SYNAGIS® (palivizumab) injection, for intramuscular use

Initial U.S. Approval: 1998

SYNAGIS® (palivizumab) injection is for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients:

• with a history of premature birth (less than or equal to 35 weeks gestational age) and who are 6 months of age or younger at the beginning of RSV season,

• with bronchopulmonary dysplasia (BPD) that required medical treatment within the previous 6 months and who are 24 months of age or younger at the beginning of RSV season,

• with hemodynamically significant congenital heart disease (CHD) and who are 24 months of age or younger at the beginning of RSV season.

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

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)

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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)

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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)
• 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, hypotension, hypotension, and anaphylactic shock with syncope. 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 hemodynamically significant congenital heart disease. Over four consecutive seasons among a total of 1287 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.
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 ± SD 30 day trough serum drug concentrations of 37 ± 21 mcg per mL after the first injection, 57 ± 41 mcg per mL after the second injection, 68 ± 51 mcg per mL after the third injection, and 72 ± 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 ± SD serum concentrations following the first and fourth injections were 61 ± 17 mcg per mL and 86 ± 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 cardiac-pulmonary bypass for open-heart surgery, the mean ± SD serum palivizumab concentration was 98 ± 52 mcg per mL before bypass and declined to 41 ± 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 infection of MA104 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=32, 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/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 K272M/D/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 site A 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-naive 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, I147V, A149T, I206L, S265G, V450I, and T455S 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-naive subjects and thus are considered treatment-associated and non-polymeric. Recombinant RSV B encoding the S265G 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 polymeric 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 ± 0.06 mcg per mL). No known polymeric or non-polymeric 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/ELIA), 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**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Placebo</th>
<th>Synagis</th>
<th>Difference Between Groups</th>
<th>Relative Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1 Impact-RSV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>500</td>
<td>1002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>53 (10.6%)</td>
<td>48 (4.8%)</td>
<td>5.8%</td>
<td>55%</td>
</tr>
<tr>
<td>Trial 2 CHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>648</td>
<td>639</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>63 (9.7%)</td>
<td>34 (5.3%)</td>
<td>4.4%</td>
<td>45%</td>
</tr>
</tbody>
</table>

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 66658-230-01
- The 50 mg vial contains 50 mg Synagis in 0.5 mL.
- 100 mg vial NDC 66658-231-01
- 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**

Advise the patient’s caregiver to read the FDA-approved patient labeling (Patient Information)

**Hypersensitivity Reactions**

Inform the patient’s caregiver of the signs and symptoms of potential hypersensitivity reactions, and advise the caregiver to seek medical attention immediately if the child experiences a severe hypersensitivity reaction to Synagis [see Contraindications (4) and Warnings and Precautions (5.1)].

**Administration**

Advise the patient’s caregiver that Synagis should be administered by a healthcare provider once a month during the RSV season by intramuscular injection and the importance of compliance with the full course of therapy [see Dosage and Administration (2)].

Synagis® is a registered trademark of Arexis AB c/o Swedish Orphan Biovitrum AB (publ).

Manufactured by:
Swedish Orphan Biovitrum AB (publ)
Stockholm, Sweden

Distributed by:
Sobi Inc.
77 4th Avenue, 3rd Floor
Waltham, MA 02451-7559

U.S License No. 1859
Issued: 11/2020
PATIENT INFORMATION
SYNAGIS® (Si-na-jis)
(palivizumab) injection

What is SYNAGIS?
SYNAGIS is a prescription medication that is used to help prevent a serious lung disease caused by Respiratory Syncytial Virus (RSV) in children:
- born prematurely (at or before 35 weeks) and who are 6 months of age or less at the beginning of RSV season,
- who have a chronic lung condition called bronchopulmonary dysplasia (BPD), that needed medical treatment within the last 6 months, and who are 24 months of age or less at the beginning of RSV season,
- born with certain types of heart disease and who are 24 months of age or less at the beginning of RSV season.

SYNAGIS contains man-made, disease-fighting proteins called antibodies.
It is not known if SYNAGIS is safe and effective to treat the symptoms of RSV in a child who already has RSV. Synagis is used to help prevent RSV disease.
It is not known if SYNAGIS is safe and effective in children who are 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. See the end of this leaflet for a complete list of ingredients in SYNAGIS. Signs and symptoms of a severe allergic reaction could include:
- severe rash, hives, or itching skin
- swelling of the lips, tongue, or face
- swelling of the throat, difficulty swallowing
- difficult, rapid, or irregular breathing
- bluish color of skin, lips, or under fingernails
- muscle weakness or floppiness
- unresponsiveness

Before your child receives SYNAGIS, tell your healthcare provider about all of your child’s medical conditions, including if your child:
- has ever had a reaction to SYNAGIS.
- has 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.

Tell your child’s healthcare provider about all the medicines your child takes, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

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 give you detailed instructions on when SYNAGIS will be given.
  o “RSV season” is the time of year when RSV infections most commonly happen, usually fall through spring, but it may begin earlier or last longer in certain areas. During this time, when RSV is most active, your child will need to receive SYNAGIS injections. Your healthcare provider can tell you when the RSV season starts in your area.
  o Your child should receive the first SYNAGIS injection before the RSV season starts to help prevent RSV infection. If the season has already started, your child should receive their first SYNAGIS injection as soon as possible to help protect them when exposure to the virus is more likely.
  o SYNAGIS is needed every 28-30 days during the RSV season. Each injection of SYNAGIS helps protect your child from severe RSV disease for about 1 month. Keep all of your child’s appointments with your 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 healthcare provider about what symptoms to look for. If your child gets a RSV infection, they should continue to receive 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. Severe allergic reactions may happen after any injection of SYNAGIS, and may be life-threatening or cause death. Call your healthcare provider or get medical help right away if your child has any of the signs or symptoms of a serious allergic reaction. See “Who should not receive SYNAGIS?”.
  The most common side effects of SYNAGIS include fever and rash. These are not all the possible side effects of SYNAGIS. 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 at 1-866-773-5274.

General information about the safe and effective use of SYNAGIS.
Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. You can ask your pharmacist or healthcare provider for information about SYNAGIS that is written for health professionals.

What are the ingredients in SYNAGIS?
Active ingredient: palivizumab
Inactive ingredients: chloride, glycine, and histidine

For more information, go to www.synagis.com or call 1-866-773-5274.

This Patient Information has been approved by the U.S. Food and Drug Administration
Revised: 11/2021 PP-8593 (v3.0) 06/22