SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Synagis 50 mg/0.5 ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of Synagis solution contains 100 mg of palivizumab*.

Each 0.5 ml vial contains 50 mg of palivizumab.
Each 1 ml vial contains 100 mg of palivizumab.

*Palivizumab is a recombinant humanised monoclonal antibody produced by DNA technology in mouse myeloma host cells.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

The solution is clear or slightly opalescent.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Synagis is indicated for the prevention of serious lower respiratory tract disease requiring hospitalisation caused by respiratory syncytial virus (RSV) in children at high risk for 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.

4.2 Posology and method of administration

Posology
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 volume (expressed in ml) of // Palivizumab // to be administered at one-monthly intervals = [patient weight in kg] multiplied by 0.15.

Where possible, the first dose should be administered prior to commencement of the RSV season. Subsequent doses should be administered monthly throughout the RSV season. The efficacy of palivizumab at doses other than 15 mg per kg or of dosing differently from monthly throughout the RSV season, has not been established.

The majority of experience including the pivotal phase III clinical trials with palivizumab has been gained with 5 injections during one season (see section 5.1). Data, although limited, are available on greater than 5 doses (see sections 4.8, 5.1 and 5.2).

To reduce risk of rehospitalisation, it is recommended that children receiving palivizumab who are hospitalised with RSV continue to receive monthly doses of palivizumab for the duration of the RSV season.

For children undergoing cardiac bypass, it is recommended that a 15 mg/kg of body weight injection of palivizumab be administered as soon as stable after surgery to ensure adequate palivizumab serum levels. Subsequent doses should resume monthly through the remainder of the RSV season for children that continue to be at high risk of RSV disease (see section 5.2).

Method of administration

Palivizumab is administered 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.

Injection volumes over 1 ml should be given as a divided dose.

Synagis solution for injection is a ready to use formulation. For instructions on special handling requirements, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1, or to other humanised monoclonal antibodies.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Allergic reactions including very rare cases of anaphylaxis and anaphylactic shock have been reported following palivizumab administration. In some cases, fatalities have been reported (see section 4.8).

Medicinal products for the treatment of severe hypersensitivity reactions, including anaphylaxis and anaphylactic shock, should be available for immediate use following administration of palivizumab.

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 mild upper respiratory infection, is not usually reason to defer administration of palivizumab.

Palivizumab should be given with caution to patients with thrombocytopaenia or any coagulation disorder.

The efficacy of palivizumab when administered to patients as a second course of treatment during an ensuing RSV season has not been formally investigated in a study performed with this objective. The possible risk of enhanced RSV infection in the season following the season in which the patients were treated with palivizumab has not been conclusively ruled out by studies performed aiming at this particular point.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interactions studies with other medicinal products were conducted. In the phase III IMpact-RSV study in the premature and bronchopulmonary dysplasia paediatric populations, 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.

Since the monoclonal antibody is specific for RSV, palivizumab is not expected to interfere with the immune response to vaccines.

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.

4.6 Fertility, Pregnancy and lactation

Not relevant. Synagis is not indicated for use in adults. Data on fertility, pregnancy and lactation are not available.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile
The most serious adverse reactions occurring with palivizumab are anaphylaxis and other acute hypersensitivity reactions. Common adverse reactions occurring with palivizumab are fever, rash, and injection site reaction.

Tabulated list of adverse reactions
Adverse reactions both clinical and laboratory, are displayed by system organ class and frequency (very common ≥ 1/10; common ≥ 1/100 to < 1/10; uncommon ≥ 1/1,000 to < 1/100; rare ≥ 1/10,000 to <1/1,000) in studies conducted in premature and bronchopulmonary dysplasia paediatric patients, and paediatric congenital heart disease patients.
The adverse reactions identified via post-marketing surveillance 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. The frequency for these "ADRs" as presented in the table below was estimated using the safety data of the two registration clinical studies. The incidences of these reactions in these studies showed no difference between the palivizumab and placebo groups and the reactions were not drug related.

Undesirable effects in clinical studies* and post-marketing reports in paediatric patients		
MedDRA system organ class	**Frequency**	**ADR**
Blood and lymphatic system disorders	Uncommon	Thrombocytopenia[#]
Immune system disorders	Not known	Anaphylaxis, anaphylactic shock (in some cases, fatalities have been reported.)[#]
Nervous system disorders	Uncommon	Convulsion[#]
Respiratory, thoracic and mediastinal disorders	Common	Apnoea[#]

Skin and subcutaneous tissue disorders	Very common Uncommon	Rash Urticaria[#]
General disorders and administrative site conditions	Very common Common	Pyrexia Injection site reaction

*For full study description, see Section 5.1 Clinical studies

ADRs identified from post-marketing surveillance

Description of selected adverse reactions

Post-marketing experience

Post-marketing serious spontaneous adverse reactions reported during palivizumab treatment between 1998 and 2002 covering four RSV seasons were evaluated. A total of 1,291 serious reports were received where palivizumab had been administered as indicated and the duration of therapy was within one season. The onset of the adverse reactions occurred after the sixth or greater dose in only 22 of these reports (15 after the sixth dose, 6 after the seventh doses and 1 after the eight dose). These adverse reactions are similar in character to those after the initial five doses.

Palivizumab treatment schedule and adverse reactions were monitored in a group of nearly 20,000 infants tracked through a patient compliance registry between 1998 and 2000. Of this group 1,250 enrolled infants had 6 injections, 183 infants had 7 injections, and 27 infants had either 8 or 9 injections. Adverse reactions observed in patients after a sixth or greater dose were similar in character and frequency to those after the initial 5 doses.

In a small open label prospective trial of 14 subjects, who received 6 doses, the adverse events reported were consistent with the known safety profile of palivizumab.

In an observational, post-marketing, database study, a small increase in the frequency of asthma was observed among preterm palivizumab recipients; however, the causal relationship is uncertain.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme:
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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 section 4.8). In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins, antiviral monoclonal antibodies; ATC Code: J06BD01.

Palivizumab is a humanised $IgG_{1\kappa}$ monoclonal antibody directed to an epitope in the A antigenic site of the fusion protein of respiratory syncytial virus (RSV). This humanised monoclonal antibody is composed of human (95%) and murine (5%) antibody sequences. It has potent neutralising and fusion-inhibitory activity against both RSV subtype A and B strains.

Palivizumab serum concentrations of approximately 30 μg/ml have been shown to produce a 99% reduction in pulmonary RSV replication in the cotton rat model.

In vitro studies of 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 titre (50% effective concentration [EC_{50}]) 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 μg/ml (mean [standard deviation] = 0.75 [0.53] μg/ml; n=69, range 0.07–2.89 μg/ml) and 0.28 μg/ml (mean [standard deviation] = 0.35 [0.23] μg/ml; n=35, range 0.03–0.88 μg/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.

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. In a genotypic analysis of 126 clinical isolates from 123 children who failed immunoprophylaxis, all RSV mutants that exhibited resistance to palivizumab (n=8) were shown to contain amino acid changes in this region of the F protein. No polymorphic or non-polymorphic sequence variations outside of the A antigenic site on the RSV F protein were shown to render RSV resistant to neutralisation by palivizumab. At least one of the palivizumab resistance-associated substitutions, N262D, K272E/Q, or S275F/L was identified in these 8 clinical RSV isolates resulting in a combined resistance-associated mutation frequency of 6.3% in these patients. A review of clinical findings did not reveal an 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%.

Immunogenicity

Antibody to palivizumab was observed in approximately 1% of patients in the IMpact-RSV during the first course of therapy. This was transient, low titre, resolved despite continued use (first and second season), and could not be detected in 55 of 56 infants during the second season (including 2 with titres during the first season). Immunogenicity was not studied in the congenital heart disease study. Antibody to palivizumab was evaluated in four additional studies in 4337 patients (children born at 35 weeks of gestation or less and 6 months of age or less, or 24 months of age or less 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 timepoints. 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.

Studies using lyophilised palivizumab

In a placebo-controlled trial of RSV disease prophylaxis in (IMpact-RSV trial) 1502 high-risk children (1002 Synagis; 500 placebo), 5 monthly doses of 15 mg/kg reduced the incidence of RSV related hospitalisation by 55% ($p = < 0.001$). The RSV hospitalisation rate was 10.6% in the placebo group. On this basis, the absolute risk reduction is 5.8% which means the number needed to treat is 17 to prevent one hospitalisation. The severity of RSV disease in children hospitalised despite prophylaxis with palivizumab in terms of days in ICU stay per 100 children and days of mechanical ventilation per 100 children was not affected.

A total of 222 children were enrolled in two separate studies to examine the safety of palivizumab when it is administered for a second RSV season. One hundred and three (103) children received monthly palivizumab injections for the first time, and 119 children received palivizumab for two consecutive seasons. No difference between groups regarding immunogenicity was observed in either study. However, as the efficacy of palivizumab when administered to patients as a second course of treatment during an ensuing RSV season has not been formally investigated in a study performed with this objective, the relevance of these data in terms of efficacy is unknown.

In an open label prospective trial pharmacokinetics and immunogenicity were evaluated after administration of 6 doses of palivizumab within a single RSV season. The pharmacokinetic data indicated that adequate mean palivizumab levels were achieved in all 14 children for whom data on 30 day trough serum concentrations after the sixth dose were available (see section 5.2). No significant elevations of anti-palivizumab antibody titer were observed in these 14 participants. 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.

In a placebo-controlled trial in 1,287 patients $\leq$ 24 months of age with haemodynamically significant congenital heart disease (639 Synagis; 648 placebo), 5 monthly doses of 15 mg/kg Synagis; reduced the incidence of RSV hospitalisations by 45% ($p = 0.003$) (congenital heart disease study). Groups were equally balanced between cyanotic and acyanotic patients. The RSV hospitalisation rate was 9.7% in the placebo group and 5.3% in the Synagis group. Secondary efficacy endpoints showed significant reductions in the Synagis group compared to placebo in total days of RSV hospitalisation (56% reduction, $p = 0.003$) and total RSV days with increased supplemental oxygen (73% reduction, $p = 0.014$) per 100 children.

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 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.

Studies using liquid palivizumab

Two clinical studies were conducted to directly compare liquid and lyophilised formulations of palivizumab. In the first study, all 153 premature infants received both formulations in different sequences. In the second study, 211 and 202 premature infants or children with chronic lung disease received liquid and lyophilised palivizumab, respectively. In two additional studies, liquid palivizumab was used as an active control (3918 paediatric subjects) to evaluate an investigational monoclonal antibody for prophylaxis of serious RSV disease in premature infants or children with BPD or hemodynamically significant CHD (see below for further details of these two studies). The overall rate and pattern of adverse events, study drug discontinuation due to AEs, and the number of deaths reported in these clinical studies were consistent with those observed during the clinical development programs for the lyophilised formulation. No deaths were considered related to palivizumab and no new ADRs were identified in these studies.

Pre-term infants and children with Chronic Lung Disease 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 15 mg/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 hospitalisation. RSV hospitalisations occurred among 62 of 3306 (1.9%) patients in the palivizumab group. The RSV hospitalisation 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 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 15 mg/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 hospitalisation. The incidence of RSV hospitalisation was 16 of 612 (2.6%) in the palivizumab group.

5.2 Pharmacokinetic properties

Lyophilised formulation of palivizumab

In studies in adult volunteers, palivizumab had a pharmacokinetic profile similar to a human IgG_1 antibody with regard to volume of distribution (mean 57 ml/kg) and half-life (mean 18 days). In prophylactic studies in premature and bronchopulmonary dysplasia paediatric populations, the mean half-life of palivizumab was 20 days and monthly intramuscular doses of 15 mg/kg achieved mean 30 day trough serum active substance concentrations of approximately 40 μg/ml after the first injection, approximately 60 μg/ml after the second injection, approximately 70 μg/ml after the third injection and fourth injection. In the congenital heart disease study, monthly intramuscular doses of 15 mg/kg achieved mean 30 day trough serum active substance concentrations of approximately 55 μg/ml after the first injection and approximately 90 μg/ml after the fourth injection.

In the open label prospective trial evaluating pharmacokinetics with administration of 6 monthly intramuscular doses of 15 mg/kg of palivizumab, mean 30 day trough serum concentrations were approximately 40 μg/ml after the first dose, 120 μg/ml after the fourth dose, and 140 μg/ml after the sixth dose.

Among 139 children in the congenital heart disease study receiving palivizumab who had cardio-pulmonary bypass and for whom paired serum samples were available, the mean serum palivizumab concentration was approximately 100 μg/ml pre-cardiac bypass and declined to approximately 40 μg/ml after bypass.

Liquid formulation of palivizumab
The pharmacokinetics and safety of palivizumab liquid formulation and palivizumab lyophilised formulation, following 15 mg/kg intramuscular administration, were compared in a cross-over 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 the liquid formulation and the lyophilised formulation and bioequivalence of the liquid and the lyophilised formulation was demonstrated.

5.3 Preclinical safety data

Single dose toxicology studies have been conducted in cynomolgus monkeys (maximum dose 30 mg/kg), rabbits (maximum dose 50 mg/kg) and rats (maximum dose 840 mg/kg). No significant findings were observed.

Studies carried out in rodents gave no indication of enhancement of RSV replication, or RSV-induced pathology or generation of virus escape mutants in the presence of palivizumab under the chosen experimental conditions.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine

Glycine

Water for injections

6.2 Incompatibilities

This medicinal product should not be mixed with other medicinal products.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator (2ºC to 8ºC).

Do not freeze.

Keep the vial in the carton in order to protect from light.

6.5 Nature and contents of container

Single-use vials: 3 ml capacity, clear, colourless type I glass vial with a chlorobutyl stopper and flip-off seal containing either 0.5 ml or 1 ml of solution for injection.

Pack size of 1.

6.6 Special precautions for disposal and other handling

Do not dilute the product.

Do not shake the vial.

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

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 into the syringe an appropriate volume of solution.

Palivizumab solution for injection does not contain a preservative, is for single use and should be administered immediately after drawing the dose into the syringe.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

AstraZeneca UK Limited,
1 Francis Crick Avenue,
Cambridge,
CB2 0AA,
UK.

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 17901/0354

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

26/03/2024