which increasing concentrations of antibody were incubated with RSV prior to addition of the human epithelial cells HEP-2. After incubation for 4-5 days, RSV antigen was measured in an ELISA assay. The neutralization titer (50% effective concentration [EC₅₀]) is expressed as the antibody concentration required to reduce detection of RSV antigen by 50% compared with untreated virus-infected cells. Palivizumab exhibited median EC₅₀ values of 0.65 mcg per mL (mean 0.75 ± 0.53 mcg per mL; n=69, range 0.07-2.89 mcg per mL) and 0.28 mcg per mL (mean 0.35 ± 0.23 mcg per mL; n=35, range 0.03-0.88 mcg per mL) against clinical RSV A and RSV B isolates, respectively. The majority of clinical RSV isolates tested (n=96) were collected from subjects across the United States (CA, CO, CT, IL, MA, NC, NY, PA, RI, TN, TX, VA), with the remainder from Japan (n=1), Australia (n=5) and Israel (n=2). These isolates encoded the most common RSV F sequence polymorphisms found among clinical isolates worldwide.

Palivizumab serum concentrations of greater than or equal to 40 mcg per mL have been shown to reduce pulmonary RSV replication in the cotton rat model of RSV infection by 100-fold.

Resistance

Palivizumab binds a highly conserved region on the extracellular domain of mature RSV F, referred to as antigenic site II or site A, which encompasses amino acids 262 to 275. All RSV mutants that exhibit resistance to palivizumab have been shown to contain amino acid changes in this region on the F protein.

F protein sequence variations within antigenic site A: Amino acid substitutions in antigenic site A selected either in cell culture, in animal models, or in human subjects that resulted in palivizumab resistance were N262D, N268I, K272E/M/N/Q/T, and S275F/L. RSV variants expressing the K272N substitution in F protein showed a 5164 ± 1731-fold decrease in susceptibility (i.e., fold increase in EC₅₀ value) when compared to the wild-type RSV, while variants containing the N262D, S275F/L, or K272E/M/N/Q/T substitutions showed a greater than 25,000-fold decrease in susceptibility to palivizumab. The N268I substitution conferred partial resistance to palivizumab; however, fold changes in susceptibility were not quantified for this mutant. Studies carried out to investigate the mechanism of virus escape from palivizumab showed a correlation between antibody binding and virus neutralization. RSV with substitutions in antigenic site A that were resistant to neutralization by palivizumab did not bind to palivizumab.

At least one of the palivizumab resistance-associated substitutions, N262D, K272E/Q, or S275F/L was identified in 8 of 126 clinical RSV (59 RSV A and 67 RSV B) isolates from subjects who failed immunoprophylaxis, resulting in a combined resistance-associated mutation frequency of 6.3%. A review of clinical findings revealed no association between antigenic A site sequence changes and RSV disease severity among children receiving palivizumab immunoprophylaxis who develop RSV lower respiratory tract disease.

Analysis of 254 clinical RSV isolates (145 RSV A and 109 RSV B) collected from immunoprophylaxis-naïve subjects revealed palivizumab resistance-associated substitutions in 2 (1 with N262D and 1 with S275F), resulting in a resistance-associated mutation frequency of 0.79%.

F protein sequence variations outside antigenic site A: In addition to the sequence variations in antigenic site A known to confer palivizumab resistance, F protein substitutions T100A, G139S, N165D/V406I; T326A, V450A in RSV A, and T74I, A147V, I206L, S285G, V450I, T455I in RSV B were identified in viruses isolated from failures of immunoprophylaxis. These substitutions were not identified in RSV F sequences derived from 254 clinical isolates from immunoprophylaxis-naïve subjects and thus are considered treatment-associated and non-polymorphic. Recombinant RSV B encoding the S285G substitution exhibited palivizumab sensitivity (EC₅₀ value = 0.39 ± 0.02 mcg per mL) similar to recombinant wild-type RSV B (EC₅₀ value = 0.17 ± 0.02 mcg per mL).

Palivizumab susceptibility of RSV encoding common F protein sequence polymorphisms located proximal to antigenic site A was evaluated. Recombinant RSV A encoding N276S (EC₅₀ value = 0.72 ± 0.07 mcg per mL), and recombinant RSV B with S276N (EC₅₀ value = 0.42 ± 0.04 mcg per mL), exhibited sensitivities comparable to the corresponding recombinant wild-type RSV A (EC₅₀ value = 0.63 ± 0.22 mcg per mL) and RSV B (EC₅₀ value = 0.23 ± 0.07 mcg per mL). Likewise, RSV B clinical isolates containing the polymorphic variation V278A were at least as sensitive to neutralization by palivizumab (EC₅₀ range 0.08-0.45 mcg per mL) as laboratory strains of wild-type RSV B (EC₅₀ value = 0.54 ± 0.08 mcg per mL). No known polymorphic or non-polymorphic sequence variations outside the antigenic site A on RSV F have been demonstrated to render RSV resistant to neutralization by palivizumab.

Interference of RSV Diagnostic Assays by Palivizumab

Interference with immunologically-based RSV diagnostic assays by palivizumab has been observed in laboratory studies. Rapid chromatographic/enzyme immunoassays (CIA/EIA), immunofluorescence assays (IFA), and direct immunofluorescence assays (DFA) using monoclonal antibodies targeting RSV F protein may be inhibited. Therefore, caution should be used in interpreting negative immunological assay results when clinical observations are consistent with RSV infection. A reverse transcriptase-polymerase chain reaction (RT-PCR) assay, which is not inhibited by palivizumab, may prove useful for laboratory confirmation of RSV infection [see *Warnings and Precautions* (5.3)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis, mutagenesis, and reproductive toxicity studies have not been performed.

14 CLINICAL STUDIES

The safety and efficacy of Synagis were assessed in two randomized, double-blind, placebo-controlled trials of prophylaxis against RSV infection in children at high risk of an RSV-related hospitalization. Trial 1 was conducted during a single RSV season and studied a total of 1502 children less than or equal to 24 months of age with BPD or infants with premature birth (less than or equal to 35 weeks gestation) who were less than or equal to 6 months of age at study entry. Trial 2 was conducted over four consecutive seasons among a total of 1287 children less than or equal to 24 months of age with hemodynamically significant congenital heart disease. In both trials participants received 15 mg per kg Synagis or an equivalent volume of placebo via intramuscular injection monthly for five injections and were followed for 150 days from randomization. In Trial 1, 99% of all subjects completed the study and 93% completed all five injections. In Trial 2, 96% of all subjects completed the study and 92% completed all five injections. The incidence of RSV hospitalization is shown in Table 1. The results were shown to be statistically significant using Fisher's exact test.

Table 1: Incidence of RSV Hospitalization by Treatment Group

Trial		Placebo	Synagis	Difference Between Groups	Relative Reduction
Trial 1 Impact-RSV	N	500	1002		
	Hospitalization	53 (10.6%)	48 (4.8%)	5.8%	55%
Trial 2 CHD	N	648	639		
	Hospitalization	63 (9.7%)	34 (5.3%)	4.4%	45%

In Trial 1, the reduction of RSV hospitalization was observed both in children with BPD (34/266 [12.8%] placebo versus 39/496 [7.9%] Synagis) and in premature infants without BPD (19/234 [8.1%] placebo versus 9/506 [1.8%] Synagis). In Trial 2, reductions were observed in acyanotic (36/305 [11.8%] placebo versus 15/300 [5.0%] Synagis) and cyanotic children (27/343 [7.9%] placebo versus 19/339 [5.6%] Synagis).

The clinical studies do not suggest that RSV infection was less severe among children hospitalized with RSV infection who received Synagis for RSV prophylaxis compared to those who received placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

Synagis is supplied in single-dose vials as a preservative-free, sterile liquid solution at 100 mg per mL for intramuscular injection.

50 mg vial NDC 60574-4114-1

The 50 mg vial contains 50 mg Synagis in 0.5 mL.

100 mg vial NDC 60574-4113-1

The 100 mg vial contains 100 mg Synagis in 1 mL.

The rubber stopper used for sealing vials of Synagis is not made with natural rubber latex.

Storage

Upon receipt and until use, Synagis should be stored between 2°C and 8°C (36°F and 46°F) in its original container. DO NOT freeze. DO NOT use beyond the expiration date.

17 PATIENT COUNSELING INFORMATION

o **“Advise the patient to read the FDA-approved patient labeling (Patient Information)”**

The healthcare provider should discuss the potential benefits and risks of Synagis with the parents or guardians of Synagis recipients. Parents or guardians should be informed of the possible side effects of Synagis and of the signs and symptoms of potential allergic reactions and should be advised of the appropriate actions. Parents or guardians should understand the dosing schedule and the importance of compliance with the full course of therapy.

Synagis® is a registered trademark of MedImmune, LLC.



Manufactured by:

MedImmune, LLC
Gaithersburg, MD 20878
U.S. License No. 1799
1-877-633-4411

RAL-SYNNV17
Component No.: 26920A

PATIENT INFORMATION
SYNAGIS® (Sĭ-nă-jĭs)
(palivizumab)
Injection

Read this Patient Information before your child starts receiving SYNAGIS and before each injection. The information may have changed. This leaflet does not take the place of talking with your child's healthcare provider about your child's condition or treatment.

What is SYNAGIS?

SYNAGIS is a prescription medication that is used to help prevent a serious lung disease caused by Respiratory Syncytial Virus (RSV). Your child is prescribed SYNAGIS because he or she is at high risk for severe lung disease from RSV.

SYNAGIS contains man-made, disease-fighting proteins called antibodies. These antibodies help prevent RSV disease. Children at high risk for severe RSV disease often do not have enough of their own antibodies. SYNAGIS is used in certain groups of children to help prevent severe RSV disease by increasing protective RSV antibodies.

SYNAGIS is not used to treat the symptoms of RSV disease once a child already has it. It is only used to prevent RSV disease.

SYNAGIS is not for adults or for children older than 24 months of age at the start of dosing.

Who should not receive SYNAGIS?

Your child should not receive SYNAGIS if they have ever had a severe allergic reaction to it. Signs and symptoms of a severe allergic reaction could include:

- severe rash, hives, or itching skin
- swelling of the lips, tongue, or face
- closing of the throat, difficulty swallowing
- difficult, rapid, or irregular breathing
- bluish color of skin, lips, or under fingernails
- muscle weakness or floppiness
- a drop in blood pressure
- unresponsiveness

What should I tell my child's healthcare provider before my child receives SYNAGIS?

Tell your child's healthcare provider about:

- **any reactions** you believe your child has ever had to SYNAGIS.
- **any bleeding or bruising problems.** SYNAGIS is given by injection. If your child has a problem with bleeding or bruises easily, an injection could cause a problem.
- **any other medical problems.**

Tell your child's healthcare provider about all the medicines your child takes, including prescription and non-prescription medicines, vitamins, and herbal supplements. Especially tell your child's healthcare provider if your child takes a blood thinner medicine.

How is SYNAGIS given?

- SYNAGIS is given as a monthly injection, usually in the thigh (leg) muscle, by your child's healthcare provider. Your child's healthcare provider will prescribe the amount of SYNAGIS that is right for your child (based on their weight).
- Your child's healthcare provider will give you detailed instructions on when SYNAGIS will be given.
 - "RSV season" is a term used to describe the time of year when RSV infections most commonly occur (usually fall through spring in most parts of the country). During this time, when RSV is most active, your child will need to receive SYNAGIS shots. Your child's healthcare provider can tell you when the RSV season starts in your area.
 - Your child should receive their **first SYNAGIS shot before the RSV season starts** to help protect them before RSV becomes active. If the season has already started, your child should receive their first SYNAGIS shot as soon as possible to help protect them when exposure to the virus is more likely.

- **SYNAGIS is needed every 28-30 days during the RSV season.** Each dose of SYNAGIS helps protect your child from severe RSV disease for about a month. **Keep all appointments with your child's healthcare provider.**

- **If your child misses an injection, talk to your healthcare provider and schedule another injection as soon as possible.**
- Your child may still get severe RSV disease after receiving SYNAGIS; talk to your child's healthcare provider about what symptoms to look for. If your child has an RSV infection, they should continue to get their scheduled SYNAGIS injections to help prevent severe disease from new RSV infections.
- If your child has certain types of heart disease and has corrective surgery, your healthcare provider may need to give your child an additional SYNAGIS injection soon after surgery.

What are the possible side effects of SYNAGIS?

Synagis may cause serious side effects including:

- Severe allergic reactions (may occur after any dose of SYNAGIS). Such reactions may be life-threatening or cause death.
 - See "Who should not take SYNAGIS?" for a list of signs and symptoms.
- Unusual bruising or groups of tiny red spots on the skin.

Call your child's healthcare provider or get medical help right away if your child has any of the serious side effects listed above after any dose of SYNAGIS.

Common side effects of SYNAGIS include:

- fever
- rash

Other possible side effects include skin reactions around the area where the shot was given (like redness, swelling, warmth, or discomfort).

These are not all the possible side effects of SYNAGIS. Tell your child's healthcare provider about any side effect that bothers your child or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to MedImmune at 1-877-633-4411.

General Information about SYNAGIS

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets.

This leaflet summarizes important information about SYNAGIS. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about SYNAGIS that is written for health professionals.

For more information, go to www.synagis.com or call 1-877-633-4411.

What are the ingredients in SYNAGIS?

Active Ingredient: palivizumab

Inactive Ingredients: chloride, glycine, and histidine

What is RSV?

Respiratory Syncytial Virus (RSV) is a common virus that is easily spread from person to person. RSV infects nearly all children by their second birthday. In most children, RSV infection is usually no worse than a bad cold. For some children, RSV infection can cause serious lung disease (like pneumonia and bronchiolitis) or breathing problems, and affected children may need to be admitted to the hospital or need emergency care.

Children who are more likely to get severe RSV disease (high-risk children) include babies born prematurely (35 weeks or less) or babies born with certain heart or lung problems.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Synagis® is a registered trademark of MedImmune, LLC.

 **MedImmune**

Manufactured by: MedImmune, LLC

Gaithersburg, MD 20878

Issued March 2014

[DATE]

[HCP First and last name, Title]

[HCP Practice name]

[HCP Address]

[HCP City, State, ZIP]

Dear [HCP First and last name, Title]:

The attached template is offered as a resource a healthcare provider could use when responding to a request from a patient's health benefits company to provide a letter of medical necessity for administering Synagis® (palivizumab). **Attachments to be included with the letter of medical necessity are [original claim form, copy of denial or explanation of benefits, and any other additional supporting documents].** A copy of the full prescribing information for Synagis is attached for your reference. If you need additional references, please contact our medical affairs department at 1-877-MEDI-411 (1-877-633-4411).

Use of the attached letter does not guarantee that the insurance company will provide reimbursement for Synagis, and is not intended to be a substitute for or an influence on the independent medical judgment of the physician.

Important Safety Information

Synagis is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in children at high risk of RSV disease. Safety and efficacy were established in children with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (≤ 35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD). The recommended dose of Synagis is 15 mg/kg of body weight given monthly by intramuscular injection. 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. Children who develop an RSV infection should continue to receive monthly doses throughout the RSV season.

The efficacy of Synagis at doses less than 15 mg/kg, or of dosing less frequently than monthly throughout the RSV season, has not been established.

Synagis is contraindicated in children who have had a previous significant hypersensitivity reaction to Synagis. Cases of anaphylaxis and anaphylactic shock, including fatal cases, have been reported following initial exposure or re-exposure to Synagis. Other acute hypersensitivity reactions, which may be severe, have also been reported on initial exposure or re-exposure to Synagis. The relationship between these reactions and the development of antibodies to Synagis is unknown. If a significant hypersensitivity reaction occurs with Synagis, its use should be permanently discontinued. If a mild hypersensitivity reaction occurs, clinical judgment should be used regarding cautious re-administration of Synagis. As with any intramuscular injection, Synagis should be given with caution to children with thrombocytopenia or any coagulation disorder. Palivizumab may interfere with immunological-based RSV diagnostic tests, such as some antigen detection-based assays.

Adverse reactions occurring greater than or equal to 10% and at least 1% more frequently than placebo are fever and rash. In post-marketing reports, cases of severe thrombocytopenia (platelet count $< 50,000$ /microliter) and injection site reactions have been reported.

Please see accompanying full Prescribing Information for Synagis, including Patient Information.

Sincerely,

The MedImmune Access 360 Team

CONFIDENTIALITY NOTE

The documents accompanying this telecopy transmission contain confidential or privileged information.

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Thank you for your assistance.

#14924A-80807

[Date]

[Contact - usually the medical director]

[Title]

[Name of Health Insurance Company]

[Address]

[City, State, ZIP Code]

Insured: [Name]

Policy Number: [Number]

Group Number: [Number]

Dear [Name of Contact]:

I am writing on behalf of my patient, [name of patient], to appeal [name of health insurance company]'s decision to deny coverage for Synagis[®] (palivizumab) which is prescribed to help prevent serious lower respiratory tract infections caused by respiratory syncytial virus (RSV). This letter documents the medical necessity for this therapy and provides information about the patient's medical history and treatment.

It is my understanding based on your letter of denial dated, [date], that coverage has been denied for the following reason(s):

[List the specific reason(s) for the denial as stated in the denial letter.]

Patient History and Diagnosis

[Provide a brief description of the patient's medical condition here.]

[Include a short summary of the patient's medical history.]

[Explain why the patient is at high risk for being hospitalized for severe RSV Disease.]

[Describe the potential consequences of the child contracting RSV and/or enduring a RSV-related hospitalization.]

[Obtain and attach supporting letters of medical necessity from any specialist that is or has provided care to the patient.]

Synagis Indication Information

Synagis is indicated for the prevention of severe lower respiratory tract disease caused by RSV in pediatric patients at high risk of RSV disease. RSV is ubiquitous, highly contagious, and potentially very serious to high-risk infants and children. RSV is the leading cause of hospitalization among infants in the US (7). The safety and efficacy of palivizumab was established in children with bronchopulmonary dysplasia (BPD) ≤ 24 months of age and infants with a history of premature birth (≤ 35 weeks gestational age) ≤ 6 months of age in a trial conducted during a single RSV season (Connor 1998). A total of 1,502 children less were included in the trial (500 placebo and 1002 palivizumab). In this trial, RSV-related hospitalization rates were significantly reduced in both the premature and BPD children: 12.8% (34/266) placebo versus 7.9% (39/496) palivizumab, and in premature infants without BPD, 8.1% (19/234) placebo versus 1.8% (9/506) palivizumab. The safety and efficacy in children with hemodynamically significant congenital heart disease (CHD) was established in a trial conducted over four consecutive RSV seasons and included total of 1287 children ≤ 24 months of age (Feltus 2003). Palivizumab patients had a 45% relative reduction in RSV-related hospitalization rate (P=0.003): 9.7% (63/648) placebo vs. 5.3% (34/639) palivizumab.

Palivizumab is administered in monthly injections of 15 mg/kg of body weight. The first dose of Synagis should be administered prior to the start of the RSV season and then continued monthly throughout the RSV season. Please see enclosed full prescribing information.

In summary, therapy with Synagis is medically necessary for this patient. Please contact me at [physician telephone number, including area code] if any additional information is required to ensure the prompt handling of this request and/or payment of the associated claims for [name of patient].

Thank you in advance for your immediate attention to this written appeal.

Sincerely,

[Physician's Name]

[Physician's Practice Name]

#14924A-80806

References

Synagis® [package insert]. Gaithersburg, MD: MedImmune, LLC.

Connor EM and the IMpact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics*. 1998;102:531-537.

Feltes TF, et al (Cardiac Synagis Study Group). Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. *J Pediatr*. 2003;143:532-540.

Leader S, Kohlhasse K. respiratory syncytial virus-coded pediatric hospitalizations, 1997-1999. *Pediatr Infect Dis J*. 2002;21:629-32.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SYNAGIS safely and effectively. See full prescribing information for SYNAGIS.

SYNAGIS® (palivizumab) injection for intramuscular use
Initial U.S. Approval: 1998

INDICATIONS AND USAGE

Synagis is a respiratory syncytial virus (RSV) F protein inhibitor monoclonal antibody indicated for the prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease.

- Safety and efficacy were established in children with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (less than or equal to 35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD).
- The safety and efficacy of Synagis have not been established for treatment of RSV disease. (1)

DOSAGE AND ADMINISTRATION

15 mg per kg of body weight, administered intramuscularly prior to commencement of the RSV season and remaining doses administered monthly throughout the RSV season. (2.1)

Children undergoing cardio-pulmonary bypass should receive an additional dose of Synagis as soon as possible after the cardio-pulmonary bypass procedure (even if sooner than a month from the previous dose). Thereafter, doses should be administered monthly as scheduled. (2.1, 12.3)

DOSAGE FORMS AND STRENGTHS

Single-dose liquid solution vials: 50 mg per 0.5 mL and 100 mg per 1 mL. (3)

FULL PRESCRIBING INFORMATION: CONTENTS*

- 1 INDICATIONS AND USAGE**
- 2 DOSAGE AND ADMINISTRATION**
 - 2.1 Dosing Information
 - 2.2 Administration Instructions
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
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 - 5.4 Treatment of RSV Disease
 - 5.5 Proper Administration
- 6 ADVERSE REACTIONS**
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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Synagis is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in children at high risk of RSV disease.

The following points should be considered when prescribing Synagis:

- Safety and efficacy were established in children with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (less than or equal to 35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD) [see *Clinical Studies* (14)].
- The safety and efficacy of Synagis have not been established for treatment of RSV disease.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of Synagis is 15 mg per kg of body weight given monthly by intramuscular injection. 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. Children who develop an RSV infection should continue to receive monthly doses throughout the RSV season. In the northern hemisphere, the RSV season typically commences in November and lasts through April, but it may begin earlier or persist later in certain communities.

Synagis serum levels are decreased after cardio-pulmonary bypass [see *Clinical Pharmacology* (12.3)]. Children undergoing cardio-pulmonary bypass should receive an additional dose of Synagis as soon as possible after the cardio-pulmonary bypass procedure (even if sooner than a month from the previous dose). Thereafter, doses should be administered monthly as scheduled.

The efficacy of Synagis at doses less than 15 mg per kg, or of dosing less frequently than monthly throughout the RSV season, has not been established.

2.2 Administration Instructions

- **DO NOT DILUTE THE PRODUCT.**
- **DO NOT SHAKE OR VIGOROUSLY AGITATE THE VIAL.**
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials exhibiting particulate matter or discoloration.

CONTRAINDICATIONS

Previous significant hypersensitivity reaction to Synagis. (4)

WARNINGS AND PRECAUTIONS

- Anaphylaxis and anaphylactic shock (including fatal cases), and other severe acute hypersensitivity reactions have been reported. Permanently discontinue Synagis and administer appropriate medications if such reactions occur. (5.1)
- As with any intramuscular injection, Synagis should be given with caution to children with thrombocytopenia or any coagulation disorder. (5.2)
- Palivizumab may interfere with immunological-based RSV diagnostic tests such as some antigen detection-based assays. (5.3, 12.4)

ADVERSE REACTIONS

Adverse reactions occurring greater than or equal to 10% and at least 1% more frequently than placebo are fever and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact MedImmune at 1-877-633-4411 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Safety and effectiveness in children greater than 24 months of age at the start of dosing have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 3/2014

7 DRUG INTERACTIONS

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*Sections or subsections omitted from the full prescribing information are not listed.

- Using aseptic techniques, attach a sterile needle to a sterile syringe. Remove the flip top from the Synagis vial and wipe the rubber stopper with a disinfectant (e.g., 70% isopropyl alcohol). Insert the needle into the vial and withdraw into the syringe an appropriate volume of solution. Administer immediately after drawing the dose into the syringe.
- Synagis should be administered in a dose of 15 mg per kg intramuscularly using aseptic technique, 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 (volume of injection in mL) per month = patient weight (kg) x 15 mg per kg ÷ 100 mg per mL of Synagis. Injection volumes over 1 mL should be given as a divided dose.
- Synagis is supplied as a single-dose vial and does not contain preservatives. Do not re-enter the vial after withdrawal of drug; discard unused portion. Only administer one dose per vial.
- Use sterile disposable syringes and needles. To prevent the transmission of hepatitis viruses or other infectious agents from one person to another, DO NOT reuse syringes and needles.

3 DOSAGE FORMS AND STRENGTHS

Single-dose liquid solution vials: 50 mg per 0.5 mL and 100 mg per 1 mL.

4 CONTRAINDICATIONS

Synagis is contraindicated in children who have had a previous significant hypersensitivity reaction to Synagis [see *Warnings and Precautions* (5.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Cases of anaphylaxis and anaphylactic shock, including fatal cases, have been reported following initial exposure or re-exposure to Synagis. Other acute hypersensitivity reactions, which may be severe, have also been reported on initial exposure or re-exposure to Synagis. Signs and symptoms may include urticaria, pruritus, angioedema, dyspnea, respiratory failure, cyanosis, hypotonia, hypotension, and unresponsiveness. The relationship between these reactions and the development of antibodies to Synagis is unknown. If a significant hypersensitivity reaction occurs with Synagis, its use should be permanently discontinued. **If anaphylaxis or other significant hypersensitivity reaction occurs, administer appropriate medications (e.g., epinephrine) and provide supportive care as required.** If a mild hypersensitivity reaction occurs, clinical judgment should be used regarding cautious readministration of Synagis.

5.2 Coagulation Disorders

Synagis is for intramuscular use only. As with any intramuscular injection, Synagis should be given with caution to children with thrombocytopenia or any coagulation disorder.

5.3 RSV Diagnostic Test Interference

Palivizumab may interfere with immunological-based RSV diagnostic tests such as some antigen detection-based assays. In addition, palivizumab inhibits virus replication in cell culture, and therefore may also interfere with viral culture assays. Palivizumab does not interfere with reverse transcriptase-polymerase chain reaction based assays. Assay interference could lead to false-negative RSV diagnostic test results. Therefore, diagnostic test results, when obtained, should be used in conjunction with clinical findings to guide medical decisions [see *Microbiology* (12.4)].

5.4 Treatment of RSV Disease

The safety and efficacy of Synagis have not been established for treatment of RSV disease.

5.5 Proper Administration

The single-dose vial of Synagis does not contain a preservative. Administration of Synagis should occur immediately after dose withdrawal from the vial. The vial should not be re-entered. Discard any unused portion.

6 ADVERSE REACTIONS

The most serious adverse reactions occurring with Synagis are anaphylaxis and other acute hypersensitivity reactions [see *Warnings and Precautions* (5.1)].

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to Synagis (n=1639) compared with placebo (n=1143) in children 3 days to 24.1 months of age at high risk of RSV-related hospitalization in two clinical trials. Trial 1 was conducted during a single RSV season and studied a total of 1502 children less than or equal to 24 months of age with BPD or infants with premature birth (less than or equal to 35 weeks gestation) who were less than or equal to 6 months of age at study entry. Trial 2 was conducted over four consecutive seasons among a total of 1287 children less than or equal to 24 months of age with hemodynamically significant congenital heart disease.

In Trials 1 and 2 combined, fever and rash were each reported more frequently among Synagis than placebo recipients, 27% versus 25%, and 12% versus 10%, respectively. Adverse reactions observed in the 153-patient crossover study comparing the liquid and lyophilized formulations were comparable for the two formulations, and were similar to those observed with Synagis in Trials 1 and 2.

Immunogenicity

In Trial 1, the incidence of anti-palivizumab antibody following the fourth injection was 1.1% in the placebo group and 0.7% in the Synagis group. In children receiving Synagis for a second season, one of the fifty-six children had transient, low titer reactivity. This reactivity was not associated with adverse events or alteration in serum concentrations. Immunogenicity was not assessed in Trial 2.

A trial of high-risk preterm children less than or equal to 24 months of age was conducted to evaluate the immunogenicity of the lyophilized formulation of Synagis (used in Trials 1 and 2 above) and the liquid formulation of Synagis. Three hundred seventy-nine children contributed to the 4 to 6 months post-final dose analysis. The rate of anti-palivizumab antibodies at this time point was low in both formulation groups (anti-palivizumab antibodies were not detected in any subject in the liquid formulation group and were detected in one subject in the lyophilized group (0.5%), with an overall rate of 0.3% for both treatment groups combined).

These data reflect the percentage of children whose test results were considered positive for antibodies to palivizumab in an enzyme-linked immunosorbent assay (ELISA) and are highly dependent on the sensitivity and specificity of the assay.

The ELISA has substantial limitations in detecting anti-palivizumab antibodies in the presence of palivizumab. Immunogenicity samples tested with the ELISA assay likely contained palivizumab at levels that may interfere with the detection of anti-palivizumab antibodies.

An electrochemical luminescence (ECL) based immunogenicity assay, with a higher tolerance for palivizumab presence compared to the ELISA, was used to evaluate the presence of anti-palivizumab antibodies in subject samples from two additional clinical trials. The rates of anti-palivizumab antibody positive results in these trials were 1.1% and 1.5%.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Synagis. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: severe thrombocytopenia (platelet count less than 50,000 per microliter)

General Disorders and Administration Site Conditions: injection site reactions

Limited information from post-marketing reports suggests that, within a single RSV season, adverse events after a sixth or greater dose of Synagis are similar in character and frequency to those after the initial five doses.

7 DRUG INTERACTIONS

No formal drug-drug interaction studies were conducted. In Trial 1, the proportions of children in the placebo and Synagis groups who received routine childhood vaccines, influenza vaccine, bronchodilators, or corticosteroids were similar and no incremental increase in adverse reactions was observed among children receiving these agents.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Synagis is not indicated for adult usage. It is not known whether Synagis can cause fetal harm or could affect reproductive capacity when administered to a pregnant woman.

Animal Data

Animal reproduction studies have not been conducted.

8.4 Pediatric Use

The safety and effectiveness of Synagis in children greater than 24 months of age at the start of dosing have not been established.

10 OVERDOSAGE

Overdoses with doses up to 85 mg per kg have been reported in clinical studies and post-marketing experience with Synagis, and in some cases, adverse reactions were reported. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

11 DESCRIPTION

Palivizumab is a humanized monoclonal antibody (IgG1 κ) produced by recombinant DNA technology, directed to an epitope in the A antigenic site of the F protein of RSV. Palivizumab is a composite of human (95%) and murine (5%) antibody sequences. The human heavy chain sequence was derived from the constant domains of human IgG1 and the variable framework regions of the V_H genes Cor and Cess. The human light chain sequence was derived from the constant domain of C κ and the variable framework regions of the V_L gene K104 with J κ -4. The murine sequences were derived from a murine monoclonal antibody, Mab 1129, in a process that involved the grafting of the murine complementarity determining regions into the human antibody frameworks. Palivizumab is composed of two heavy chains and two light chains and has a molecular weight of approximately 148,000 Daltons.

Synagis is supplied as a sterile, preservative-free liquid solution at 100 mg per mL to be administered by intramuscular injection. Thimerosal or other mercury-containing salts are not used in the production of Synagis. The solution has a pH of 6.0 and should appear clear or slightly opalescent.

Each 100 mg single-dose vial of Synagis liquid solution contains 100 mg of palivizumab and also contains chloride (0.5 mg), glycine (0.1 mg), and histidine (3.9 mg), in a volume of 1 mL. Each 50 mg single-dose vial of Synagis liquid solution contains 50 mg of palivizumab and also contains chloride (0.2 mg), glycine (0.06 mg), and histidine (1.9 mg), in a volume of 0.5 mL.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Palivizumab is a recombinant humanized monoclonal antibody with anti-RSV activity [see *Microbiology* (12.4)].

12.3 Pharmacokinetics

In children less than or equal to 24 months of age without congenital heart disease (CHD), the mean half-life of palivizumab was 20 days and monthly intramuscular doses of 15 mg per kg achieved mean \pm SD 30 day trough serum drug concentrations of 37 \pm 21 mcg per mL after the first injection, 57 \pm 41 mcg per mL after the second injection, 68 \pm 51 mcg per mL after the third injection, and 72 \pm 50 mcg per mL after the fourth injection. Trough concentrations following the first and fourth Synagis dose were similar in children with CHD and in non-cardiac patients. In children given Synagis for a second season, the mean \pm SD serum concentrations following the first and fourth injections were 61 \pm 17 mcg per mL and 86 \pm 31 mcg per mL, respectively.

In 139 children less than or equal to 24 months of age with hemodynamically significant CHD who received Synagis and underwent cardio-pulmonary bypass for open-heart surgery, the mean \pm SD serum palivizumab concentration was 98 \pm 52 mcg per mL before bypass and declined to 41 \pm 33 mcg per mL after bypass, a reduction of 58% [see *Dosage and Administration* (2.1)]. The clinical significance of this reduction is unknown.

Specific studies were not conducted to evaluate the effects of demographic parameters on palivizumab systemic exposure. However, no effects of gender, age, body weight, or race on palivizumab serum trough concentrations were observed in a clinical study with 639 children with CHD (less than or equal to 24 months of age) receiving five monthly intramuscular injections of 15 mg per kg of Synagis.

The pharmacokinetics and safety of Synagis liquid solution and Synagis lyophilized formulation administered via intramuscular injection at 15 mg per kg were studied in a cross-over trial of 153 infants less than or equal to 6 months of age with a history of prematurity. The results of this trial indicated that the trough serum concentrations of palivizumab were comparable between the liquid solution and the lyophilized formulation, which was the formulation used in the clinical studies. A population pharmacokinetic analysis was performed across 22 studies in 1800 patients (1684 pediatric and 116 adult patients) to characterize palivizumab pharmacokinetics and inter-subject variability in serum concentrations. Palivizumab pharmacokinetics was described by a two-compartment linear model with an elimination half-life of 24.5 days in pediatric patients. Clearance of palivizumab in a typical pediatric patient (body weight 4.5 kg) less than or equal to 24 months of age without CHD was estimated to be 11 mL per day with a bioavailability of 70% following intramuscular administration. The inter-patient variability in drug clearance was 48.7% (CV%). Covariate analysis did not identify any factors that could account for the inter-patient variability in order to predict serum concentrations a priori in an individual patient.

12.4 Microbiology

Mechanism of Action

Palivizumab, a recombinant humanized monoclonal antibody which provides passive immunity against RSV, acts by binding the RSV envelope fusion protein (RSV F) on the surface of the virus and blocking a critical step in the membrane fusion process. Palivizumab also prevents cell-to-cell fusion of RSV-infected cells.

Antiviral Activity

The antiviral activity of palivizumab was assessed in a microneutralization assay in which increasing concentrations of antibody were incubated with RSV prior to addition of the human epithelial cells HEP-2. After incubation for 4-5 days, RSV antigen was measured in an ELISA assay. The neutralization titer (50% effective concentration [EC₅₀]) is expressed as the antibody concentration required to reduce detection of RSV antigen by 50% compared with untreated virus-infected cells. Palivizumab exhibited median EC₅₀ values of 0.65 mcg per mL (mean 0.75 ± 0.53 mcg per mL; n=69, range 0.07-2.89 mcg per mL) and 0.28 mcg per mL (mean 0.35 ± 0.23 mcg per mL; n=35, range 0.03-0.88 mcg per mL) against clinical RSV A and RSV B isolates, respectively. The majority of clinical RSV isolates tested (n=96) were collected from subjects across the United States (CA, CO, CT, IL, MA, NC, NY, PA, RI, TN, TX, VA), with the remainder from Japan (n=1), Australia (n=5) and Israel (n=2). These isolates encoded the most common RSV F sequence polymorphisms found among clinical isolates worldwide.

Palivizumab serum concentrations of greater than or equal to 40 mcg per mL have been shown to reduce pulmonary RSV replication in the cotton rat model of RSV infection by 100-fold.

Resistance

Palivizumab binds a highly conserved region on the extracellular domain of mature RSV F, referred to as antigenic site II or site A, which encompasses amino acids 262 to 275. All RSV mutants that exhibit resistance to palivizumab have been shown to contain amino acid changes in this region on the F protein.

F protein sequence variations within antigenic site A: Amino acid substitutions in antigenic site A selected either in cell culture, in animal models, or in human subjects that resulted in palivizumab resistance were N262D, N268I, K272E/M/N/Q/T, and S275F/L. RSV variants expressing the K272N substitution in F protein showed a 5164 ± 1731-fold decrease in susceptibility (i.e., fold increase in EC₅₀ value) when compared to the wild-type RSV, while variants containing the N262D, S275F/L, or K272E/M/N/Q/T substitutions showed a greater than 25,000-fold decrease in susceptibility to palivizumab. The N268I substitution conferred partial resistance to palivizumab; however, fold changes in susceptibility were not quantified for this mutant. Studies carried out to investigate the mechanism of virus escape from palivizumab showed a correlation between antibody binding and virus neutralization. RSV with substitutions in antigenic site A that were resistant to neutralization by palivizumab did not bind to palivizumab.

At least one of the palivizumab resistance-associated substitutions, N262D, K272E/Q, or S275F/L was identified in 8 of 126 clinical RSV (59 RSV A and 67 RSV B) isolates from subjects who failed immunoprophylaxis, resulting in a combined resistance-associated mutation frequency of 6.3%. A review of clinical findings revealed no association between antigenic A site sequence changes and RSV disease severity among children receiving palivizumab immunoprophylaxis who develop RSV lower respiratory tract disease.

Analysis of 254 clinical RSV isolates (145 RSV A and 109 RSV B) collected from immunoprophylaxis-naïve subjects revealed palivizumab resistance-associated substitutions in 2 (1 with N262D and 1 with S275F), resulting in a resistance-associated mutation frequency of 0.79%.

F protein sequence variations outside antigenic site A: In addition to the sequence variations in antigenic site A known to confer palivizumab resistance, F protein substitutions T100A, G139S, N165D/V406I; T326A, V450A in RSV A, and T74I, A147V, I206L, S285G, V450I, T455I in RSV B were identified in viruses isolated from failures of immunoprophylaxis. These substitutions were not identified in RSV F sequences derived from 254 clinical isolates from immunoprophylaxis-naïve subjects and thus are considered treatment-associated and non-polymorphic. Recombinant RSV B encoding the S285G substitution exhibited palivizumab sensitivity (EC₅₀ value = 0.39 ± 0.02 mcg per mL) similar to recombinant wild-type RSV B (EC₅₀ value = 0.17 ± 0.02 mcg per mL).

Palivizumab susceptibility of RSV encoding common F protein sequence polymorphisms located proximal to antigenic site A was evaluated. Recombinant RSV A encoding N276S (EC₅₀ value = 0.72 ± 0.07 mcg per mL), and recombinant RSV B with S276N (EC₅₀ value = 0.42 ± 0.04 mcg per mL), exhibited sensitivities comparable to the corresponding recombinant wild-type RSV A (EC₅₀ value = 0.63 ± 0.22 mcg per mL) and RSV B (EC₅₀ value = 0.23 ± 0.07 mcg per mL). Likewise, RSV B clinical isolates containing the polymorphic variation V278A were at least as sensitive to neutralization by palivizumab (EC₅₀ range 0.08-0.45 mcg per mL) as laboratory strains of wild-type RSV B (EC₅₀ value = 0.54 ± 0.08 mcg per mL). No known polymorphic or non-polymorphic sequence variations outside the antigenic site A on RSV F have been demonstrated to render RSV resistant to neutralization by palivizumab.

Interference of RSV Diagnostic Assays by Palivizumab

Interference with immunologically-based RSV diagnostic assays by palivizumab has been observed in laboratory studies. Rapid chromatographic/enzyme immunoassays (CIA/EIA), immunofluorescence assays (IFA), and direct immunofluorescence assays (DFA) using monoclonal antibodies targeting RSV F protein may be inhibited. Therefore, caution should be used in interpreting negative immunological assay results when clinical observations are consistent with RSV infection. A reverse transcriptase-polymerase chain reaction (RT-PCR) assay, which is not inhibited by palivizumab, may prove useful for laboratory confirmation of RSV infection [see *Warnings and Precautions* (5.3)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis, mutagenesis, and reproductive toxicity studies have not been performed.

14 CLINICAL STUDIES

The safety and efficacy of Synagis were assessed in two randomized, double-blind, placebo-controlled trials of prophylaxis against RSV infection in children at high risk of an RSV-related hospitalization. Trial 1 was conducted during a single RSV season and studied a total of 1502 children less than or equal to 24 months of age with BPD or infants with premature birth (less than or equal to 35 weeks gestation) who were less than or equal to 6 months of age at study entry. Trial 2 was conducted over four consecutive seasons among a total of 1287 children less than or equal to 24 months of age with hemodynamically significant congenital heart disease. In both trials participants received 15 mg per kg Synagis or an equivalent volume of placebo via intramuscular injection monthly for five injections and were followed for 150 days from randomization. In Trial 1, 99% of all subjects completed the study and 93% completed all five injections. In Trial 2, 96% of all subjects completed the study and 92% completed all five injections. The incidence of RSV hospitalization is shown in Table 1. The results were shown to be statistically significant using Fisher's exact test.

Table 1: Incidence of RSV Hospitalization by Treatment Group

Trial		Placebo	Synagis	Difference Between Groups	Relative Reduction
Trial 1 Impact-RSV	N	500	1002		
	Hospitalization	53 (10.6%)	48 (4.8%)	5.8%	55%
Trial 2 CHD	N	648	639		
	Hospitalization	63 (9.7%)	34 (5.3%)	4.4%	45%

In Trial 1, the reduction of RSV hospitalization was observed both in children with BPD (34/266 [12.8%] placebo versus 39/496 [7.9%] Synagis) and in premature infants without BPD (19/234 [8.1%] placebo versus 9/506 [1.8%] Synagis). In Trial 2, reductions were observed in acyanotic (36/305 [11.8%] placebo versus 15/300 [5.0%] Synagis) and cyanotic children (27/343 [7.9%] placebo versus 19/339 [5.6%] Synagis).

The clinical studies do not suggest that RSV infection was less severe among children hospitalized with RSV infection who received Synagis for RSV prophylaxis compared to those who received placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

Synagis is supplied in single-dose vials as a preservative-free, sterile liquid solution at 100 mg per mL for intramuscular injection.

50 mg vial NDC 60574-4114-1

The 50 mg vial contains 50 mg Synagis in 0.5 mL.

100 mg vial NDC 60574-4113-1

The 100 mg vial contains 100 mg Synagis in 1 mL.

The rubber stopper used for sealing vials of Synagis is not made with natural rubber latex.

Storage

Upon receipt and until use, Synagis should be stored between 2°C and 8°C (36°F and 46°F) in its original container. DO NOT freeze. DO NOT use beyond the expiration date.

17 PATIENT COUNSELING INFORMATION

o **“Advise the patient to read the FDA-approved patient labeling (Patient Information)”**

The healthcare provider should discuss the potential benefits and risks of Synagis with the parents or guardians of Synagis recipients. Parents or guardians should be informed of the possible side effects of Synagis and of the signs and symptoms of potential allergic reactions and should be advised of the appropriate actions. Parents or guardians should understand the dosing schedule and the importance of compliance with the full course of therapy.

Synagis® is a registered trademark of MedImmune, LLC.



Manufactured by:

MedImmune, LLC
Gaithersburg, MD 20878
U.S. License No. 1799
1-877-633-4411

RAL-SYNNV17
Component No.: 26920A

PATIENT INFORMATION
SYNAGIS® (Sĭ-nă-jĭs)
(palivizumab)
Injection

Read this Patient Information before your child starts receiving SYNAGIS and before each injection. The information may have changed. This leaflet does not take the place of talking with your child's healthcare provider about your child's condition or treatment.

What is SYNAGIS?

SYNAGIS is a prescription medication that is used to help prevent a serious lung disease caused by Respiratory Syncytial Virus (RSV). Your child is prescribed SYNAGIS because he or she is at high risk for severe lung disease from RSV.

SYNAGIS contains man-made, disease-fighting proteins called antibodies. These antibodies help prevent RSV disease. Children at high risk for severe RSV disease often do not have enough of their own antibodies. SYNAGIS is used in certain groups of children to help prevent severe RSV disease by increasing protective RSV antibodies.

SYNAGIS is not used to treat the symptoms of RSV disease once a child already has it. It is only used to prevent RSV disease.

SYNAGIS is not for adults or for children older than 24 months of age at the start of dosing.

Who should not receive SYNAGIS?

Your child should not receive SYNAGIS if they have ever had a severe allergic reaction to it. Signs and symptoms of a severe allergic reaction could include:

- severe rash, hives, or itching skin
- swelling of the lips, tongue, or face
- closing of the throat, difficulty swallowing
- difficult, rapid, or irregular breathing
- bluish color of skin, lips, or under fingernails
- muscle weakness or floppiness
- a drop in blood pressure
- unresponsiveness

What should I tell my child's healthcare provider before my child receives SYNAGIS?

Tell your child's healthcare provider about:

- **any reactions** you believe your child has ever had to SYNAGIS.
- **any bleeding or bruising problems.** SYNAGIS is given by injection. If your child has a problem with bleeding or bruises easily, an injection could cause a problem.
- **any other medical problems.**

Tell your child's healthcare provider about all the medicines your child takes, including prescription and non-prescription medicines, vitamins, and herbal supplements. Especially tell your child's healthcare provider if your child takes a blood thinner medicine.

How is SYNAGIS given?

- SYNAGIS is given as a monthly injection, usually in the thigh (leg) muscle, by your child's healthcare provider. Your child's healthcare provider will prescribe the amount of SYNAGIS that is right for your child (based on their weight).
- Your child's healthcare provider will give you detailed instructions on when SYNAGIS will be given.
 - "RSV season" is a term used to describe the time of year when RSV infections most commonly occur (usually fall through spring in most parts of the country). During this time, when RSV is most active, your child will need to receive SYNAGIS shots. Your child's healthcare provider can tell you when the RSV season starts in your area.
 - Your child should receive their **first SYNAGIS shot before the RSV season starts** to help protect them before RSV becomes active. If the season has already started, your child should receive their first SYNAGIS shot as soon as possible to help protect them when exposure to the virus is more likely.

- **SYNAGIS is needed every 28-30 days during the RSV season.** Each dose of SYNAGIS helps protect your child from severe RSV disease for about a month. **Keep all appointments with your child's healthcare provider.**

- **If your child misses an injection, talk to your healthcare provider and schedule another injection as soon as possible.**
- Your child may still get severe RSV disease after receiving SYNAGIS; talk to your child's healthcare provider about what symptoms to look for. If your child has an RSV infection, they should continue to get their scheduled SYNAGIS injections to help prevent severe disease from new RSV infections.
- If your child has certain types of heart disease and has corrective surgery, your healthcare provider may need to give your child an additional SYNAGIS injection soon after surgery.

What are the possible side effects of SYNAGIS?

Synagis may cause serious side effects including:

- Severe allergic reactions (may occur after any dose of SYNAGIS). Such reactions may be life-threatening or cause death.
 - See "Who should not take SYNAGIS?" for a list of signs and symptoms.
- Unusual bruising or groups of tiny red spots on the skin.

Call your child's healthcare provider or get medical help right away if your child has any of the serious side effects listed above after any dose of SYNAGIS.

Common side effects of SYNAGIS include:

- fever
- rash

Other possible side effects include skin reactions around the area where the shot was given (like redness, swelling, warmth, or discomfort).

These are not all the possible side effects of SYNAGIS. Tell your child's healthcare provider about any side effect that bothers your child or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to MedImmune at 1-877-633-4411.

General Information about SYNAGIS

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets.

This leaflet summarizes important information about SYNAGIS. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about SYNAGIS that is written for health professionals.

For more information, go to www.synagis.com or call 1-877-633-4411.

What are the ingredients in SYNAGIS?

Active Ingredient: palivizumab

Inactive Ingredients: chloride, glycine, and histidine

What is RSV?

Respiratory Syncytial Virus (RSV) is a common virus that is easily spread from person to person. RSV infects nearly all children by their second birthday. In most children, RSV infection is usually no worse than a bad cold. For some children, RSV infection can cause serious lung disease (like pneumonia and bronchiolitis) or breathing problems, and affected children may need to be admitted to the hospital or need emergency care.

Children who are more likely to get severe RSV disease (high-risk children) include babies born prematurely (35 weeks or less) or babies born with certain heart or lung problems.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Synagis® is a registered trademark of MedImmune, LLC.



Manufactured by: MedImmune, LLC

Gaithersburg, MD 20878

Issued March 2014

[DATE]

[HCP First and last name, Title]

[HCP Practice name]

[HCP Address]

[HCP City, State, ZIP]

Dear [HCP First and last name, Title]:

The attached template is offered as a resource a healthcare provider could use when responding to a request from a patient's health benefits company to provide a letter of medical necessity for administering Synagis[®] (palivizumab). **Attachments to be included with the letter of medical necessity are [original claim form, copy of denial or explanation of benefits, and any other additional supporting documents].** A copy of the full prescribing information for Synagis is attached for your reference. If you need additional references, please contact our medical affairs department at 1-877-MEDI-411 (1-877-633-4411).

Use of the attached letter does not guarantee that the insurance company will provide reimbursement for Synagis, and is not intended to be a substitute for or an influence on the independent medical judgment of the physician.

Important Safety Information

Synagis is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in children at high risk of RSV disease. Safety and efficacy were established in children with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (≤ 35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD). The recommended dose of Synagis is 15 mg/kg of body weight given monthly by intramuscular injection. 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. Children who develop an RSV infection should continue to receive monthly doses throughout the RSV season.

The efficacy of Synagis at doses less than 15 mg/kg, or of dosing less frequently than monthly throughout the RSV season, has not been established.

Synagis is contraindicated in children who have had a previous significant hypersensitivity reaction to Synagis. Cases of anaphylaxis and anaphylactic shock, including fatal cases, have been reported following initial exposure or re-exposure to Synagis. Other acute hypersensitivity reactions, which may be severe, have also been reported on initial exposure or re-exposure to Synagis. The relationship between these reactions and the development of antibodies to Synagis is unknown. If a significant hypersensitivity reaction occurs with Synagis, its use should be permanently discontinued. If a mild hypersensitivity reaction occurs, clinical judgment should be used regarding cautious re-administration of Synagis. As with any intramuscular injection, Synagis should be given with caution to children with thrombocytopenia or any coagulation disorder. Palivizumab may interfere with immunological-based RSV diagnostic tests, such as some antigen detection-based assays.

Adverse reactions occurring greater than or equal to 10% and at least 1% more frequently than placebo are fever and rash. In post-marketing reports, cases of severe thrombocytopenia (platelet count $< 50,000/\text{microliter}$) and injection site reactions have been reported.

Please see accompanying full Prescribing Information for Synagis, including Patient Information.

Sincerely,

The MedImmune Access 360 Team

CONFIDENTIALITY NOTE

The documents accompanying this telecopy transmission contain confidential or privileged information.

The information is intended to be for the use of the individual or entity named on this transmission sheet. If you are not the intended recipient, be aware that any disclosure, copying, distribution or use of the contents of this telecopied information is prohibited. If you have received this telecopy in error, please notify us by telephone immediately so that we can arrange for the retrieval of the original document at no cost to your office.

Thank you for your assistance.

#14433A-81006

[Date]

[Contact - usually the medical director]

[Title]

[Name of Health Insurance Company]

[Address]

[City, State, ZIP Code]

Insured: [Name]

Policy Number: [Number]

Group Number: [Number]

Dear [Name of Contact]:

I am writing on behalf of my patient, [name of patient], to request that [name of health insurance company] approve coverage for Synagis® (palivizumab) to help prevent severe RSV disease. This letter documents the medical necessity for this therapy and provides information about the patient's medical history and treatment.

Patient History and Diagnosis

[Name of patient] is a [male/female] baby who was born prematurely at [Gestational age] weeks gestation. [Name of patient] is now [chronological age] and has risk factors that increase [his/her] chances of contracting RSV. These risk factors include [list risk factors].

Treatment Information

I am requesting Synagis for this patient based on evidence-based medicine noted in the package insert of the drug, which states that Synagis should be given 15mg/kg of body weight, IM, prior to the commencement of the RSV season and administered monthly throughout the season. This seasonality is captured by the CDC in their tracking of RSV virology. I have included a copy of the RSV virology for my state as reported by the CDC.

There are no data from clinical trials evaluating the safety and efficacy of Synagis dosing less frequently than monthly throughout the RSV season. Human pharmacokinetic studies and animal studies of effective serum concentrations indicated that monthly dosing is required to maintain serum levels adequate for RSV prophylaxis. The IMPact-RSV trial found a wide variety of serum trough levels in the subjects studied. It is noted in the study that the trough serum drug concentration levels of Synagis were found to be 37 ± 21 mcg/mL after the first dose, 57 ± 41 mcg/mL after the second dose and 68 ± 51 mcg/mL after the third dose. A target level of 42 mcg/ml is based on the cotton rat model. It is also important to note that these trough levels in the study were measured in highly compliant subjects, whose dosing regimen was strictly adhered to, which is not always the case in real life situations. A palivizumab population pharmacokinetic (PK) study involving 22 clinical studies and 1684 who contributed 4095 plasma palivizumab samples was reported (Robbie 2012). With a three monthly doses schedule, serum concentrations declined to levels well below those maintained by monthly doses so that by months 4 and 5 palivizumab concentrations in 31.9% and 67.7% of patients, respectively, were below the 5th percentile of concentrations achieved with the 5 monthly dosage schedule in the IMPact trial (Figure 1). The efficacy of Synagis at doses less than 15 mg per kg, or of dosing less frequently than monthly throughout the RSV season, has not been established.

A seasonal dosing regimen of 3 doses in children less than 90 days of age is inconsistent with the FDA-approved Synagis package insert or the studies that support its label. I therefore request based upon the available evidence that this child be given the full season of dosing in order to keep them protected from RSV. This is in accordance to the FDA-approved label of the drug and the supporting CDC RSV virology data, showing that RSV is currently widespread in this area. The American Academy of Pediatrics (AAP) guidelines also states that healthcare providers should base their dosing decisions on the level of RSV activity in their area in conjunction with their clinical knowledge and judgment.

If you have any further questions, please feel free to contact me at [physician telephone number, including area code]. Thank you for assisting me in keeping this fragile baby protected from RSV and the complications associated with this disease.

Sincerely,

[Physician's Name]

[Physician's Practice Name]

#14433A-81503

References

Synagis® [package insert]. Gaithersburg, MD: MedImmune, LLC.

Connor EM and the IMPact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics*. 1998;102:531-537.

Robbie GJ, et al. Population pharmacokinetics of palivizumab, a humanized anti-RSV monoclonal antibody, in adults and children. *Antimicrob Agents Chemother*. 2012;56:4927-36.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SYNAGIS safely and effectively. See full prescribing information for SYNAGIS.

SYNAGIS® (palivizumab) injection for intramuscular use
Initial U.S. Approval: 1998

INDICATIONS AND USAGE

Synagis is a respiratory syncytial virus (RSV) F protein inhibitor monoclonal antibody indicated for the prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease.

- Safety and efficacy were established in children with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (less than or equal to 35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD).
- The safety and efficacy of Synagis have not been established for treatment of RSV disease. (1)

DOSAGE AND ADMINISTRATION

15 mg per kg of body weight, administered intramuscularly prior to commencement of the RSV season and remaining doses administered monthly throughout the RSV season. (2.1)

Children undergoing cardio-pulmonary bypass should receive an additional dose of Synagis as soon as possible after the cardio-pulmonary bypass procedure (even if sooner than a month from the previous dose). Thereafter, doses should be administered monthly as scheduled. (2.1, 12.3)

DOSAGE FORMS AND STRENGTHS

Single-dose liquid solution vials: 50 mg per 0.5 mL and 100 mg per 1 mL. (3)

FULL PRESCRIBING INFORMATION: CONTENTS*

- 1 INDICATIONS AND USAGE
- 2 DOSAGE AND ADMINISTRATION
 - 2.1 Dosing Information
 - 2.2 Administration Instructions
- 3 DOSAGE FORMS AND STRENGTHS
- 4 CONTRAINDICATIONS
- 5 WARNINGS AND PRECAUTIONS
 - 5.1 Hypersensitivity Reactions
 - 5.2 Coagulation Disorders
 - 5.3 RSV Diagnostic Test Interference
 - 5.4 Treatment of RSV Disease
 - 5.5 Proper Administration
- 6 ADVERSE REACTIONS
 - 6.1 Clinical Studies Experience
 - 6.2 Postmarketing Experience

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Synagis is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in children at high risk of RSV disease.

The following points should be considered when prescribing Synagis:

- Safety and efficacy were established in children with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (less than or equal to 35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD) [see *Clinical Studies* (14)].
- The safety and efficacy of Synagis have not been established for treatment of RSV disease.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of Synagis is 15 mg per kg of body weight given monthly by intramuscular injection. 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. Children who develop an RSV infection should continue to receive monthly doses throughout the RSV season. In the northern hemisphere, the RSV season typically commences in November and lasts through April, but it may begin earlier or persist later in certain communities.

Synagis serum levels are decreased after cardio-pulmonary bypass [see *Clinical Pharmacology* (12.3)]. Children undergoing cardio-pulmonary bypass should receive an additional dose of Synagis as soon as possible after the cardio-pulmonary bypass procedure (even if sooner than a month from the previous dose). Thereafter, doses should be administered monthly as scheduled.

The efficacy of Synagis at doses less than 15 mg per kg, or of dosing less frequently than monthly throughout the RSV season, has not been established.

2.2 Administration Instructions

- **DO NOT DILUTE THE PRODUCT.**
- **DO NOT SHAKE OR VIGOROUSLY AGITATE THE VIAL.**
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials exhibiting particulate matter or discoloration.

CONTRAINDICATIONS

Previous significant hypersensitivity reaction to Synagis. (4)

WARNINGS AND PRECAUTIONS

- Anaphylaxis and anaphylactic shock (including fatal cases), and other severe acute hypersensitivity reactions have been reported. Permanently discontinue Synagis and administer appropriate medications if such reactions occur. (5.1)
- As with any intramuscular injection, Synagis should be given with caution to children with thrombocytopenia or any coagulation disorder. (5.2)
- Palivizumab may interfere with immunological-based RSV diagnostic tests such as some antigen detection-based assays. (5.3, 12.4)

ADVERSE REACTIONS

Adverse reactions occurring greater than or equal to 10% and at least 1% more frequently than placebo are fever and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact MedImmune at 1-877-633-4411 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Safety and effectiveness in children greater than 24 months of age at the start of dosing have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 3/2014

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.4 Pediatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
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- 12.4 Microbiology

13 NONCLINICAL TOXICOLOGY

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14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

- Using aseptic techniques, attach a sterile needle to a sterile syringe. Remove the flip top from the Synagis vial and wipe the rubber stopper with a disinfectant (e.g., 70% isopropyl alcohol). Insert the needle into the vial and withdraw into the syringe an appropriate volume of solution. Administer immediately after drawing the dose into the syringe.
- Synagis should be administered in a dose of 15 mg per kg intramuscularly using aseptic technique, 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 (volume of injection in mL) per month = patient weight (kg) x 15 mg per kg ÷ 100 mg per mL of Synagis. Injection volumes over 1 mL should be given as a divided dose.
- Synagis is supplied as a single-dose vial and does not contain preservatives. Do not re-enter the vial after withdrawal of drug; discard unused portion. Only administer one dose per vial.
- Use sterile disposable syringes and needles. To prevent the transmission of hepatitis viruses or other infectious agents from one person to another, DO NOT reuse syringes and needles.

3 DOSAGE FORMS AND STRENGTHS

Single-dose liquid solution vials: 50 mg per 0.5 mL and 100 mg per 1 mL.

4 CONTRAINDICATIONS

Synagis is contraindicated in children who have had a previous significant hypersensitivity reaction to Synagis [see *Warnings and Precautions* (5.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Cases of anaphylaxis and anaphylactic shock, including fatal cases, have been reported following initial exposure or re-exposure to Synagis. Other acute hypersensitivity reactions, which may be severe, have also been reported on initial exposure or re-exposure to Synagis. Signs and symptoms may include urticaria, pruritus, angioedema, dyspnea, respiratory failure, cyanosis, hypotonia, hypotension, and unresponsiveness. The relationship between these reactions and the development of antibodies to Synagis is unknown. If a significant hypersensitivity reaction occurs with Synagis, its use should be permanently discontinued. **If anaphylaxis or other significant hypersensitivity reaction occurs, administer appropriate medications (e.g., epinephrine) and provide supportive care as required.** If a mild hypersensitivity reaction occurs, clinical judgment should be used regarding cautious readministration of Synagis.

5.2 Coagulation Disorders

Synagis is for intramuscular use only. As with any intramuscular injection, Synagis should be given with caution to children with thrombocytopenia or any coagulation disorder.

5.3 RSV Diagnostic Test Interference

Palivizumab may interfere with immunological-based RSV diagnostic tests such as some antigen detection-based assays. In addition, palivizumab inhibits virus replication in cell culture, and therefore may also interfere with viral culture assays. Palivizumab does not interfere with reverse transcriptase-polymerase chain reaction based assays. Assay interference could lead to false-negative RSV diagnostic test results. Therefore, diagnostic test results, when obtained, should be used in conjunction with clinical findings to guide medical decisions [see *Microbiology* (12.4)].

5.4 Treatment of RSV Disease

The safety and efficacy of Synagis have not been established for treatment of RSV disease.

5.5 Proper Administration

The single-dose vial of Synagis does not contain a preservative. Administration of Synagis should occur immediately after dose withdrawal from the vial. The vial should not be re-entered. Discard any unused portion.

6 ADVERSE REACTIONS

The most serious adverse reactions occurring with Synagis are anaphylaxis and other acute hypersensitivity reactions [see *Warnings and Precautions* (5.1)].

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to Synagis (n=1639) compared with placebo (n=1143) in children 3 days to 24.1 months of age at high risk of RSV-related hospitalization in two clinical trials. Trial 1 was conducted during a single RSV season and studied a total of 1502 children less than or equal to 24 months of age with BPD or infants with premature birth (less than or equal to 35 weeks gestation) who were less than or equal to 6 months of age at study entry. Trial 2 was conducted over four consecutive seasons among a total of 1287 children less than or equal to 24 months of age with hemodynamically significant congenital heart disease.

In Trials 1 and 2 combined, fever and rash were each reported more frequently among Synagis than placebo recipients, 27% versus 25%, and 12% versus 10%, respectively. Adverse reactions observed in the 153-patient crossover study comparing the liquid and lyophilized formulations were comparable for the two formulations, and were similar to those observed with Synagis in Trials 1 and 2.

Immunogenicity

In Trial 1, the incidence of anti-palivizumab antibody following the fourth injection was 1.1% in the placebo group and 0.7% in the Synagis group. In children receiving Synagis for a second season, one of the fifty-six children had transient, low titer reactivity. This reactivity was not associated with adverse events or alteration in serum concentrations. Immunogenicity was not assessed in Trial 2.

A trial of high-risk preterm children less than or equal to 24 months of age was conducted to evaluate the immunogenicity of the lyophilized formulation of Synagis (used in Trials 1 and 2 above) and the liquid formulation of Synagis. Three hundred seventy-nine children contributed to the 4 to 6 months post-final dose analysis. The rate of anti-palivizumab antibodies at this time point was low in both formulation groups (anti-palivizumab antibodies were not detected in any subject in the liquid formulation group and were detected in one subject in the lyophilized group (0.5%), with an overall rate of 0.3% for both treatment groups combined).

These data reflect the percentage of children whose test results were considered positive for antibodies to palivizumab in an enzyme-linked immunosorbent assay (ELISA) and are highly dependent on the sensitivity and specificity of the assay.

The ELISA has substantial limitations in detecting anti-palivizumab antibodies in the presence of palivizumab. Immunogenicity samples tested with the ELISA assay likely contained palivizumab at levels that may interfere with the detection of anti-palivizumab antibodies.

An electrochemical luminescence (ECL) based immunogenicity assay, with a higher tolerance for palivizumab presence compared to the ELISA, was used to evaluate the presence of anti-palivizumab antibodies in subject samples from two additional clinical trials. The rates of anti-palivizumab antibody positive results in these trials were 1.1% and 1.5%.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Synagis. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: severe thrombocytopenia (platelet count less than 50,000 per microliter)

General Disorders and Administration Site Conditions: injection site reactions

Limited information from post-marketing reports suggests that, within a single RSV season, adverse events after a sixth or greater dose of Synagis are similar in character and frequency to those after the initial five doses.

7 DRUG INTERACTIONS

No formal drug-drug interaction studies were conducted. In Trial 1, the proportions of children in the placebo and Synagis groups who received routine childhood vaccines, influenza vaccine, bronchodilators, or corticosteroids were similar and no incremental increase in adverse reactions was observed among children receiving these agents.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Synagis is not indicated for adult usage. It is not known whether Synagis can cause fetal harm or could affect reproductive capacity when administered to a pregnant woman.

Animal Data

Animal reproduction studies have not been conducted.

8.4 Pediatric Use

The safety and effectiveness of Synagis in children greater than 24 months of age at the start of dosing have not been established.

10 OVERDOSAGE

Overdoses with doses up to 85 mg per kg have been reported in clinical studies and post-marketing experience with Synagis, and in some cases, adverse reactions were reported. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

11 DESCRIPTION

Palivizumab is a humanized monoclonal antibody (IgG1 κ) produced by recombinant DNA technology, directed to an epitope in the A antigenic site of the F protein of RSV. Palivizumab is a composite of human (95%) and murine (5%) antibody sequences. The human heavy chain sequence was derived from the constant domains of human IgG1 and the variable framework regions of the V_H genes Cor and Cess. The human light chain sequence was derived from the constant domain of C κ and the variable framework regions of the V_L gene K104 with J κ -4. The murine sequences were derived from a murine monoclonal antibody, Mab 1129, in a process that involved the grafting of the murine complementarity determining regions into the human antibody frameworks. Palivizumab is composed of two heavy chains and two light chains and has a molecular weight of approximately 148,000 Daltons.

Synagis is supplied as a sterile, preservative-free liquid solution at 100 mg per mL to be administered by intramuscular injection. Thimerosal or other mercury-containing salts are not used in the production of Synagis. The solution has a pH of 6.0 and should appear clear or slightly opalescent.

Each 100 mg single-dose vial of Synagis liquid solution contains 100 mg of palivizumab and also contains chloride (0.5 mg), glycine (0.1 mg), and histidine (3.9 mg), in a volume of 1 mL. Each 50 mg single-dose vial of Synagis liquid solution contains 50 mg of palivizumab and also contains chloride (0.2 mg), glycine (0.06 mg), and histidine (1.9 mg), in a volume of 0.5 mL.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Palivizumab is a recombinant humanized monoclonal antibody with anti-RSV activity [see *Microbiology* (12.4)].

12.3 Pharmacokinetics

In children less than or equal to 24 months of age without congenital heart disease (CHD), the mean half-life of palivizumab was 20 days and monthly intramuscular doses of 15 mg per kg achieved mean \pm SD 30 day trough serum drug concentrations of 37 \pm 21 mcg per mL after the first injection, 57 \pm 41 mcg per mL after the second injection, 68 \pm 51 mcg per mL after the third injection, and 72 \pm 50 mcg per mL after the fourth injection. Trough concentrations following the first and fourth Synagis dose were similar in children with CHD and in non-cardiac patients. In children given Synagis for a second season, the mean \pm SD serum concentrations following the first and fourth injections were 61 \pm 17 mcg per mL and 86 \pm 31 mcg per mL, respectively.

In 139 children less than or equal to 24 months of age with hemodynamically significant CHD who received Synagis and underwent cardio-pulmonary bypass for open-heart surgery, the mean \pm SD serum palivizumab concentration was 98 \pm 52 mcg per mL before bypass and declined to 41 \pm 33 mcg per mL after bypass, a reduction of 58% [see *Dosage and Administration* (2.1)]. The clinical significance of this reduction is unknown.

Specific studies were not conducted to evaluate the effects of demographic parameters on palivizumab systemic exposure. However, no effects of gender, age, body weight, or race on palivizumab serum trough concentrations were observed in a clinical study with 639 children with CHD (less than or equal to 24 months of age) receiving five monthly intramuscular injections of 15 mg per kg of Synagis.

The pharmacokinetics and safety of Synagis liquid solution and Synagis lyophilized formulation administered via intramuscular injection at 15 mg per kg were studied in a cross-over trial of 153 infants less than or equal to 6 months of age with a history of prematurity. The results of this trial indicated that the trough serum concentrations of palivizumab were comparable between the liquid solution and the lyophilized formulation, which was the formulation used in the clinical studies. A population pharmacokinetic analysis was performed across 22 studies in 1800 patients (1684 pediatric and 116 adult patients) to characterize palivizumab pharmacokinetics and inter-subject variability in serum concentrations. Palivizumab pharmacokinetics was described by a two-compartment linear model with an elimination half-life of 24.5 days in pediatric patients. Clearance of palivizumab in a typical pediatric patient (body weight 4.5 kg) less than or equal to 24 months of age without CHD was estimated to be 11 mL per day with a bioavailability of 70% following intramuscular administration. The inter-patient variability in drug clearance was 48.7% (CV%). Covariate analysis did not identify any factors that could account for the inter-patient variability in order to predict serum concentrations a priori in an individual patient.

12.4 Microbiology

Mechanism of Action

Palivizumab, a recombinant humanized monoclonal antibody which provides passive immunity against RSV, acts by binding the RSV envelope fusion protein (RSV F) on the surface of the virus and blocking a critical step in the membrane fusion process. Palivizumab also prevents cell-to-cell fusion of RSV-infected cells.

Antiviral Activity

The antiviral activity of palivizumab was assessed in a microneutralization assay in which increasing concentrations of antibody were incubated with RSV prior to addition of the human epithelial cells HEP-2. After incubation for 4-5 days, RSV antigen was measured in an ELISA assay. The neutralization titer (50% effective concentration [EC₅₀]) is expressed as the antibody concentration required to reduce detection of RSV antigen by 50% compared with untreated virus-infected cells. Palivizumab exhibited median EC₅₀ values of 0.65 mcg per mL (mean 0.75 ± 0.53 mcg per mL; n=69, range 0.07-2.89 mcg per mL) and 0.28 mcg per mL (mean 0.35 ± 0.23 mcg per mL; n=35, range 0.03-0.88 mcg per mL) against clinical RSV A and RSV B isolates, respectively. The majority of clinical RSV isolates tested (n=96) were collected from subjects across the United States (CA, CO, CT, IL, MA, NC, NY, PA, RI, TN, TX, VA), with the remainder from Japan (n=1), Australia (n=5) and Israel (n=2). These isolates encoded the most common RSV F sequence polymorphisms found among clinical isolates worldwide.

Palivizumab serum concentrations of greater than or equal to 40 mcg per mL have been shown to reduce pulmonary RSV replication in the cotton rat model of RSV infection by 100-fold.

Resistance

Palivizumab binds a highly conserved region on the extracellular domain of mature RSV F, referred to as antigenic site II or site A, which encompasses amino acids 262 to 275. All RSV mutants that exhibit resistance to palivizumab have been shown to contain amino acid changes in this region on the F protein.

F protein sequence variations within antigenic site A: Amino acid substitutions in antigenic site A selected either in cell culture, in animal models, or in human subjects that resulted in palivizumab resistance were N262D, N268I, K272E/M/N/Q/T, and S275F/L. RSV variants expressing the K272N substitution in F protein showed a 5164 ± 1731-fold decrease in susceptibility (i.e., fold increase in EC₅₀ value) when compared to the wild-type RSV, while variants containing the N262D, S275F/L, or K272E/M/N/Q/T substitutions showed a greater than 25,000-fold decrease in susceptibility to palivizumab. The N268I substitution conferred partial resistance to palivizumab; however, fold changes in susceptibility were not quantified for this mutant. Studies carried out to investigate the mechanism of virus escape from palivizumab showed a correlation between antibody binding and virus neutralization. RSV with substitutions in antigenic site A that were resistant to neutralization by palivizumab did not bind to palivizumab.

At least one of the palivizumab resistance-associated substitutions, N262D, K272E/Q, or S275F/L was identified in 8 of 126 clinical RSV (59 RSV A and 67 RSV B) isolates from subjects who failed immunoprophylaxis, resulting in a combined resistance-associated mutation frequency of 6.3%. A review of clinical findings revealed no association between antigenic A site sequence changes and RSV disease severity among children receiving palivizumab immunoprophylaxis who develop RSV lower respiratory tract disease.

Analysis of 254 clinical RSV isolates (145 RSV A and 109 RSV B) collected from immunoprophylaxis-naïve subjects revealed palivizumab resistance-associated substitutions in 2 (1 with N262D and 1 with S275F), resulting in a resistance-associated mutation frequency of 0.79%.

F protein sequence variations outside antigenic site A: In addition to the sequence variations in antigenic site A known to confer palivizumab resistance, F protein substitutions T100A, G139S, N165D/V406I; T326A, V450A in RSV A, and T74I, A147V, I206L, S285G, V450I, T455I in RSV B were identified in viruses isolated from failures of immunoprophylaxis. These substitutions were not identified in RSV F sequences derived from 254 clinical isolates from immunoprophylaxis-naïve subjects and thus are considered treatment-associated and non-polymorphic. Recombinant RSV B encoding the S285G substitution exhibited palivizumab sensitivity (EC₅₀ value = 0.39 ± 0.02 mcg per mL) similar to recombinant wild-type RSV B (EC₅₀ value = 0.17 ± 0.02 mcg per mL).

Palivizumab susceptibility of RSV encoding common F protein sequence polymorphisms located proximal to antigenic site A was evaluated. Recombinant RSV A encoding N276S (EC₅₀ value = 0.72 ± 0.07 mcg per mL), and recombinant RSV B with S276N (EC₅₀ value = 0.42 ± 0.04 mcg per mL), exhibited sensitivities comparable to the corresponding recombinant wild-type RSV A (EC₅₀ value = 0.63 ± 0.22 mcg per mL) and RSV B (EC₅₀ value = 0.23 ± 0.07 mcg per mL). Likewise, RSV B clinical isolates containing the polymorphic variation V278A were at least as sensitive to neutralization by palivizumab (EC₅₀ range 0.08-0.45 mcg per mL) as laboratory strains of wild-type RSV B (EC₅₀ value = 0.54 ± 0.08 mcg per mL). No known polymorphic or non-polymorphic sequence variations outside the antigenic site A on RSV F have been demonstrated to render RSV resistant to neutralization by palivizumab.

Interference of RSV Diagnostic Assays by Palivizumab

Interference with immunologically-based RSV diagnostic assays by palivizumab has been observed in laboratory studies. Rapid chromatographic/enzyme immunoassays (CIA/EIA), immunofluorescence assays (IFA), and direct immunofluorescence assays (DFA) using monoclonal antibodies targeting RSV F protein may be inhibited. Therefore, caution should be used in interpreting negative immunological assay results when clinical observations are consistent with RSV infection. A reverse transcriptase-polymerase chain reaction (RT-PCR) assay, which is not inhibited by palivizumab, may prove useful for laboratory confirmation of RSV infection [see *Warnings and Precautions* (5.3)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis, mutagenesis, and reproductive toxicity studies have not been performed.

14 CLINICAL STUDIES

The safety and efficacy of Synagis were assessed in two randomized, double-blind, placebo-controlled trials of prophylaxis against RSV infection in children at high risk of an RSV-related hospitalization. Trial 1 was conducted during a single RSV season and studied a total of 1502 children less than or equal to 24 months of age with BPD or infants with premature birth (less than or equal to 35 weeks gestation) who were less than or equal to 6 months of age at study entry. Trial 2 was conducted over four consecutive seasons among a total of 1287 children less than or equal to 24 months of age with hemodynamically significant congenital heart disease. In both trials participants received 15 mg per kg Synagis or an equivalent volume of placebo via intramuscular injection monthly for five injections and were followed for 150 days from randomization. In Trial 1, 99% of all subjects completed the study and 93% completed all five injections. In Trial 2, 96% of all subjects completed the study and 92% completed all five injections. The incidence of RSV hospitalization is shown in Table 1. The results were shown to be statistically significant using Fisher's exact test.

Table 1: Incidence of RSV Hospitalization by Treatment Group

Trial		Placebo	Synagis	Difference Between Groups	Relative Reduction
Trial 1 Impact-RSV	N	500	1002		
	Hospitalization	53 (10.6%)	48 (4.8%)	5.8%	55%
Trial 2 CHD	N	648	639		
	Hospitalization	63 (9.7%)	34 (5.3%)	4.4%	45%

In Trial 1, the reduction of RSV hospitalization was observed both in children with BPD (34/266 [12.8%] placebo versus 39/496 [7.9%] Synagis) and in premature infants without BPD (19/234 [8.1%] placebo versus 9/506 [1.8%] Synagis). In Trial 2, reductions were observed in acyanotic (36/305 [11.8%] placebo versus 15/300 [5.0%] Synagis) and cyanotic children (27/343 [7.9%] placebo versus 19/339 [5.6%] Synagis).

The clinical studies do not suggest that RSV infection was less severe among children hospitalized with RSV infection who received Synagis for RSV prophylaxis compared to those who received placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

Synagis is supplied in single-dose vials as a preservative-free, sterile liquid solution at 100 mg per mL for intramuscular injection.

50 mg vial NDC 60574-4114-1

The 50 mg vial contains 50 mg Synagis in 0.5 mL.

100 mg vial NDC 60574-4113-1

The 100 mg vial contains 100 mg Synagis in 1 mL.

The rubber stopper used for sealing vials of Synagis is not made with natural rubber latex.

Storage

Upon receipt and until use, Synagis should be stored between 2°C and 8°C (36°F and 46°F) in its original container. DO NOT freeze. DO NOT use beyond the expiration date.

17 PATIENT COUNSELING INFORMATION

o **“Advise the patient to read the FDA-approved patient labeling (Patient Information)”**

The healthcare provider should discuss the potential benefits and risks of Synagis with the parents or guardians of Synagis recipients. Parents or guardians should be informed of the possible side effects of Synagis and of the signs and symptoms of potential allergic reactions and should be advised of the appropriate actions. Parents or guardians should understand the dosing schedule and the importance of compliance with the full course of therapy.

Synagis® is a registered trademark of MedImmune, LLC.



Manufactured by:

MedImmune, LLC
Gaithersburg, MD 20878
U.S. License No. 1799
1-877-633-4411

RAL-SYNNV17
Component No.: 26920A

PATIENT INFORMATION
SYNAGIS® (Sĭ-nă-jĭs)
(palivizumab)
Injection

Read this Patient Information before your child starts receiving SYNAGIS and before each injection. The information may have changed. This leaflet does not take the place of talking with your child's healthcare provider about your child's condition or treatment.

What is SYNAGIS?

SYNAGIS is a prescription medication that is used to help prevent a serious lung disease caused by Respiratory Syncytial Virus (RSV). Your child is prescribed SYNAGIS because he or she is at high risk for severe lung disease from RSV.

SYNAGIS contains man-made, disease-fighting proteins called antibodies. These antibodies help prevent RSV disease. Children at high risk for severe RSV disease often do not have enough of their own antibodies. SYNAGIS is used in certain groups of children to help prevent severe RSV disease by increasing protective RSV antibodies.

SYNAGIS is not used to treat the symptoms of RSV disease once a child already has it. It is only used to prevent RSV disease.

SYNAGIS is not for adults or for children older than 24 months of age at the start of dosing.

Who should not receive SYNAGIS?

Your child should not receive SYNAGIS if they have ever had a severe allergic reaction to it. Signs and symptoms of a severe allergic reaction could include:

- severe rash, hives, or itching skin
- swelling of the lips, tongue, or face
- closing of the throat, difficulty swallowing
- difficult, rapid, or irregular breathing
- bluish color of skin, lips, or under fingernails
- muscle weakness or floppiness
- a drop in blood pressure
- unresponsiveness

What should I tell my child's healthcare provider before my child receives SYNAGIS?

Tell your child's healthcare provider about:

- **any reactions** you believe your child has ever had to SYNAGIS.
- **any bleeding or bruising problems.** SYNAGIS is given by injection. If your child has a problem with bleeding or bruises easily, an injection could cause a problem.
- **any other medical problems.**

Tell your child's healthcare provider about all the medicines your child takes, including prescription and non-prescription medicines, vitamins, and herbal supplements. Especially tell your child's healthcare provider if your child takes a blood thinner medicine.

How is SYNAGIS given?

- SYNAGIS is given as a monthly injection, usually in the thigh (leg) muscle, by your child's healthcare provider. Your child's healthcare provider will prescribe the amount of SYNAGIS that is right for your child (based on their weight).
- Your child's healthcare provider will give you detailed instructions on when SYNAGIS will be given.
 - "RSV season" is a term used to describe the time of year when RSV infections most commonly occur (usually fall through spring in most parts of the country). During this time, when RSV is most active, your child will need to receive SYNAGIS shots. Your child's healthcare provider can tell you when the RSV season starts in your area.
 - Your child should receive their **first SYNAGIS shot before the RSV season starts** to help protect them before RSV becomes active. If the season has already started, your child should receive their first SYNAGIS shot as soon as possible to help protect them when exposure to the virus is more likely.

- **SYNAGIS is needed every 28-30 days during the RSV season.** Each dose of SYNAGIS helps protect your child from severe RSV disease for about a month. **Keep all appointments with your child's healthcare provider.**

- **If your child misses an injection, talk to your healthcare provider and schedule another injection as soon as possible.**
- Your child may still get severe RSV disease after receiving SYNAGIS; talk to your child's healthcare provider about what symptoms to look for. If your child has an RSV infection, they should continue to get their scheduled SYNAGIS injections to help prevent severe disease from new RSV infections.
- If your child has certain types of heart disease and has corrective surgery, your healthcare provider may need to give your child an additional SYNAGIS injection soon after surgery.

What are the possible side effects of SYNAGIS?

Synagis may cause serious side effects including:

- Severe allergic reactions (may occur after any dose of SYNAGIS). Such reactions may be life-threatening or cause death.
 - See "Who should not take SYNAGIS?" for a list of signs and symptoms.
- Unusual bruising or groups of tiny red spots on the skin.

Call your child's healthcare provider or get medical help right away if your child has any of the serious side effects listed above after any dose of SYNAGIS.

Common side effects of SYNAGIS include:

- fever
- rash

Other possible side effects include skin reactions around the area where the shot was given (like redness, swelling, warmth, or discomfort).

These are not all the possible side effects of SYNAGIS. Tell your child's healthcare provider about any side effect that bothers your child or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to MedImmune at 1-877-633-4411.

General Information about SYNAGIS

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets.

This leaflet summarizes important information about SYNAGIS. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about SYNAGIS that is written for health professionals.

For more information, go to www.synagis.com or call 1-877-633-4411.

What are the ingredients in SYNAGIS?

Active Ingredient: palivizumab

Inactive Ingredients: chloride, glycine, and histidine

What is RSV?

Respiratory Syncytial Virus (RSV) is a common virus that is easily spread from person to person. RSV infects nearly all children by their second birthday. In most children, RSV infection is usually no worse than a bad cold. For some children, RSV infection can cause serious lung disease (like pneumonia and bronchiolitis) or breathing problems, and affected children may need to be admitted to the hospital or need emergency care.

Children who are more likely to get severe RSV disease (high-risk children) include babies born prematurely (35 weeks or less) or babies born with certain heart or lung problems.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Synagis® is a registered trademark of MedImmune, LLC.



Manufactured by: MedImmune, LLC

Gaithersburg, MD 20878

Issued March 2014

[DATE]

[HCP First and last name, Title]

[HCP Practice name]

[HCP Address]

[HCP City, State, ZIP]

Dear [HCP First and last name, Title]:

The attached template is offered as a resource a healthcare provider could use when responding to a request from a patient's health benefits company to provide a letter of medical necessity for administering Synagis® (palivizumab). **Attachments to be included with the letter of medical necessity are [original claim form, copy of denial or explanation of benefits, and any other additional supporting documents].** A copy of the full prescribing information for Synagis is attached for your reference. If you need additional references, please contact our medical affairs department at 1-877-MEDI-411 (1-877-633-4411).

Use of the attached letter does not guarantee that the insurance company will provide reimbursement for Synagis, and is not intended to be a substitute for or an influence on the independent medical judgment of the physician.

Important Safety Information

Synagis is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in children at high risk of RSV disease. Safety and efficacy were established in children with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (≤ 35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD). The recommended dose of Synagis is 15 mg/kg of body weight given monthly by intramuscular injection. 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. Children who develop an RSV infection should continue to receive monthly doses throughout the RSV season.

The efficacy of Synagis at doses less than 15 mg/kg, or of dosing less frequently than monthly throughout the RSV season, has not been established.

Synagis is contraindicated in children who have had a previous significant hypersensitivity reaction to Synagis. Cases of anaphylaxis and anaphylactic shock, including fatal cases, have been reported following initial exposure or re-exposure to Synagis. Other acute hypersensitivity reactions, which may be severe, have also been reported on initial exposure or re-exposure to Synagis. The relationship between these reactions and the development of antibodies to Synagis is unknown. If a significant hypersensitivity reaction occurs with Synagis, its use should be permanently discontinued. If a mild hypersensitivity reaction occurs, clinical judgment should be used regarding cautious re-administration of Synagis. As with any intramuscular injection, Synagis should be given with caution to children with thrombocytopenia or any coagulation disorder. Palivizumab may interfere with immunological-based RSV diagnostic tests, such as some antigen detection-based assays.

Adverse reactions occurring greater than or equal to 10% and at least 1% more frequently than placebo are fever and rash. In post-marketing reports, cases of severe thrombocytopenia (platelet count $< 50,000/\text{microliter}$) and injection site reactions have been reported.

Please see accompanying full Prescribing Information for Synagis, including Patient Information.

Sincerely,

The MedImmune Access 360 Team

CONFIDENTIALITY NOTE

The documents accompanying this telecopy transmission contain confidential or privileged information.

The information is intended to be for the use of the individual or entity named on this transmission sheet. If you are not the intended recipient, be aware that any disclosure, copying, distribution or use of the contents of this telecopied information is prohibited. If you have received this telecopy in error, please notify us by telephone immediately so that we can arrange for the retrieval of the original document at no cost to your office.

Thank you for your assistance.

#14432A-81301

[Date]

[Contact - usually the medical director]

[Title]

[Name of Health Insurance Company]

[Address]

[City, State, ZIP Code]

Insured: [Name]

Policy Number: [Number]

Group Number: [Number]

Dear [Name of Contact]:

I am writing on behalf of my patient, [name of patient], to request that [name of health insurance company] approve coverage for Synagis® (palivizumab) to help prevent severe RSV disease. This letter documents the medical necessity for this therapy and provides information about the patient's medical history and treatment.

Patient History and Diagnosis

[Name of patient] is a [chronological age,] [male/female] baby who was born prematurely at [Gestational age] weeks gestation. [Name of patient] being of young chronological age increases [his/her] chances of contracting RSV.

Treatment Information

I am requesting Synagis for this baby because of the evidence from population-based epidemiologic studies of RSV-related hospitalization in young children clearly demonstrates that infants ≤ 6 months of age have the greatest burden of hospitalizations. In studies from the US and Europe of children 0-3 month old infants account for 34 to 55% and those 4 to 6 months old infants account for 21 to 23% of the RSV-related admissions (Berner 2001, Clarke 1978, Lanari 2002, Nielson 2003, Paramore 2004, Shay 1999, Vicente 2003). While infants <3 months of age experience the highest rate of RSV-related hospitalization, the 4-6 month age group account for the second largest percentage within the first year of life. When examining the patterns of age at admission for RSV-related hospitalizations among the 32 to 35 week gestational age infants, those up to 6 months of age also have the greatest burden (Boye 2000, Heikkinen 2005, McCormick 2002, Vincente 2003).

Interrupted lung development and low levels of maternally-transmitted RSV-neutralizing antibodies contribute significantly to the high risk of the premature infant for RSV-related illness throughout infancy (DeVincenzo 2005). It has been demonstrated that preterm infants have substantially lower serum IgG levels and maternally-transmitted anti-RSV antibodies as compared to term infants and that these antibodies decrease steadily over the first three months with a nadir at 6 months (Hacimustafaoglu 2004, Wang 1999; Yeung 1968). A study from the Danish National Birth Cohort found that cord blood RSV neutralizing antibody levels were inversely related to RSV-related hospitalizations in infants <6 months of age (IRR=0.74; 95% CI, 0.62-.087) (Stensballe 2008).

In summary, therapy with Synagis (palivizumab) is medically necessary for this prematurely born patient because [his/her] chronological age (≤ 6 months of age prior to the start of the RSV season) puts them at an increased risk of developing severe RSV disease. Thank you in advance for assisting me in keeping this fragile baby protected from RSV and the complications associated with this disease.

If you have any further questions, please feel free to contact me at [physician telephone number, including area code]. Thank you in advance for your immediate attention to this request.

Sincerely,

[Physician's Name]

[Physician's Practice Name]

References

Synagis® [package insert]. Gaithersburg, MD: MedImmune, LLC.

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Yeung CY and Hobbs JR. Serum-gamma G-globulin levels in normal, premature, post-mature and “small-for-dates” newborn babies. *Lancet*. 1968;1:1167-1170.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SYNAGIS safely and effectively. See full prescribing information for SYNAGIS.

SYNAGIS® (palivizumab) injection for intramuscular use
Initial U.S. Approval: 1998

INDICATIONS AND USAGE

Synagis is a respiratory syncytial virus (RSV) F protein inhibitor monoclonal antibody indicated for the prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease.

- Safety and efficacy were established in children with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (less than or equal to 35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD).
- The safety and efficacy of Synagis have not been established for treatment of RSV disease. (1)

DOSAGE AND ADMINISTRATION

15 mg per kg of body weight, administered intramuscularly prior to commencement of the RSV season and remaining doses administered monthly throughout the RSV season. (2.1)

Children undergoing cardio-pulmonary bypass should receive an additional dose of Synagis as soon as possible after the cardio-pulmonary bypass procedure (even if sooner than a month from the previous dose). Thereafter, doses should be administered monthly as scheduled. (2.1, 12.3)

DOSAGE FORMS AND STRENGTHS

Single-dose liquid solution vials: 50 mg per 0.5 mL and 100 mg per 1 mL. (3)

FULL PRESCRIBING INFORMATION: CONTENTS*

- 1 INDICATIONS AND USAGE**
- 2 DOSAGE AND ADMINISTRATION**
 - 2.1 Dosing Information
 - 2.2 Administration Instructions
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
 - 5.1 Hypersensitivity Reactions
 - 5.2 Coagulation Disorders
 - 5.3 RSV Diagnostic Test Interference
 - 5.4 Treatment of RSV Disease
 - 5.5 Proper Administration
- 6 ADVERSE REACTIONS**
 - 6.1 Clinical Studies Experience
 - 6.2 Postmarketing Experience

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Synagis is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in children at high risk of RSV disease.

The following points should be considered when prescribing Synagis:

- Safety and efficacy were established in children with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (less than or equal to 35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD) [see *Clinical Studies* (14)].
- The safety and efficacy of Synagis have not been established for treatment of RSV disease.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of Synagis is 15 mg per kg of body weight given monthly by intramuscular injection. 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. Children who develop an RSV infection should continue to receive monthly doses throughout the RSV season. In the northern hemisphere, the RSV season typically commences in November and lasts through April, but it may begin earlier or persist later in certain communities.

Synagis serum levels are decreased after cardio-pulmonary bypass [see *Clinical Pharmacology* (12.3)]. Children undergoing cardio-pulmonary bypass should receive an additional dose of Synagis as soon as possible after the cardio-pulmonary bypass procedure (even if sooner than a month from the previous dose). Thereafter, doses should be administered monthly as scheduled.

The efficacy of Synagis at doses less than 15 mg per kg, or of dosing less frequently than monthly throughout the RSV season, has not been established.

2.2 Administration Instructions

- **DO NOT DILUTE THE PRODUCT.**
- **DO NOT SHAKE OR VIGOROUSLY AGITATE THE VIAL.**
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials exhibiting particulate matter or discoloration.

CONTRAINDICATIONS

Previous significant hypersensitivity reaction to Synagis. (4)

WARNINGS AND PRECAUTIONS

- Anaphylaxis and anaphylactic shock (including fatal cases), and other severe acute hypersensitivity reactions have been reported. Permanently discontinue Synagis and administer appropriate medications if such reactions occur. (5.1)
- As with any intramuscular injection, Synagis should be given with caution to children with thrombocytopenia or any coagulation disorder. (5.2)
- Palivizumab may interfere with immunological-based RSV diagnostic tests such as some antigen detection-based assays. (5.3, 12.4)

ADVERSE REACTIONS

Adverse reactions occurring greater than or equal to 10% and at least 1% more frequently than placebo are fever and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact MedImmune at 1-877-633-4411 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Safety and effectiveness in children greater than 24 months of age at the start of dosing have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 3/2014

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.4 Pediatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics
- 12.4 Microbiology

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

- Using aseptic techniques, attach a sterile needle to a sterile syringe. Remove the flip top from the Synagis vial and wipe the rubber stopper with a disinfectant (e.g., 70% isopropyl alcohol). Insert the needle into the vial and withdraw into the syringe an appropriate volume of solution. Administer immediately after drawing the dose into the syringe.
- Synagis should be administered in a dose of 15 mg per kg intramuscularly using aseptic technique, 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 (volume of injection in mL) per month = patient weight (kg) x 15 mg per kg ÷ 100 mg per mL of Synagis. Injection volumes over 1 mL should be given as a divided dose.
- Synagis is supplied as a single-dose vial and does not contain preservatives. Do not re-enter the vial after withdrawal of drug; discard unused portion. Only administer one dose per vial.
- Use sterile disposable syringes and needles. To prevent the transmission of hepatitis viruses or other infectious agents from one person to another, DO NOT reuse syringes and needles.

3 DOSAGE FORMS AND STRENGTHS

Single-dose liquid solution vials: 50 mg per 0.5 mL and 100 mg per 1 mL.

4 CONTRAINDICATIONS

Synagis is contraindicated in children who have had a previous significant hypersensitivity reaction to Synagis [see *Warnings and Precautions* (5.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Cases of anaphylaxis and anaphylactic shock, including fatal cases, have been reported following initial exposure or re-exposure to Synagis. Other acute hypersensitivity reactions, which may be severe, have also been reported on initial exposure or re-exposure to Synagis. Signs and symptoms may include urticaria, pruritus, angioedema, dyspnea, respiratory failure, cyanosis, hypotonia, hypotension, and unresponsiveness. The relationship between these reactions and the development of antibodies to Synagis is unknown. If a significant hypersensitivity reaction occurs with Synagis, its use should be permanently discontinued. **If anaphylaxis or other significant hypersensitivity reaction occurs, administer appropriate medications (e.g., epinephrine) and provide supportive care as required.** If a mild hypersensitivity reaction occurs, clinical judgment should be used regarding cautious readministration of Synagis.

5.2 Coagulation Disorders

Synagis is for intramuscular use only. As with any intramuscular injection, Synagis should be given with caution to children with thrombocytopenia or any coagulation disorder.

5.3 RSV Diagnostic Test Interference

Palivizumab may interfere with immunological-based RSV diagnostic tests such as some antigen detection-based assays. In addition, palivizumab inhibits virus replication in cell culture, and therefore may also interfere with viral culture assays. Palivizumab does not interfere with reverse transcriptase-polymerase chain reaction based assays. Assay interference could lead to false-negative RSV diagnostic test results. Therefore, diagnostic test results, when obtained, should be used in conjunction with clinical findings to guide medical decisions [see *Microbiology* (12.4)].

5.4 Treatment of RSV Disease

The safety and efficacy of Synagis have not been established for treatment of RSV disease.

5.5 Proper Administration

The single-dose vial of Synagis does not contain a preservative. Administration of Synagis should occur immediately after dose withdrawal from the vial. The vial should not be re-entered. Discard any unused portion.

6 ADVERSE REACTIONS

The most serious adverse reactions occurring with Synagis are anaphylaxis and other acute hypersensitivity reactions [see *Warnings and Precautions* (5.1)].

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to Synagis (n=1639) compared with placebo (n=1143) in children 3 days to 24.1 months of age at high risk of RSV-related hospitalization in two clinical trials. Trial 1 was conducted during a single RSV season and studied a total of 1502 children less than or equal to 24 months of age with BPD or infants with premature birth (less than or equal to 35 weeks gestation) who were less than or equal to 6 months of age at study entry. Trial 2 was conducted over four consecutive seasons among a total of 1287 children less than or equal to 24 months of age with hemodynamically significant congenital heart disease.

In Trials 1 and 2 combined, fever and rash were each reported more frequently among Synagis than placebo recipients, 27% versus 25%, and 12% versus 10%, respectively. Adverse reactions observed in the 153-patient crossover study comparing the liquid and lyophilized formulations were comparable for the two formulations, and were similar to those observed with Synagis in Trials 1 and 2.

Immunogenicity

In Trial 1, the incidence of anti-palivizumab antibody following the fourth injection was 1.1% in the placebo group and 0.7% in the Synagis group. In children receiving Synagis for a second season, one of the fifty-six children had transient, low titer reactivity. This reactivity was not associated with adverse events or alteration in serum concentrations. Immunogenicity was not assessed in Trial 2.

A trial of high-risk preterm children less than or equal to 24 months of age was conducted to evaluate the immunogenicity of the lyophilized formulation of Synagis (used in Trials 1 and 2 above) and the liquid formulation of Synagis. Three hundred seventy-nine children contributed to the 4 to 6 months post-final dose analysis. The rate of anti-palivizumab antibodies at this time point was low in both formulation groups (anti-palivizumab antibodies were not detected in any subject in the liquid formulation group and were detected in one subject in the lyophilized group (0.5%), with an overall rate of 0.3% for both treatment groups combined).

These data reflect the percentage of children whose test results were considered positive for antibodies to palivizumab in an enzyme-linked immunosorbent assay (ELISA) and are highly dependent on the sensitivity and specificity of the assay.

The ELISA has substantial limitations in detecting anti-palivizumab antibodies in the presence of palivizumab. Immunogenicity samples tested with the ELISA assay likely contained palivizumab at levels that may interfere with the detection of anti-palivizumab antibodies.

An electrochemical luminescence (ECL) based immunogenicity assay, with a higher tolerance for palivizumab presence compared to the ELISA, was used to evaluate the presence of anti-palivizumab antibodies in subject samples from two additional clinical trials. The rates of anti-palivizumab antibody positive results in these trials were 1.1% and 1.5%.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Synagis. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: severe thrombocytopenia (platelet count less than 50,000 per microliter)

General Disorders and Administration Site Conditions: injection site reactions

Limited information from post-marketing reports suggests that, within a single RSV season, adverse events after a sixth or greater dose of Synagis are similar in character and frequency to those after the initial five doses.

7 DRUG INTERACTIONS

No formal drug-drug interaction studies were conducted. In Trial 1, the proportions of children in the placebo and Synagis groups who received routine childhood vaccines, influenza vaccine, bronchodilators, or corticosteroids were similar and no incremental increase in adverse reactions was observed among children receiving these agents.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Synagis is not indicated for adult usage. It is not known whether Synagis can cause fetal harm or could affect reproductive capacity when administered to a pregnant woman.

Animal Data

Animal reproduction studies have not been conducted.

8.4 Pediatric Use

The safety and effectiveness of Synagis in children greater than 24 months of age at the start of dosing have not been established.

10 OVERDOSAGE

Overdoses with doses up to 85 mg per kg have been reported in clinical studies and post-marketing experience with Synagis, and in some cases, adverse reactions were reported. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

11 DESCRIPTION

Palivizumab is a humanized monoclonal antibody (IgG1 κ) produced by recombinant DNA technology, directed to an epitope in the A antigenic site of the F protein of RSV. Palivizumab is a composite of human (95%) and murine (5%) antibody sequences. The human heavy chain sequence was derived from the constant domains of human IgG1 and the variable framework regions of the V_H genes Cor and Cess. The human light chain sequence was derived from the constant domain of C κ and the variable framework regions of the V_L gene K104 with J κ -4. The murine sequences were derived from a murine monoclonal antibody, Mab 1129, in a process that involved the grafting of the murine complementarity determining regions into the human antibody frameworks. Palivizumab is composed of two heavy chains and two light chains and has a molecular weight of approximately 148,000 Daltons.

Synagis is supplied as a sterile, preservative-free liquid solution at 100 mg per mL to be administered by intramuscular injection. Thimerosal or other mercury-containing salts are not used in the production of Synagis. The solution has a pH of 6.0 and should appear clear or slightly opalescent.

Each 100 mg single-dose vial of Synagis liquid solution contains 100 mg of palivizumab and also contains chloride (0.5 mg), glycine (0.1 mg), and histidine (3.9 mg), in a volume of 1 mL. Each 50 mg single-dose vial of Synagis liquid solution contains 50 mg of palivizumab and also contains chloride (0.2 mg), glycine (0.06 mg), and histidine (1.9 mg), in a volume of 0.5 mL.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Palivizumab is a recombinant humanized monoclonal antibody with anti-RSV activity [see *Microbiology* (12.4)].

12.3 Pharmacokinetics

In children less than or equal to 24 months of age without congenital heart disease (CHD), the mean half-life of palivizumab was 20 days and monthly intramuscular doses of 15 mg per kg achieved mean \pm SD 30 day trough serum drug concentrations of 37 \pm 21 mcg per mL after the first injection, 57 \pm 41 mcg per mL after the second injection, 68 \pm 51 mcg per mL after the third injection, and 72 \pm 50 mcg per mL after the fourth injection. Trough concentrations following the first and fourth Synagis dose were similar in children with CHD and in non-cardiac patients. In children given Synagis for a second season, the mean \pm SD serum concentrations following the first and fourth injections were 61 \pm 17 mcg per mL and 86 \pm 31 mcg per mL, respectively.

In 139 children less than or equal to 24 months of age with hemodynamically significant CHD who received Synagis and underwent cardio-pulmonary bypass for open-heart surgery, the mean \pm SD serum palivizumab concentration was 98 \pm 52 mcg per mL before bypass and declined to 41 \pm 33 mcg per mL after bypass, a reduction of 58% [see *Dosage and Administration* (2.1)]. The clinical significance of this reduction is unknown.

Specific studies were not conducted to evaluate the effects of demographic parameters on palivizumab systemic exposure. However, no effects of gender, age, body weight, or race on palivizumab serum trough concentrations were observed in a clinical study with 639 children with CHD (less than or equal to 24 months of age) receiving five monthly intramuscular injections of 15 mg per kg of Synagis.

The pharmacokinetics and safety of Synagis liquid solution and Synagis lyophilized formulation administered via intramuscular injection at 15 mg per kg were studied in a cross-over trial of 153 infants less than or equal to 6 months of age with a history of prematurity. The results of this trial indicated that the trough serum concentrations of palivizumab were comparable between the liquid solution and the lyophilized formulation, which was the formulation used in the clinical studies. A population pharmacokinetic analysis was performed across 22 studies in 1800 patients (1684 pediatric and 116 adult patients) to characterize palivizumab pharmacokinetics and inter-subject variability in serum concentrations. Palivizumab pharmacokinetics was described by a two-compartment linear model with an elimination half-life of 24.5 days in pediatric patients. Clearance of palivizumab in a typical pediatric patient (body weight 4.5 kg) less than or equal to 24 months of age without CHD was estimated to be 11 mL per day with a bioavailability of 70% following intramuscular administration. The inter-patient variability in drug clearance was 48.7% (CV%). Covariate analysis did not identify any factors that could account for the inter-patient variability in order to predict serum concentrations a priori in an individual patient.

12.4 Microbiology

Mechanism of Action

Palivizumab, a recombinant humanized monoclonal antibody which provides passive immunity against RSV, acts by binding the RSV envelope fusion protein (RSV F) on the surface of the virus and blocking a critical step in the membrane fusion process. Palivizumab also prevents cell-to-cell fusion of RSV-infected cells.

Antiviral Activity

The antiviral activity of palivizumab was assessed in a microneutralization assay in which increasing concentrations of antibody were incubated with RSV prior to addition of the human epithelial cells HEP-2. After incubation for 4-5 days, RSV antigen was measured in an ELISA assay. The neutralization titer (50% effective concentration [EC₅₀]) is expressed as the antibody concentration required to reduce detection of RSV antigen by 50% compared with untreated virus-infected cells. Palivizumab exhibited median EC₅₀ values of 0.65 mcg per mL (mean 0.75 ± 0.53 mcg per mL; n=69, range 0.07-2.89 mcg per mL) and 0.28 mcg per mL (mean 0.35 ± 0.23 mcg per mL; n=35, range 0.03-0.88 mcg per mL) against clinical RSV A and RSV B isolates, respectively. The majority of clinical RSV isolates tested (n=96) were collected from subjects across the United States (CA, CO, CT, IL, MA, NC, NY, PA, RI, TN, TX, VA), with the remainder from Japan (n=1), Australia (n=5) and Israel (n=2). These isolates encoded the most common RSV F sequence polymorphisms found among clinical isolates worldwide.

Palivizumab serum concentrations of greater than or equal to 40 mcg per mL have been shown to reduce pulmonary RSV replication in the cotton rat model of RSV infection by 100-fold.

Resistance

Palivizumab binds a highly conserved region on the extracellular domain of mature RSV F, referred to as antigenic site II or site A, which encompasses amino acids 262 to 275. All RSV mutants that exhibit resistance to palivizumab have been shown to contain amino acid changes in this region on the F protein.

F protein sequence variations within antigenic site A: Amino acid substitutions in antigenic site A selected either in cell culture, in animal models, or in human subjects that resulted in palivizumab resistance were N262D, N268I, K272E/M/N/Q/T, and S275F/L. RSV variants expressing the K272N substitution in F protein showed a 5164 ± 1731-fold decrease in susceptibility (i.e., fold increase in EC₅₀ value) when compared to the wild-type RSV, while variants containing the N262D, S275F/L, or K272E/M/N/Q/T substitutions showed a greater than 25,000-fold decrease in susceptibility to palivizumab. The N268I substitution conferred partial resistance to palivizumab; however, fold changes in susceptibility were not quantified for this mutant. Studies carried out to investigate the mechanism of virus escape from palivizumab showed a correlation between antibody binding and virus neutralization. RSV with substitutions in antigenic site A that were resistant to neutralization by palivizumab did not bind to palivizumab.

At least one of the palivizumab resistance-associated substitutions, N262D, K272E/Q, or S275F/L was identified in 8 of 126 clinical RSV (59 RSV A and 67 RSV B) isolates from subjects who failed immunoprophylaxis, resulting in a combined resistance-associated mutation frequency of 6.3%. A review of clinical findings revealed no association between antigenic A site sequence changes and RSV disease severity among children receiving palivizumab immunoprophylaxis who develop RSV lower respiratory tract disease.

Analysis of 254 clinical RSV isolates (145 RSV A and 109 RSV B) collected from immunoprophylaxis-naïve subjects revealed palivizumab resistance-associated substitutions in 2 (1 with N262D and 1 with S275F), resulting in a resistance-associated mutation frequency of 0.79%.

F protein sequence variations outside antigenic site A: In addition to the sequence variations in antigenic site A known to confer palivizumab resistance, F protein substitutions T100A, G139S, N165D/V406I; T326A, V450A in RSV A, and T74I, A147V, I206L, S285G, V450I, T455I in RSV B were identified in viruses isolated from failures of immunoprophylaxis. These substitutions were not identified in RSV F sequences derived from 254 clinical isolates from immunoprophylaxis-naïve subjects and thus are considered treatment-associated and non-polymorphic. Recombinant RSV B encoding the S285G substitution exhibited palivizumab sensitivity (EC₅₀ value = 0.39 ± 0.02 mcg per mL) similar to recombinant wild-type RSV B (EC₅₀ value = 0.17 ± 0.02 mcg per mL).

Palivizumab susceptibility of RSV encoding common F protein sequence polymorphisms located proximal to antigenic site A was evaluated. Recombinant RSV A encoding N276S (EC₅₀ value = 0.72 ± 0.07 mcg per mL), and recombinant RSV B with S276N (EC₅₀ value = 0.42 ± 0.04 mcg per mL), exhibited sensitivities comparable to the corresponding recombinant wild-type RSV A (EC₅₀ value = 0.63 ± 0.22 mcg per mL) and RSV B (EC₅₀ value = 0.23 ± 0.07 mcg per mL). Likewise, RSV B clinical isolates containing the polymorphic variation V278A were at least as sensitive to neutralization by palivizumab (EC₅₀ range 0.08-0.45 mcg per mL) as laboratory strains of wild-type RSV B (EC₅₀ value = 0.54 ± 0.08 mcg per mL). No known polymorphic or non-polymorphic sequence variations outside the antigenic site A on RSV F have been demonstrated to render RSV resistant to neutralization by palivizumab.

Interference of RSV Diagnostic Assays by Palivizumab

Interference with immunologically-based RSV diagnostic assays by palivizumab has been observed in laboratory studies. Rapid chromatographic/enzyme immunoassays (CIA/EIA), immunofluorescence assays (IFA), and direct immunofluorescence assays (DFA) using monoclonal antibodies targeting RSV F protein may be inhibited. Therefore, caution should be used in interpreting negative immunological assay results when clinical observations are consistent with RSV infection. A reverse transcriptase-polymerase chain reaction (RT-PCR) assay, which is not inhibited by palivizumab, may prove useful for laboratory confirmation of RSV infection [see *Warnings and Precautions* (5.3)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis, mutagenesis, and reproductive toxicity studies have not been performed.

14 CLINICAL STUDIES

The safety and efficacy of Synagis were assessed in two randomized, double-blind, placebo-controlled trials of prophylaxis against RSV infection in children at high risk of an RSV-related hospitalization. Trial 1 was conducted during a single RSV season and studied a total of 1502 children less than or equal to 24 months of age with BPD or infants with premature birth (less than or equal to 35 weeks gestation) who were less than or equal to 6 months of age at study entry. Trial 2 was conducted over four consecutive seasons among a total of 1287 children less than or equal to 24 months of age with hemodynamically significant congenital heart disease. In both trials participants received 15 mg per kg Synagis or an equivalent volume of placebo via intramuscular injection monthly for five injections and were followed for 150 days from randomization. In Trial 1, 99% of all subjects completed the study and 93% completed all five injections. In Trial 2, 96% of all subjects completed the study and 92% completed all five injections. The incidence of RSV hospitalization is shown in Table 1. The results were shown to be statistically significant using Fisher's exact test.

Table 1: Incidence of RSV Hospitalization by Treatment Group

Trial		Placebo	Synagis	Difference Between Groups	Relative Reduction
Trial 1 Impact-RSV	N	500	1002		
	Hospitalization	53 (10.6%)	48 (4.8%)	5.8%	55%
Trial 2 CHD	N	648	639		
	Hospitalization	63 (9.7%)	34 (5.3%)	4.4%	45%

In Trial 1, the reduction of RSV hospitalization was observed both in children with BPD (34/266 [12.8%] placebo versus 39/496 [7.9%] Synagis) and in premature infants without BPD (19/234 [8.1%] placebo versus 9/506 [1.8%] Synagis). In Trial 2, reductions were observed in acyanotic (36/305 [11.8%] placebo versus 15/300 [5.0%] Synagis) and cyanotic children (27/343 [7.9%] placebo versus 19/339 [5.6%] Synagis).

The clinical studies do not suggest that RSV infection was less severe among children hospitalized with RSV infection who received Synagis for RSV prophylaxis compared to those who received placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

Synagis is supplied in single-dose vials as a preservative-free, sterile liquid solution at 100 mg per mL for intramuscular injection.

50 mg vial NDC 60574-4114-1

The 50 mg vial contains 50 mg Synagis in 0.5 mL.

100 mg vial NDC 60574-4113-1

The 100 mg vial contains 100 mg Synagis in 1 mL.

The rubber stopper used for sealing vials of Synagis is not made with natural rubber latex.

Storage

Upon receipt and until use, Synagis should be stored between 2°C and 8°C (36°F and 46°F) in its original container. DO NOT freeze. DO NOT use beyond the expiration date.

17 PATIENT COUNSELING INFORMATION

o **“Advise the patient to read the FDA-approved patient labeling (Patient Information)”**

The healthcare provider should discuss the potential benefits and risks of Synagis with the parents or guardians of Synagis recipients. Parents or guardians should be informed of the possible side effects of Synagis and of the signs and symptoms of potential allergic reactions and should be advised of the appropriate actions. Parents or guardians should understand the dosing schedule and the importance of compliance with the full course of therapy.

Synagis® is a registered trademark of MedImmune, LLC.



Manufactured by:

MedImmune, LLC
Gaithersburg, MD 20878
U.S. License No. 1799
1-877-633-4411

RAL-SYNNV17
Component No.: 26920A

PATIENT INFORMATION
SYNAGIS® (Sĭ-nă-jĭs)
(palivizumab)
Injection

Read this Patient Information before your child starts receiving SYNAGIS and before each injection. The information may have changed. This leaflet does not take the place of talking with your child's healthcare provider about your child's condition or treatment.

What is SYNAGIS?

SYNAGIS is a prescription medication that is used to help prevent a serious lung disease caused by Respiratory Syncytial Virus (RSV). Your child is prescribed SYNAGIS because he or she is at high risk for severe lung disease from RSV.

SYNAGIS contains man-made, disease-fighting proteins called antibodies. These antibodies help prevent RSV disease. Children at high risk for severe RSV disease often do not have enough of their own antibodies. SYNAGIS is used in certain groups of children to help prevent severe RSV disease by increasing protective RSV antibodies.

SYNAGIS is not used to treat the symptoms of RSV disease once a child already has it. It is only used to prevent RSV disease.

SYNAGIS is not for adults or for children older than 24 months of age at the start of dosing.

Who should not receive SYNAGIS?

Your child should not receive SYNAGIS if they have ever had a severe allergic reaction to it. Signs and symptoms of a severe allergic reaction could include:

- severe rash, hives, or itching skin
- swelling of the lips, tongue, or face
- closing of the throat, difficulty swallowing
- difficult, rapid, or irregular breathing
- bluish color of skin, lips, or under fingernails
- muscle weakness or floppiness
- a drop in blood pressure
- unresponsiveness

What should I tell my child's healthcare provider before my child receives SYNAGIS?

Tell your child's healthcare provider about:

- **any reactions** you believe your child has ever had to SYNAGIS.
- **any bleeding or bruising problems.** SYNAGIS is given by injection. If your child has a problem with bleeding or bruises easily, an injection could cause a problem.
- **any other medical problems.**

Tell your child's healthcare provider about all the medicines your child takes, including prescription and non-prescription medicines, vitamins, and herbal supplements. Especially tell your child's healthcare provider if your child takes a blood thinner medicine.

How is SYNAGIS given?

- SYNAGIS is given as a monthly injection, usually in the thigh (leg) muscle, by your child's healthcare provider. Your child's healthcare provider will prescribe the amount of SYNAGIS that is right for your child (based on their weight).
- Your child's healthcare provider will give you detailed instructions on when SYNAGIS will be given.
 - "RSV season" is a term used to describe the time of year when RSV infections most commonly occur (usually fall through spring in most parts of the country). During this time, when RSV is most active, your child will need to receive SYNAGIS shots. Your child's healthcare provider can tell you when the RSV season starts in your area.
 - Your child should receive their **first SYNAGIS shot before the RSV season starts** to help protect them before RSV becomes active. If the season has already started, your child should receive their first SYNAGIS shot as soon as possible to help protect them when exposure to the virus is more likely.

- **SYNAGIS is needed every 28-30 days during the RSV season.** Each dose of SYNAGIS helps protect your child from severe RSV disease for about a month. **Keep all appointments with your child's healthcare provider.**

- **If your child misses an injection, talk to your healthcare provider and schedule another injection as soon as possible.**
- Your child may still get severe RSV disease after receiving SYNAGIS; talk to your child's healthcare provider about what symptoms to look for. If your child has an RSV infection, they should continue to get their scheduled SYNAGIS injections to help prevent severe disease from new RSV infections.
- If your child has certain types of heart disease and has corrective surgery, your healthcare provider may need to give your child an additional SYNAGIS injection soon after surgery.

What are the possible side effects of SYNAGIS?

Synagis may cause serious side effects including:

- Severe allergic reactions (may occur after any dose of SYNAGIS). Such reactions may be life-threatening or cause death.
 - See "Who should not take SYNAGIS?" for a list of signs and symptoms.
- Unusual bruising or groups of tiny red spots on the skin.

Call your child's healthcare provider or get medical help right away if your child has any of the serious side effects listed above after any dose of SYNAGIS.

Common side effects of SYNAGIS include:

- fever
- rash

Other possible side effects include skin reactions around the area where the shot was given (like redness, swelling, warmth, or discomfort).

These are not all the possible side effects of SYNAGIS. Tell your child's healthcare provider about any side effect that bothers your child or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to MedImmune at 1-877-633-4411.

General Information about SYNAGIS

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets.

This leaflet summarizes important information about SYNAGIS. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about SYNAGIS that is written for health professionals.

For more information, go to www.synagis.com or call 1-877-633-4411.

What are the ingredients in SYNAGIS?

Active Ingredient: palivizumab

Inactive Ingredients: chloride, glycine, and histidine

What is RSV?

Respiratory Syncytial Virus (RSV) is a common virus that is easily spread from person to person. RSV infects nearly all children by their second birthday. In most children, RSV infection is usually no worse than a bad cold. For some children, RSV infection can cause serious lung disease (like pneumonia and bronchiolitis) or breathing problems, and affected children may need to be admitted to the hospital or need emergency care.

Children who are more likely to get severe RSV disease (high-risk children) include babies born prematurely (35 weeks or less) or babies born with certain heart or lung problems.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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Manufactured by: MedImmune, LLC

Gaithersburg, MD 20878

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