PRESCRIBING INFORMATION

Abbosynagis 50 mg
Powder and solvent for solution for injection
Abbosynagis 100 mg
Powder and solvent for solution for injection

1. NAME OF THE MEDICINAL PRODUCT

Abbosynagis 50 mg
Powder and solvent for solution for injection
Abbosynagis 100 mg
Powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Abbosynagis 50 mg
One vial contains 50 mg palivizumab, providing 100 mg/ml of palivizumab when reconstituted as recommended.

Abbosynagis 100 mg
One vial contains 100 mg palivizumab, providing 100 mg/ml of palivizumab when reconstituted as recommended.

For a full list of excipients, see "List of excipients".

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.
The powder is a white to off-white cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Abbosynagis is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV). Safety and efficacy were established in:

- infants with bronchopulmonary dysplasia (BPD)
- infants with a history of prematurity (35 weeks gestational age)
- Children less then 2 years of age and with haemodynamically significant congenital heart disease (CHD)

4.2 Posology and method of administration

Recommended dose

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. 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 majority of experience including the pivotal phase III clinical trials with palivizumab has been gained with 5 injections during one season (see "Pharmacodynamic properties"). Data, although limited, are available on greater than 5 doses (see "Undesirable effects" and "Pharmacodynamic properties"), therefore the benefit in terms of protection beyond 5 doses has not been established.

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 "Pharmacokinetic properties").

Method of administration

Palivizumab is administered in a dose of 15 mg/kg of body weight once a month intramuscularly, preferably in the anterolateral aspect of the thigh. The gluteal muscle should not be used routinely as an injection site because of the risk of damage to the sciatic nerve. The injection should be given using standard aseptic technique.

The volume (expressed in mL) of palivizumab to be administered at one-monthly intervals = [patient weight in kg] multiplied by 0.15

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

To ensure the correct volume is reconstituted for Abbosynagis, see "Instructions for use, handling and disposal".

4.3 Contraindications

Known hypersensitivity to the active substance or to any of the excipients (see "List of excipients"), or other humanised monoclonal antibodies.

4.4 Special warnings and special precautions for use

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 "Undesirable effects").

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.

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

The single-use vial of Abbosynagis does not contain a preservative. Injections should be given within 3 hours after reconstitution. Any remaining contents should be discarded after use.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies with other medicinal products were conducted, however no interactions have been described to date. In the phase III IMpact-RSV study in the premature and bronchopulmonary dysplasia paediatric population, 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, Abbosynagis is not expected to interfere with the immune response to vaccines.

4.6 Pregnancy and lactation

Not applicable. Abbosynagis is not indicated for use in adults. Data on pregnancy and lactation are not available.

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

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

Adverse events at least possibly causally-related to palivizumab, both clinical and laboratory, are displayed by system organ class and frequency (common ≥ 1/100 to < 1/10; uncommon ≥ 1/1,000 to < 1/100) in studies conducted in premature and bronchopulmonary dysplasia paediatric patients, and congenital heart disease patients (Tables 1 and 2, respectively).

Within each frequency grouping, adverse reactions have been presented in order of decreasing seriousness.

Table 1. Undesirable Effects in Prophylactic Clinical Studies with Premature and Bronchopulmonary Dysplasia Paediatric Populations

Infections and infestations	Uncommon	Upper respiratory infection Viral infection
Blood and lymphatic system disorders	Uncommon	Leucopenia
Psychiatric disorders	Common	Nervousness
Respiratory, thoracic and mediastinal disorders	Uncommon	Rhinitis Cough Wheeze
Gastrointestinal disorders	Common Uncommon	Diarrhoea Vomiting
Skin and subcutaneous tissue disorders	Uncommon	Rash
General disorders and administration site conditions	Common Uncommon	Fever Injection site reaction Pain
Investigations	Uncommon	AST increase Abnormal liver function test ALT increase

No medically important differences were observed during the prophylactic studies carried out in the premature and bronchopulmonary dysplasia paediatric population in ADRs by body system or when evaluated in subgroups of children by clinical category, gender, age, gestational age, country, race/ethnicity or quartile serum palivizumab concentration. No significant difference in safety profile was observed between children without active RSV infection and those hospitalised for RSV. Permanent discontinuation of palivizumab due to ADRs was rare (0.2%). Deaths were balanced between the integrated placebo and palivizumab groups and were not drug-related.

Table 2. Undesirable Effects in the Prophylactic Paediatric Congenital Heart Disease Clinical Study

Infections and infestations	Uncommon	Upper respiratory infection Gastroenteritis
Psychiatric disorders	Uncommon	Nervousness
Nervous system disorders	Uncommon	Somnolence Hyperkinesia
Vascular disorders	Uncommon	Haemorrhage
Respiratory, thoracic and mediastinal disorders	Uncommon	Rhinitis
Gastrointestinal disorders	Uncommon	Diarrhoea Vomiting Constipation
Skin and subcutaneous tissue disorders	Uncommon	Rash Eczema
General disorders and administration site conditions	Common Uncommon	Injection site reaction Fever Asthenia

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

Post-marketing experience:

The following events were reported during post-marketing experience of palivizumab. Because these events 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.

Blood and lymphatic system disorders: thrombocytopenia

Immune system disorders: anaphylaxis, anaphylactic shock (in some cases, fatalities have been reported.)

Nervous system disorders: convulsion

Respiratory, thoracic and mediastinal disorders: apnoea

Skin and subcutaneous tissue disorders: urticaria

Post-marketing serious spontaneous adverse events 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 event occurred after the sixth or greater dose in only 22 of these reports (15 after the sixth dose, 6 after the seventh dose and 1 after the eighth dose). These events are similar in character to those after the initial five doses.

Palivizumab treatment schedule and adverse events 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 events observed in patients after a sixth or greater dose were similar in character and frequency to those after the initial 5 doses.

Human anti-human antibody (HAHA) response:

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 55/56 infants during the second season (including 2 with titres during the first season). Therefore, HAHA responses appear to be of no clinical relevance.

Immunogenicity was not studied in the congenital heart disease study.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: specific immunoglobulins; ATC Code: J06BB16

Palivizumab is a humanised IgG_{1K} 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.

Clinical studies

In a placebo-controlled trial of RSV disease prophylaxis in (IMpact-RSV trial) 1502 high-risk children (1002 Abbosynagis; 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 (ARR) is 5.8% which means the number needed to treat (NNT) 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 designed to evaluate pharmacokinetics, safety and immunogenicity after administration of 7 doses palivizumab with a single RSV season, pharmacokinetic data indicated that adequate mean palivizumab levels were achieved in all 18 children enrolled. Transient, low levels of antipalivizumab 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 ≤ 24 months of age with haemodynamically significant congenital heart disease (639 Abbosynagis; 648 placebo), 5 monthly doses of 15 mg/kg Abbosynagis 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 Abbosynagis group. Secondary efficacy endpoints showed significant reductions in the Abbosynagis 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 Abbosynagis 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 Abbosynagis prophylaxis compared with children who did not receive prophylaxis.

5.2 Pharmacokinetic properties

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.

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.

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

Powder:
Histidine
Glycine
Mannitol
Solvent:
Water for Injections

6.2 Incompatibilities

Abbosynagis should not be mixed with any medicinal product or diluents other than Water for Injections.

6.3 Shelf-life

3 years

Solution must be administered within 3 hours (at 20-24ºC) of reconstitution.

6.4 Special precautions for storage

Store in a refrigerator (2ºC to 8ºC). Do not freeze.

Store in the original container.

For storage conditions of the reconstituted medicinal product, see section "Shelf-life".

6.5 Nature and contents of container

Abbosynagis powder: clear, colourless, type I glass vial with stopper and flip-off seal.

Water for Injections: clear, colourless, type I glass ampoule containing 1 ml water for injections.

One vial of Abbosynagis powder and one ampoule of Water for Injections per pack.

50 mg vial - When reconstituted as recommended, the final concentration is 100 mg/ml.

100 mg vial - When reconstituted as recommended, the final concentration is 100 mg/ml.

6.6 Instructions for use, handling and disposal

The 50 mg vial contains an overfill to allow the withdrawal of 50 mg when reconstituted if following the directions described below.

The 100 mg vial contains an overfill to allow the withdrawal of 100 mg when reconstituted if following the directions described below.

To reconstitute, remove the tab portion of the vial cap and clean the rubber stopper with 70% ethanol or equivalent.

Abbosynagis 50 mg - Add 0.6 ml of Water for Injections

Abbosynagis 100 mg - Add 1.0 ml of Water for Injections

SLOWLY add the Water for Injections along the inside wall of the vial to minimise foaming. After the water is added, tilt the vial slightly and gently rotate the vial for 30 seconds. DO NOT SHAKE THE VIAL.

Palivizumab solution should stand at room temperature for a minimum of 20 minutes until the solution clarifies. Palivizumab solution does not contain a preservative and should be administered within 3 hours of preparation. Any remaining contents should be discarded after use.

When reconstituted as recommended, the final concentration is 100 mg/ml.

The appearance of the reconstituted solution is clear to slightly opalescent.

הוראות שימוש

על מנת להכין את התמיסה יש להסיר את החלק הנשלף של כיסוי האלומיניום ולנקות את הגומי שנמצא מתחת עם אתנול 70%.

אבוסינגיס 50 מ"ג – הוסף 0.6 מ"ל מים להזרקה.

אבוסינגיס 100 מ"ג – הוסף 1.0 מ"ל מים להזרקה.

יש להוסיף את המים להזרקה באיטיות לאורך הדופן של הבקבוקון על מנת למנוע היווצרות קצף. לאחר הוספת המים יש לערבב את הבקבוקון בעדינות בתנועות סיבוביות למשך 30 שניות. אין לנער את הבקבוקון!

יש להעמיד את התמיסה המתקבלת בטמפרטורת החדר למשך מינימום של 20 דקות עד שהתמיסה הופכת לצלולה.

התמיסה אינה מכילה חומרים משמרים ולפיכך יש להשתמש בה תוך 3 שעות מרגע הכנתה. את השארית יש להשמיד לאחר השימוש.

לאחר המיהול מתקבלת תמיסה של 100 מ"ג/מ"ל.

הוראות אחסנה

במקרר בין 2-8 מעלות צלזיוס. אסור להקפיא.

יש להשתמש תוך 3 שעות (20-24ºC) מרגע המיהול.

Manufacturer: Abbott Srl, Italy.
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The format of this leaflet was determined by the Ministry of Health and its content was checked and approved

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