

PRODUCT MONOGRAPH

PrSYNAGIS®
palivizumab
lyophilized powder (50 mg and 100 mg)

Passive Immunizing Agent (Humanized Monoclonal Antibody)

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SYNAGIS[®]

palivizumab

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Non-medical Ingredients
intramuscular injection	lyophilized powder / 50 mg lyophilized powder / 100 mg	glycine, histidine, and mannitol <i>For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

DESCRIPTION

SYNAGIS[®] (palivizumab) is a humanized monoclonal antibody (IgG1 κ) 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 (95%) human and (5%) murine amino acid 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 and Cess. The human light chain sequence was derived from the constant domain of C κ and the variable framework regions of the V_L gene K104 with J κ ⁻⁴. The murine sequences were derived from a murine monoclonal antibody, Mab 1129, in a process which 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.

INDICATIONS AND CLINICAL USE

SYNAGIS[®] (palivizumab) is indicated for:

- 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 prematurity (≤ 35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD). See (**CLINICAL TRIALS**).

Distribution restrictions - this product should be administered under the supervision of a qualified health professional.

Geriatrics (≥ 65 years of age):

SYNAGIS[®] is not indicated for adult usage.

Pediatrics (≤ 35 weeks gestational age):

See (**INDICATIONS AND CLINICAL USE**) section.

CONTRAINDICATIONS

- SYNAGIS[®] (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. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- If anaphylaxis, anaphylactic shock or severe allergic reaction occurs, administer epinephrine in appropriate pediatric dosage, and provide supportive care as required.

General

No studies have been performed to assess the administration of more than seven SYNAGIS[®] doses in an RSV season.

The single-use vial of SYNAGIS[®] does not contain a preservative. Injections should be given within six hours after reconstitution.

Carcinogenesis and Mutagenesis

Carcinogenesis and mutagenesis studies have not been performed with SYNAGIS[®].

Hematologic

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.

Hypersensitivity

Allergic reactions including very rare cases of anaphylaxis and anaphylactic shock have been reported following SYNAGIS[®] administration. In some cases, fatalities have been reported. See (**ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).

Symptoms of immediate hypersensitivity and anaphylaxis were observed in two adult volunteers receiving 30 mg/kg in one of the pharmacodynamic studies.

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

Immune

In Study I, the incidence of anti-humanized 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 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 Study II.

These data reflect the percentage of patients whose test results were considered positive for antibodies to 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.

In the Extended Dose Study (Study IV), transient, low levels of antipalivizumab antibody (1:20) were observed in one child after the second dose of SYNAGIS[®] that dropped to undetectable levels (< 1:10) at the fifth and seventh dose.

Respiratory

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

Sexual Function/Reproduction

Reproductive toxicity studies have not been performed with SYNAGIS[®].

Special Populations

Pregnant Women

SYNAGIS[®] 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 whether it could affect reproductive capacity.

Pediatrics (≤ 35 weeks gestational age):

See (INDICATIONS AND CLINICAL USE) section.

Geriatrics (≥ 65 years of age):

SYNAGIS[®] is not indicated for adult usage.

Monitoring and Laboratory Tests

There is not known interference between SYNAGIS[®] and laboratory tests.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In the combined pediatric prophylaxis studies of pediatric patients with BPD or prematurity involving 520 subjects receiving placebo and 1168 subjects receiving SYNAGIS[®] (palivizumab), the proportions of subjects in the placebo and SYNAGIS[®] groups who experienced any adverse event or any serious adverse event were similar.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Study I

Adverse events which occurred in more than 1% of patients receiving SYNAGIS[®] in Study I for which the incidence in the SYNAGIS[®] group was 1% greater than in the placebo group are presented in **Table 1**.

Table 1. Adverse Events Occurring in Study I at Greater Frequency in the SYNAGIS[®] Group

	SYNAGIS [®] n = 1002 (%)	Placebo n = 500 (%)
Body as a Whole	49.6	49.4
Upper respiratory infection	52.6	49.0
Otitis media	41.9	40.0
Rhinitis	28.7	23.4
Rash	25.6	22.4
Pain	8.5	6.8
Hernia	6.3	5.0
SGOT increased	4.9	3.8
Pharyngitis	2.6	1.4

Other adverse events reported in more than 1% of the SYNAGIS[®] group included:

Blood and Lymphatic System Disorders: Anemia.

Ear and Labyrinth Disorders: Ear disorder.

Gastrointestinal Disorders: Constipation, diarrhea, flatulence, gastrointestinal disorder and vomiting.

General Disorders and Administration Site Conditions:	Fever and study drug injection site reaction.
Hepato-biliary disorders:	Liver function abnormality.
Infections and Infestations:	Bronchitis, bronchiolitis, croup, conjunctivitis, flu syndrome, fungal dermatitis, gastroenteritis, oral moniliasis, pneumonia, RSV, sinusitis and viral infection.
Injury, Poisoning and Procedural Complications:	Accidental injury and miscellaneous procedure.
Investigations:	SGPT increase.
Metabolism and Nutrition Disorders:	Failure to thrive and feeding abnormalities.
Psychiatric Disorders:	Nervousness.
Respiratory, Thoracic and Mediastinal Disorders:	Asthma, apnea, cough, dyspnea, respiratory disorder and wheeze.
Skin and Subcutaneous Tissue Disorders:	Eczema and seborrhoea.

There were no statistically significant differences in the incidence of adverse events between the SYNAGIS[®] and placebo groups.

Study II

In the randomized, double-blind, placebo-controlled trial of RSV disease prophylaxis among children with hemodynamically significant congenital heart disease, the proportion of subjects in the placebo and SYNAGIS[®] groups who experienced any adverse event or any serious adverse events were similar. No significant differences in morbidity or mortality were observed.

Adverse events that occurred in more than 1% of patients receiving SYNAGIS[®] and for which the incidence was 1% greater in the SYNAGIS[®] group than in the placebo group are shown in **Table 2**.

Table 2 Adverse Events Occurring in Study II at Greater Frequency in the SYNAGIS[®] Group

	SYNAGIS [®] n=639 (%)	Placebo n=648 (%)
Upper respiratory infection	47.4	46.1
Fever	27.1	23.9
Conjunctivitis	11.3	9.3%
Cyanosis	9.1	6.9%
Infection	5.6	2.9%
Study drug injection site reaction	3.4	2.2%
Arrhythmia	3.1	1.7%

Other adverse events reported in 1% or more of the SYNAGIS[®] group included:

Blood and Lymphatic System Disorders:	Anemia, coagulation disorder and thrombocytopenia.
Cardiac Disorders:	Bradycardia, congestive heart failure, heart failure, cardiovascular disorder, pericardial effusion and tachycardia.
Ear and Labyrinth Disorders:	Ear disorder.
Gastrointestinal Disorders:	Constipation, diarrhea, flatulence, gastrointestinal disorder, pain (primarily teething) and vomiting.
General Disorders and Administration Site Conditions:	Asthenia and edema.
Infections and Infestations:	Bacterial infection, bronchitis, bronchiolitis, croup, flu syndrome, fungal infection, fungal dermatitis, gastroenteritis, otitis media, oral moniliasis, pneumonia, pharyngitis, RSV, rhinitis, urinary tract infection, sepsis, sinusitis and viral infection.
Injury, Poisoning and Procedural Complications:	Accidental injury.
Metabolism and Nutrition Disorders:	Failure to thrive, feeding abnormalities and hypokalemia.
Nervous System Disorders:	Hyperkinesia and somnolence.
Psychiatric Disorders:	Nervousness
Respiratory, Thoracic and Mediastinal Disorders:	Apnea, atelectasis, cough, dyspnea, hypoxia, hyperventilation, lung edema, respiratory disorders, pleural effusion, pulmonary hypertension, pneumothorax, stridor and wheeze.
Skin and Subcutaneous Tissue Disorders:	Eczema and rash.
Vascular Disorders	Hemorrhage.

Study IV

No reported adverse events were considered related to SYNAGIS[®] and no deaths were reported in any of the 18 patients in this study.

Less Common Clinical Trial Adverse Drug Reactions (< 1%)

Both clinical and laboratory adverse drug reactions are displayed by system organ class.

Gastrointestinal Disorders:	Diarrhea and vomiting.
General Disorders and Administration Site Conditions:	Pain.

Infections and Infestations: Upper respiratory infections, rhinitis and viral infection.

Investigations: Aspartate aminotransferase (AST) increase, abnormal liver function test, and alanine aminotransferase (ALT) increase.

Respiratory, Thoracic and Mediastinal Disorders: Cough and wheeze.

Skin and Subcutaneous Tissue Disorders: Rash.

Abnormal Hematologic and Clinical Chemistry Findings

Mild or moderate elevations of AST occurred in 1.6% placebo and 3.7% SYNAGIS[®]; for ALT, these percentages were 2.0% and 2.3% respectively. Reported adverse events related to the liver and deemed by the blinded investigator to be related to study drug were balanced between the two groups.

Post-Market Adverse Drug Reactions

The following adverse reactions have been reported with SYNAGIS[®] 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 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

SYNAGIS[®] 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. Fifteen (1%) adverse events were observed in patients following a sixth or greater dose. All 15 of the adverse events occurred following the administration of the sixth dose and not with subsequent doses (up to 9 doses). Adverse events from this registry as well as through routine post-marketing surveillance were similar in character and frequency to those after the initial 5 doses.

Congenital Heart Disease (CHD) Post-marketing Study

A retrospective observational study was conducted in young children with hemodynamically significant congenital heart disease (HSCHD) comparing the occurrence of primary serious adverse events (PSAEs: infection, arrhythmia, and death) between those who did (1009) and historical controls who did not receive SYNAGIS[®] prophylaxis (1009) matched by age, type of cardiac lesion, and prior corrective surgery. The incidence of arrhythmia and death PSAEs was similar in children who did and did not receive prophylaxis. The incidence of infection PSAEs was lower in children who received prophylaxis as compared to those children who did not receive prophylaxis. The results of the study indicate no increased risk of serious infection, serious arrhythmia, or death in children with HSCHD associated with SYNAGIS[®] prophylaxis compared with children who did not receive prophylaxis.

DRUG INTERACTIONS

Overview

No formal drug-drug interaction studies were conducted. In Study I, 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, in either of the two groups. Since the monoclonal antibody is specific for RSV, SYNAGIS[®] is not expected to interfere with the immune response to vaccines, including live viral vaccines.

Drug-Drug Interactions

No formal drug-drug interaction studies were conducted with SYNAGIS®.

Drug-Food Interactions

Interactions with food have not been established with SYNAGIS®.

Drug-Herb Interactions

Interactions with herbal products have not been established with SYNAGIS®.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established with SYNAGIS®.

Drug-Lifestyle Interactions

No data available.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

The recommended dose of SYNAGIS® (palivizumab) is 15 mg/kg of body weight, **INTRAMUSCULAR INJECTION ONLY**, given once a month during anticipated periods of RSV risk in the community. Where possible, the first dose should be administered prior to commencement of the RSV season, and subsequent doses should be administered monthly throughout the RSV season. To avoid risk of reinfection, it is recommended that children receiving SYNAGIS® who become infected with RSV continue to receive monthly doses of SYNAGIS® throughout the RSV season.

In temperate climates, the RSV season typically commences in the fall months and lasts through the spring; however, there have been reported cases during the summer. During this period, children normally receive 5 consecutive monthly intramuscular doses of palivizumab. See **(WARNINGS AND PRECAUTIONS)**.

Missed Dose

If your child misses an injection of SYNAGIS®, you should contact your doctor as soon as possible. Each injection of SYNAGIS® can only help protect your child for about one month before another injection is needed.

Administration

SYNAGIS® should be administered in a once monthly 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.

Reconstituted SYNAGIS[®] is to be administered by **INTRAMUSCULAR INJECTION ONLY**.

Reconstitution

Parenteral Products

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
50 mg	0.6 mL	0.6 mL	50 mg / 0.5 mL
100 mg	1.0 mL	1.0 mL	100 mg / mL

Note: Both the 50 mg and 100 mg vial contain an overfill to allow the withdrawal of 50 mg or 100 mg respectively when reconstituted if following the directions described below.

Reconstituted product is stable for up to 6 hours when left at room temperature. **However, since the single-use vial of SYNAGIS[®] does not contain a preservative, unless it is reconstituted under controlled and validated aseptic conditions, the product should be administered within 3 hours of reconstitution.**

SYNAGIS[®] should not be mixed with any medications or diluents other than sterile Water for Injection (WFI). WFI is provided in the SYNAGIS[®] kit and it is to be used solely for reconstitution with SYNAGIS[®].

Reconstitution of the 50 mg Vial

- Using aseptic technique, to reconstitute, remove the tab portion of the vial cap and clean the rubber stopper with 70% ethanol or equivalent.
- Carefully tap the top of the ampoule of sterile water for injection, provided in the kit, until all the droplets have fallen to the bottom of the ampoule. In one hand, hold the ampoule with the red dot facing you. With the other hand, hold a 2x2 gauze pad or equivalent at the top, near the red dot, and snap off the upper portion of the ampoule away from you. The glass will break off cleanly and easily.
- To minimize foaming, SLOWLY add **0.6 mL** of sterile Water for Injection, provided in the kit, along the inner side of the **50 mg vial**. Ideally, the sterile water should be “dripped in” along the inner side of the vial. Rotate the sides of the vial after half the sterile water has been added to the SYNAGIS[®] powder, and add the balance of the sterile water down the other side of the vial.
- After removing the syringe from the vial, gently turn the vial between your fingers for approximately 30 seconds. This allows you to visually ensure that all the SYNAGIS[®] has **BEEN SATURATED** by the sterile water. **DO NOT SHAKE OR VIGOROUSLY AGITATE THE VIAL.**
- **DO NOT INVERT THE VIAL DURING THE RECONSTITUTION PROCESS.**

Reconstitution of the 100 mg Vial

- Using aseptic technique, to reconstitute, remove the tab portion of the vial cap and clean the rubber stopper with 70% ethanol or equivalent.

- Carefully tap the top of the ampoule of sterile water for injection, provided in the kit, until all the droplets have fallen to the bottom of the ampoule. In one hand, hold the ampoule with the red dot facing you. With the other hand, hold a 2x2 gauze pad or equivalent at the top, near the red dot, and snap off the upper portion of the ampoule away from you. The glass will break off cleanly and easily.
- To minimize foaming, SLOWLY add **1.0 mL** of sterile Water for Injection, provided in the kit, along the inner side of the **100 mg vial**. Ideally, the sterile water should be “dripped in” along the inner side of the vial. Rotate the sides of the vial after half the sterile water has been added to the SYNAGIS[®] powder and add the balance of the sterile water down the other side of the vial.
- After removing the syringe from the vial, gently turn the vial between your fingers for approximately 30 seconds. This allows you to visually ensure that all the SYNAGIS[®] has **BEEN SATURATED** by the sterile water. **DO NOT SHAKE OR VIGOROUSLY AGITATE THE VIAL.**
- **DO NOT INVERT THE VIAL DURING THE RECONSTITUTION PROCESS.**

Reconstituted SYNAGIS[®] should stand undisturbed at room temperature for a minimum of 20 minutes until the solution clarifies. If excessive foaming has occurred and a full dose of either 1.0 mL or 0.5 mL is required, allow more time for the foam to dissipate (typically 1 hour or longer). The reconstituted solution should appear clear or slightly opalescent.

Before drawing up the solution, invert the vial for approximately 30 seconds. This allows the solution to collect at the bottom of the vial, and facilitates the withdrawal process.

It is most important to work slowly and not rush the reconstitution process.

Reconstituted product is stable for up to 6 hours when left at room temperature. **SYNAGIS[®] is supplied as a single-use vial and does not contain a preservative. It is recommended that unless it is reconstituted under controlled and validated aseptic conditions, the product should be administered within 3 hours of reconstitution.**

Single-use vial. Discard any unused product.

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

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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 as high as 60 mg/kg have been reported without any untoward medical events.

No clinical data are available from human subjects who have received more than 7 monthly SYNAGIS[®] doses during a single RSV season.

ACTION AND 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 clinical RSV isolates were all neutralized by SYNAGIS[®]. 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 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.

Pharmacodynamics

A discussion on animal pre-clinical studies can be found under **(DETAILED PHARMACOLOGY, Animal, Pharmacodynamics)**.

Pharmacokinetics

Absorption

Adult (intramuscular and intravenous)

Palivizumab has a time to maximum serum concentration of 1.6 hours when administered intravenously, and 5 days when administered intramuscularly.

In adult volunteer studies, SYNAGIS[®] administered either intravenously or intramuscularly had a pharmacokinetic profile similar to a human IgG1 antibody in regards to the volume of distribution (mean 57 mL/kg) and the half-life (mean 18 days).

Pediatric (intramuscular and intravenous)

In pediatric patients less than 24 months of age, the mean half-life of palivizumab was 20 days (range 16.8 to 26.8 days), and monthly intramuscular doses of 15 mg/kg achieved mean \pm SD 30-day trough serum drug concentrations of 37 ± 21 mcg/mL after the first injection, 57 ± 41 mcg/mL after the second injection, 68 ± 51 mcg/mL after the third injection, and 72 ± 50 mcg/mL after the fourth injection. In pediatric patients given palivizumab for a second season, the mean \pm SD serum concentrations following the first and fourth injections were 61 ± 17 mcg/mL and 86 ± 31 mcg/mL, respectively.

Thirty days after the first intravenous infusion, the mean trough concentration in patients receiving 15 mg/kg was 60.6 mcg/mL (range 21.4 to 149.8 mcg/mL). Thirty days after the second infusion, the mean trough concentration in patients receiving 15 mg/kg was 70.7 mcg/mL (range 20.2 to 112.6 mcg/mL).

In pediatric patients ≤ 24 months of age with hemodynamically significant congenital heart disease (CHD) who received palivizumab and underwent cardio-pulmonary bypass for open-heart surgery, the mean serum palivizumab concentration was 98 ± 52 mcg/mL before bypass and declined to 41 ± 33 mcg/mL after bypass, a reduction of 58%.

The results of a prospective, phase 2, open-label trial designed to evaluate pharmacokinetics, safety and immunogenicity after administration of 7 doses of palivizumab within a single RSV season showed that adequate mean palivizumab target levels (30 mcg/mL or greater) were achieved in all 18 children enrolled. See [DETAILED PHARMACOLGY, Human, Pharmacokinetics, Extended Dose Study (Study IV)].

Special Populations and Conditions

Pediatrics

See [ACTION and CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption, Pediatric (intramuscular and intravenous)] for details.

Geriatrics

SYNAGIS[®] pharmacokinetics has not been studied in geriatric population. SYNAGIS[®] is not indicated for adult usage.

Gender

No gender related pharmacokinetic differences have been observed in adult patients.

Race

Pharmacokinetics differences due to race have not been identified.

Hepatic Insufficiency

No pharmacokinetic data are available in patients with hepatic impairment.

Renal Insufficiency

No pharmacokinetic data are available in patients with renal impairment.

Genetic Polymorphism

No data available on genetic polymorphism.

STORAGE AND STABILITY

Upon receipt and until reconstitution for use, SYNAGIS[®] should be stored between 2 and 8°C in its original container. Do not freeze. Do not use beyond the expiration date.

SPECIAL HANDLING INSTRUCTIONS

After Reconstitution

Reconstituted SYNAGIS[®] should stand at room temperature for a minimum of 20 minutes until the solution clarifies. The reconstituted solution should appear clear or slightly opalescent.

Reconstituted product is stable for up to 6 hours when left at room temperature. **However, since the single-use vial of SYNAGIS[®] does not contain a preservative, unless it is reconstituted under controlled and validated aseptic conditions, the product should be administered within 3 hours of reconstitution.**

Single-use vial. Discard any unused product.

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

SYNAGIS[®] (palivizumab) is available in two strengths: 50 mg and 100 mg.

SYNAGIS[®] 50 mg is supplied as a kit in single-use 4 mL vials containing 50 mg of lyophilized powder with a 1 mL ampoule of sterile Water for Injection. See (**DOSAGE AND ADMINISTRATION, Administration, Reconstitution, Parenteral Products**) and (**SPECIAL HANDLING INSTRUCTIONS, After Reconstitution**) for more information on the reconstituted solution.

SYNAGIS[®] 100 mg is supplied as a kit, in single-use 10 mL vial containing 100 mg of lyophilized powder with a 1 mL ampoule of sterile Water for Injection. See (**DOSAGE AND ADMINISTRATION, Administration, Reconstitution, Parenteral Products**) and (**SPECIAL HANDLING INSTRUCTIONS, After Reconstitution**) for more information on the reconstituted solution.

Listing of Non-Medicinal Ingredients

Each SYNAGIS[®] 50 mg kit contains the following non-medicinal ingredients: glycine, histidine, mannitol and sterile Water for Injection.

Each SYNAGIS[®] 100 mg kit contains the following non-medicinal ingredients: glycine, histidine, mannitol and sterile Water for Injection.

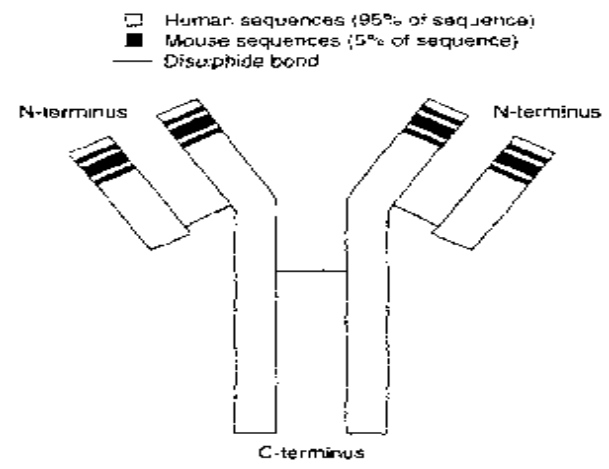
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: palivizumab

Structural formula:



Product characteristics:

Palivizumab is produced by recombinant DNA technology in a mammalian cell (NSO) suspension culture. The anti-RSV antibody is purified by affinity and ion-exchange chromatography steps. The purification process includes specific viral inactivation and removal procedures. 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). Palivizumab specifically binds with high affinity ($K_d = 0.96$ nM) to the F protein of RSV. Palivizumab is a composite of (95%) human and (5%) murine amino acid sequences. The antibody contains about 1 to 2% carbohydrate by weight which is composed of N-acetyl-glucosamine, mannose, fructose, and galactose.

This humanized monoclonal antibody is composed of two heavy chains (50.6 kDa each) and two light chains (27.6 kDa each), has a molecular weight of approximately 148,000 Daltons and an isoelectric point of greater than 9.0.

CLINICAL TRIALS

Study Demographics and Trial Design

The safety and efficacy of SYNAGIS[®] (palivizumab) were assessed in a randomized, double-blind, placebo-controlled trial (Study I) of respiratory syncytial virus (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 (Study II).

Study Results

Study I

Study I, conducted at 139 centres 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 (CHD) were excluded from enrollment. In this trial, 500 patients were randomized to receive five monthly placebo injections and 1002 patients were randomized to receive five monthly injections of 15 mg/kg of SYNAGIS[®]. Subjects were randomized into the study and were followed for safety and efficacy. 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[®] 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[®]) and patients enrolled with a diagnosis of prematurity without BPD (19/234 [8.1%] placebo vs 9/506 [1.8%] SYNAGIS[®]). The reduction of RSV hospitalization was observed throughout the course of the RSV season.

Among secondary endpoints, the incidence of intensive care unit (ICU) admission during hospitalization for RSV infection was lower among subjects receiving SYNAGIS[®] (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[®] and who required hospitalization due to RSV infection than among placebo patients who required hospitalization due to RSV infection. SYNAGIS[®] did not alter the incidence and mean duration of hospitalization for non-RSV respiratory illness or the incidence of otitis media.

Study II

Study II, 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 SYNAGIS[®]. 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.

Respiratory Syncytial Virus hospitalizations occurred among 63 of 648 (9.7%) patients in the placebo group and 34 of 639 (5.3%) patients in the SYNAGIS[®] 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 SYNAGIS[®] 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, $p = 0.014$).

Study III - Reduction of Viral Load in Tracheal Aspirates

A study was conducted in children hospitalized and intubated with RSV infection to determine whether SYNAGIS[®] reduced RSV titers in tracheal secretions; 17 children were randomized to receive a single intravenous infusion of 15 mg/kg SYNAGIS[®] and 18 children to receive placebo. The results are presented in **Table 3**.

Table 3 Quantitative RSV Plaque Assay Titer (\log_{10}) Tracheal Aspirates

	Placebo (SE)	SYNAGIS [®] (SE)	p-value
Mean Titer at Study Entry	4.8 (0.3)	4.8 (0.3)	
Decrease in Titer on Day 1	0.6 (0.2)	1.7 (0.3)	0.004
Decrease in Titer on Day 2	1.0 (0.4)	2.5 (0.3)	0.012
Decrease in Titer on Day 3	1.9 (0.7)	2.8 (0.4)	0.288
Decrease in Titer on Day 4	2.1 (0.7)	2.8 (0.5)	0.500
Decrease in Titer on Day 5	1.8 (0.7)	2.7 (0.5)	0.417

definitions: SE = standard error

SYNAGIS[®] was found to reduce the tracheal RSV titer significantly when compared to placebo. However, despite the antiviral effect of SYNAGIS[®] observed, no difference in the severity of RSV disease was observed in the three treatment studies; days of RSV hospitalization, days of mechanical ventilation and days of hospitalization with a supplemental oxygen requirement were similar in the placebo and SYNAGIS[®] groups.

DETAILED PHARMACOLOGY

Pre-Clinical

In vitro Studies of Binding RSV

In vitro studies demonstrated the potent binding activity of palivizumab to the RSV F protein. The *in vitro* studies performed are listed in **Table 4**.

Table 4. Summary of In vitro Studies Performed with Palivizumab

Property	Experiment
Affinity	ELISA Kinetic analysis
Neutralization of RSV	Microneutralization Plaque reduction Neutralization of clinical isolates

The studies demonstrate that the K_d of palivizumab is approximately 1nM, which is equal to or better than that of an isotype matched chimeric version of the parent MAb. Neutralization studies indicate that palivizumab is at least equivalent to the chimeric version of MAb 1129 in a microneutralization assay and that palivizumab effectively neutralizes both A and B laboratory subtypes.

To confirm the expected efficacy in the clinical setting, a diverse panel of clinical isolates of both A and B subtype RSV from European and North American sites were evaluated.

Palivizumab was tested against a panel of 57 clinical isolates of RSV, of both the A and B subtypes, isolated between 1987 and 1993 from different geographic areas of the United States. The origin and subtype of these isolates is presented in **Table 5**. The microneutralization assay was used with the concentration of antibody fixed (400 ng/mL) while the virus was serially diluted. Polyclonal RespiGam[®] served as a positive control and a non-neutralizing human antibody developed at MedImmune as a negative control. All 57 of the North American clinical isolates tested were neutralized by palivizumab.

Table 5. Neutralization of Clinical Isolates by Palivizumab (North American Data)

Source	RSV-A	RSV-B	Total
Rochester	6	4	10
Huston	9	7	16
St.Louis	2	5	7
Nashville	5	1	6
Long Beach	4	1	5
Denver	3	2	5
Other	5	3	8
Total	34	23	57

In addition to the isolates obtained from the North American studies, twenty laboratory adapted RSV isolates were obtained from Europe, as presented in **Table 6**.

Table 6. Neutralization of Clinical Isolates by Palivizumab (European Data)

Source	RSV-A	RSV-B	Total
UK	10	4	14
Spain	3	1	4
Sweden	1	1	2
Total	14	6	20

All 20 isolates were neutralized by palivizumab.

These studies demonstrate that palivizumab is effective in neutralizing a range of RSV-A and RSV-B subtypes that occur clinically in North America and in Europe.

Animal

Pharmacodynamics

Cotton Rat *in-vivo* Activity

Respiratory Syncytial Virus bronchiolitis and interstitial pneumonia can be experimentally induced in the cotton rat, producing pathology qualitatively similar, but less severe, to that seen in the human. Three efficacy studies were conducted using the cotton rat model for RSV bronchopneumonia. The studies evaluated the reduction in pulmonary viral load and/or histopathology after either intravenous or intramuscular administration as prophylaxis or treatment of RSV.

Intravenous infusion in the treatment of RSV in cotton rats

SYNAGIS[®] (palivizumab) was evaluated for its ability to treat an ongoing infection in cotton rats using intravenous infusion at doses of 0.63 to 10.0 mg/kg. Bovine serum albumin (BSA) and RespiGam[®] were used as negative and positive controls, respectively, for this experiment. One day after treatment, the animals were sacrificed and the circulating human antibody and pulmonary RSV titer were determined. The results of this experiment are summarized in **Table 7**.

Table 7. Therapy of RSV Infection by Palivizumab in Cotton Rats

Sample	Dose (mg/kg)	Humanized IgG (mcg/mL)	Lung RSV Titer pfu/g (mean log ₁₀ ± SE)
BSA	10	0	5.99 ± 0.1
Palivizumab	0.63	4.1	5.13 ± 0.16
Palivizumab	1.25	18.8	4.74 ± 0.08
Palivizumab	2.5	20.2	4.94 ± 0.19
Palivizumab	5	60.2	3.37 ± 0.13
Palivizumab	10	106	2.81 ± 0.27
RSV-IGIV	500	3100	< 2 ± 0

Definitions: BSA = Bovine serum albumin; RSV-IGIV = RespiGam[®]; SE = standard error.

These results demonstrated a dose response where a 10 mg/kg palivizumab treatment resulted in circulating levels of approximately 100 mcg/mL at the time of sacrifice and a reduction in RSV titer of three orders of magnitude (three log₁₀). Thus, palivizumab is effective in reducing viral titer when administered to RSV infected cotton rats.

Intramuscular injection in cotton rats

Intramuscular dose-ranging studies were conducted in the cotton rat model. Palivizumab or RespiGam[®] was administered by intramuscular injection. The doses of palivizumab consisted of 5 mg/kg (body weight), 1.67 mg/kg, and 0.56 mg/kg. For comparison, polyclonal human RespiGam[®] was administered at doses of 250 mg/kg, 50 mg/kg, and 16.7 mg/kg (Experiment I) or 250 mg/kg, 83.3 mg/kg, and 27.8 mg/kg (Experiment II). In both experiments bovine serum albumin (BSA) at 5.0 mg/kg was used as the negative control. Twenty-four hours after administration of palivizumab, the animals were bled and infected intranasally with RSV. Four days after inoculation, animals were sacrificed, and their lungs were harvested and titered *in vitro*. Human antibody concentration in the serum at the time of challenge was determined. Results of these experiments are presented in **Table 8**.

Table 8. Assessment of Potential for Palivizumab to Treat RSV (Long Strain) Infection in Cotton Rats Following a Single Intramuscular Injection (Part I)

Compound	Number of Animals	Dose (mg/kg)	Serum [Human IgG] at Challenge (mcg/mL)	Lung Viral Titer pfu/g (mean log ₁₀ ± SE)
Experiment I				
BSA	4	5.0	0	5.20 ± 0.07
Palivizumab	4	0.56	2	4.66 ± 0.07
Palivizumab	4	1.67	11	2.66 ± 0.38
Palivizumab	4	5.0	30	2.17 ± 0.17
RSV-IGIV	4	16.7	125	4.48 ± 0.04
RSV-IGIV	4	50	298	3.87 ± 0.11
RSV-IGIV	4	250	1450	2.29 ± 0.29
Experiment II				
BSA	4	5.0	0	3.75 ± 0.24
Palivizumab	4	0.56	4	2.15 ± 0.09
Palivizumab	4	1.67	13	2.08 ± 0.08
Palivizumab	4	5.0	47	4.32 ± 0.08
RSV-IGIV	4	27.8	64	3.49 ± 0.19
RSV-IGIV	4	83.3	295	2.0 ± 0
RSV-IGIV	4	250	1400	4.80 ± 0.08

Definitions: BSA = Bovine Serum Albumin; RSV-IGIV = RespiGam[®]; SE = standard error.

A greater than 2 log reduction in RSV titer was obtained at a palivizumab dose of 1.67 mg/kg, corresponding to serum antibody levels of 11 and 13 mcg/mL (Experiments I and II respectively) at the time of RSV challenge when compared to the negative controls.

Additional experiments were performed to compare the potency of palivizumab against A and B subtypes of RSV in cotton rats dosed with palivizumab intramuscularly at doses of 0.625, 1.25, 2.5, or 5.0 mg/kg.

The results of all intramuscular studies show at least a 50-fold increase in potency with palivizumab when compared to RespiGam[®] administered intramuscularly. Both A and B RSV subtypes were susceptible to palivizumab. A greater than 2 log reduction in RSV titer was obtained at doses of 1.67 to 2.5 mg/kg, corresponding to serum antibody levels of 11 to 21 mcg/mL at the time of RSV challenge.

Intravenous Administration for Prophylaxis in Cotton Rats

Three dose ranging studies evaluating palivizumab, administered by an intravenous route, for prophylaxis of RSV infection in cotton rats were performed. The purpose of these studies was to determine a serum concentration of palivizumab which results in at least a 99% (2 log₁₀) reduction of RSV lung titer.

In the first two studies, cotton rats were anesthetised and infused intravenously with Bovine Serum Albumin (BSA) (10 mg/kg) or palivizumab at doses of 10 mg/kg, 5.0 mg/kg, 2.5 mg/kg, 1.25 mg/kg, 0.625 mg/kg, or 0.312 mg/kg. The third experiment was identical except that the 0.312 mg/kg dose of palivizumab was omitted. One day after infusion, the animals were anesthetised, bled and challenged by intranasal instillation with RSV. Serum palivizumab levels at the time of challenge were determined using ELISA. Four days after RSV challenge all animals were sacrificed, lungs were harvested, homogenized and RSV titers were determined. **Table 9** represents the combined data from the three studies.

Table 9. Intravenous Prophylaxis in Cotton Rats (All Experiments Combined)"Determination of serum concentration of Palivizumab which results in at least a 99% (2 log₁₀) reduction of RSV lung titer"

Compound	Number of Animals	Dose (mg/kg)	Mean ± SE Concentration of Human IgG at Challenge (mcg/mL)	Geometric Mean ± SE Lung Viral Titer (pfu/g)
BSA	18	10	0	1.3 x 10 ⁵ ± 1.2
Palivizumab	7	0.312	2.67 ± 0.60	4.6 x 10 ⁴ ± 1.5
Palivizumab	17	0.625	5.27 ± 0.27	2.7 x 10 ⁴ ± 1.3
Palivizumab	18	1.25	10.1 ± 0.29	3.3 x 10 ³ ± 1.4
Palivizumab	17	2.5	28.6 ± 2.15	9.6 x 10 ² ± 1.5
Palivizumab	15	5.0	55.6 ± 3.43	1.3 x 10 ² ± 1.2
Palivizumab	18	10.0	117.6 ± 5.09	1.0 x 10 ² ± 1.0

Definitions: BSA = Bovine Serum Albumin; SE = standard error.

The data indicated that a dose of 2.5 mg/kg and, more importantly, a corresponding circulating level of palivizumab of about 30 mcg/mL correlated with a greater than 2 log reduction in viral pulmonary RSV titer.

Potential Enhancement of Infection (cotton rats)

Potential Enhancement of Infection and/or Selection for Escape Mutants of RSV

The cotton rat model was used to determine whether the presence of palivizumab at non-inhibitory levels could enhance viral replication or virus-induced pathology during a primary RSV infection. In addition, the experiment was also designed to analyze the virus isolated from the lungs of the palivizumab-treated animals for the presence of antibody-resistant variants.

Animals each were administered BSA at 10 mg/kg (Group A) or palivizumab at 0.0032 mg/kg, 0.016 mg/kg, 0.08 mg/kg, 0.4 mg/kg, 2.0 mg/kg, and 10 mg/kg (Groups B through G), intramuscularly. Twenty-four hours, later all animals were challenged with RSV. Four days later the animals were sacrificed and the lung tissue was analyzed for RSV levels, and prepared for histopathology. The results of this study are summarized in **Table 10**.

Table 10. Analysis of Potential Enhancement of Infection and/or Selection for Escape Mutants of RSV during Prophylaxis with Palivizumab in Cotton Rats

Group	Dose (mg/kg)	Mean Log \pm SE RSV Titer* (pfu/g)	Animals with RSV related pathology	Severity of lesions observed (N - 4)**
A	0 (BSA)	3.23 \pm 0.08	4/4	1
B	0.0032	3.2 \pm 0.02	4/4	1
C	0.016	3.3 \pm 0.22	4/4	1
D	0.08	3.35 \pm 0.16	3/4	0
E	0.4	2.98 \pm 0.06	4/4	1
F	2.0	2.28 \pm 0.16	2/4	0
G	10	<2 \pm 0	0/4	0

* RSV Titer measured in 0.1 mg/mL BSA

** N (Normal), 1 (Minimal), 2 (Mild), 3 (Moderate), 4 (Marked).

Definitions: BSA = Bovine Serum Albumin; SE = standard error.

Lung changes consistent with RSV infection were found in four of four animals each from Groups A, B, C, and E, three of four animals from Group D, two of four animals from group F and none of four animals from group G. The data indicate that palivizumab protects from RSV-induced lesions in cotton rats at a dose of 2 mg/kg (partial protection) and 10 mg/kg (complete protection). No enhancement of pathology was observed at sub-effective doses of palivizumab. Based on these results, palivizumab does not induce antibody-dependent enhancement in a primary infection of cotton rats.

Re-challenge of Previously Infected Cotton Rats

Again using the cotton rat model, a study was conducted to analyze the potential for enhancement of pulmonary virus of RSV associated histopathology in previously infected animals. Cotton rats were divided into three Groups. Group 1 animals were administered 10 mg/kg BSA and Group 2 received 10 mg/kg palivizumab intravenously one day prior to challenge with RSV (10^5 pfu/Long strain). Group 3 was not dosed and was mock challenged with medium only. Four animals from each group were sacrificed four days after infection and pulmonary virus titers were determined. The remaining animals were bled bi-weekly until palivizumab was no longer detectable in Group 2 animals. At that time, the remaining animals were re-challenged with a low dose of RSV (10^3 pfu) and sacrificed on day four after challenge. Lungs were divided and prepared for histopathology and virus titration as previously described above. The results of the challenge and rechallenge are summarized in **Table 11**.

Table 11. Results of Re-challenge of Previously Infected Cotton Rats: Analysis for Potential Enhancement of Pulmonary Virus or RSV Associated Histopathology (Study No. III)

Group	Dose	1° RSV challenge (mean log pfu/g ± SE)	2° RSV challenge (mean log pfu/g ± SE)	Animals with RSV Associated Pathology	Range of Severity (N - 4)
1	10 mg/kg BSA	5.51 ± 0.05	< 2 ± 0	0/7	0
2	10 mg/kg palivizumab	< 2 ± 0	< 2 ± 0	0/5	0-1
3	None	Mock Challenged	2.46 ± 0.14	1/8	0-1

** N (Normal), 1 (Minimal), 2 (Mild), 3 (Moderate), 4 (Marked).

Definitions: BSA = Bovine Serum Albumin; SE = standard error.

Inflammation of the bronchiole consistent with RSV infection was diagnosed in one of eight untreated control animals but not any other animal of the study. Other lesions (inflammation associated with foreign material, histiocytosis and pigmentation) were considered incidental lesions not related to treatment. Since the untreated controls (Group 3) had not received a primary challenge with RSV on study day one, the data suggest that the secondary challenge (rechallenge) with 10^3 pfu/animal of RSV did not induce extensive pulmonary lesions detectable microscopically four days after challenge. Viral titers were also consistent with a low level of infection in the Group 3 animals, as intended. Except for the foreign material inflammation of one animal of Group 2, lesions were not seen in the lungs of Group 1 and 2 animals indicating lack of residual changes attributable to RSV, BSA, or palivizumab. Thus, no enhancement of either virus replication or virus-induced pathology was observed in a secondary RSV infection. Furthermore, the animals protected by palivizumab from an initial RSV challenge were also shown to be resistant to a secondary challenge of RSV.

Pharmacokinetics

Non-clinical pharmacokinetics was assessed in the Cynomolgus monkey, a macaque surrogate of humans. These investigations revealed considerable interanimal variability but a consistent biphasic pattern, attributable to the distribution and the elimination phases. Some of this variability might be due in part to difficulties matching age, physical characteristics, health and nutritional status in these wild-caught monkeys. Although the elimination phase is quite long, the dosing strategy in humans specifies one month between each injection in order to assure acceptable trough levels.

Absorption

An intravenous infusion of liquid, unfiltered palivizumab at 10 mg/kg was provided to two female Cynomolgus monkeys (Figure 1). Standard hematology, clinical chemistry and urinalyses assays were performed at the initiation and conclusion of the study. Samples were removed from a contralateral vein for kinetic analysis at 5, 15, 30, 60, 120, 180, 360 and 720 minutes, as well as days 1, 2, 4, 7, 10, 15 and 21 post-dosing. The C_{max} was approximately 200 mcg/mL or nearly 7 times the effective concentration in human plasma. Consistent with the study above, the distributional phase or alpha half-life was 8.8 to 12.6 hours, while the elimination phase or beta half-life was approximately 8.6 days. There was no evidence for intolerance of this dosage in this model.

Kinetic data were also obtained during the acute toxicity study performed in Cynomolgus monkeys. Single dosages of liquid, unfiltered palivizumab at 10 and 30 mg/kg were given

intravenously, equating up to two times the human maximum clinical dose, to two monkeys of each sex.

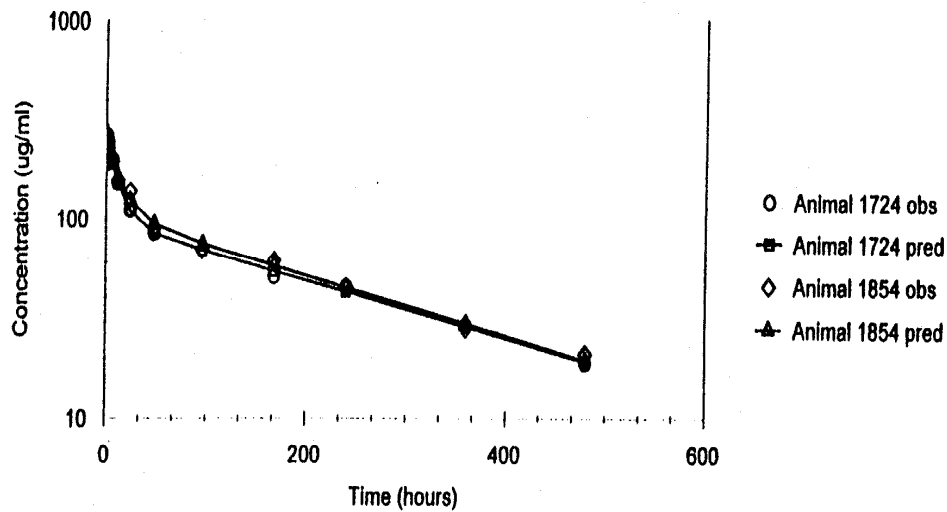


Figure 1. Pharmacokinetic Analysis of Palivizumab in Cynomolgus Monkeys

The pharmacokinetic curves in Figure 1 were generated from time course samples at 5, 15, 30, 60, 120, 180, 320, 720 minutes and day 1, 2, 4, 7, 15 and 20 for animal #1724 (†) and #1854 (□).

These dosages provided mean C_{max} concentrations of 286 and 595 mcg/mL, respectively, approximately 10 and 20 times the effective concentration (30 mcg/mL) defined as efficacious in the cotton rat model and later confirmed in human trials. Considerable interanimal variability was noted in the biphasic half-life of the drug in these animals, with the alpha phase lasting from 0.24 hours to 30.66 hours; the beta phase was more prolonged, lasting from 4.2 days to 5.9 days. Thus, total clearance is quite protracted in the Cynomolgus monkey.

Human

Pharmacokinetics

Extended Dose Study (Study IV)

An open, prospective safety and pharmacokinetics study examined the safety, tolerance and pharmacokinetics of SYNAGIS[®] 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. SYNAGIS[®] 15 mg/kg was injected once per month, for up to 7 months during the RSV season. Safety data are based on all 18 subjects who received SYNAGIS[®], 17 of whom received all 7 doses.

Palivizumab serum concentrations were not available for all subjects at all visits (**Table 12**). Target serum trough palivizumab levels (30 mcg/mL or greater) were achieved. No significant elevations of anti-palivizumab antibody titer were observed. These study results suggest that seven SYNAGIS[®] doses are non-immunogenic and not associated with increased adverse events.

Table 12. Summary of SYNAGIS[®] Blood Assay Results (Study IV)

Study Visit*	Number of subjects					Mean ± Standard Deviation
	≥ 30mcg/mL	< 30mcg/mL	< LOQ	NRP	Total	
Visit 1	0	0	17	1	18	0 ± 0
Visit 2	16	0	1	1	18	44.72 ± 18.67
Visit 5	16	0	0	2	18	121.06 ± 36.23
Visit 7	14	0	0	4	18	144.36 ± 47.54

* Blood was drawn prior to study drug administration at each visit.

Definitions: LOQ = Limit of quantification; mcg/mL = mcg/mL of SYNAGIS[®]; NRP = Not reported.

TOXICOLOGY

Acute Toxicity

Rabbits

New Zealand White rabbits were treated with intramuscular or subcutaneous injections of either 15 or 50 mg/kg of palivizumab or control vehicle (2x Formulation Buffer; 0.15 or 0.5 mL/kg) and sacrificed on Day 4 (interim) or Day 15 (terminal). Body weights were collected prior to dosing and prior to interim and terminal sacrifice, and weight changes were determined. Weight changes in the animals that were sacrificed on Day 4 or Day 15 were not adversely affected by any exposure route or any dose of either the vehicle control or palivizumab. Slight (Day 2) and very slight (Days 3 and 4) erythema was observed in one of eight animals treated with an intramuscular injection of 50 mg/kg of palivizumab (Group 5). Very slight erythema was also observed on Days 2 and 3 in one of the eight animals treated with a subcutaneous injection of 15 mg/kg of palivizumab (Group 4). A hematoma was observed on Day 2 in one of the eight animals treated with subcutaneous injection of 50 mg/kg of palivizumab (Group 6). The hematoma was not observed after Day 2. A lesion was observed during the necropsy (Day 4) in

one of the four animals treated with an intramuscular injection of 0.15 mL/kg of the control vehicle (Group 1). Any lesions observed macroscopically are most likely attributable to trauma caused during the injection procedure. Microscopic evaluation of the injection site from animals necropsied on Days 4 and 15 confirmed that treatment with palivizumab did not result in any lesions attributable to the test article.

Tissue damage from palivizumab was evaluated in a Good Laboratory Practices-compliant study in New Zealand White rabbits. The lyophilized product was injected in vehicle both intramuscularly and subcutaneously into the thigh muscles of 2 rabbits/sex/group; one group served as a vehicle control (5.6% mannitol, 3.0 mM glycine, 47 mM histidine), while the other 2 received either 15 or 50 mg/kg injected in a bolus. The lower dosage is equivalent to the maximum recommended human dosage, while the higher dosage provided over three times the human dosage. The animals tolerated the treatments without evidence for systemic toxicity. On evaluation Days 4 and 15, some injection sites were erythematous, while most were unremarkable. One rabbit in the higher dosage group developed a hematoma at the injection site, presumably due to accidental injection into or near a major blood vessel. Histologic examination of the injection sites revealed no evidence for local intolerance.

Rats

A 14-day single dose toxicity study in Sprague-Dawley rats (6/sex/group) provided single, intravenous doses up to 840 mg/kg or 56 times the maximum human dose of 15 mg/kg. Based on pre-study body weights of male and female rats, dosages were adjusted to the mean weight of each group. Male rats received a 210 mg/kg (1.2 mL), 420 mg/kg (2.4 mL) or 840 mg/kg (5.0 mL) dose of palivizumab or a 5.0 mL injection of the buffer control solution. Female rats received a 210 mg/kg (1.0 mL), 420 mg/kg (1.9 mL) or 840 mg/kg (3.9 mL) dose of palivizumab or a 3.9 mL injection of the formulation buffer as a control. All doses of the test article were administered at a concentration of 57 mg/mL. Although the preferred route for clinical use is intramuscular, not intravenous, this parenteral route provided an efficacious response in cotton rats infected with RSV and higher maximum plasma concentrations (C_{max}) achieved via the intravenous route were more likely to demonstrate systemic toxicity. These dosages were anticipated to provide up to 8 times the human exposure, based on surface area calculations. Cage side observations were recorded twice daily, and all rats were observed at approximately one hour after dose administration for mortality or pharmacotoxic signs, and weekly for clinical signs and abnormality. Ophthalmic examinations were performed during the pretreatment and prior to necropsy. These rats were observed for 14 days, including traditional assessments of clinical signs, body weight changes, food consumption, ophthalmoscopy, hematology, clinical and anatomic pathology. Despite these considerable multiples of the human exposure, there was no evidence for systemic toxicity. Superficial corneal lesions were described but attributed to the repeated bleeding via the infraorbital sinus.

Blood samples were collected and serum harvested for the sponsor during the pretreatment week, on Days 0, 1, 3, 5, 7 and prior to necropsy (Day 14). Blood samples were also collected for hematology evaluations during pretreatment, on Day 3 and at time of necropsy. Serum samples for clinical chemistry evaluations were collected during the pretreatment week (retained frozen for possible evaluation) and prior to necropsy. A complete necropsy was performed on all rats in all groups on Day 14. All retained tissues from animals in Groups 1 (0 mg/kg), 2 (210 mg/kg) and 4 (840 mg/kg) were processed and evaluated histologically. Since no treatment-related gross or histologic lesions were observed in these groups, tissues from animals in Group 3 (420 mg/kg) were not examined.

All animals survived until scheduled sacrifice. The only abnormal clinical signs noted were for one male rat animal in Group 1 on Days 7 (exophthalmos and eye opacity) and 14 (eye opacity) and for one Group 1 female on Days 7 and 14 (eye opacity). These rats were judged to be clinically normal at all other physical examination intervals. No abnormal ophthalmic findings were noted before dosing. Panophthalmitis was observed in the right eye of one male rat and one female rat in Group 1. Retinal detachment was observed in the right eye of one Group 2 male and retinal detachment with hemorrhage was observed in the right eye of one Group 4 female. These lesions were considered secondary to previous blood collections from the infraorbital sinus. No significant changes in body weight or food consumption were observed during the study.

Statistically significant group differences, relative to control group values of the same sex, that were observed in clinical pathology data were considered to be chance occurrences and not indicative of a drug-related toxic effect. Findings noted at necropsy were not attributed to administration of the test material. No significant changes in group organ weights were observed. Histopathologically, no treatment-related lesions were observed in any tissue of any treatment group. Sporadic lesions commonly seen in these rats under laboratory conditions were rare.

Under the conditions of this study, a single intravenous injection of palivizumab, when administered to male or female rats at doses of 210, 420 or 840 mg/kg did not produce evidence of toxicity.

Cynomolgus Monkeys

The acute toxicity study of palivizumab administered intravenously to Cynomolgus monkeys consisted of three groups of two monkeys/sex/group. Group 1 animals were administered phosphate buffer saline (PBS) which served as control and Group 2 and 3 animals were dosed with 10 and 30 mg/kg of the test article, respectively (equating to 2 times the human maximum dose). Dose administration was performed via intravenous infusion through a percutaneous catheter placed in a peripheral vein of each monkey. Animals were individually restrained in slings and infusion of vehicle or test article was performed over a 15 minute period, without tranquilization, on Day 1 of the study.

Animals were observed for 14 or 29 days; one animal/sex/group was subjected to a complete gross necropsy on Days 15 and 30. Various parameters were analyzed to assess the toxicity of the test material.

Daily clinical observations revealed findings such as abrasions, scabs, erythema, bruises, swelling (on various body sites), pale mucous membranes, alopecia, salivation, and discoloured feces in test article-treated and vehicle-treated (which had the most findings) groups. These findings were not considered to be associated with treatment with the test article but appeared to be due to the multiple bleeding procedures and the associated stress and trauma. The body weight, food consumption, physical examination, blood pressure and body temperature measurements did not exhibit any remarkable changes that could be attributed to the test material.

Clinical pathology data analysis revealed decreasing hemoglobin (HGB) and hematocrit (HCT) values, especially in one Group 2 and two Group 1 and 3 females during the first few days after dosing. However, the animals were in the process of recovery from this deficiency by Day 8 as was demonstrated by the increased reticulocyte counts and the upward trend in HGB and HCT.

These reductions were judged to have been due to repeated venoclysis for the pharmacokinetic analyses.

Analysis of serum chemistry parameters revealed high creatine kinase (CK), lactate dehydrogenase (LDH) and aspartate aminotransferase (AST) values in all animals on Days 1-2 and in a few animals on Day 3 in both vehicle and test article treated groups. These elevations were thought to be due to the restraining procedure used for dose administration in these animals, which caused their muscle enzymatic activities to increase and were not considered to be related to treatment with the test article. A decrease in blood urea nitrogen (BUN) values in all Group 1 and 2 animals and Group 3 females on Day 3 only, was difficult to interpret but was not considered a test article effect since it was also found in concurrent control animals.

No remarkable treatment changes were found in blood coagulation and urinalysis data as compared to the control animals. Organ weight analysis did exhibit changes in several Group 2 and 3 tissue weights as compared to corresponding weights from Group 1 animals, but since the available data was only from one animal/sex/group, the significance of this variation could not be determined.

Gross necropsy observation showed many single red/purple foci around the saphenous vein of five monkeys on Day 15 and four monkeys on Day 30 and subcutaneous hemorrhage and edema in one Group 2 male. These findings were considered to be due to the catheterization procedure used for dose administration.

Microscopic examination revealed a golden brown globular pigment consistent with hemosiderin in the renal tubule and a few other organs of one Group 3 female. Similar pigment, but more consistent with lipofuscin, was found in the tubular epithelial cells of one Group 1 female. One Group 3 male and two females, one each in Groups 1 and 2, also exhibited renal tubular pigments on Day 30. These hemosiderin-like pigments were considered incidental, not related to palivizumab, and without consequence to the well-being of the primate. The above-mentioned Group 3 female also exhibited some crystalline material in its cortical tubules, the reason for which could not be specifically ascertained with the available data. Microscopic observation also revealed acute inflammation at the administration site in all animals and mild to moderate hemorrhage at the saphenous vein in the Group 1 and 2 males. Also observed were a trauma-related lesion and subcapsular focus in a section of liver in one Group 3 male and one Group 2 female, respectively.

There were no microscopic findings observed that could be attributed specifically to the test article.

The data obtained from this study did not exhibit any potential toxicity following an intravenous infusion of test material up to a dose level of 30 mg/kg in *Cynomolgus* monkeys when observed for 30 days.

Long-Term Toxicity

No long-term toxicity studies were performed, owing to the absence of tissue reactivity from palivizumab, the likely neutralization of the humanized antibody, the expectation of anaphylaxis or immune complex formation to the foreign protein, and the considerable time separation between human exposures.

Mutagenicity and Carcinogenicity

Carcinogenicity studies have not been performed with SYNAGIS®.

Mutagenicity studies have not been performed with SYNAGIS®, nor are they normally required for monoclonal antibody products.

Reproduction and Teratology

Reproduction studies have not been performed with SYNAGIS®.

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PART III: CONSUMER INFORMATION

PrSYNAGIS[®] palivizumab

This leaflet is PART III of a three-part “Product Monograph” published when SYNAGIS[®] was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about SYNAGIS[®]. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- The prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease.

What it does:

SYNAGIS[®] exhibits neutralizing activity against RSV. These activities inhibit RSV replication in laboratory experiments.

When it should not be used:

SYNAGIS[®] is contraindicated in patients with known hypersensitivity to palivizumab or to any of its ingredients. It is also contraindicated in patients with known hypersensitivity to other humanized monoclonal antibodies.

What the medicinal ingredient is:

palivizumab

What the important non-medicinal ingredients are:

SYNAGIS[®] also contains glycine, histidine, and mannitol.

For a full listing of non-medicinal ingredients see PART I of the Product Monograph.

What dosage forms it comes in:

50 mg of lyophilized powder. Once reconstituted, the vial contains a solution of 50 mg / 0.5 mL.

100 mg of lyophilized powder. Once reconstituted, the vial contains a solution of 100 mg / mL.

WARNINGS AND PRECAUTIONS

BEFORE you use SYNAGIS[®] talk to your doctor or pharmacist if:

- your child is unwell, as the use of SYNAGIS[®] may need to be delayed.
- your child has any bleeding disorder, as SYNAGIS[®] is usually injected into the thigh.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with SYNAGIS[®] include:

- The monoclonal antibody is specific for RSV. SYNAGIS[®] is not expected to interfere with the immune response to vaccines, including live viral vaccines.

PROPER USE OF THIS MEDICATION

Usual dose:

The recommended dose of SYNAGIS[®] is 15 mg/kg of body weight, **INTRAMUSCULAR INJECTION ONLY**, given once a month during anticipated periods of RSV risk in the community.

Overdose:

From the post-marketing experience, overdoses as high as 60 mg/kg have been reported without any untoward medical events.

Missed Dose:

If your child misses an injection, you should contact your doctor as soon as possible. Each injection of SYNAGIS[®] can only help protect your child for about one month before another injection is needed.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, SYNAGIS[®] can cause side effects.

Some of the common side effects that your child may have while on SYNAGIS[®] include fever, nervousness, redness or swelling at the injection site. Less common side effects include colds, coughs, runny nose, wheeze, vomiting, rash, diarrhea, pain, viral infections and increase in liver function tests. A pause in breathing or other breathing difficulties may occur rarely and severe allergic reactions very rarely.

If a child shows **ANY** side effects after receiving SYNAGIS[®] you should contact your doctor. You should also notify your doctor of any side effects experienced that are not mentioned in this section.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Fever		√	
	Nervousness		√	
	Redness or swelling at the injection site		√	
Uncommon	Colds		√	
	Coughs		√	
	Runny nose		√	
	Wheeze		√	
	Vomiting		√	
	Rash		√	
	Diarrhea		√	
	Pain		√	
	Viral infection		√	
	Increase in liver function tests		√	
Rare	A pause in breathing or any other breathing difficulties		√	
Very rare	Severe allergic reaction		√	

This is not a complete list of side effects. For any unexpected effects while taking SYNAGIS® contact your doctor or pharmacist.

HOW TO STORE IT

Upon receipt and until reconstitution for use, SYNAGIS® should be stored between 2 and 8°C in its original container. Do not freeze. Do not use beyond the expiration date.

Reconstituted product is stable for up to 6 hours when left at room temperature. **However, since the single-use vial of SYNAGIS® does not contain a preservative, unless it is reconstituted under controlled and validated aseptic conditions, the product should be administered as soon as possible, preferably within 3 hours of reconstitution.**

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report on line at:**
www.healthcanada.gc.ca/medeffect
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
 - **Fax toll-free to 1-866-678-6789**
 - **Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701C
Ottawa, ON K1A 0K9**

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at <http://www.healthcanada.gc.ca/medeffect>

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at:

<http://www.abbott.ca>

or by contacting the sponsor, Abbott Laboratories, Limited, Saint-Laurent, Qc H4S 1Z1 at:
1-800-699-9948

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