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SYNAGIS® (PALIVIZUMAB)

for Intramuscular Administration

DESCRIPTION: Synagis® (palivizumab) is a humanized monoclonal antibody (IgG1κ) produced by recombinant DNA technology, directed to an epitope in the A antigenic site of the F protein of respiratory syncytial virus (RSV). Synagis® 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 (1) and Cess (2). The human light chain sequence was derived from the constant domain of Cκ and the variable framework regions of the V_L gene K104 with Jκ-4 (3). The murine sequences were derived from a murine monoclonal antibody, Mab 1129 (4), in a process that involved the grafting of the murine complementarity determining regions into the human antibody frameworks. Synagis® is composed of two heavy chains and two light chains and has a molecular weight of approximately 148,000 Daltons.

Synagis® is available in two formulations: a lyophilized powder and a liquid solution.

Lyophilized Powder: Synagis® is supplied as a sterile lyophilized product for reconstitution with sterile water for injection. Reconstituted Synagis® (100 mg/mL) is to be administered by intramuscular injection (IM) only. The reconstituted solution should appear clear or slightly opalescent with pH of 6.0.

Each 100 mg single-use vial of Synagis® lyophilized powder is formulated in 67.5 mg of mannitol, 8.7 mg histidine and 0.3 mg of glycine and is designed to deliver 100 mg of Synagis® in 1.0 mL when reconstituted with 1.0 mL of sterile water for injection.

Each 50 mg single-use vial of Synagis® lyophilized powder is formulated in 40.5 mg mannitol, 5.2 mg of histidine and 0.2 mg of glycine and is designed to deliver 50 mg of Synagis® in 0.5 mL when reconstituted with 0.6 mL of sterile water for injection.

Liquid Solution: Synagis® (100 mg/mL) is supplied as a sterile, preservative-free solution to be administered by intramuscular injection (IM) only. The solution should appear clear or slightly opalescent with pH of 6.0.

Each 100 mg single-use vial of Synagis® liquid solution is formulated in 4.7 mg of histidine and 0.1 mg of glycine in a volume of 1.2 mL to and is designed to deliver 100 mg of Synagis® in 1.0 mL.

Each 50 mg single-use vial of Synagis® liquid solution is formulated in 2.7 mg of histidine and 0.08 mg of glycine in a volume of 0.7 mL to and is designed to deliver 50 mg of Synagis® in 0.5 mL.

CLINICAL PHARMACOLOGY: *Mechanism of Action:* Synagis® exhibits neutralizing and fusion-inhibitory activity against RSV. These activities inhibit RSV replication in laboratory experiments. Although resistant RSV strains may be isolated in laboratory studies, a panel of 57 clinical RSV isolates were all neutralized by Synagis® (5). Synagis® serum concentrations of = 40 µg/mL have been shown to reduce pulmonary RSV replication in the cotton rat model of RSV infection by 100-fold (5). The *in vivo* neutralizing activity of the active ingredient in Synagis® was assessed in a randomized, placebo-controlled study of 35 pediatric patients tracheally intubated because of RSV disease. In these patients,

Synagis® significantly reduced the quantity of RSV in the lower respiratory tract compared to control patients (6).

Pharmacokinetics: In pediatric patients less than 24 months of age without congenital heart disease, the mean half-life of Synagis® was 20 days and monthly intramuscular doses of 15 mg/kg achieved mean ±SD 30 day trough serum drug concentrations of 37+ 21 µg/mL after the first injection, 57 ± 41 µg/mL after the second injection, 68 ± 51 µg/mL after the third injection and 72 ± 50 µg/mL after the fourth injection (7). Trough concentrations following the first and fourth Synagis® dose were similar in children with congenital heart disease and in non-cardiac patients. In pediatric patients given Synagis® for a second season, the mean ±SD serum concentrations following the first and fourth injections were 61 ± 17 µg/mL and 86 ±31µg/mL, respectively.

In 139 pediatric patients ≤ 24 months of age with hemodynamically significant congenital heart disease (CHD) who received Synagis® and underwent cardio-pulmonary bypass for open-heart surgery, the mean ± SD serum Synagis® concentration was 98± 52 µg/mL before bypass and declined to 41± 33 µg/mL after bypass, a reduction of 58% (see *DOSAGE AND ADMINISTRATION*). The clinical significance of this reduction is unknown.

Specific studies were not conducted to evaluate the effects of demographic parameters on Synagis® systemic exposure. However, no effects of gender, age, body weight or race on Synagis® serum trough concentrations were observed in a clinical study with 639 pediatric patients with congenital heart disease (=24 months of age) receiving five monthly intramuscular injections of 15 mg/kg of Synagis®.

Trough serum Synagis® concentrations were comparable between the Synagis® liquid and Synagis® lyophilized formulations administered IM at 15 mg/kg in a cross-over trial in 153 pediatric patients ≤6 months of age with a history of prematurity.

CLINICAL STUDIES: The safety and efficacy of Synagis® (palivizumab) were assessed in two randomized, double-blind, placebo-controlled trials of prophylaxis against RSV infection in pediatric patients at high risk of an RSV-related hospitalization. Trial 1 was conducted during a single RSV season and studied a total of 1,502 patients = 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 (7). Trial 2 was conducted over four consecutive seasons among a total of 1287 patients = 24 months of age with hemodynamically significant congenital heart disease. In both trials 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. 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.

Table 1: **Incidence of RSV Hospitalization by Treatment Group**

Trial		Placebo	Synagis	Difference between groups	Relative Reduction	p-Value
Trial 1	N	500	1002			
Impact-RSV	Hospitalization	53 (10.6%)	48 (4.8%)	5.8%	55	<0.001
Trial 2	n	648	639			
CHD	Hospitalization	63 (9.7%)	34 (5.3%)	4.4%	45%	0.003

In Trial 1, the reduction of RSV hospitalization was observed both in patients with BPD (34/266 [12.8%] placebo vs. 39/496 [7.9%] Synagis®), and in premature infants without BPD (19/234 [8.1%] placebo vs. 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 RSV hospitalized patients who received Synagis® compared to those who received placebo.

INDICATIONS AND USAGE: Synagis® is indicated 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 infants with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (= 35 weeks gestational age), and children with hemodynamically significant CHD. (See *CLINICAL STUDIES*)

CONTRAINDICATIONS: Synagis® should not be used in pediatric patients with a history of a severe prior reaction to Synagis® or other components of this product.

WARNINGS: Very rare cases of anaphylaxis (<1 case per 100,000 patients) have been reported following re-exposure to Synagis® (see *ADVERSE REACTIONS, POSTMARKETING EXPERIENCE)*. Rare severe acute hypersensitivity reactions have also been reported on initial exposure or re-exposure to Synagis®. If a severe hypersensitivity reaction occurs, therapy with Synagis® should be permanently discontinued. If milder hypersensitivity reactions occur, caution should be used on readministration of Synagis®. **If anaphylaxis or severe allergic reactions occur, administer appropriate medications (e.g., epinephrine) and provide supportive care as required.**

PRECAUTIONS: *General:* Synagis® is for intramuscular use only. As with any intramuscular injection, Synagis® should be given with caution to patients with thrombocytopenia or any coagulation disorder.

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

The single-use vial of Synagis® (palivizumab) does not contain a preservative. Lyophilized Synagis® must be used within 6 hours of reconstitution. Administration of either reconstituted Synagis® or liquid Synagis® should occur immediately after withdrawal from vial. The vial should not be re-entered. Discard any unused portion.

Drug Interactions: No formal drug-drug interaction studies were conducted. In Trial 1, the proportions of patients 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 patients receiving these agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis, mutagenesis and reproductive toxicity studies have not performed.

Pregnancy: Pregnancy Category C: Synagis® is not indicated for adult usage and animal reproduction studies have not been conducted. It is also not known whether Synagis® can cause fetal harm when administered to a pregnant woman or could affect reproductive capacity.

ADVERSE REACTIONS:

The most serious adverse reactions occurring with Synagis® treatment are anaphylaxis and other acute hypersensitivity reactions (see *WARNINGS*). The adverse reactions most commonly observed in Synagis®-treated patients were upper respiratory tract infection, otitis media, fever, rhinitis, rash, diarrhea, cough, vomiting, gastroenteritis, and wheezing. Upper respiratory tract infection, otitis media, fever, and rhinitis occurred at a rate of 1% or greater in the Synagis® group compared to placebo (Table 2).

Because clinical trials are conducted under widely varying conditions, adverse event 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 adverse reaction information does, however, provide a basis for identifying the adverse events that appear to be related to drug use and a basis for approximating rates.

The data described reflect Synagis® exposure for 1641 pediatric patients of age 3 days to 24.1 months in Trials 1 and 2. Among these patients, 496 had bronchopulmonary dysplasia, 506 were premature birth infants less than 6 months of age, and 639 had congenital heart disease. Adverse events observed in the 153 patient crossover study comparing the liquid and lyophilized formulations were similar between the two formulations, and similar to the adverse events observed with Synagis® in Trials 1 and 2.

Table 2 - Adverse events occurring at a rate of 1% or greater more frequently in patients† receiving Synagis®

Event	Synagis® (n=1641) n (%)	Placebo (n=1148) n (%)
Upper respiratory infection	830 (50.6)	544 (47.4)
Otitis media	597 (36.4)	397 (34.6)
Fever	446 (27.1)	289 (25.2)
Rhinitis	439 (26.8)	282 (24.6)
Hernia	68 (4.1)	30 (2.6)
SGOT Increase	49 (3.0)	20 (1.7)
†Cyanosis (Synagis® [9.1%]/ placebo [6.9%]) and arrythmia (Synagis® [3.1%]/placebo [1.7%]) were reported during Trial 2 in congenital heart disease patients.		

Immunogenicity

In the Trial 1, the incidence of anti-Synagis® antibody following the fourth injection was 1.1% in the placebo group and 0.7% in the Synagis® group. In pediatric patients receiving Synagis® for a second season, one of the fifty-six patients 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.

These data reflect the percentage of patients whose test results were considered positive for antibodies to Synagis® (palivizumab) in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Synagis® with the incidence of antibodies to other products may be misleading.

Post-Marketing Experience

The following adverse reactions have been identified and reported during post-approval use of Synagis®. Because the reports of these reactions are voluntary and the population is of uncertain size, it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to drug exposure.

Based on experience in over 400,000 patients who have received Synagis® (>2 million doses), rare severe acute hypersensitivity reactions have been reported on initial or subsequent exposure. Very rare cases of anaphylaxis (<1 case per 100,000 patients) have also been reported following re-exposure *(*See *WARNINGS)*. None of the reported hypersensitivity reactions were fatal. Hypersensitivity

reactions may include dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia and unresponsiveness. The relationship between these reactions and the development of antibodies to Synagis® is unknown.

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.

OVER DOSAGE: No data from clinical studies are available on over dosage. No toxicity was observed in rabbits administered a single intramuscular or subcutaneous injection of Synagis® at a dose of 50 mg/kg.

DOSAGE AND ADMINISTRATION: The recommended dose of Synagis® is 15 mg/kg of body weight. Patients, including those who develop an RSV infection, should continue to receive monthly doses throughout the RSV season. The first dose should be administered prior to commencement of 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*). Patients undergoing cardio-pulmonary bypass should receive a 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.

Synagis® should be administered in a dose of 15 mg/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 per month = patient weight (kg) x 15 mg/kg ÷ 100 mg/mL of Synagis®. Injection volumes over 1 mL should be given as a divided dose.

Preparation of Lyophilized Product for Administration:

- To reconstitute, remove the tab portion of the vial cap and clean the rubber stopper with 70% ethanol or equivalent.
- Both the 50 mg and 100 mg vials contain an overfill to allow the withdrawal of 50 milligrams or 100 milligrams respectively when reconstituted following the directions described below.
- SLOWLY add 0.6 mL of sterile water for injection to the 50 mg vial or add 1.0 mL of sterile water for injection to the 100 mg vial. The vial should be tilted slightly and gently rotated for 30 seconds to avoid foaming. DO NOT SHAKE or VIGOROUSLY AGITATE the VIAL. This is a critical step to avoid prolonged foaming.
- Reconstituted Synagis® should stand undisturbed at room temperature for a minimum of 20 minutes until the solution clarifies.
- Reconstituted Synagis® (palivizumab) should be inspected visually for particulate matter or discoloration prior to administration. The reconstituted solution should appear clear or slightly opalescent (a thin layer of micro-bubbles on the surface is normal and will not affect dosage). Do not use if there is particulate matter or if the solution is discolored.
- Reconstituted Synagis® does not contain a preservative and should be administered within 6 hours of reconstitution. Administer immediately after withdrawal from vial. Synagis® is supplied in single-use vials DO NOT re-enter the vial. Discard any unused portion.

Preparation of Liquid Product for Administration:

- Remove the tab portion of the vial cap and clean the rubber stopper with 70% ethanol or equivalent.
- Both the 50 mg and 100 mg vials contain an overfill to allow the withdrawal of 50 milligrams or 100 milligrams.
- Synagis® does not contain a preservative and should be administered immediately after withdrawal from vial. Synagis® is supplied in single-use vials. DO NOT re-enter the vial. Discard any unused portion.

To prevent the transmission of hepatitis viruses or other infectious agents from one person to another, sterile disposable syringes and needles should be used. Do not reuse syringes and needles.

HOW SUPPLIED: Synagis® is available in two formulations: a lyophilized powder and liquid solution.

Lyophilized Powder: Synagis® is supplied in single-use vials as lyophilized powder to deliver either 50 milligrams or 100 milligrams when reconstituted with sterile water for injection.

50 mg vial NDC 60574-4112-1
Upon reconstitution the 50 mg vial contains 50 milligrams Synagis® in 0.5 mL.

100 mg vial NDC 60574-4111-1
Upon reconstitution the 100 mg vial contains 100 milligrams Synagis® in 1.0 mL.

Liquid Solution: Synagis® is supplied in single-use vials as a preservative free, sterile solution at 100 mg/mL in 0.5 mL and 1.0 mL to deliver either 50 milligrams or 100 milligrams, respectively for IM injection.

50 mg vial NDC 60574-4114-1
The 50 mg vial contains 50 milligrams Synagis® in 0.5 mL.

100 mg vial NDC 60574-4113-1
The 100 mg vial contains 100 milligrams Synagis® in 1.0 mL.

Upon receipt and until use, Synagis® should be stored between 2 and 8°C (35.6° and 46.4°F) in its original container. Do not freeze. Do not use beyond the expiration date.

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