Product Package Insert

PRODUCT NAME

Palivizumab

TRADE NAME

Synagis®

DESCRIPTION

Palivizumab is a humanized IgG1 monoclonal antibody directed to an epitope in the A antigenic site of the fusion protein of respiratory syncytial virus (RSV).

This humanized monoclonal antibody is composed of 95% human and 5% murine amino acid sequences. Palivizumab is composed of two heavy chains and two light chains having a molecular weight of approximately 148,000 Daltons.

Palivizumab is supplied as a sterile solution for intramuscular injection. Palivizumab contains the following excipients: 25 mM histidine and 1.6mM glycine and the active ingredient, palivizumab, at a concentration of 100 milligrams per mL the solution is clear or slightly opalescent.

INDICATIONS

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.

- Children born at 35 weeks of gestation or less and less than 6 months of age at the onset of the RSV season.

- Children less than 2 years of age and requiring treatment for bronchopulmonary dysplasia within the last 6 months.

- Children less than 2 years of age and with haemodynamically significant congenital heart disease.

DOSAGE AND ADMINISTRATION

The recommended dose of palivizumab is 15 mg/kg of body weight, given once a month during anticipated periods of RSV risk in the community. The first dose should be administered prior to commencement of the RSV season and subsequent doses should be administered monthly throughout the RSV season. In the northern hemisphere, the RSV season typically commences in November and lasts through April, but RSV activity may begin earlier or persist later in a community. To avoid risk of reinfection, it is recommended that children receiving palivizumab who become infected with RSV continue to receive monthly doses of palivizumab for the duration of the RSV season.

Palivizumab is administered in a dose of 15 mg/kg once a month intramuscularly, 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 injection should be given using standard aseptic technique. The dose per month = patient weight (kg) x 15mg/kg ÷ 100 mg/ml of palivizumab. Injection volumes over 1 mL should be given as a divided dose.

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.

Palivizumab is to be administered by intramuscular injection only.

To prevent the transmission of infectious diseases, sterile disposable syringes and needles should be used. Do not reuse syringes and needles.

Preparation for Administration

Liquid Formulation (100 mg/mL in 0.5 mL or 1 mL vials)
Liquid palivizumab should not be mixed with any medications or diluents.

Administration Instructions (Liquid Formulation)

Both the 0.5 mL and 1 mL vials contain an overfill to allow the withdrawal of 50 mg or 100 mg, respectively.

- **DO NOT DILUTE THE PRODUCT.**
- **DO NOT SHAKE VIAL.**
- To administer, remove the tab portion of the vial cap and clean the stopper with 70%
- ethanol or equivalent. Insert the needle into the vial and withdraw an appropriate volume of
- solution into the syringe.
- Palivizumab does not contain a preservative and should be administered immediately after drawing the dose into the syringe.
- Single-use vial. Do not re-enter the vial after withdrawal of drug. Discard unused contents.

CONTRAINDICATIONS

Palivizumab is contraindicated in patients with known hypersensitivity to palivizumab or to any of its excipients. It is also contraindicated in patients with known hypersensitivity to other humanized monoclonal antibodies.

WARNINGS AND PRECAUTIONS

Allergic reactions including very rare anaphylaxis and anaphylactic shock have been reported following palivizumab administration. In some cases, fatalities have been reported (see **ADVERSE REACTIONS/ Post-marketing Experience**).

Medications for the treatment of severe hypersensitivity reactions, including anaphylaxis and anaphylactic shock, should be available for immediate use following administration of palivizumab. If a severe hypersensitivity reaction occurs, therapy with palivizumab should be discontinued. As with other agents administered to this population, if milder hypersensitivity reactions occur, caution should be used on re-administration of palivizumab.

As with any intramuscular injection, palivizumab should be given with caution to patients with thrombocytopenia or any coagulation disorder.

The single-use vial of palivizumab does not contain a preservative.

A moderate to severe acute infection or febrile illness may warrant delaying the use of palivizumab, unless, in the opinion of the physician, withholding palivizumab entails a greater risk. A mild febrile illness, such as a mild upper respiratory infection, is not usually reason to defer administration of palivizumab.

DRUG INTERACTIONS

No formal drug-drug interaction studies were conducted, however no interactions have been described to date. In the IMpact RSV Study, the proportions of patients in the placebo and 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 in either of the two groups. Since the monoclonal antibody is specific for RSV, palivizumab is not expected to interfere with the immune response to vaccines, including live viral vaccines.

Drug/Laboratory Test Interaction

Palivizumab may interfere with immune-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.

PREGNANCY AND LACTATION

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

ADVERSE REACTIONS

Adverse events at least possibly causally related to palivizumab (ADRs) are displayed by system organ class and frequency (very common: ≥ 1/10; common: ≥ 1/100 to < 1/10; uncommon: ≥ 1/1000 to < 1/100; rare: ≥ 1/10000 to < 1/1000) in studies conducted in premature and bronchopulmonary dysplasia patients and pediatric congenital heart disease patients (Table 1).

Adverse drug reactions (ADRs) reported in the prophylactic pediatric studies were similar in the placebo and palivizumab groups. The majority of ADRs were transient and mild to moderate in severity.

IMpact-RSV Study

In the study of premature infants and children with bronchopulmonary dysplasia, no medically important differences in ADRs by body system or in subgroups of children categorized by gender, age, gestational age, country, race/ethnicity or quartile serum palivizumab concentration were observed. No significant difference in safety profile was observed between children without active

RSV infection and those hospitalised for RSV. Permanent discontinuation of palivizumab because of ADRs was rare (0.2%). Deaths were balanced between the placebo and palivizumab treatment groups and were not drug-related.

CHD Study

In the congenital heart disease study, no medically important differences were observed in ADRs by body system or when evaluated in subgroups of children by cardiac category (cyanotic versus acyanotic). The incidence of serious adverse events was significantly lower in the palivizumab group, as compared to the placebo group. No serious adverse events related to palivizumab were reported. The incidences of cardiac surgeries classified as planned, earlier than planned, or urgent, were balanced between the groups. Deaths associated with RSV infection occurred in 2 patients in the palivizumab group and 4 patients in the placebo group and were not drug-related.

Table 1 Summary of Adverse Drug Reactions in Prophylactic Clinical Studies with Premature and Bronchopulmonary Dysplasia or Congenital Heart Disease Pediatric Populations (IMpact-RSV and CHD Studies)*

MedDRA System Organ Class	**Frequency**	**ADR**
Skin and subcutaneous tissue disorders	Very common	Rash
General disorders and administrative site conditions	Very common Common	Pyrexia Injection site reaction

*For full study description, see **CLINICAL STUDIES** section.

Extended Dose Study

No reported adverse events were considered related to palivizumab and no deaths were reported in this study.

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 palivizumab group. In pediatric patients receiving 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 palivizumab serum concentrations. Immunogenicity was not assessed in the CHD Study.

Antibody to palivizumab was also evaluated in four additional studies in 4337 palivizumab- treated patients (children born at 35 weeks of gestation or less and 6 months of age or less, or < 24 months of age with bronchopulmonary dysplasia or with haemodynamically significant congenital heart disease were included in these studies) and was observed in 0% – 1.5% of patients at different study time points. There was no association observed between the presence of antibody and adverse events. Therefore, anti-drug antibody (ADA) responses appear to be of no clinical relevance.

In the Extended Dose Study, transient, low levels of anti-palivizumab antibody were observed in one child after the second dose of palivizumab that dropped to undetectable levels at the fifth and seventh

dose.

Post-marketing Experience

The following adverse reactions have been reported with palivizumab therapy. 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 palivizumab exposure (see also **WARNINGS AND PRECAUTIONS**).

Blood and the lymphatic system disorders

Thrombocytopenia

Immune system disorders

Anaphylaxis, anaphylactic shock (In some cases, fatalities have been reported)

Nervous system disorders

Convulsion

Skin and subcutaneous tissue disorders

Urticaria

Palivizumab treatment schedule and adverse events were monitored in a group of nearly 20,000 infants tracked through a patient compliance registry, the REACH program. Of this group, 1250 enrolled infants received 6 injections, 183 infants received 7 injections, and 27 infants received either 8 or 9 injections, each respectively. Adverse events observed in patients following a sixth or greater dose from this registry as well as through routine post marketing surveillance were similar in character and frequency to those after the initial 5 doses.

OVERDOSAGE

In clinical studies, three children received an overdose of more than 15 mg/kg. These doses were 20.25 mg/kg, 21.1 mg/kg and 22.27 mg/kg. No medical consequences were identified in these instances.

From the post-marketing experience, overdoses with doses up to 85 mg/kg have been reported and in some cases, adverse reactions were reported which did not differ from those observed with 15 mg/kg dose (see ADVERSE REACTIONS). In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

PHARMACOLOGIC PROPERTIES

Mechanism of Action

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 clinical RSV isolates were all neutralized by palivizumab. Palivizumab serum concentrations of approximately 30 mcg/mL have been shown to produce a mean 99% reduction in pulmonary RSV replication in the cotton rat model.

The *in vivo* neutralizing activity of the active ingredient in 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.

Pharmacokinetic Properties

The pharmacokinetics and safety of palivizumab liquid formulation and palivizumab lyophilized formulation, following 15 mg per kg intramuscular administration, were compared in a crossover trial of 153 infants less than or equal to 6 months of age with a history of prematurity (less than or equal to 35 weeks gestational age). The results of this trial indicated that the trough serum concentrations of palivizumab were similar between liquid formulation and the lyophilized formulation and bioequivalence of the liquid and the lyophilized formulation was demonstrated.

MICROBIOLOGY

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 enzyme-linked immunosorbent assay (ELISA). 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 [standard deviation] = 0.75 [0.53] mcg per mL; n=69, range 0.07–2.89 mcg per mL) and 0.28 mcg per mL (mean [standard deviation] = 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 in the United States 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.

Resistance

Palivizumab binds a highly conserved region on the extracellular domain of mature RSV F protein, referred to as antigenic site II or A antigenic site, 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. No known polymorphic or non-polymorphic sequence variations outside of the A antigenic site on RSV F protein have been demonstrated to render RSV resistant to neutralization by palivizumab. At least one of the palivizumab resistance-associated substitutions, N262D, K272E/Q, or S275F/L was identified in 8 of 126 clinical RSV 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 A antigenic 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 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%.

PRE-CLINICAL SAFETY DATA

In a human tissue cross-reactivity study, biotinylated palivizumab did not stain in a specific fashion to the more than 30 human adult and neonatal tissues studied.

Acute toxicity studies in three species, the Sprague Dawley rat, the cynomolgus monkey and the NZW rabbit demonstrated tolerance at the site of injection as well as lack of specific systemic toxicity.

Immunogenicity data in cynomolgus monkeys showed no generation of antibody against palivizumab.

In the cotton rat model, pretreatment with palivizumab was shown to reduce mean pulmonary viral titers (replication) by a mean of 99% at serum concentrations of approximately 30 mcg/mL. At no concentration was increased viral replication seen, nor was there an increase in pulmonary inflammation or histopathology at any palivizumab concentration examined. No RSV mutants escaped therapy, and reinfection with RSV after palivizumab exposure did not enhance RSV viral titers (replication) or the resultant pulmonary histopathology.

Binding and neutralization studies have been performed on RSV isolates collected from around the world, to determine whether palivizumab has specificity for a wide range of subtypes. Over 600 isolates, collected from 19 countries on 5 continents have been tested for binding and palivizumab bound to all samples. A subset of more than 100 of these isolates was evaluated for neutralization by palivizumab, and all samples were neutralized.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

CLINICAL STUDIES

The safety and efficacy of palivizumab were assessed in a randomized, double-blind, placebo-controlled trial (IMpact-RSV Trial) of RSV disease prophylaxis among children with premature birth and children with bronchopulmonary dysplasia, and in a randomized, double-blind, placebo-controlled trial of RSV disease prophylaxis among children with hemodynamically significant congenital heart disease (CHD Study). Additional clinical studies conducted following the initial approval of palivizumab have provided further data on the safety and effectiveness of palivizumab prophylaxis for the prevention of RSV related diseases among the similar pediatric populations.

IMpact-RSV Trial

This trial, conducted at 139 centers in the United States, Canada and the United Kingdom, studied patients less than or equal to 24 months of age with bronchopulmonary dysplasia (BPD) and patients 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. 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 lyophilized palivizumab. Subjects were randomized into the study, 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 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%] palivizumab) and patients enrolled with a diagnosis of prematurity without BPD (19/234 [8.1%] placebo vs. 9/506 [1.8%] 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 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 palivizumab and who required hospitalization due to RSV infection than among placebo patients who required hospitalization due to RSV infection. Palivizumab did not alter the incidence and mean duration of hospitalization for non-RSV respiratory illness or the incidence of otitis media.

Pre-term Infants and Children with CLD of Prematurity (CLDP)

This trial, conducted at 347 centers in the North America, European Union and 10 other countries, studied patients less than or equal to 24 months of age with CLDP and patients 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. Patients with hemodynamically significant congenital heart disease were excluded from enrollment in this study and were studied in a separate study. In this trial, patients were randomized to receive 5 monthly injections of 15mg/kg of liquid palivizumab (N=3306) used as active control for an investigational monoclonal antibody (N=3329). Subjects were followed for safety and efficacy for 150 days. Ninety- eight percent of all subjects receiving palivizumab completed the study and 97% received all five injections. The primary endpoint was the incidence of RSV hospitalization. RSV hospitalizations occurred among 62 of 3306 (1.9%) patients in the palivizumab group. The RSV hospitalization rate observed in patients enrolled with a diagnosis of CLDP was 28/723 (3.9%) and in patients enrolled with a diagnosis of prematurity without CLDP was 34/2583 (1.3%).

CHD Study

This trial, conducted at 76 centers in the United States, Canada, France, Germany, Poland, Sweden and the United Kingdom, studied patients less than or equal to 24 months of age with hemodynamically significant CHD. In this trial, 648 patients were randomized to receive five monthly placebo injections and 639 patients were randomized to receive five monthly injections of 15 mg/kg of palivizumab. The trial was conducted during four consecutive RSV seasons. Subjects were stratified by cardiac lesion (cyanotic vs. other) and were followed for safety and efficacy for 150 days. Ninety-six percent (96%) of all subjects completed the study and 92% received all five injections. The primary endpoint was the incidence of RSV hospitalization.

RSV hospitalizations occurred among 63 of 648 (9.7%) patients in the placebo group and 34 of 639 (5.3%) patients in the palivizumab group, a 45% reduction ($p=0.003$). The reduction of RSV hospitalization was consistent over time, across geographic regions, across stratification by anatomic cardiac lesion (cyanotic vs. other), and within subgroups of children defined by gender, age, weight, race, and presence of RSV neutralizing antibody at entry. The secondary efficacy endpoints that showed significant reductions in the palivizumab group compared to placebo, included total days of RSV hospitalization (56% reduction, $p=0.003$) and total RSV days with increased supplemental

oxygen (73% reduction, p=0.014).

CHD Study 2

This trial, conducted at 162 centers in North America, European Union and 4 other countries over two RSV seasons, studied patients less than or equal to 24 months of age with hemodynamically significant CHD. In this trial, patients were randomized to receive 5 monthly injections of 15mg/kg of liquid palivizumab (N=612) used as active control for an investigational monoclonal antibody (N=624). Subjects were stratified by cardiac lesion (cyanotic vs. other) and were followed for safety and efficacy for 150 days. Ninety-seven percent of all subjects receiving palivizumab completed the study and 95% received all five injections. The primary endpoint was a summary of adverse events and serious adverse events, and the secondary endpoint was the incidence of RSV hospitalization. The incidence of RSV hospitalization was 16 of 612 (2.6%) in the palivizumab group.

CHD Post-marketing Study

A postmarketing retrospective, observational, noninterventional cohort study was conducted in children with hemodynamically significant congenital heart disease (HSCHD) in 32 sites in 10 European countries (Austria, Belgium, France, Germany, Italy, Norway, Poland, Slovenia, Spain, United Kingdom). Children with HSCHD who were less than 24 months of age when the first dose of lyophilized Synagis was administered (N=1009) were compared for the occurrence of primary serious adverse events (PSAEs) over an 8-month observational period with a historical cohort of matched children who were also diagnosed with HSCHD but did not receive lyophilized Synagis during the first 24 months of life (N=1009). Children were matched by age, type of cardiac lesion, and prior corrective cardiac surgery. PSAEs were defined as the SAEs of infection, arrhythmia, and death.

PSAEs of infection during the 8-month chart review period were reported at a statistically significantly lower rate in prophylaxed children (27.8% [281/1009]) compared to non- prophylaxed children (32.6% [329/1009]) (P=0.023). The incidence of arrhythmia PSAEs was 4.1% (41/1009) in prophylaxed children and 3.9% (39/1009) in non-prophylaxed children (P>0.100). The incidence of death PSAEs was numerically lower for prophylaxed children (0.9% [9/1009]) compared to non-prophylaxed children (1.0% [10/1009]).

The results of the study indicate no increased risk of serious infections, serious arrhythmias, or death in children with HSCHD associated with lyophilized Synagis prophylaxis compared with matched non-prophylaxed children.

Extended Dose Study

An open label, prospective safety and pharmacokinetics study examined the safety, tolerance and pharmacokinetics of palivizumab when administered for up to 7 months in Saudi Arabia, a subtropical region where the reported RSV season is frequently longer than in temperate countries. Eighteen preterm infants (less than 34 weeks gestation), ranging in age from newborn to 29 weeks, with or without chronic lung disease (CLD), judged to be at risk for RSV infection, and palivizumab naïve, were included in the study. Lyophilized palivizumab 15 mg/kg was injected once per month, for up to 7 months during the RSV season.

Palivizumab levels in the extended dose study were comparable to those achieved in the Impact RSV trial. No significant elevations of anti-palivizumab antibody titer were observed.

STORAGE

Store at 2 to 8ºC (35.6 and 46.4ºF). Do not freeze. Store in original container.
Do not use beyond the expiration date.

HOW SUPPLIED

Palivizumab single-use vial: 3 mL capacity, clear, colorless type I glass vial with stopper and flip-off seal containing 0.5 mL palivizumab solution for injection with a concentration of 100 mg/mL.

Palivizumab single-use vial: 3 mL capacity, clear, colorless type I glass vial with stopper and flip-off seal containing 1 mL palivizumab solution for injection with a concentration of 100 mg/mL.

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

Manufactured by:
Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Straße 65, D-88397 Biberach an der Riss, Germany.

Packed by:
AbbVie S.R.L., S.R. 148 Pontina km 52 SNC, 04011 Campoverde di Aprilia (LT) – Italy

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