

## **SYNAGIS® (PALIVIZUMAB)** **for Intramuscular Administration**

**DESCRIPTION:** Synagis® (palivizumab) is a humanized monoclonal antibody (IgG1 $\kappa$ ) produced by recombinant DNA technology, directed to an epitope in the A antigenic site of the F protein of respiratory syncytial virus (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<sub>H</sub> genes Cor (1) and Cess (2). The human light chain sequence was derived from the constant domain of C $\kappa$  and the variable framework regions of the V<sub>L</sub> gene K104 with J $\kappa$ -4 (3). The murine sequences were derived from a murine monoclonal antibody, Mab 1129 (4), in a process which involved the grafting of the murine complementarity determining regions into the human antibody frameworks. Synagis® (palivizumab) is composed of two heavy chains and two light chains and has a molecular weight of approximately 148,000 Daltons.

Synagis® (palivizumab) is supplied as a sterile lyophilized product for reconstitution with sterile water for injection. Reconstituted Synagis® (palivizumab) is to be administered by intramuscular injection only. Upon reconstitution, Synagis® (palivizumab) contains the following excipients: 47 mM histidine, 3.0 mM glycine and 5.6% mannitol and the active ingredient, palivizumab, at a concentration of 100 milligrams per mL solution. The reconstituted solution should appear clear or slightly opalescent.

**CLINICAL PHARMACOLOGY:** *Mechanism of Action:* Synagis® (palivizumab) 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® (palivizumab) (5). Synagis® (palivizumab) serum concentrations of = 40  $\mu\text{g}/\text{mL}$  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® (palivizumab) was assessed in a randomized, placebo-controlled study of 35 pediatric patients tracheally intubated because of RSV disease. In these patients, palivizumab significantly reduced the quantity of RSV in the lower respiratory tract compared to control patients (6).

*Pharmacokinetics:* In studies in adult volunteers Synagis® (palivizumab) had a pharmacokinetic profile similar to a human IgG1 antibody in regard to the volume of distribution and the half-life (mean 18 days). In pediatric patients less than 24 months of age, the mean half-life of Synagis® (palivizumab) was 20 days and monthly intramuscular doses of 15 mg/kg achieved mean  $\pm$ SD 30 day trough serum drug concentrations of 37  $\pm$ 21  $\mu\text{g}/\text{mL}$  after the first injection, 57  $\pm$ 41  $\mu\text{g}/\text{mL}$  after the second injection, 68  $\pm$ 51  $\mu\text{g}/\text{mL}$  after the third injection and 72  $\pm$ 50  $\mu\text{g}/\text{mL}$  after the fourth injection (7). In pediatric patients given Synagis® (palivizumab) for a second season, the mean  $\pm$ SD serum concentrations following the first and fourth injections were 61  $\pm$ 17  $\mu\text{g}/\text{mL}$  and 86  $\pm$ 31  $\mu\text{g}/\text{mL}$ , respectively.

**CLINICAL STUDIES:** The safety and efficacy of Synagis® (palivizumab) were assessed in a randomized, double-blind, placebo-controlled trial (IMpact-RSV Trial) of RSV disease prophylaxis among high-risk pediatric patients (7). This trial, conducted at 139 centers in the United States, Canada and the United Kingdom, studied patients = 24 months of age with bronchopulmonary dysplasia (BPD) and patients with premature birth (= 35 weeks gestation) who were = 6 months of age at study entry. Patients with uncorrected congenital heart disease were excluded from enrollment. In this trial, 500 patients were randomized to receive five monthly placebo injections and 1,002 patients were randomized to receive five monthly injections of 15 mg/kg of Synagis® (palivizumab). Subjects were randomized into the study from November 15 to December 13, 1996, and were followed for safety and efficacy for 150 days. Ninety-nine percent of all subjects

completed the study and 93% received all five injections. The primary endpoint was the incidence of RSV hospitalization.

RSV hospitalizations occurred among 53 of 500 (10.6%) patients in the placebo group and 48 of 1002 (4.8%) patients in the Synagis® (palivizumab) group, a 55% reduction ( $p < 0.001$ ). The reduction of RSV hospitalization was observed both in patients enrolled with a diagnosis of BPD (34/266 [12.8%] placebo vs. 39/496 [7.9%] Synagis® [palivizumab]) and patients enrolled with a diagnosis of prematurity without BPD (19/234 [8.1%] placebo vs. 9/506 [1.8%] Synagis® [palivizumab]). The reduction of RSV hospitalization was observed throughout the course of the RSV season.

Among secondary endpoints, the incidence of ICU admission during hospitalization for RSV infection was lower among subjects receiving Synagis® (palivizumab) (1.3%) than among those receiving placebo (3.0%), but there was no difference in the mean duration of ICU care between the two groups for patients requiring ICU care. Overall, the data do not suggest that RSV illness was less severe among patients who received Synagis® (palivizumab) and who required hospitalization due to RSV infection than among placebo patients who required hospitalization due to RSV infection. Synagis® (palivizumab) did not alter the incidence and mean duration of hospitalization for non-RSV respiratory illness or the incidence of otitis media.

**INDICATIONS AND USAGE:** Synagis® (palivizumab) 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) and infants with a history of prematurity (= 35 weeks gestational age). (See *Clinical Studies* section)

**CONTRAINDICATIONS:** Synagis® (palivizumab) should not be used in pediatric patients with a history of a severe prior reaction to Synagis® (palivizumab) 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 (palivizumab) [see Adverse Reactions, Post-Marketing Experience]. Rare severe acute hypersensitivity reactions have also been reported on initial exposure or re-exposure to palivizumab. If a severe hypersensitivity reaction occurs, therapy with palivizumab should be permanently discontinued. If milder hypersensitivity reactions occur, caution should be used on readministration of palivizumab. **If anaphylaxis or severe allergic reactions occur, administer appropriate medications (e.g., epinephrine) and provide supportive care as required.**

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

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

The single-use vial of Synagis® (palivizumab) does not contain a preservative. Injections should be given within 6 hours after reconstitution.

*Drug Interactions:* No formal drug-drug interaction studies were conducted. In the IMpact-RSV trial, the proportions of patients in the placebo and Synagis® (palivizumab) 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® (palivizumab) is not indicated for adult usage and animal reproduction studies have not been conducted. It is also not known whether Synagis® (palivizumab) can cause fetal harm when administered to a pregnant woman or could affect reproductive capacity.

**ADVERSE REACTIONS:** In the combined pediatric prophylaxis studies of pediatric patients with BPD or prematurity involving 520 subjects receiving placebo and 1168 subjects receiving 5 monthly doses of Synagis® (palivizumab), the proportions of subjects in the placebo and Synagis® (palivizumab) groups who experienced any adverse event or any serious adverse event were similar.

Most of the safety information was derived from the IMpact-RSV trial. In this study, Synagis® (palivizumab) was discontinued in five patients: two because of vomiting and diarrhea, one because of erythema and moderate induration at the site of the fourth injection, and two because of pre-existing medical conditions which required management (one with congenital anemia and one with pulmonary venous stenosis requiring cardiac surgery). Seizures were reported in 0.6% of the placebo group and 0.4% of the Synagis® group. Deaths in study patients occurred in five of 500 placebo recipients and four of 1,002 Synagis® (palivizumab) recipients. Sudden infant death syndrome was responsible for two of these deaths in the placebo group and one death in the Synagis® (palivizumab) Adverse events which occurred in more than 1% of patients receiving Synagis® (palivizumab) in the IMpact-RSV study for which the incidence in the Synagis® (palivizumab) group was 1% greater than in the placebo group are shown in Table 1.

**Table 1. Adverse Events Occurring in IMPact-RSV Study at Greater Frequency in the Synagis® (palivizumab) Group**

<b>% of patients with:</b>	<b>Placebo n = 500</b>	<b>Synagis® (palivizumab) n = 1,002</b>
upper respiratory infection	49.0%	52.6%
otitis media	40.0%	41.9%
rhinitis	23.4%	28.7%
rash	22.4%	25.6%
pain	6.8%	8.5%
hernia	5.0%	6.3%
SGOT increased	3.8%	4.9%
Pharyngitis	1.4%	2.6%

Other adverse events reported in more than 1% of the Synagis® (palivizumab) group included: fever, cough, wheeze, bronchiolitis, pneumonia, bronchitis, asthma, croup, dyspnea, sinusitis, apnea, failure to thrive, nervousness, diarrhea, vomiting, and gastroenteritis, SGPT increase, liver function abnormality, study drug injections site reaction, conjunctivitis, viral infection, oral monilia, fungal dermatitis, eczema, seborrhea, anemia and flu syndrome. The incidence of these adverse events was similar between the Synagis® (palivizumab) and placebo groups.

#### Immunogenicity

In the IMpact-RSV trial, the incidence of anti-palivizumab antibody following the fourth injection was 1.1% in the placebo group and 0.7% in the Synagis® (palivizumab) group. In pediatric patients receiving Synagis® (palivizumab) 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 Synagis® (palivizumab) serum concentrations.

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® (palivizumab) 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® (palivizumab). 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. None of the reported hypersensitivity reactions were fatal. Hypersensitivity reactions may include dyspnea, cyanosis, respiratory failure, urticaria, pruritis, angioedema, hypotonia and unresponsiveness. The relationship between these reactions and the development of antibodies to Synagis® (palivizumab) 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® (palivizumab) are similar in character and frequency to those after the initial five doses.

**OVERDOSAGE:** No data from clinical studies are available on overdosage. No toxicity was observed in rabbits administered a single intramuscular or subcutaneous injection of Synagis® (palivizumab) at a dose of 50 mg/kg.

**DOSAGE AND ADMINISTRATION:** The recommended dose of Synagis® (palivizumab) is 15 mg/kg of body weight. Patients, including those who develop an RSV infection, should 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® (palivizumab) 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® (palivizumab)]. Injection volumes over 1 mL should be given as a divided dose.

*Preparation 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 gently swirled for 30 seconds to avoid foaming. **DO NOT SHAKE VIAL.**
- Reconstituted Synagis® (palivizumab) should stand at room temperature for a minimum of 20 minutes until the solution clarifies.
- Reconstituted Synagis® (palivizumab) does not contain a preservative and should be administered within 6 hours of reconstitution.

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® (palivizumab) 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® (palivizumab) in 0.5 mL.

100 mg vial NDC 60574-4111-1

Upon reconstitution the 100 mg vial contains 100 milligrams Synagis® (palivizumab) in 1.0 mL.

Upon receipt and until reconstitution for use, Synagis® (palivizumab) 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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