1.5.5.2 PROFESSIONAL INFORMATION (PROPOSED CLEAN)

PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

SYNAGIS® 100 mg/mL solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SYNAGIS contains 100 mg/mL palivizumab.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection

Clear to slightly opalescent, non-turbid liquid; some small translucent particles may be visible.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

SYNAGIS is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in paediatric patients at high risk of RSV disease. Safety and efficacy were established in infants with bronchopulmonary dysplasia (BPD), infants with a history of prematurity (less than or equal to 35 weeks gestational age), and children with haemodynamically significant congenital heart disease (CHD).

4.2 Posology and method of administration

Posology

The recommended dose of SYNAGIS is 15 mg/kg of body weight, given once a month during anticipated periods of RSV risk in the community. The first dose should be administered prior to

commencement of the RSV season and subsequent doses should be administered monthly throughout the RSV season. In temperate climates, RSV season typically commences in the fall months and lasts through the spring; however, there have been reported cases during summer. In tropical climates, RSV season coincides with the rainy season. To avoid the risk of reinfection, it is recommended that children receiving SYNAGIS who become infected with RSV continue to receive monthly doses of SYNAGIS for the duration of the RSV season.

SYNAGIS is administered in a dose of 15 mg/kg once a month intramuscularly, preferably in the anterolateral aspect of the thigh. The gluteal muscle should not be used routinely as an injection site because of the risk of damage of the sciatic nerve. The injection should be given using standard aseptic technique. The dose per month = patient weight (kg) x 15 mg/kg ÷ 100 mg/mL of palivizumab. Injection volumes over 1 mℓ should be given as a divided dose.

The efficacy of SYNAGIS at doses less than 15 mg/kg, or of dosing less frequently than monthly throughout the RSV season has not been established.

Method of administration

SYNAGIS is to be administered by intramuscular injection only.

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

SYNAGIS should not be mixed with any medicines or diluents.

Both the 0,5 mL and 1 mL vials contain an overfill to allow the withdrawal of 50 mg or 100 mg, respectively.

- **DO NOT DILUTE SYNAGIS.**
- **DO NOT SHAKE VIAL.**

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

4.3 Contraindications

SYNAGIS 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.

4.4 Special warnings and precautions for use

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

Medicines 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 discontinued. If milder hypersensitivity reactions occur, caution should be used on re-administration of SYNAGIS.

SYNAGIS should be given with caution to patients with thrombocytopenia or any coagulation disorder.

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.

4.5 Interaction with other medicines and other forms of interaction

No formal interactions studies were conducted, however no interactions have been described to date. In the IMpact RSV Study, the proportions of patients in the placebo and palivizumab groups who received routine childhood vaccines, influenza vaccine, bronchodilators or corticosteroids were similar and no incremental increase in adverse reactions was observed among patients receiving these medicines 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.

Medicine/Laboratory Test Interaction

SYNAGIS may interfere with immune-based RSV diagnostic tests, such as some antigen detection-based assays. In addition, SYNAGIS inhibits virus replication in cell culture and, therefore, may also interfere with viral culture assays. SYNAGIS 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

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

4.7 Effects on ability to drive and use machines

No information available

4.8 Undesirable effects

b. Tabulated list of adverse reactions

Adverse events are displayed by system organ class and frequency (very common: ≥ 1/10; common: ≥ 1/100 to < 1/10; uncommon: ≥ 1/1000 to < 1/100; rare: ≥ 1/10000 to < 1/1000) in studies conducted in premature and bronchopulmonary dysplasia patients and paediatric congenital heart disease patients.

MedDRA system organ class	**Frequency**	**ADR**
Blood and lymphatic system disorders	Uncommon	Thrombocytopaenia[#]
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	Rash
	Uncommon	Urticaria[#]
General disorders and administration site conditions	Very common	Pyrexia
	Common	Injection site reaction
[#]ADRs identified from post-marketing surveillance		

c. Description of selected adverse reactions

Post-marketing experience

Post-marketing serious spontaneous adverse reactions reported during SYNAGIS treatment between 1998 and 2002 covering four RSV seasons were evaluated. A total of 1,291 serious reports were received where SYNAGIS had been administered as indicated and the duration of therapy was within one season. The onset of the adverse reaction 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.

SYNAGIS 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.

Immunogenicity

In the Impact-RSV trial, the incidence of anti-palivizumab antibody following the fourth injection was 1,1 % in the placebo group and 0,7 % in the palivizumab group. In paediatric patients receiving palivizumab for a second season, one of the fifty-six patients had transient, low titer reactivity. This reactivity was not associated with adverse events or alteration in palivizumab serum concentrations. Immunogenicity was not assessed in the CHD Study.

Antibody to palivizumab was also evaluated in four additional studies in 4337 palivizumab-treated patients (children born at 35 weeks of gestation or less and 6 months of age or less, or < 24 months of age with bronchopulmonary dysplasia or with haemodynamically significant congenital heart disease were included in these studies) and was observed in 0 % to 1,5 % of patients at different study time points. There was no association observed between the presence of antibody and adverse events. Therefore, anti-drug antibody (ADA) responses appear to be of no clinical relevance.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to

report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

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 overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.30.1 – Antibodies

Palivizumab is a humanised IgG1 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 95 % human and 5 % murine amino acid sequences. Palivizumab is composed of two heavy chains and two light chains having a molecular weight of approximately 148,000 Daltons.

Palivizumab exhibits neutralizing and fusion-inhibitory activity against RSV. These activities inhibit RSV replication in laboratory experiments. Although resistant RSV strains may be isolated in laboratory studies, a panel of clinical RSV isolates were all neutralized by palivizumab. Palivizumab serum concentrations of approximately 30 µg/mℓ have been shown to produce a mean 99 % reduction in pulmonary RSV replication in the cotton rat model.

The *in vivo* neutralizing activity of the active ingredient in palivizumab was assessed in a randomized, placebo-controlled study of 35 paediatric patients tracheally intubated because of RSV disease. In these patients, palivizumab significantly reduced the quantity of RSV in the lower respiratory tract compared to control patients.

5.2 Pharmacokinetic properties

In studies in adult volunteers, palivizumab had a pharmacokinetic profile similar to a human IgG1 antibody with regard to volume of distribution (mean 57 mL/kg) and half-life (mean 18 days). In studies in children, the mean half-life of palivizumab was 20 days and monthly intramuscular doses of 15 mg/kg achieved mean 30 day trough serum drug concentrations of approximately 40 mcg/mL after the first injection, approximately 60 mcg/mL after the second injection, and approximately 70 mcg/mL after the third injection and fourth injection. In pediatric patients given palivizumab for a second season, the mean serum concentrations following the first and fourth injections were approximately 60 and 90 mcg/mL, respectively.

In pediatric patients less than or equal to 24 months of age with hemodynamically significant congenital heart disease (HS CHD) who received palivizumab and underwent cardiopulmonary bypass for open-heart surgery, the mean serum palivizumab concentration was approximately 100 mcg/mL pre-cardiac bypass and declined to approximately 40 mcg/mL after bypass.

A prospective, phase II, open-label trial designed to evaluate pharmacokinetics, safety and immunogenicity after administration of 7 doses of palivizumab within a single RSV season, indicated that adequate mean palivizumab levels were achieved in all 18 children enrolled.

The pharmacokinetics and safety of palivizumab liquid formulation and palivizumab lyophilized formulation, following 15 mg per 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 liquid formulation and the lyophilized formulation and bioequivalence of the liquid and the lyophilized formulation was demonstrated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine

Glycine

6.2 Incompatibilities

No information available

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at 2 - 8 °C.

6.5 Nature and contents of container

SYNAGIS single-use vial:

- 3 mL capacity, clear, colourless type I glass vial with grey chlorobutyl, Teflon-faced, siliconised stopper and lacquered aluminium crimping seal with a polypropylene flip-off disc containing 0,5 mL palivizumab solution for injection with a concentration of 100 mg/mL.
- 3 mL capacity, clear, colourless type I glass vial with grey chlorobutyl, Teflon-faced, siliconised stopper and lacquered aluminium crimping seal with a polypropylene flip-off disc containing 1 mL palivizumab solution for injection with a concentration of 100 mg/mL.

6.6 Special precautions for disposal and other handling

No information available

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER

50/30.1/0148

9 DATE OF FIRST AUTHORISATION

26 October 2018

10 DATE OF REVISION OF THE TEXT

28 June 2021