

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Synagis 50 mg/0.5 ml solution for injection  
Synagis 100 mg/1 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 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.

### **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  $\geq 1/10$ ; common  $\geq 1/100$  to  $< 1/10$ ; uncommon  $\geq 1/1,000$  to  $< 1/100$ ; rare  $\geq 1/10,000$  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.

<b>Undesirable effects in clinical studies* and post-marketing reports in paediatric patients</b>		
<b>MedDRA system organ class</b>	<b>Frequency</b>	<b>ADR</b>
Blood and lymphatic system disorders	Uncommon	Thrombocytopenia <sup>#</sup>
Immune system disorders	Not known	Anaphylaxis, anaphylactic shock (in some cases, fatalities have been reported.) <sup>#</sup>
Nervous system disorders	Uncommon	Convulsion <sup>#</sup>
Respiratory, thoracic and mediastinal disorders	Common	Apnoea <sup>#</sup>
Skin and subcutaneous tissue disorders	Very common	Rash
	Uncommon	Urticaria <sup>#</sup>
General disorders and administrative site conditions	Very common	Pyrexia
	Common	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 eighth 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 national reporting system listed in Appendix V.](#)

## **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<sub>1κ</sub> 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<sub>50</sub>]) 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<sub>50</sub> 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<sub>1</sub> 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 (2°C to 8°C).  
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 AB  
SE-151 85 Södertälje  
Sweden

**8.    MARKETING AUTHORISATION NUMBERS**

EU/1/99/117/003  
EU/1/99/117/004

**9.    DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 13 August 1999  
Date of latest renewal: 27 July 2009

**10.   DATE OF REVISION OF THE TEXT**

Detailed information on this product is available on the website of the European Medicines Agency:  
<http://www.ema.europa.eu>.

## **ANNEX II**

- A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

**A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer(s) of the biological active substance

Boehringer Ingelheim Pharma GmbH & Co. KG  
D-88397 Biberach an der Riss  
Germany

AstraZeneca Pharmaceuticals Limited Partnership (AZPLP)  
660 MedImmune Court / 633 Research Court, Frederick, Maryland,  
USA

Name and address of the manufacturer(s) responsible for batch release

AbbVie S.r.l.  
04011 Campoverde di Aprilia (LT)  
Italy

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to medical prescription.

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

• **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

• **Risk management plan (RMP)**

The marketing authorization holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Outer Carton of 0.5 ml vial**

**1. NAME OF THE MEDICINAL PRODUCT**

Synagis 50 mg/0.5 ml solution for injection  
palivizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each 0.5 ml vial contains 50 mg of palivizumab. Concentration of 100 mg/ml solution for injection.

**3. LIST OF EXCIPIENTS**

Also contains: histidine, glycine and water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection  
50 mg/0.5 ml

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
**Do not shake.**

Intramuscular use.

Single-use vial.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP



**9. SPECIAL STORAGE CONDITIONS**

**Store in a refrigerator.**

**Do not freeze.**

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

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

AstraZeneca AB  
SE-151 85 Södertälje  
Sweden

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/99/117/003

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Outer Carton of 1.0 ml vial**

**1. NAME OF THE MEDICINAL PRODUCT**

Synagis 100 mg/1 ml solution for injection  
palivizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each 1 ml vial contains 100 mg of palivizumab. Concentration of 100 mg/ml solution for injection.

**3. LIST OF EXCIPIENTS**

Also contains: histidine, glycine and water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection  
100 mg/1 ml

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
**Do not shake.**

Intramuscular use.

Single-use vial.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

**Store in a refrigerator.**  
**Do not freeze.**

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

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

AstraZeneca AB  
SE-151 85 Södertälje  
Sweden

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/99/117/004

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**Label of 0.5 ml vial**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Synagis 50 mg/0.5 ml solution for injection  
palivizumab  
IM

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

AstraZeneca

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

100 mg/ml

**6. OTHER**

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**Label of 1.0 ml vial**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Synagis 100 mg/1 ml solution for injection  
palivizumab  
IM

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

AstraZeneca

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

100 mg/ml

**6. OTHER**

**B. PACKAGE LEAFLET**

## **Package leaflet: Information for the user**

**Synagis 50 mg/0.5 ml solution for injection**

**Synagis 100 mg/1 ml solution for injection**

Active substance: palivizumab

**Read all of this leaflet carefully before your child is given this medicine because it contains important information for you and your child.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- If any of the side effects get serious, or if you notice that your child has any side effects not listed in this leaflet, please tell your doctor or pharmacist. See section 4.

### **What is in this leaflet**

1. What Synagis is and what it is used for
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#### **1. What Synagis is and what it is used for**

Synagis contains an active ingredient called palivizumab which is an antibody that works specifically against a virus called respiratory syncytial virus, RSV.

Your child is at high risk of getting an illness caused by a virus called respiratory syncytial virus (RSV).

Children who are more likely to get severe RSV disease (high-risk children) include babies born prematurely (35 weeks or less) or babies born with certain heart or lung problems.

Synagis is a medicine to help protect your child from getting severe RSV illness.

#### **2. What you need to know before Synagis is given to your child**

##### **Your child should not be given Synagis**

If he/she is allergic to palivizumab or any of the other ingredients of this medicine (listed in section 6).

Signs and symptoms of a severe allergic reaction include:

- severe rash, hives, or itching skin
- swelling of the lips, tongue, or face
- closing of the throat, difficulty swallowing
- difficult, rapid, or irregular breathing
- bluish colour of skin, lips, or under fingernails
- muscle weakness or floppiness
- a drop in blood pressure
- unresponsiveness

## **Warnings and precautions**

Take special care with Synagis

- if your child is unwell. Please tell your doctor if your child is unwell, as the use of Synagis may need to be delayed.
- if your child has any bleeding disorders as Synagis is usually injected into the thigh.

## **Other medicines and Synagis**

Synagis is not known to interact with other medicines. However, you should inform your doctor of all medicines your child is currently taking before starting Synagis.

## **3. How will my child receive Synagis**

*How often will Synagis be given to my child?*

Synagis should be given to your child at a dose of 15 mg/kg body weight once a month for as long as the risk of RSV infection remains. For your child's best protection, it is necessary to take the doctor's advice about when to return for additional doses of Synagis.

If your child is to have a heart operation (cardiac bypass surgery), he or she may be given an extra dose of Synagis after the operation. Your child can then go back to the original planned injections.

*How will my child receive Synagis?*

Synagis will be given by injection to your child into a muscle, usually in the outer part of the thigh.

*What should you do if your child misses an injection of Synagis?*

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.

Always use this medicine exactly as your doctor or pharmacist has told you. If you are not sure about how this product will be given to your child, ask your doctor or pharmacist.

## **4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

*Synagis may cause serious side effects including:*

- severe allergic reactions, such reactions may be life threatening or fatal (see "Your child should not be given Synagis" for a list of signs and symptoms).
- unusual bruising or groups of tiny red spots on the skin.

Call your doctor or get medical help right away if your child has any of the serious side effects listed above after receiving any dose of Synagis.

### **Additional side effects**

Very common (affects at least 1 user in 10):

- rash
- fever

Common (affects 1 to 10 users in 100):

- pain, redness or swelling at the injection site
- a pause in breathing or other breathing difficulties



Uncommon (affects less than 1 user in 100):

- fits
- hives

### **Reporting of side effects**

If your child gets any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store Synagis**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label after 'EXP'. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C).

Do not freeze.

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

## **6. Contents of the pack and other information**

### **What Synagis contains**

- The active substance is palivizumab. One ml of Synagis solution for injection contains 100 mg of palivizumab.
- Each 0.5 ml vial contains 50 mg of palivizumab.
- Each 1 ml vial contains 100 mg of palivizumab.
- The other ingredients are histidine, glycine and water for injections.

### **What Synagis looks like and contents of the pack**

Synagis solution for injection is a clear or slightly opalescent solution and is available in vials of either 0.5 ml or 1 ml.

Pack size of 1.

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Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>.

The following information is intended for medical or healthcare professionals only:

### **Administrator's Instructions**

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

Palivizumab should not be mixed with any medicinal products 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 the product.**

**Do not shake the 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 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.

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

When using Palivizumab 100 mg/1 ml, the volume (expressed in ml) of Palivizumab to be administered at one-monthly intervals = [patient weight in kg] multiplied by 0.15

For example, for a baby with a body weight of 3 kg, the calculation becomes:

$(3 \times 0.15) \text{ ml} = 0.45 \text{ ml palivizumab per month.}$