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

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

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

For a full list of excipients, see section 6.1.

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 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

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 efficacy of Abbosynagis at doses other than 15 mg/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 and 5.1), 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 section 5.2).

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 section 6.6.

4.3 Contraindications
Known hypersensitivity to the active substance or to any of the excipients (see section 6.1), or other humanised monoclonal antibodies.

4.4 Special warnings and 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 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.

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.

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, 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 Pregnancy and lactation

Not relevant. 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 relevant.

4.8 Undesirable effects

Summary of the safety profile

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.

No medically important differences were observed during the prophylactic studies carried out in the premature and bronchopulmonary dysplasia paediatric populations 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 uncommon (0.2%). Deaths were balanced between the integrated placebo and palivizumab groups and were not drug-related.

In the congenital heart disease study, no medically important differences were observed in ADRs by body system or when evaluated in subgroups of children by cardiac category (cyanotic versus acyanotic). 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.

Tabulated list of adverse reactions

Adverse events at least possibly causally-related to palivizumab, 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 events 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 events in these studies showed no difference between the palivizumab and placebo groups and the events were not drug related.

Undesirable effects in clinical studies* and post-marketing reports in paediatric patients		
MedDRA System Organ Class	**Frequency**	**ADR**
Skin and subcutaneous tissue disorders	Very common	Rash
General disorders and administrative site conditions	Very common Common	Pyrexia Injection site reaction
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	Uncommon	Urticaria[#]

*For full study description, see section 5.1 Clinical studies
ADRs identified from post-marketing surveillance

Post-marketing experience:

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.

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.

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 4,337 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.

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

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: 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.

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 EC_{50} 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%.

Clinical studies

In a placebo-controlled trial of RSV disease prophylaxis in (IMpact-RSV trial) 1502 high-risk children (1,002 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 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 designed to evaluate pharmacokinetics, safety and immunogenicity after administration of 7 doses of palivizumab within 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 (1,009) and did not receive Abbosynagis prophylaxis (1,009) 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
Any remaining contents should be discarded after use.
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 6.3.

6.5 Nature and contents of container

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

Water for Injections: 1 ml of Water for Injections in an ampoule (type I glass).

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 Special precautions for disposal and other handling

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.

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

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

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

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 ההכנה 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 הכנת התמיסה.

7. Manufacturer: AbbVie Srl, Italy.

8. License Holder: AbbVie Biopharmaceuticals Ltd., 4 Haharash St., Hod Hasharon, Israel

9. Registration Numbers:

Abbosynagis 50 mg: 119-63-30030-00
Abbosynagis 100 mg: 119-01-29909-00

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved.