SYNAGIS® (palivizumab) injection, for intramuscular use

Limitations of Use:

The safety and efficacy of Synagis have not been established for treatment of RSV disease. (1)

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**DOSE AND ADMINISTRATION**

- **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 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. (1)

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**Dosage and Administration**

- 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. (2.1, 12.3)

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**Dosing Information**

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SYNAGIS® (palivizumab) injection, for intramuscular use

- 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) × 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 anaphylactoid 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, and anaphylaxis. The risk of hypersensitivity reactions following re-exposure to Synagis is increased when Synagis is given to children who have had a prior significant hypersensitivity reaction to Synagis or other agents used prophylactically for RSV prevention. Initial use of Synagis in children with RSV who have had a prior significant hypersensitivity reaction to Synagis is not recommended.

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 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 1592 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

Risk Summary

Synagis is not indicated for use in females of reproductive potential.

8.2 Lactation

Risk Summary

Synagis is not indicated for use in females of reproductive potential.

8.4 Pediatric Use

The safety and effectiveness of Synagis in children older than 24 months of age at the start of dosing have not been established [see Clinical Studies (14)].

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 overdose, 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 (IgG1k) 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 Vh genes Cor and Cess. The human light chain sequence was derived from the constant domain of Ck and the variable framework regions of the Vk gene K104 with Jk -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.
Palivizumab is a recombinant humanized monoclonal antibody with anti-RSV activity [see Microbiology (12.4)].

**12 CLINICAL PHARMACOLOGY**

**12.1 Mechanism of Action**
Palivizumab is mechanism-based inhibition of RSV replication in the human airway 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 also prevents cell-to-cell fusion of RSV-infected cells.

**12.2 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 injection were 37 ± 21 mcg per mL and 57 ± 41 mcg per mL, respectively.

In 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) was less than or equal to 24 months of age without CHD was estimated to be 11 mcL 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 blocking the RSV envelope 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 also prevents cell-to-cell fusion of RSV-infected cells.

RSV respiratory tract disease.

**13 NONCLINICAL TOXICOLOGY**

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**
Carcinogenesis, mutagenesis, and reproductive toxicity studies have not been performed.
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.
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.

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 1866-773-5274.

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
Manufactured by: Swedish Orphan Biovitrum AB (publ), Stockholm, Sweden
Synagis® is a registered trademark of Arexis AB c/o Swedish Orphan Biovitrum AB (publ).

For more information, go to www.synagis.com or call 1866-773-5274.