Risk Management Plan for Palivizumab/Synagis®

AbbVie Inc. (AbbVie)

Active substance (INN or common name):	Palivizumab
Pharmaco-therapeutic group (ATC Code):	J06BB16
Name of Marketing Authorisation Holder or Applicant:	AbbVie Ltd
Number of medicinal product to which this RMP refers:	1
Product concerned (brand name):	Synagis®

Data lock point for this RMP:	31 Dec 2012
Version number:	1.0
Date of final sign off:	Sep 2013

Part I Product(s) Overview

Administrative Information on the RMP

Part	Module/Annex	Date last updated for submission (sign-off date)	Version number of RMP when last submitted
Part II Safety Specification	SI Epidemiology of the indication and target population(s)	NA[a]	NA[a]
	SII Non-clinical part of the safety specification		
	SIII Clinical trial exposure		
	SIV Populations not studied in clinical trials		
	SV Post-authorisation experience		
	SVI Additional EU requirements for the safety specification		
	SVII Identified and potential risks		
	SVIII Summary of the safety concerns		
Part III Pharmacovigilance Plan		NA[a]	NA[a]
Part IV Plan for Post-authorisation Efficacy Studies		NA[a]	NA[a]
Part V Risk Minimisation Measures		NA[a]	NA[a]
Part VI Summary of RMP		NA[a]	NA[a]
Part VII Annexes	Annex 2 Current or proposed SmPC/PIL	NA[a]	NA[a]
	Annex 3 Worldwide marketing status by country		
	Annex 4 Synopsis of clinical trial programme		

Part	Module/Annex	Date last updated for submission (sign-off date)	Version number of RMP when last submitted
	Annex 5 Synopsis of pharmacoepidemiological study programme		
	Annex 6 Protocols for proposed and on-going studies in Part III		
	Annex 7 Specific adverse event follow-up forms		
	Annex 8 Protocols for studies in Part IV		
	Annex 9 Synopsis of newly available study reports in Parts III-IV		
	Annex 10 Details of proposed additional risk minimisation activities		
	Annex 11 Mock up examples		
	Annex 12 Other supporting data		

a. This is the first iteration of the Synagis RMP (ed 1.0).

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Overview of Versions

Version number of last agency agreed RMP:	NA
Version number agreed within	NA

Current RMP Versions Under Evaluation

RMP Version Number	Submitted on:	Submitted within:
NA		

List of Abbreviations

AAP	American Academy of Pediatrics
AEs	adverse events
AGA	Appropriate for gestational age
aOR	Adjusted odds ratio
BPD	bronchopulmonary dysplasia
CHD	congenital heart disease
CI	confidence interval
CLD	chronic lung disease
CLDP	CLD of prematurity
EPAR	European Public Assessment Report
F protein	Fusion protein
GA	gestational age
HIV	human immunodeficiency virus
HSCHD	hemodynamically significant congenital heart disease
IBD	International Birth Date
IgG	immunoglobulin G
IM	intramuscular
IV	intravenous
MAH	Marketing Authorization Holder
NEC	necrotizing enterocolitis
NICU	neonatal intensive care unit
OR	odds ratio
PDA	patent ductus arteriosus
PK	pharmacokinetics
PL	package leaflet
PMDA	Pharmaceuticals and Medical Devices Agency
PV	Pharmacovigilance
RDS	Respiratory Distress Syndrome
RR	Relative risk
RSV	respiratory syncytial virus
SGA	Small for gestational age
SIDS	sudden infant death syndrome
SmPC	Summary of Product Characteristics
VLBW	Very low birth weight

For Each Product in the RMP

Invented name(s) in the European Economic Area (EEA)	Synagis®
Authorisation procedure	Centralised
Authorisation number(s)	EU/1/99/117/001, EU/1/99/117/002
Brief description of product	Chemical class: Specific immunoglobulins Mode of action: Palivizumab is a recombinant, humanized immunoglobulin G (IgG)1 monoclonal antibody which targets an epitope in the A antigenic site of the fusion (F) protein of respiratory syncytial virus (RSV) and prevents viral entry into host cells. It exhibits neutralizing and fusion-inhibitory activity against both RSV subtype A and B strains. Composition: Palivizumab is composed of human (95%) and murine (5%) antibody amino acid sequences.
Indication(s) in the EEA	Current: Synagis is indicated for the prevention of serious lower respiratory tract disease requiring hospitalization caused by 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 (BPD) within the last 6 months. • Children less than 2 years of age and with hemodynamically significant congenital heart disease (HSCHD). Proposed (if applicable): Not applicable.

Posology and route of administration in the EEA	Current: 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 3 clinical trials with palivizumab has been gained with 5 injections during one season. Data, although limited, are available on greater than 5 doses, therefore the benefit in terms of protection beyond 5 doses has not been established. To reduce risk of rehospitalization, it is recommended that children receiving palivizumab who are hospitalized 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. 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. Proposed (if applicable): NA

Pharmaceutical form(s) and strength(s)	Current: Synagis 50 mg powder and solvent for solution for injection. Each vial contains 50 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. Synagis 100 mg powder and solvent for solution for injection. 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. **Proposed additional medicinal product:** Liquid solution Synagis 100 mg/mL solution for injection Each 1 mL of Synagis solution contains 100 mg of palivizumab* and excipients * Palvizumab is a recombinant humanised monoclonal antibody produced by DNA technology in mouse myeloma host cells.

Country and date of first authorisation worldwide:	19 June 1998 – US
Country and date of first launch worldwide:	19 June 1998 – US
Country and date of first authorization in the EEA:	13 August 1999 – European Union (EU)
Is the product subject to additional monitoring in the EU?	No

Part II

Module SI: Epidemiology of the Indication(s) and Target Population

Indication: Palivizumab is indicated for the prevention of serious lower respiratory tract disease requiring hospitalization caused by 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 BPD within the last 6 months.
- Children less than 2 years of age and with HSCHD.

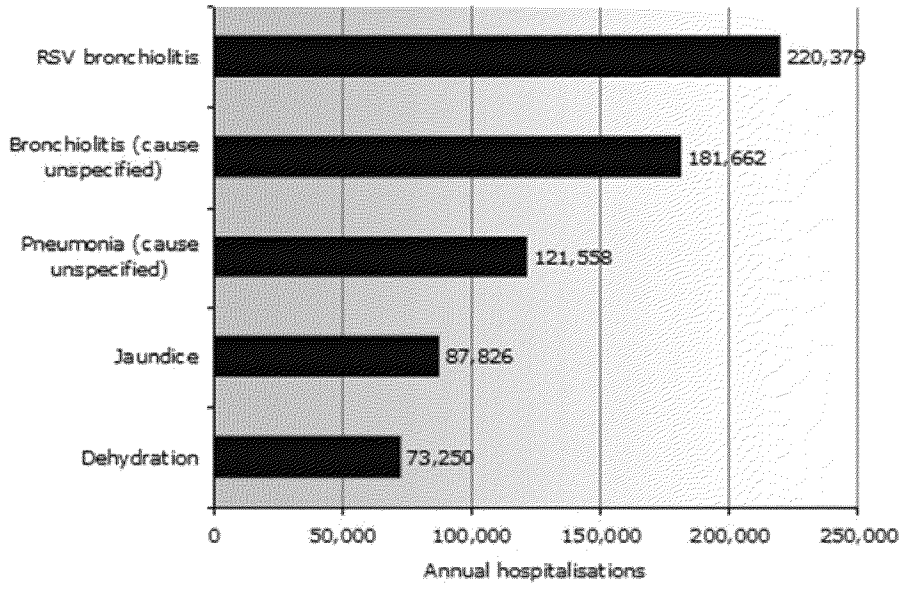
Brand Name of Concerned Products (with this indication): Synagis

SI.1 Epidemiology of the Disease

Overview of Worldwide Epidemiology of RSV:

RSV is an important respiratory pathogen for infants and young children, causing annual epidemics of bronchiolitis and pneumonia worldwide. Up to 69% of children are infected with RSV during their first year of life and up to 99% are infected by the age of 2 (Glenzen 1986; Prober 1997). One study estimated 33.8 million new episodes of RSV-associated acute lower respiratory tract infection worldwide in children younger than 5 years of age (Nair 2010). Peak rates of RSV infection occur in infants aged 6 weeks to 6 months (Simoes 1999). Among infants, RSV has been estimated to cause up to 90% of all hospitalizations resulting from bronchiolitis and up to 50% of all pneumonia admissions (Prober 1997). RSV bronchiolitis is a leading cause of hospitalization in infants in the United States (US) (Leader 2002) (Figure 1 derived from Table 1 of the Leader 2002).

Figure 1. RSV Bronchiolitis Is a Leading Cause of Infant Hospitalization in the United States



Lower respiratory tract infections caused by RSV account for more than 125,000 paediatric hospitalizations in infants and approximately 3.2 deaths per 100,000 person-years among children up to 4 years of age in the US (Shay 1999, Shay 2001). Overall the hospitalization rate from RSV infection in infants less than 1 year old is approximately 1% to 2% (Thompson 2003; Heilman 1990; Hall 1979; Groothuis 1988). A large descriptive analysis of US National Hospital Discharge data from 1980 to 1996 revealed that 57% of RSV hospitalizations occurred among children younger than 6 months of age and 81% among those younger than 1 year (Shay 1999). Data from the Danish Respiratory Syncytial Virus Database illustrate that boys are 1.3 times more likely to be infected with RSV than girls, and that the incidence of infection declines with increasing age (Stensballe 2002). Recent US data showed that RSV-coded hospitalizations accounted for 24% of an estimated 5.5 million lower respiratory tract infection hospitalizations among children < 5 years of age during the

10 study years, 1997 to 2006. The RSV-coded hospitalization rate in infants < 1 year old was 26.0 per 1000, with no significant difference between study years. The hospitalization rate was highest among infants < 3 months old (48.9 per 1000), followed by infants 3 to 5 months old (28.4 per 1000), and lower among those > 1 year old (1.8 per 1000). An estimated 132,000 to 172,000 RSV-associated hospitalizations occurred annually in children < 5 years of age (Stockman 2012).

RSV-Related Diseases in High Risk Children

The incidence, prevalence, mortality, and demographic profiles of the palivizumab-indicated populations are presented in the following tables: RSV infection among premature infants (children born at ≤ 35 weeks of gestation and less than 6 months of age at the onset of the RSV season) (Table 1), RSV infection among children less than 2 years of age and requiring treatment for BPD/chronic lung disease (CLD, or CLD of prematurity [CLDP]) within the last 6 months (Table 2), and RSV infection among children less than 2 years of age and with HSCHD (Table 3). In all patient populations, hospitalization due to RSV disease was used as an indicator for incidence of serious lower respiratory tract infection.

Epidemiology of RSV hospitalization among children with BPD or CLD is presented in Table 2. Chronic lung disease in children represents a heterogeneous group of many distinct clinicopathological entities. Bronchopulmonary dysplasia of prematurity is a subset of the broader CLD group (Rossi 2005), the definition of which has changed overtime (Kair 2012). Data presented below captures both BPD and CLD. In some publications, it was not possible to separate them.

Table 1. Epidemiology of RSV Disease Among Infants (< 6 Months of Age) with a History of Premature Birth (≤ 35 Weeks Gestational Age)

Incidence	**NORTH AMERICA:** United States: From a retrospective study conducted among Tennessee, USA Medicaid infants born at < 29 weeks gestation, the incidence of hospitalization due to RSV was 187.5/1000 child-years among those ≤ 6 months of age and 92.1/1000 child-years among infants 6 to 11 months of age (Boyce 2000). In other studies conducted in the US, the incidence rates of hospitalization due to RSV infection in premature infants (≤ 32 weeks gestational age) have been reported to be between 10.7% and 20% (Atkins 2000, Stevens 2000, Law 2002). Canada: The incidence of hospitalization due to RSV infection in premature infants (≤ 6 months of age) born between 33 and 35 weeks gestation was 3.6% (Law 2004). Infants born between 23 and 32 weeks gestational age were 2.6 times more likely to be hospitalized for RSV infection than those born at 33 to 36 weeks gestation (odds ratio [OR] = 2.6, 95% confidence interval [CI] = 1.4 to 5.1) (Joffe 1999). **EUROPE:** United Kingdom: 34.9% of all premature infants (≤ 32 weeks gestation) in a London hospital were rehospitalized with a confirmed RSV infection before a corrected age of 1 year (Broughton 2005). Investigators using a hospital-based cohort study in Shropshire found the hospitalization rate from RSV among infants ≤ 6 months of age and between 24 to 32 and 33 to 36 weeks gestational age to be 7.5% and 6.6%, respectively (Deshpande 2003). Spain: In a large prospective epidemiologic study which included almost 10% of the entire Spanish population of preterm infants ≤ 32 weeks of gestation, the rate of readmission for RSV disease was estimated to be 13.4%. (Carbonell-Estrany 2000). An additional study conducted in Spain reported the incidence rate as 3.7% in premature infants born between 32 and 35 weeks gestation (Figueras-Aloy 2008). Switzerland: The incidence of hospitalization due to RSV infection was reported to be 60.0 per 1,000 infants < 12 months of age with a history of prematurity (≤ 35 weeks gestation) (Duppenthaler 2001). Denmark: Using national data, the incidence of hospitalization from RSV infection in infants born < 28 weeks gestation or < 1000 g was 16.0% (Pedersen 2003). Ireland: Of the 2,113 RSV-positive samples from 1,790 paediatric patients in the neonatal intensive care unit (NICU), children born ≤ 35 weeks of gestation had readmission rate of 6.4%. Children born ≤ 32 weeks of gestation had a readmission rate of 7.3% (McCormick 2002).
Prevalence	Our review of the literature found no studies of the prevalence of RSV infection in infants < 6 months of age with a history of premature birth.

Table 1. Epidemiology of RSV Disease Among Infants (< 6 Months of Age) with a History of Premature Birth (≤ 35 Weeks Gestational Age) (Continued)

<table>
<tr><td>Demographics of target population</td><td>NORTH AMERICA:
United States: RSV hospitalized children 71.8% male, 28.2% female (< 32 weeks gestation, mean age: 27.6 weeks) (Atkins 2000).
Canada: RSV hospitalized children 54.7% male, 45.3% female (33 to 35 weeks gestation, ≤ 6 months of age) (Law 2004).

EUROPE:
United Kingdom: RSV hospitalized children in Scotland were 55.3% male (< 33 weeks gestation (Zeitlin 2002).
Spain: RSV hospitalized children 59.9% male, 40.1% female (32 to 35 weeks gestation, < 12 months of age) (Figueras-Aloy 2008).</td></tr>
<tr><td>Mortality in target indication</td><td>Canada: The mortality rate was 8.1% in infants < 1 year of age and 32 to 35 weeks gestation hospitalized for RSV infection (Sampalis 2003).
United States: RSV-related mortality rates were 61.8 per 100,000 infants born at ≤ 35 weeks gestation and < 2500 g birth weight (Leader 2003).</td></tr>
<tr><td>Risk factors for RSV disease</td><td>Approximately 40% of infants hospitalized with RSV infection have an underlying condition such as low birth weight or cardiopulmonary disease (Hall 2001).
Following table is a list about the risk of hospitalization from RSV:
<table>
<tr><th>Prematurity Risk Group</th><th>Adjusted Incidence Rate Ratio* (95% CI)</th></tr>
<tr><td>< 29 weeks gestational age</td><td>2.4 (1.8 – 3.3)</td></tr>
<tr><td>29 to < 33 weeks gestational age</td><td>2.2 (1.8 – 2.7)</td></tr>
<tr><td>33 to < 36 weeks gestational age</td><td>1.8 (1.6 – 2.6)</td></tr>
</table>
* Compared to children ≥ 37 weeks of gestation.

Data from the Danish Respiratory Syncytial Virus Database illustrate that boys are 1.3 times more likely to be infected with RSV than girls, and that the incidence of infection declines with increasing age (Stensballe 2002). In addition, living with school age siblings, exposure to tobacco smoke, and a chronologic age of < 3 months at the onset of the RSV season were also identified as potential risk factors (Simoes 2003). A case-control study also identified chronological age at the beginning of RSV season (adjusted odds ration [aOR] = 8.46; 95% CI: 3.09 – 23.18); birth weight category (aOR = 7.70; 95% CI: 1.29 – 45.91); birth order (aOR = 1.92; 95% CI: 1.21 – 3.06) as risk factors for RSV hospitalization (Rossi 2007).</td></tr>
</table>

Table 1. Epidemiology of RSV Disease Among Infants (< 6 Months of Age) with a History of Premature Birth (≤ 35 Weeks Gestational Age) (Continued)

Risk factors for RSV disease (continued)	Other less well documented risk factors include the following: recurrent wheezing, pulmonary function abnormalities, airway hyper-reactivity, chronic reactive airway disease, nosocomial infection, viral co-infection, increased length of hospitalization, mechanical ventilation. Some of these listed conditions may also be the consequences of RSV infection.
Treatment options	No products, except for aerosolized ribavirin, are approved for treatment of RSV infection; however, clinical management of RSV infection is usually supportive care as indicated by the clinical condition of the patient. Oxygen, beta-2 agonists, racemic epinephrine, aerosolized recombinant human DNase, inhaled and systemic corticosteroids, ribavirin, nasopharyngeal suctioning, helium-oxygen gas mixtures, nitric oxide, extracorporeal membrane oxygenation, nebulized hypertonic saline, fluids.

Table 2. Epidemiology of RSV Disease Among Children (< 2 Years of Age) with Bronchopulmonary Dysplasia/Chronic Lung Disease

Incidence	**NORTH AMERICA:** In a Canadian study, 6% of all infants hospitalized with RSV infection had underlying CLD (Wang 1997). In a US study, 14% of children < 2 years of age admitted to the PICU for RSV infections had underlying CLD (Buckingham 2001). **EUROPE:** A retrospective cohort study of children born in Finland from 1991 – 2000 found that 12% of children hospitalized with RSV infection had underlying CLD (Heikkinen 2005). In a review of 14 studies of infants born in North American and Europe, the hospitalization rate of RSV-infected children with CLD who were < 2 years of age was 18.4% (Simoes 2002). In a multicenter, randomized, double-blind clinical trial conducted in the US, Canada, and the UK among children < 24 months of age and a clinical diagnosis of BPD found that the hospitalization rate due to RSV was 12.8% in the placebo group compared with 7.9% in the palivizumab group (The IMpact-RSV Study Group 1998). The incidence rate of hospitalizations due to RSV-confirmed infection in Switzerland was 160.0 per 1,000 infants under 12 months of age with CLD of prematurity (≤ 35 weeks gestation) (Duppenthaler 2001). A retrospective cohort study conducted in Denmark found that 30% of all infants either born at gestational age < 28 weeks or born with a birth weight < 1000g also had BPD/CLD and were rehospitalized for RSV infection (Pedersen 2003). A prospective cohort study conducted in Germany found that 15% of children < 1 year of age with CLD of prematurity (< 35 weeks gestation) were subsequently rehospitalized for RSV-related infection (Liese 2003). An additional prospective study in Germany found that the hospitalization rate for RSV infection was 26% among premature infants (< 37 weeks gestation) (Simon 2007). A prospective study in London found that 39% of premature infants (< 32 weeks gestation and corrected age of 1 year) with BPD were rehospitalized for RSV infection (Broughton 2005). A retrospective study in Spain found that the hospitalization rate for RSV infection was 19.7% in premature infants (≤ 32 weeks gestation and ≤ 6 months at onset of RSV season) (Pedraz 2003). United Kingdom: 15.6% of preterm infants (< 37 weeks gestation) with CLD had an RSV related hospitalization before their second birthday (Deshpande 2003). Austria: A prospective cohort study found that 4% of all premature infants < 1 year of age and 29 to 32 weeks gestation hospitalized for RSV infection also had BPD (Resch 2006).

Table 2. Epidemiology of RSV Disease Among Children (< 2 Years of Age) with Bronchopulmonary Dysplasia/Chronic Lung Disease (Continued)

Prevalence	Our review of the literature found no studies of the prevalence of RSV infection in children < 2 years of age with CLD.
Demographics of target population	Our review of the literature found no studies comparing demographic profiles of children < 2 years of age with chronic lung disease who are at risk of developing RSV disease.
Mortality in target indication	Canada: RSV-related mortality rates were 3.5% in infants with CLD (Navas 1992).
Risk factors for RSV disease	Risk of RSV hospitalization shows about a 10-fold increase in patients with BPD compared to those without BPD (Hall 2001). In addition, living with school age siblings, exposure to tobacco smoke, and a chronologic age of < 3 months at the onset of the RSV season were also identified as potential risk factors (Simoes 2003). A case-control study also identified chronological age at the beginning of RSV season (aOR = 8.46; 95% CI: 3.09 – 23.18); birth weight category (aOR = 7.70; 95% CI: 1.29 – 45.91); birth order (aOR = 1.92; 95% CI: 1.21 – 3.06) as risk factors for RSV hospitalization (Rossi 2007). Other less well documented risk factors include the following: recurrent wheezing, pulmonary function abnormalities, airway hyper-reactivity, chronic reactive airway disease, nosocomial infection, viral co-infection, increased length of hospitalization, mechanical ventilation. Some of these listed conditions may also be the consequences of RSV infection.
Treatment Options	No products, except for aerosolized ribavirin, are approved for treatment of RSV; however, clinical management of RSV infection is usually supportive care as indicated by the clinical condition of the patient. Oxygen, beta-2 agonists, racemic epinephrine, aerosolized recombinant human DNase, inhaled and systemic corticosteroids, ribavirin, nasopharyngeal suctioning, helium-oxygen gas mixtures, nitric oxide, extracorporeal membrane oxygenation, nebulized hypertonic saline, fluids.

Table 3. Epidemiology of RSV Disease Among Children (< 2 Years of Age) with Hemodynamically Significant Congenital Heart Disease

Incidence	**NORTH AMERICA**: United States: The incidence of hospitalizations due to confirmed RSV infection among infants with congenital heart disease (CHD) in a study of Medicaid patients in Tennessee was 92.2 per 1,000 children < 12 months of age (Boyce 2000). Published data from a multicenter, randomized, double-blind, placebo-controlled trial of 1287 children with HSCHD reported an RSV hospitalization rate of 9.7% (63/648) (Feltes 2003). One study used the California statewide hospital discharge data from the California Office of Health Planning and Development (Chang 2010) that defined HSCHD using specific ICD 9 diagnosis and procedure codes. This study compared incidence of RSV hospitalization between pre-palivizumab era vs post palivizumab era. Of all RSV hospitalizations, 3.0% were among children with CHD, and 0.50% among children with HSCHD. HSCHD children accounted for 0.56% of RSV hospitalizations in 2000 – 2002, compared to 0.46% RSV hospitalizations in 2004 – 2006. That represents a 19% reduction in RSV hospitalizations among HSCHD children after 2003. The 19% decrease in RSV hospitalizations equates to 7 fewer hospitalizations (76 hospital days) per year among HSCHD children. In a large hospital cardiology database, Altman (Altman 2000) found 6% of all RSV hospitalization was associated with significant CHD. Canada: The hospitalization rate for RSV infection among children < 2 years of age with CHD was 16.7% (MacDonald 1982). **EUROPE:** Switzerland: The RSV hospitalization rates for children with CHD was 2.5 per 100 child-years (95% CI: 0.8 – 5.6) in children < 6 months of age, 2.0 per 100 child-years (95% CI: 0.8 – 5.6) in children < 12 months of age, 0.5 per 100 child-years (95% CI: 0.1 – 1.8) in children 12 to 24 months of age, and 1.3 per 100 child-years (95% CI: 0.6 – 2.3) in children < 24 months of age (Duppenthaler 2004). Ireland: The incidence rate of hospitalization due to RSV infection among infants (> 35 weeks gestation) with CHD was 14% (McCormick 2002). **REST OF THE WORLD:** Japan: The incidence rate of rehospitalization among children < 2 years of age with CHD was 4.42% (Saji 2008).

Table 3. Epidemiology of RSV Disease Among Children (< 2 Years of Age) with Hemodynamically Significant Congenital Heart Disease (Continued)

Prevalence	A review of the literature found no studies of the prevalence of RSV infection in children (< 2 years of age) with HSCHD.
Demographics of target population	A review of the literature found no studies comparing demographic profiles of RSV infection in children (< 2 years of age) with HSCHD.
Mortality in target indication	Between 2.5% and 3.4% of infants with CHD who are hospitalized with RSV disease will die from complications of RSV infection (Feltes 2003). United States: The RSV-related mortality rate was 2.5% in infants with CHD (Moler 1992). Canada: The RSV-related mortality rate was 3.4% in infants with CHD (Navas 1992, MacDonald 1982). In a multicenter study conducted in the US, Canada, Sweden, Germany, Poland, France and the UK found the RSV-related mortality rate among children < 24 months of age with CHD was 4.2% (Feltes 2003).
Risk factors for RSV infection	Risk of RSV hospitalization shows about a 3-fold increase in patients with CHD compared to those without CHD (Hall 2001). Infants hospitalized in the first few months of life with uncorrected cyanotic CHD are at particular risk. More complicated or serious illness has been associated with cyanotic congenital heart conditions and those accompanied by pulmonary hypertension. Nevertheless, all types of congenital cardiac abnormalities with functional impairment have been associated with increased risk for hospitalization with RSV infection, especially if the congenital cardiac abnormality needed surgical correction (Hall 2010). Children, living with school age siblings, exposure to tobacco smoke and a chronologic age of < 3 months at the onset of the RSV season were also identified as potential risk factors in all premature children (Simoes 2003). A case-control study also identified chronological age at the beginning of RSV season (aOR = 8.46; 95% CI: 3.09 – 23.18); birth weight category (aOR = 7.70; 95% CI: 1.29 – 45.91); birth order (aOR = 1.92; 95% CI: 1.21 – 3.06) as risk factors for RSV hospitalization (Rossi 2007). Other less well documented risk factors include the following: recurrent wheezing, pulmonary function abnormalities, airway hyper-reactivity, chronic reactive airway disease, nosocomial infection, viral co-infection, increased length of hospitalization, mechanical ventilation. Some of these listed conditions may also be the consequences of RSV.

Table 3. Epidemiology of RSV Disease Among Children (< 2 Years of Age) with Hemodynamically Significant Congenital Heart Disease (Continued)

Main treatment options	No products, except for aerosolized ribavirin, are approved for treatment of RSV; however, clinical management of RSV infection is usually supportive care as indicated by the clinical condition of the patient. Oxygen, beta-2 agonists, racemic epinephrine, aerosolized recombinant human DNase, inhaled and systemic corticosteroids, ribavirin, nasopharyngeal suctioning, helium-oxygen gas mixtures, nitric oxide, extracorporeal membrane oxygenation, nebulized hypertonic saline, fluids.

SI.2 Concomitant Medication(s) in the Target Population

Concomitant medications in the target paediatric patient population have been consistent with the subject's developmental age and/or underlying condition or disease. The most commonly used medications by indicated patient populations are listed in Table 4.

Table 4. Concomitant Medications

Indication by sub-population	Co-prescribed medicinal products
Children born at 35 weeks of gestation or less and less than 6 months of age at the onset of the RSV season.	Antibiotics Diuretics Glucocorticosteroids (systemic or inhaled) Bronchodilators Immunoglobulins Surfactants Vaccines
Children less than 2 years of age and requiring treatment for BPD within the last 6 months.	Diuretics Corticosteroids Bronchodilators Immunoglobulins Surfactants Vaccines
Children less than 2 years of age and with HSCHD.	Antibiotics Antifungals Ribavirin Bronchodilators Cardiac inotropes Diuretics Immunoglobulins Analgesics Vaccines

SI.3 Important Co-Morbidities Found in the Target Population

The morbidities in the target paediatric population are presented per patient population. The significant co-morbid conditions have been characterised in as much detail as available.

SI.3.1 Co-Morbidities among Premature Infants (< 6 Months of Age, ≤ 35 Weeks Gestational Age)

Comorbidities that may occur in premature infants (< 6 months of age at the onset of RSV season) born at ≤ 35 weeks gestation who are at risk for hospitalization with serious lower

respiratory tract disease caused by RSV include BPD/CLD (Table 5), apnea of prematurity (Table 6), paediatric gastroesophageal reflux disease (Table 7), sudden infant death syndrome (Table 8), sepsis/infection (Table 9), necrotizing enterocolitis (NEC) (Table 10), patent ductus arteriosus (Table 11), respiratory distress syndrome (Table 12), and cerebral palsy (Table 13).

Table 5. Co-Morbid Bronchopulmonary Dysplasia in Infants (< 6 Months of Age) with a History of Premature Birth (≤ 35 Weeks Gestational Age)

Incidence in target indication	**USA:** In a nationally representative sample of 16 participating centers of the National Institute of Child Health & Human Development Neonatal Research Network study, the incidence of BPD was: 42%, 25%, 11%, and 4% in infants with birth weight of 501 – 750g, 751 – 1000g, 1001 – 1250g, and 1251 – 1500 g, respectively (Fanaroff 2007). Although, these rates were not presented by gestational age, given the strong correlation between the low birth weight and gestational age, the majority of the above population are likely to include children ≤ 35 weeks of gestation. **EUROPE:** In premature infants, the incidence of BPD was greater in males compared with females (Farstad 2011, Gortner 2011) with an OR = 1.5 and a 95% CI: 1.2 – 1.8 (Gortner 2011). Norway: In infants born between 22 and 25 weeks of gestation, the incidence of BPD was 67.3%. The incidence of BPD in infants between 26 and 30 weeks of gestation was 36.6% (Farstad 2011). Sweden: In infants < 27 weeks of gestation, the incidence of BPD was 73% (EXPRESS 2010).
Prevalence in target indication	Norway: In infants between 22 and 25 weeks gestation, the prevalence of BPD was 67.3% compared with 36.6% ($P = 0.0004$) in infants 26 to 30 weeks gestation (Farstad 2011).
Mortality in target indication	Information on mortality is very limited. Neonatal Research Network for very low birth weight (VLBW) Registry in USA reported 89% mortality among 195 infants weighing 401 to 500 grams with nearly all survivors developing CLD (Lemons 2001). Northway and co-workers showed very high mortality (67%) from CLD in infants who had received high concentrations of oxygen and mechanical ventilation from birth (Kinsella 2006). In a study including 35 infants with severe BPD at a single center in Michigan, there were 19 deaths (54%) (Shankaran 1984).

Table 6. Co-Morbid Apnea of Prematurity in Infants (< 6 Months of Age) with a History of Premature Birth (≤ 35 Weeks Gestational Age)

Incidence in target indication	**NORTH AMERICA:** The incidence of apnea of prematurity is found in > 50% of premature infants and nearly 100% of infants who weigh < 1000 g at birth (Finer 2006). Approximately 70% of premature infants < 34 weeks gestation have clinically significant apnea, bradycardia, or O_2 desaturation (Finer 2006). United States: In a 5-year retrospective study, 84% of 161 premature neonates (mean gestational age: 27 weeks, range: 19 to 34 weeks) showed symptoms of apnea within 84 hours of admission to a hospital neonatal intensive care unit (Alden 1972). **EUROPE:** Turkey: In infants born between 34 and 37 weeks of gestation, the incidence of apnea was 1.6% (Kalyoncu 2010). No other information in children < 34 weeks of gestation is available in Europe.
Prevalence in target indication	United States: The prevalence of apnea of prematurity decreases with increasing gestation age – 0.4% at 35 weeks gestation and 0.2% at 35 weeks gestation (Hibbard 2010).
Mortality in target indication	Limited information is available on mortality of children with apnea of prematurity. One study based on data prior to 1972 showed a very high mortality rate (85%) for apnea of prematurity (Alden 1972).

Table 7. Co-Morbid Paediatric Gastroesophageal Reflux Disease in Infants (< 6 Months of Age) with a History of Premature Birth (≤ 35 Weeks Gestational Age)

Incidence in target indication	In premature infants with a mean gestational age of 30 weeks (range unknown), the incidence of gastroesophageal reflux disease (GERD) was 63% (Marino 1995).
Prevalence in target indication	The prevalence of GERD in preterm infants with a maximum age of 2 years (range unknown) was 26.7% (Kase 2009) with a decreased frequency of GERD with increasing gestation age ($P < 0.05$).
Mortality in target indication	A review of the literature found no studies of mortality from gatroesophageal reflux disease in premature infants.

Table 8. Co-Morbid Sudden Infant Death Syndrome in Infants (< 6 Months of Age) with a History of Premature Birth (≤ 5 Weeks Gestational Age)

Incidence in target indication	United States: In premature infants born between 24 and 32 weeks gestation, the incidence of sudden infant death syndrome (SIDS) was 2.2 per 1000 births (Malloy 2004).
Prevalence in target indication	United States: An increased risk of SIDS was reported with decreasing gestation age. Compared with infants born between 40 to 42 weeks gestation, infants born between 29 to 32 weeks had an increased risk of SIDS with an OR = 2.9, 95% CI: 2.6 – 3.2; between 33 to 35 weeks OR = 2.1, 95% CI: 1.9 – 2.3; and between 36 to 37 weeks OR = 1.5, 95% CI: 1.2 – 1.8 (Malloy 2004).
Mortality in target indication	United States: In premature infants born between 24 and 32 weeks gestation, the incidence of SIDS was 2.2 per 1000 births (Malloy 2004).

Table 9. Co-Morbid Sepsis/Infection in Infants (< 6 Months of Age) with a History of Premature Birth (≤ 35 Weeks Gestational Age)

Incidence in target indication	Austria: A retrospective cohort analysis of 42 premature infants (< 37 weeks gestational age) hospitalized due to RSV infection identified concurrent nosocomial bacterial infections in 9.5% of the preterm infants compared with 3.1% of full-term infants (relative risk [RR] = 3.1, 95% CI = 1.3–7.6) (Resch 2006). Switzerland: In infants between 24 and 27 weeks of gestation, 25% were diagnosed with sepsis (Schlapbach 2011). United States: The rate of sepsis in infants, 28 weeks gestation age was 53% (Kobaly 2008). China: The incidence of sepsis was 5.9% in late preterm infants born between 34 and 36 weeks gestation (Ma 2009).
Prevalence in target indication	A review of the literature found no studies of the prevalence of sepsis/infection in premature infants ≤ 35 weeks gestation hospitalized for RSV.
Mortality in target indication	A review of the literature found no studies of mortality due to sepsis/infections in premature infants ≤ 35 weeks gestation hospitalized for RSV.

Table 10. Co-Morbid Necrotizing Enterocolitis in Infants (< 6 Months of Age) with a History of Premature Birth (≤ 35 Weeks Gestational Age)

<table>
<tr><td>Incidence in target indication</td><td>United States: In infants with a gestational age < 28 weeks, the incidence of NEC was 7% (Kobaly 2008). Neonatal Research Network for VLBW Registry in USA reported incidence of NEC to be 7% among children with birth weight 500 – 1500 grams (Lemons 2001).
Canada: In a population-based cohort of 16669 infants with gestational age (GA) < 33 weeks, admitted to 25 NICUs participating in Canadian Neonatal Network, the incidence rate of NEC was 5.1% (Yee 2012).
Sweden: In infants with a gestational age < 27 weeks, the incidence of NEC was 5.8% (EXPRESS Group 2010).
Turkey: In infants with a gestational age between 34 and 36 weeks, the incidence of NEC was 4.8% (Kalyoncu 2010).</td></tr>
<tr><td>Prevalence in target indication</td><td>A review of the literature found no studies of the prevalence of NEC in premature infants.</td></tr>
<tr><td>Mortality in target indication</td><td>While NEC is associated with mortality, this association increases with decreased gestational age. A retrospective cohort study from California reported that the mortality from NEC ranged between 6.4% among children born at gestational age 34 to 35.9% among those born at 24 weeks of gestation (Jelin 2012).
United States: Among very low birth weight infants, the risk of mortality from NEC increased with decreasing birth weight as shown in the table below (Fizgibbons 2009).
<table>
<tr><th>Birth Weight (g)</th><th>NEC Mortality (%)</th></tr>
<tr><td>501 – 750</td><td>42.0</td></tr>
<tr><td>751 – 1,000</td><td>29.4</td></tr>
<tr><td>1,001 – 1,250</td><td>21.3</td></tr>
<tr><td>1,251 – 1,500</td><td>15.9</td></tr>
</table>
The mortality rate among low birth weight neonates (< 2,500 g) hospitalized for NEC was 15.9% (Holman 2006).
Among neonates born between 23 and 34 weeks gestation who were hospitalized for NEC, the rate of mortality was 12% (Guthrie 2003).</td></tr>
</table>

Table 11. Co-Morbid Patent Ductus Arteriosus in Infants (< 6 Months of Age) with a History of Premature Birth (≤ 35 Weeks Gestational Age)

Incidence in target indication	United States: In infants with a gestational age < 28 weeks, the incidence of patent ductus arteriosus (PDA) was 74% (Kobaly 2008). Sweden: In infants with a gestational age < 27 weeks, the incidence of PDA was 61% (EXPRESS Group). In another study, infants with a mean gestational age of 29 weeks had an incidence of PDA of 20% (Hentschel 2005).
Prevalence in target indication	A review of the literature found no studies of the prevalence of patent ductus arteriosus in premature infants.
Mortality in target indication	A review of the literature found no studies of the mortality from patent ductus arteriosus in premature infants.

Table 12. Co-Morbid Respiratory Distress Syndrome in Infants (< 6 Months of Age) with a History of Premature Birth (≤ 35 Weeks Gestational Age)

<table>
<tr>
<td>Incidence in target indication</td>
<td>
NORTH AMERICA:
Canada: In infants of gestation age < 33 weeks, 62% had respiratory distress syndrome (RDS) (Yee 2012).
The incidence of RDS among neonates with birth weights < 2500 g in the US and Canada is 10 to 15%, as reported in one literature review (Ishisaka 1996).
Literature review showed that RDS affects 33% of infants born at 28 to 34 weeks gestation, but occurs in less than 5% of those born after 34 weeks gestation (Hermansen 2007).
United States: In a population-based retrospective study of 46,246 births (Strandjord 2000), the incidence of RDS among white, black, Native American, and Hispanic infants by gestational age was estimated to be as follows:
<table>
<tr><th>Gestational Age</th><th>White</th><th>Black</th><th>Native American</th><th>Hispanic</th></tr>
<tr><td>< 28 weeks</td><td>51.1%</td><td>52.5%</td><td>68.2%</td><td>53.3%</td></tr>
<tr><td>28 to 29 weeks</td><td>61.8%</td><td>63.2%</td><td>50.0%</td><td>33.3%</td></tr>
<tr><td>30 to 31 weeks</td><td>37.0%</td><td>37.5%</td><td>33.3%</td><td>30.0%</td></tr>
<tr><td>32 to 33 weeks</td><td>18.0%</td><td>11.9%</td><td>12.5%</td><td>7.8%</td></tr>
<tr><td>34 to 35 weeks</td><td>10.8%</td><td>2.7%</td><td>6.1%</td><td>4.5%</td></tr>
</table>
EUROPE:
Sweden: In a retrospective study of all preterm infants (< 33 weeks gestation) born and hospitalized in a Swedish neonatal intensive care unit between 1985 and 1994, investigators compared the incidence of RDS between infants with birth weights appropriate for gestational age (AGA), defined as birth weight + 24% (+2 SD), and infants with birth weights small for gestational age (SGA). The frequency of RDS by gestational age in SGA and AGA infants, respectively, were reported as follows: 25 weeks, 100% vs. 60%; 26 weeks, 69% vs. 71%; 27 weeks, 76% vs. 58%; 28 weeks, 77% vs. 63%; 29 weeks, 55% vs. 59%; 30 weeks, 26% vs. 42%; 31 weeks, 15% vs. 38%; 32 weeks, 15% vs. 25% (Ley 1997). A large difference observed in the incidence of RDS in very premature SGA children compared to AGA children points to the importance of both low birth weight and gestational age in the incidence of RDS.
</td>
</tr>
</table>

Table 12. Co-Morbid Respiratory Distress Syndrome in Infants (< 6 Months of Age) with a History of Premature Birth (≤ 35 Weeks Gestational Age) (Continued)

Incidence in target indication (continued)	Finland: In 529 infants born at 22 weeks gestation, 76% were diagnosed with RDS (Tommiska 2001). Italy: The incidence of RDS by gestational age in a 12-month prospective study of 63,537 infants was reported as follows: 22 weeks, 100%; 23 weeks, 100%; 24 weeks, 54.5%; 25 weeks, 43.8%; 26 weeks, 46.7%; 27 weeks, 47.9%; 28 weeks, 45.6%; 29 weeks, 47.3%; 30 weeks, 35.9%; 31 weeks, 33.4%; 32 weeks, 25.6%; 33 weeks, 11.9%; 34 weeks, 6.4%; 35 weeks 4.1% (Rubaltelli 1998b). From the trend in RDS incidence by gestational age presented above, one can conclude that RDS is almost a certainty in very premature born children and as expected the incidence decreases with greater gestational age. An additional 3-month prospective study of neonatal respiratory disorders in 17,192 Italian infants born in 65 hospitals in 17 Italian regions estimated the incidence rate of RDS by gestational age as follows: < 27 weeks, 41.5%; 27 to 28 weeks, 54.0%; 29 to 30 weeks, 44.6%; 31 to 32 weeks, 37.2%; 33 to 34 weeks, 12.0% (Rubaltelli 1998a). France: The incidence rate of RDS among 2,181 premature neonates by gestational age was reported as follows: 30 weeks, 43.8%; 31 weeks, 32.8%; 32 weeks, 23.9%; 33 weeks, 13.6%; 34 weeks, 2.6% (Marret 2007). **REST OF WORLD**: China: In infants born between 34 and 36 weeks gestation, the incidence of RSD was 42.1%. Compared with full-term infants, these infants had an OR = 2.1, 95% CI: 1.9 – 2.4 (Ma 2009).
Prevalence in target indication	A review of the literature found no studies of the prevalence of respiratory distress syndrome in premature infants ≤ 35 weeks gestation.
Mortality in target indication	Italy: The case fatality rate of RDS among newborn infants by gestational age was as follows: 24 weeks, 77%; 27 weeks, 46.9%; 30 weeks, 16.3% (Rubaltelli 1998b). Italy: The case fatality rate of RDS among newborn infants by gestational age was reported as follows: < 27 weeks, 90.0%; 27 to 28 weeks, 52.9%; 29 to 30 weeks, 22.0%; 31 to 32 weeks, 3.4%; 33 to 34 weeks, 7.1% (Rubaltelli 1998a). China: The in-hospital rate of mortality for RDS in infants born between 34 and 36 weeks gestation was 0.8% compared with 0.4% for full-term infants (Ma 2009).

Table 13. Co-Morbid Cerebral Palsy in Infants (< 6 Months of Age) with a History of Premature Birth (≤ 35 Weeks Gestational Age)

Incidence in target indication	**NORTH AMERICA:** In infants of gestational age < 27 weeks, the incidence of cerebral palsy was 2.1% (Natarajan 2012).
Prevalence in target indication	A review of the literature found no studies of the prevalence of cerebral palsy in premature children.
Mortality in target indication	A review of the literature found no studies of the mortality from cerebral palsy in premature children.

SI.3.2 Co-Morbidities Among Children with Bronchopulmonary Dysplasia (< 2 Years of Age)

Co-morbidities that may occur in children with BPD (< 2 years of age) with or without prematurity who are at risk for hospitalization with serious lower respiratory tract disease caused by RSV include cerebral palsy (Table 14), persistent respiratory distress syndrome (Table 15), infection (Table 16), pulmonary hypertension/edema (Table 17), and wheezing (Table 18).

Table 14. Co-Morbid of Cerebral Palsy in Children (< 2 Years of Age) with a History of Bronchopulmonary Dysplasia

Incidence in target indication	**NORTH AMERICA:** In infants of gestational age < 27 weeks, the incidence of cerebral palsy among those with BPD was 7% (Natarajan 2012). Among infants of very low birth weight, 15% of those with BPD had comorbid cerebral palsy (Skidmore 1990).
Prevalence in target indication	A review of the literature found no studies of the prevalence of cerebral palsy in children with BPD.
Mortality in target indication	A review of the literature found no studies of the mortality from cerebral palsy in children with BPD.

Table 15. Co-Morbid Respiratory Distress Syndrome in Children (< 2 Years of Age) with a History of Bronchopulmonary Dysplasia

Incidence in target indication	**REST OF WORLD:** Australia: In infants born between 26 to 33 weeks gestation who were admitted to the neonatal intensive care unit, the rate of RDS was 98% in infants with BPD and 54% among those without BPD (Gray 1995). Korea: In infants born after 32 weeks gestation, the rate of RDS was 58.6% (An 2010).
Prevalence in target indication	A review of the literature found no studies of the prevalence of RDS in children with BPD.
Mortality in target indication	A review of the literature found no studies of the mortality from persistent respiratory distress syndrome in children with BPD.

Table 16. Co-Morbid Infection in Children (< 2 Years of Age) with a History of Bronchopulmonary Dysplasia

Incidence in target indication	**NORTH AMERICA:** In infants born at less than 27 weeks gestation with low birth weight, a higher rate of blood born infection was observed in infants with BPD (54%) compared with infants without BPD (33.5%) during their NICU follow-up (Nataranjan 2012). United States: In a nationally representative sample of 16 participating centers of the National Institute of Child Health & Human Development Neonatal Research Network study, the incidence of BPD was: 42%, 25%, 11%, and 4% in infants with birth weight of 501 – 750, 751 – 1,000, 1,001 – 1,250, and 1,251 – 1,500 g, respectively (Fanaroff 2007). Although, these rates were not presented by gestational age, given the strong correlation between the low birth weight and gestational age, the majority of the above population is likely to include children ≤ 35 weeks of gestation (Fanaroff 2007). **EUROPE:** In infants born at less than 33 weeks gestation, a higher rate of postnatal infection ($P = 0.03$) was reported in infants with BPD (100%) compared with infants without BPD (74%) (May 2011).
Prevalence in target indication	A review of the literature found no studies of the prevalence of infection in children with BPD.
Mortality in target indication	A review of the literature found no studies of mortality from infection in children with BPD.

Table 17. Co-Morbid Pulmonary Hypertension/Edema in Children (< 2 Years of Age) with a History of Bronchopulmonary Dysplasia

Incidence in target indication	**NORTH AMERICA:** In infants born at a median gestational age of 26 weeks, infants with pulmonary hypertension were significantly more likely ($P < 0.01$) to have BPD compared with infants without BPD (Bhat 2012). Moreover, BPD was more severe in infants with pulmonary hypertension.
Prevalence in target indication	**REST OF WORLD:** Korea: In infants born at less than 32 weeks gestation with BPD, pulmonary hypertension was also diagnosed in 25% of the infants. Moreover, the pulmonary hypertension was more severe in the presence of BPD ($P < 0.01$) (An 2010).
Mortality in target indication	**REST OF WORLD:** In a study including 116 preterm infants born at less than 32 weeks, 3 infant deaths were attributed to pulmonary hypertension (An 2010).

Table 18. Co-Morbid Wheezing in Children (< 2 Years of Age) with a History of Bronchopulmonary Dysplasia

Incidence in target indication	**NORTH AMERICA:** Rates of wheezing were compared among children at age 7 who were born premature between 24 and 31 weeks of gestation, with and without BPD, and children born full-term between 38 to 42 weeks of gestation. The rate of wheezing was 30% in children born prematurely with BPD ($P < 0.001$ compared to full term children), 24% in children born prematurely without BPD ($P < 0.005$ compared to full term children), and 7% in children born full term (Gross 1998). **REST OF WORLD:** Australia: Rates of wheezing were 37% in school age children who were born prematurely between 26 and 33 weeks gestation. The rate in infants born prematurely with BPD did not differ significantly ($P = 0.35$) from infants born prematurely without BPD (Gray 2008).
Prevalence in target indication	A review of the literature found no studies of the prevalence of wheezing in children with BPD.
Mortality in target indication	A review of the literature found no studies of mortality from wheezing in children with BPD.

SI.3.3 Co-Morbidities Among HSCHD Children (< 2 Years of Age)

Co-morbidities that may occur in children with HSCHD children (< 2 years of age) who are at risk for hospitalization with serious lower respiratory tract disease caused by RSV include asthma (Table 19), cerebral palsy (Table 20), developmental and functional outcomes (Table 21), Down syndrome (Table 22), and extracardiac anomalies (Table 23). If available, data on HSCHD were presented, otherwise, information on overall CHD was presented.

Table 19. Co-Morbidity of Asthma in Children (< 2 Years of Age) with a History of HSCHD

Incidence in target indication	A review of the literature found no studies of incidence of asthma in children with HSCHD.
Prevalence in target indication	**EUROPE:** Finland: In infants who were surgically-treated for CHD, the rate of asthma was 4.6%, as determined from prescription records, compared with 2.8% for sex-matched controls without CHD (RR = 1.8; 95% CI: 1.5 – 2.1) (Nieminen 2010).
Mortality in target indication	A review of the literature found no studies of mortality associated with asthma in children with HSCHD.

Table 20. Co-Morbid Cerebral Palsy in Children (< 2 Years of Age) with a History of HSCHD

Incidence in target indication	**NORTH AMERICA:** United States: The rate of moderate to severe cerebral palsy was 12% (6/49) in patients with CHD and 7% (544/7,778) in subjects without CHD (Pappas 2012). However, proportion of HSCHD is unknown.
Prevalence in target indication	A review of the literature found no studies of prevalence of cerebral palsy in children with HSCHD.
Mortality in target indication	A review of the literature found no studies of mortality from cerebral palsy in children with CHD.

Table 21. Co-Morbid Developmental and Functional Outcomes Mental Retardation in Children (< 2 Years of Age) with a History of HSCHD

Incidence in target indication	**NORTH AMERICA:** Canada: In 5-year old children who had undergone surgery for CHD as a newborn or infant, 22.4% had a full scale IQ test that was below cutoff point, 80, indicating lower IQ. Moreover, 11% of children in this cohort had significant functional overall impairment (cognition, mobility, and self-care) (Majnemer 2008).
Prevalence in target indication	**EUROPE:** Denmark: The risk of mental retardation was significantly increased, hazard ratio = 6.2, 95% CI: 4.5 – 8.4, in children with CHD compared with the general population (Olsen 2011).
Mortality in target indication	A review of the literature found no studies of mortality from mental retardation in children with HSCHD.

Table 22. Co-Morbid of Down Syndrome in Children (< 2 Years of Age) with a History of HSCHD

Incidence in target indication	**NORTH AMERICA:** United States: In premature infants (median gestation age = 36 weeks) with CHD requiring surgery, the rate of Down syndrome was 1.9% (Ades 2010). **EUROPE:** England: In children born with CHD, 6.4% also had Down syndrome (Dadvand 2009). Norway: In children born with CHD, 4.7% also had Down syndrome (Meberg 2007). Malta: The prevalence of children born with CHD and Down syndrome was 0.73/1000 births (95% CI: 0.45 – 1.16) (Grech 1999).
Prevalence in target indication	**NORTH AMERICA:** United States: In premature infants (median gestation age = 36 weeks) with CHD requiring surgery, the rate of Down syndrome was 1.9%. **EUROPE:** England: In children born with CHD, 4.6% also had Down syndrome (Dadvand 2009). Norway: In children born with CHD, 4.7% also had Down syndrome (Meberg 2007). Malta: The prevalence of children born with CHD and Down syndrome was 0.73/1000 births (95% CI: 0.45 – 1.16) (Grech 1999).
Mortality in target indication	A review of the literature found no studies of mortality from Down syndrome in children with HSCHD.

Table 23. Co-Morbid Extracardiac Anomalies in Children (< 2 Years of Age) with a History of HSCHD

Incidence in target indication	**NORTH AMERICA:** United States: In full term infants with CHD, the incidence of extracardiac anomalies was 29% (Licht 2009).
Prevalence in target indication	**NORTH AMERICA:** United States: In premature infants (median gestation age = 36 weeks) with CHD requiring surgery, the rate of extracardiac anomalies was 32% (Ades 2010). **EUROPE:** Norway: In children born with CHD, 46% had extracardiac anomalies (Meberg 2007).
Mortality in target indication	A review of the literature found no studies of mortality from extracardiac anomalies in children with HSCHD.

Module SII Non-Clinical Part of the Safety Specification

Key Safety Findings (from Non-Clinical Studies)	Relevance To Human Usage
Toxicity	
Single and repeat dose toxicity: Single intravenous (IV) doses up to 840 mg/kg palivizumab in rats, single SC or intramuscular (IM) doses up to 50 mg/kg of palivizumab in New Zealand White rabbits, and single IV doses of up to 30 mg/kg of palivizumab in cynomolgus monkeys were well tolerated; no treatment-related gross findings or histologic abnormalities were observed. In a repeat-dose toxicity study in cynomolgus monkeys, weekly IV doses of 60 and 120 mg/kg of palivizumab for 5- and 14-weeks were well tolerated without any adverse findings; no significant abnormalities in clinical, laboratory, or histological parameters were observed.	Palivizumab was well tolerated in 3 different animal species at higher doses than used in humans.
Reproductive toxicity: No study was conducted because palivizumab will be used only in a paediatric population.	Based on the intended use in humans, palivizumab is not expected to have any effect on reproduction in paediatric humans.
Developmental toxicity No study was conducted because of the short-term use in paediatric humans.	Based on the mode of action, no developmental toxicity is expected in humans.
Nephrotoxicity: There was no evidence of renal toxicity in animal studies.	Studies in cynomolgus monkey did not indicate any nephrotoxicity risk for humans.
Hepatotoxicity: There was no evidence of hepatotoxicity in animal studies.	Studies in cynomolgus monkey did not indicate any hepatotoxicity risk for humans.
Genotoxicity: Genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals and, therefore, are not needed.	It is not expected that palivizumab would interact directly with DNA or chromosomal material; there is no genotoxic risk for humans.

Key Safety Findings (from Non-Clinical Studies)	Relevance To Human Usage
Toxicity (continued)	
Carcinogenicity: Carcinogenicity studies are not warranted with a biologic due to the short-term human exposure and the lack of any direct interaction with DNA or chromosomes.	Based on the mode of action of palivizumab, no carcinogenic risk is expected in humans.
General Safety Pharmacology	
Cardiovascular (including potential for QT interval prolongation): In vitro tissue cross-reactivity (TCR) did not show any binding to heart tissue, nor was there any effect on ECG in monkeys after weekly IV doses for 5 and 14 weeks.	Data do not indicate an effect on the cardiovascular system in humans.
Nervous system: TCR study did not show any binding.	No effect on CNS expected in humans.
In vitro tissue cross-reactivity (TCR): The binding of biotinylated palivizumab at concentrations of 2.5 µg/mL and 25 µg/mL was evaluated in more than 30 human adult and neonatal tissues, and no specific tissue staining was observed.	Based on this data, no binding to human tissues is expected.
Mechanisms for drug interactions: No dedicated study was conducted.	Based on the mechanism of action, no drug interactions are expected in humans.
Other toxicity-related information or data.	None.

Because animals do not express the RSV target for palivizumab, animal studies are only useful in evaluating the potential for off-target effects. The absence of safety findings in animal studies supports a low safety risk for humans. Studies in juvenile animals were not conducted to support the use in children aged 2 years and less because of the lack of a pharmacologically relevant species.

Conclusions on Non-Clinical Data

Findings from non-clinical studies with palivizumab were assessed with the original marketing authorisation application for the prevention of serious lower respiratory tract

disease requiring hospitalization caused by RSV in children at high risk for RSV disease. Non-clinical studies did not reveal any safety findings of concern.

Module SIII Clinical Trial Exposure

SIII.1 Brief Overview of Development

Palivizumab is a humanized monoclonal antibody composed of 95% human and 5% murine amino acid sequences. Lyophilised palivizumab was originally developed and approved based on the 2 registration studies (Studies MI-CP018 and MI-CP048) for the prevention of serious lower respiratory tract disease requiring hospitalization caused by 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 BPD within the last 6 months; and children less than 2 years of age and with HSCHD. A number of additional clinical studies (see Module SIII.2) after the approval of lyophilised formulation were subsequently conducted and the data obtained confirmed the safety and efficacy that had been established in the registration studies in the paediatric populations for which palivizumab is indicated.

Lyophilised palivizumab was first approved in the US on 19 June 1998 and in the EU on 13 August 1999 via the centralised procedure. MedImmune is the innovator and license holder for palivizumab in the US. AbbVie (Marketing Authorization Holder [MAH]) is the ex-US license holder.

In 2004, liquid palivizumab was approved in the US for the same indication and patient populations as lyophilised formulation. In 2012, liquid palivizumab was approved in Japan. As of 01 March 2013, palivizumab, in lyophilised and/or liquid formulations, is approved in over 80 countries

On November 2012, AbbVie applied to the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan to expand the indication of palivizumab to include young children (≤ 24 months) with immunocompromised medical conditions following a request by the Japan Ministry of Health, Labor and Welfare. A clinical study (Study M12-420) conducted in Japanese children demonstrating bioequivalent serum concentrations (trough value) and consistent safety profile of palivizumab in immunocompromised children to

those found in Japanese premature infants, children treated for BPD and children with HSCHD was submitted.

SIII.2 Clinical Trial Exposure

The clinical safety database includes results from studies conducted with liquid and lyophilised palivizumab. The cutoff date for the clinical trial data inclusion was 31 December 2012. Of note, Studies MI-CP097 and MI-CP116 included both lyophilised palivizumab and liquid palivizumab; thus, the exposure to palivizumab was counted separately under each formulation. Patient exposure categorized by palivizumab formulation studied (lyophilised formulation, liquid formulation) in these clinical studies is presented in Table 24. In subsequent tables (Table 25 through Table 31), exposure is tabulated by indicated patient population, i.e., Prematurity and/or BPD versus HSCHD. If a study enrolled 2 patient populations of prematurity/BPD and HSCHD, patients were included in the appropriate high risk category.

The lyophilised formulation of palivizumab was investigated in 5 randomized, double-blind studies, (Studies MI-CP005, MI-CP018, MI-CP048, MI-CP097, and MI-CP116) and 6 open-label studies (Studies MI-CP011, MI-CP012, MI-CP036, MI-CP045, W00-350, and W10-664). The liquid formulation of palivizumab was investigated in 6 studies (Studies MI-CP097, MI-CP116, MI-CP110, MI-CP118, MI-CP124, and MI-CP127).

Study MI-CP097 was a double-blind, randomized cross-over study and was conducted in paediatric patients specifically to compare the liquid and lyophilised formulations. Study MI-CP116 was conducted to assess the immune reactivity of liquid and lyophilised formulations. Studies MI-CP110, MI-CP118, MI-CP124, and MI-CP127 were conducted to compare motavizumab, an investigational monoclonal antibody, with liquid palivizumab for the prophylaxis of serious RSV disease in high-risk children. None of the studies conducted with liquid palivizumab were placebo-controlled.

Clinical studies performed in healthy adults and in paediatric patients with bone marrow transplant, cystic fibrosis, immunocompromised medical conditions, or RSV infection were not included in the exposure data (Table 24) because these studies were not conducted in the approved indicated patient populations. Seven open-label clinical studies (Studies MI-CP007, MI-CP017, MI-CP035, MI-CP080, MI-RSV-MAb-9401a, MI-RSV-MAb-9401b, and MI-RSV-MAb-9401c) were conducted in the US in 122 healthy adults, all of whom received palivizumab. These studies were conducted to determine safety, tolerance, and pharmacokinetics (PK) of palivizumab. Two additional open-label, Phase 1 studies, Studies MI-CP004 and MI-CP034, were conducted in the US in 21 bone marrow transplant patients with an age range of 2 to 58 years of age to investigate the safety, tolerance, and PK of palivizumab administered intravenously. One double-blind, randomized, placebo-controlled, Phase 4, safety study (Study MI-MA001) was conducted in 186 children with cystic fibrosis, of which 92 subjects received palivizumab for prophylaxis of RSV disease. Three additional double-blind, placebo-controlled studies (Studies MI-CP009, MI-CP013, and MI-CP026) were conducted in a total of 109 healthy children hospitalized with RSV infection, of which 54 children received palivizumab, to investigate the safety, tolerance, and PK of palivizumab. Finally, an open-label study (Study M12-420) was conducted in Japan in 28 paediatric patients with immunocompromised medical conditions (ICC) aged $\leq$ 2 years, all of whom received palivizumab for prophylaxis of serious RSV disease.

Table 24. Total Paediatric Subject Exposure to Liquid or Lyophilised Palivizumab

Study Type	Number of Subjects Exposed N
	Liquid palivizumab
Randomized, blinded studies[a]	4503
All studies[a]	4503
	Lyophilised palivizumab
Randomized, blinded studies[b]	2036
All studies[c]	2331

a. Includes palivizumab recipients from Studies MI-CP110, MI-CP124, MI-CP097, MI-CP116, MI-CP118, and MI-CP127 (including both palivizumab/motavizumab group and motavizumab/palivizumab group).

b. Includes palivizumab recipients from Studies MI-CP097, MI-CP116, MI-CP005, MI-CP018, and MI-CP048.

c. Includes palivizumab recipients from Studies MI-CP097, MI-CP116, MI-CP005, MI-CP018, MI-CP048, MI-CP045, MI-CP011, MI-CP012, MI-CP036, W00-350 and W10-664.

Note: In Study MI-CP097, all subjects received both liquid and lyophilised palivizumab in a cross-over fashion. One subject may be counted for both liquid and lyophilised group. Study MI-CP116 has both liquid and lyophilised treatment groups. In Study MI-CP118, only subjects exposed to palivizumab in the second season and in Study MI-CP127, only subjects exposed to palivizumab are included. Subjects participating in both Studies MI-CP018 and MI-CP036 will be counted once for exposure.

Table 25. Total Paediatric Subject Exposure to Liquid or Lyophilised Palivizumab by Indicated Population

Study Population	Number of Subjects Exposed		
	Liquid Palivizumab N	**Lyophilised Palivizumab N**	**Total Palivizumab N**
Randomized, blinded studies			
Prematurity and/or BPD	3893[a]	1398[b]	5139
Congenital heart disease	610[c]	638[d]	1248
Total	4503	2036	6387
All studies			
Prematurity and/or BPD	3893[a]	1664[e]	5405
Congenital heart disease	610[c]	667[f]	1277
Total	4503	2331	6682

a. Includes data from Studies MI-CP097, MI-CP116, MI-CP110, MI-CP118, and MI-CP127.

b. Includes data from Studies MI-CP097, MI-CP116, MI-CP005, and MI-CP018.

c. Includes data from Study MI-CP124.

d. Includes data from Study MI-CP048.

e. Includes data from Studies MI-CP097, MI-CP116, MI-CP005, MI-CP018, MI-CP045, MI-CP011, MI-CP012, MI-CP036, W00-350, and W10-664.

f. Includes data from Studies MI-CP048 and W10-664.

Note: In Study MI-CP097, all subjects received both liquid and lyophilised palivizumab in a cross-over fashion. One subject may be counted for both liquid and lyophilised groups. Therefore the total number will not equal the sum of the two numbers of the subgroups. Study MI-CP116 has both liquid and lyophilised treatment groups.

Table 26. Total Paediatric Subject Exposure to Liquid or Lyophilised Palivizumab by Number of Doses (Prematurity and/or Bronchopulmonary Dysplasia)

	Number of Children Exposed				
	Liquid Palivizumab		Lyophilised Palivizumab		
Number of Doses	Randomized, Blinded Studies[a] N	All Studies[a] N	Randomized, Blinded Studies[b] N	All Studies[c] N	Total Palivizumab N
1 Dose	181	181	177	189	66[d]
2 Doses	100	100	9	68	320[d]
3 Doses	114	114	34	35	149
4 Doses	43	43	49	83	126
5 Doses	3455	3455	1129	1216	4671
6 Doses	0	0	0	0	0
7 Doses	0	0	0	18	18
8 Doses	0	0	0	0	0
9 Doses	0	0	0	0	0
10 Doses	0	0	0	55	55
> 10 Doses	0	0	0	0	0
Total	3893	3893	1398	1664	5405

a. Includes data from Studies MI-CP097, MI-CP116, MI-CP110, MI-CP118, and MI-CP127.

b. Includes data from Studies MI-CP097, MI-CP116, MI-CP005, and MI-CP018.

c. Includes data from Studies MI-CP097, MI-CP116, MI-CP005, MI-CP018, MI-CP045, MI-CP011, MI-CP012, MI-CP036, W00-350, and W10-664.

d. For Study MI-CP097, if a subject was given 1 dose each of liquid and lyophilised palivizumab, the subject exposure will be counted as 1 dose for each of the liquid and lyophilised palivizumab groups. For the total palivizumab group, the subject exposure will be counted as 2 doses for the same subject.

Note: Subjects received lyophilised palivizumab in Study MI-CP018 during the first RSV season and then received lyophilised palivizumab in the second RSV season in Study MI-CP036. The doses will be added up for the same subject participating in the 2 studies. Studies MI-CP097 and MI-CP116 have both liquid and lyophilised treatment groups.

Table 27. Total Paediatric Subject Exposure to Liquid or Lyophilised Palivizumab by Number of Doses (Congenital Heart Disease)

	Number of Children Exposed				
	Liquid Palivizumab		Lyophilised Palivizumab		
Exposure	Randomized, Blinded Studies[a] N	All Studies[a] N	Randomized, Blinded Studies[b] N	All Studies[c] N	Total Palivizumab N
1 Dose	5	5	14	15	20
2 Doses	6	6	6	6	12
3 Doses	6	6	8	10	16
4 Doses	14	14	16	20	34
5 Doses	579	579	594	614	1193
6 Doses	0	0	0	2	2
7 Doses	0	0	0	0	0
> 7 Doses	0	0	0	0	0
Total	610	610	638	667	1277

a. Includes data from Study MI-CP124.

b. Includes data from Study MI-CP048.

c. Includes data from Studies MI-CP048 and W10-664.

Table 28. Total Paediatric Subject Exposure to Liquid or Lyophilised Palivizumab by Age Group and Gender (Prematurity and/or Bronchopulmonary Dysplasia)

	Number of Subjects Exposed					
	Liquid Palivizumab[a]		Lyophilised Palivizumab[b]		Total Palivizumab	
Age Group	Female N	Male N	Female N	Male N	Female N	Male N
All Studies						
≤ 6 mo	1557	1816	580	671	2066	2406
> 6 mo – ≤ 1 yr	115	186	102	158	217	344
> 1 yr – ≤ 2 yr	96	123	62	87	158	210
> 2 yr	0	0	1	3	1	3
Total	1768	2125	745	919	2442	2963

mo = month; yr = year

a. Includes data from Studies MI-CP097, MI-CP116, MI-CP110, MI-CP118, and MI-CP127.

b. Includes data from Studies MI-CP097, MI-CP116, MI-CP005, MI-CP018, MI-CP045, MI-CP011, MI-CP012, MI-CP036, W00-350, and W10-664.

Table 29. Total Paediatric Subject Exposure to Liquid or Lyophilised Palivizumab by Age Group and Gender (Congenital Heart Disease)

	Number of Subjects Exposed					
	Liquid Palivizumab[a]		Lyophilised Palivizumab[b]		Total Palivizumab	
Age Group	Female N	Male N	Female N	Male N	Female N	Male N
All Studies						
≤ 6 mo	136	163	182	198	318	361
> 6 mo – ≤ 1 yr	70	69	74	98	144	167
> 1 yr – ≤ 2 yr	92	80	48	67	140	147
> 2 yr	0	0	0	0	0	0
Total	298	312	304	363	602	675

mo = month; yr = year

a. Includes data from Study MI-CP124.

b. Includes data from Studies MI-CP048 and W10-664.

Table 30. Total Paediatric Subject Exposure to Liquid or Lyophilised Palivizumab by Racial Origin (Prematurity and/or Bronchopulmonary Dysplasia)

	Number of Subjects Treated		
Racial Origin	**Liquid Palivizumab[a] N**	**Lyophilised Palivizumab[b] N**	**Total Palivizumab N**
All Studies			
White/Non-Hispanic	2871	991	3787
Black	339	355	651
Hispanic	490	183	650
Asian	47	31	74
Other	145	104	242
Missing	1	0	1
Total	3893	1664	5405

a. Includes data from Studies MI-CP097, MI-CP116, MI-CP110, MI-CP118, and MI-CP127.

b. Includes data from Studies MI-CP097, MI-CP116, MI-CP005, MI-CP018, MI-CP045, MI-CP011, MI-CP012, MI-CP036, W00-350, and W10-664.

Table 31. Total Paediatric Subject Exposure to Liquid or Lyophilised Palivizumab by Racial Origin (Congenital Heart Disease)

	Number of Subjects Treated		
Racial Origin	**Liquid Palivizumab[a] N**	**Lyophilised Palivizumab[b] N**	**Total Palivizumab N**
All Studies			
White/Non-Hispanic	528	481	1009
Black	20	52	72
Hispanic	23	77	100
Asian	8	15	23
Other	31	42	73
Missing	0	0	0
Total	610	667	1277

a. Includes data from Study MI-CP124.

b. Includes data from Studies MI-CP048 and W10-664.

Module SIV Populations Not Studied in Clinical Trials

SIV.1 Limitations of Adverse Drug Reaction Detection Common to Clinical Trial Development Programmes

The total palivizumab exposure is 6682 patients based on the clinical trials conducted within the approved palivizumab indication and presented in Section SIII.2. The estimated cumulative postmarketing patient exposure since the International Birth Date (IBD) through 31 December 2012 is approximately 3 million seasonal courses of therapy. While the clinical trial patient exposure may not be adequate for the identification of "infrequent" or "rare" events, the overall patient exposure to palivizumab in both clinical trial and postmarketing use spanning approximately 14 years allows the MAH to detect adverse reactions with very rare occurrence. The safety data from these sources of exposure are adequate for monitoring for the appearance of new reactions on an ongoing basis.

SIV.2 Effect of Exclusion Criteria in the Clinical Trial Development Plan

Except for known allergy to other humanized monoclonal antibodies (product of human immunoglobulin genes), none of the other exclusion criteria used in the clinical trials resulted in any contraindication in the Summary of Product Characteristics (SmPC).

Exclusion Criteria Which Will Remain as Contraindications	
Criteria	**Implications for Target Population**
Known allergy to immunoglobulin products	If a patient is known to have a hypersensitivity to palivizumab, any of its excipients, or other monoclonal antibodies, the patient will not qualify for administration of palivizumab. However, based on the clinical trial data, there were very few reports of hypersensitivity and no reports of anaphylaxis or anaphylactic shock in patients who received palivizumab prophylaxis. Therefore, it is assumed that the number of patients at risk of hypersensitivity is very small and, thus, the impact of hypersensitivity to palivizumab in the target populations will be minimal.

Exclusion Criteria Which Are Not Contraindications		
Criteria	**Reason for Being an Exclusion Criterion**	**Justification for Not Being a Contraindication**
Preterm infants and young children with BPD		
Hospitalization at time of randomization	RSV hospitalization was the primary study endpoint.	Hospitalized patients may now receive palivizumab if they fulfill criteria for indication.
Mechanical ventilation	Mechanical ventilation was a secondary study endpoint.	Patients receiving mechanical ventilation may now receive palivizumab if they fulfill criteria for indication.
Life expectancy < 6 months	Study design was planned to follow subjects up to 6 months.	Life expectancy of < 6 months would be considered in the risk benefit of palivizumab for an individual patient.
Active RSV infection	RSV infection was part of the primary study endpoint.	Since a patient may be reinfected with RSV, current recommendation is to continue palivizumab prophylaxis if infected.
Renal impairment, hepatic dysfunction, chronic seizure disorder, immunodeficiency	Safety was an endpoint, so significant underlying diseases were excluded to best profile the safety of palivizumab as the causative agent of the event.	No safety concern identified in patients with these concurrent conditions.
Congenital heart disease	CHD was to be studied in Study MI-CP048.	Palivizumab is approved for patients with HSCHD.
Young children with HSCHD		
Unstable cardiac or respiratory status	These conditions will complicate the interpretation of the study results.	No safety concern identified in patients with these concurrent conditions.
Hospitalization	RSV hospitalization was the primary study endpoint.	Hospitalized patients may now receive palivizumab, if they fulfill criteria for indication.
Mechanical ventilation, extracorporeal membrane oxygenation, continuous positive airway pressure	Mechanical ventilation was a secondary study endpoint.	Patients receiving mechanical ventilation may receive palivizumab if they fulfill criteria for indication.

Exclusion Criteria Which Are Not Contraindications		
Criteria	**Reason for Being an Exclusion Criterion**	**Justification for Not Being a Contraindication**
Young children with HSCHD (continued)		
Associated non-cardiac anomalies or end organ dysfunction with resultant survival of < 6 months	Study design was planned to follow subjects up to 6 months.	Life expectancy of < 6 months would be considered in the risk benefit of palivizumab for an individual patient.
Human immunodeficiency virus (HIV) positive	Safety was an endpoint, so significant underlying diseases were excluded to best profile the safety of palivizumab as the etiologic agent.	No safety concern identified in patients with these concurrent conditions.
Active RSV infection	RSV infection was part of the primary study endpoint.	Since a patient may get re-infected with RSV, current recommendation is to continue palivizumab prophylaxis if infected.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Studies of palivizumab evaluated the safety of palivizumab prophylaxis in infants and young children at high risk for RSV disease, including preterm infants (≤ 35 weeks gestational age) under 6 months of age and children with BPD or HSCHD under 2 years of age. Outside the indicated population, patients with the following medical conditions have not been appropriately studied in the registration clinical development programs for palivizumab subjects > 2 years of age, including elderly persons and pregnant or lactating women, term children with underlying medical conditions (e.g., cystic fibrosis, bone marrow transplant recipients, Down syndrome) or without underlying medical conditions, children who are immunocompromised (e.g., patients with HIV), or who have neuromuscular disorders.

Children

Palivizumab was specifically developed and studied in infants and young children less than 2 years of age who are at high risk for serious RSV disease. In this very young population, the natural history of RSV infection and its epidemiology support prophylaxis in this age range. In contrast, the incidence of RSV infection remarkably decreases after 2 years of age and, with a more developed immune system, the children may be less susceptible to serious RSV infection. In addition, the disease presentation becomes milder as the child matures anatomically and, therefore, may require only symptomatic relief. As a result, the benefit of palivizumab prophylaxis is expected to be significantly reduced in children older than 2 years of age. Therefore, palivizumab for prophylaxis of serious RSV disease has not been studied in subjects > 2 years of age.

Elderly

Palivizumab has been developed and approved for paediatric patients < 2 years of age with high risk for serious RSV infection. There are no data available on the efficacy and safety of palivizumab in the elderly population.

Pregnant or Breastfeeding Women

The patient population indicated for palivizumab is paediatric patients < 2 years of age; therefore, this is not applicable.

Patients with Hepatic or Renal Impairment

Paediatric patients within the currently indicated populations who also have hepatic or renal impairment have not been directly studied in palivizumab clinical trials. Since palivizumab is a protein, it is likely to be metabolized in a similar fashion as other human antibodies; the metabolism of which is not significantly impaired even in patients with end stage liver or kidney disease.

Patients with Other Relevant Co-Morbidity

Immunocompromised Medical Conditions:

Patients with immunocompromised medical conditions were not studied in the registration clinical development programs. However, upon the Japan PMDA request, a Phase 3, multicenter, open-label, uncontrolled clinical study (Study M12-420) was conducted in Japan to evaluate safety, efficacy, and pharmacokinetics of palivizumab in 28 Japanese newborns, infants, and young children at the age of 24 months or less with immunocompromised medical conditions (e.g., organ transplantation, immunosuppressive chemotherapy, steroid therapy). The study results confirmed a positive benefit-risk profile of palivizumab prophylaxis in this limited patient population. However, because of the limited number of patients involved in the study, it is difficult to extrapolate the data to a wider application. The Amecican Academy of Paediatrics in its Synagis Authorization Guideline noted that "Synagis® has not been evaluated in randomized trials in immunocompromised children. However, children with severe immunodeficiencies (such as severe combined immunodeficiency syndrome or advanced AIDS) may benefit from prophylaxis." (American Academy of Paediatrics 2009). Furthermore, the estimated number of patients with these medical conditions is not expected to be large.

Down Syndrome:

Nearly half of patients with Down syndrome present with congenital heart defects (Urbano 2010). Some of these patients have CHD that is considered hemodynamically significant, a condition for which palivizumab prophylaxis is indicated. Although patients with Down syndrome were not specifically studied in the palivizumab clinical development programs, those with HSCHD may have been included as study participants for palivizumab prophylaxis. There are also literature reports on the use of palivizumab in preventing serious RSV infection in patients with Down syndrome (Paolo 2009). A few patients with Down syndrome were also studied in the Japan clinical trial of palivizumab prophylaxis for RSV disease (Study M12-420). No specific safety concerns have been identified in the use of palivizumab for prophylaxis for serious RSV infection in patients

with Down syndrome. However, there is no convincing data from well-designed clinical trials to evaluate the efficacy and safety of palivizumab prophylaxis in patients with Down syndrome.

Cystic Fibrosis:

Epidemiological studies have indicated that children with cystic fibrosis may be at high risk for RSV infection (Abman 1988; Hiatt 1999; Lieberman 1999). Data from retrospective and open-label studies provided information without clear benefit on the potential use of palivizumab prophylaxis in this patient population (Giebels 2008; McCormick 2007; Robinson 2009). One randomized, placebo-controlled, double-blind study (Study MI-MA001) investigated the prophylactic use of palivizumab in 186 children (92 palivizumab and 94 placebo) $\leq$ 2 years of age with cystic fibrosis. The results indicated that palivizumab administration at the dose of 15 mg/kg was safe and well tolerated. However, based on the information available, the American Academy of Paediatrics (AAP) Committee on Infectious Diseases (COID) in its Red Book 2012 recommendations on RSV prophylaxis states, "Limited studies suggest that some patients with cystic fibrosis may be at increased risk of RSV infection. Whether RSV infection exacerbates the CLD of cystic fibrosis is not known. In addition, insufficient data exist to determine the effectiveness of palivizumab use in this patient population. Therefore, a recommendation for routine prophylaxis in patients with cystic fibrosis cannot be made (AAP COID 2012)."

Neuromuscular Disorders:

Paediatric patients with neuromuscular disorders are at high risk for severe RSV infection. Palivizumab prophylaxis for these uncommon underlying conditions is under consideration (Simon 2011). However, prospective studies are needed to determine the burden of RSV disease and the effectiveness of palivizumab prophylaxis in these children.

Patients with a Disease Severity Different from the Inclusion Criteria in the Clinical Trial Population

Palivizumab is indicated for the prevention of hospitalization due to severe RSV disease in high risk children. Therefore, the disease severity does not apply to the patient populations who are to receive palivizumab prophylaxis.

Sub-Populations Carrying Known and Relevant Polymorphisms

There are no known relevant genetic polymorphisms that effect metabolism degradation or pharmacological effects of palivizumab.

Patients of Different Racial and/or Ethnic Origin

Palivizumab binds directly to the conserved region of RSV Fusion protein (F protein) and does not act pharmacologically on human organs or tissues. There is no expected impact of genetic variations on both efficacy and safety among people with various racial or ethnic backgrounds. Palivizumab has been extensively studied in subject populations including males and females of a variety of racial backgrounds in clinical trials. There have been no safety signals identified for particular racial groups in clinical trials or in postmarketing surveillance.

SIV.4 Conclusions on the Populations Not Studied and Other Limitations of the Clinical Trial Development Programme

The large patient exposure to palivizumab in clinical studies and postmarketing experience for patients < 2 years of age at high risk for serious RSV disease should allow the detection of adverse drug reactions with infrequent occurrences. The missing or limited information on the populations not studied or under-represented in clinical trial programs discussed above is not anticipated to constitute an important safety risk to the target population indicated for palivizumab prophylaxis.

Module SV Post-Authorisation Experience

SV.1 Action Taken by Regulatory Authorities and/or Marketing Authorisation Holders for Safety Reasons

No regulatory action has been taken in any country since palivizumab (Synagis) was first approved on 19 June 1998 in the US and 13 August 1999 in EU.

SV.2 Non-Study Post-Authorisation Exposure

SV.2.1 Method Used to Calculate Exposure

Since the approval of palivizumab for the prevention of serious lower respiratory tract disease requiring hospitalization caused by RSV in children at high risk for RSV disease in the US on 19 June 1998 and on 13 August 1999 in the EU, considerable global postmarketing exposure has accrued.

An estimate of the number of patients treated with palivizumab was calculated from internal AbbVie and MedImmune distribution data for the period of IBD through 31 December 2012. The patient exposure estimate is approximate because palivizumab is dosed at 15 mg/kg and an individual may receive more or less than 5 doses in any given season. For these calculations, it was assumed that the average patient would receive approximately 4.25 vials of 100 mg palivizumab each season as determined by previously conducted studies and market surveys. Two 50-mg vials were considered to be equivalent to 100 mg. The number of 100-mg equivalent doses was divided by 4.25 (the estimated number of vials per patient during a season) to arrive at an estimate of the number of courses of therapy distributed. Using this methodology, the estimated seasonal courses of therapy distributed were calculated. Therefore, we presented exposure as number of estimated seasonal courses in the table below.

SV.2.2 Exposure

Based on the method provided in SV.2.1, AbbVie estimated the worldwide postmarketing exposure data from IBD to 31 December 2012 by region (Table 32).

Table 32. Postmarketing (Non-Study) Palivizumab Exposure (Seasonal Courses of Therapy) By Region, Country, and Year – 19 June 1998 Through 31 December 2012[a]

Region	1998 %[b]	1999 %[b]	2000 %[b]	2001 %[b]	2002 %[b]	2003 %[b]	2004 %[b]	2005 %[b]	2006 %[b]	2007 %[b]	2008 %[b]	2009 %[b]	2010 %[b]	2011 %[b]	2012 %[b]	Total IBD-2012
European Total	68 (1.4%)	771 (1.0%)	5,042 (4.5%)	9,880 (7.2%)	13,544 (7.4%)	18,444 (8.5%)	23,313 (10.0%)	28,957 (11.4%)	32,310 (12.8%)	37,996 (14.2%)	43,443 (16.2%)	48,590 (19.0%)	49,988 (20.8%)	53,735 (22.6%)	25,463 (20.2%)	391,543 (13.6%)
Latin American Total	0 (0.0%)	95 (0.1%)	413 (0.4%)	518 (0.4%)	484 (0.3%)	470 (0.2%)	457 (0.2%)	1,162 (0.5%)	2,549 (1.0%)	4,938 (1.8%)	8,712 (3.3%)	12,692 (5.0%)	15,548 (6.5%)	11,237 (4.7%)	9,377 (7.4%)	68,651 (2.4%)
North America Canada	92	1,380	3,141	3,580	4,058	4,455	5,456	5,853	7,694	6,050	8,079	8,185	7,577	8,153	4,671	78,423
US	4,701	77,130	104,056	123,513	160,413	186,863	193,194	201,055	183,633	184,740	166,146	139,236	114,048	103,424	51,783	1,993,936
Total	4,793 (98.6%)	78,510 (98.9%)	107,197 (95.1%)	127,093 (92.1%)	164,471 (89.8%)	191,318 (87.7%)	198,650 (85.0%)	206,908 (81.4%)	191,327 (75.7%)	190,790 (71.3%)	174,226 (65.1%)	147,421 (57.7%)	121,625 (50.7%)	111,577 (46.9%)	56,454 (44.7%)	2,072,358 (72.2%)
Pacific Total	0 (0.0%)	13 (0.0%)	24 (0.0%)	16 (0.0%)	24 (0.0%)	33 (0.0%)	55 (0.0%)	61 (0.0%)	77 (0.0%)	52 (0.0%)	170 (0.1%)	196 (0.1%)	297 (0.1%)	237 (0.1%)	192 (0.2%)	1,447 (0.1%)
Asia Total	0 (0.0%)	27 (0.0%)	81 (0.1%)	497 (0.4%)	4,613 (2.5%)	7,828 (3.6%)	11,168 (4.8%)	16,702 (6.6%)	26,011 (10.3%)	33,146 (12.4%)	40,450 (15.1%)	46,089 (18.0%)	51,605 (21.5%)	58,450 (24.6%)	31,124 (24.6%)	327,790 (11.4%)
Africa Total	0 (0.0%)	1 (0.0%)	5 (0.0%)	15 (0.0%)	24 (0.0%)	70 (0.0%)	129 (0.1%)	253 (0.1%)	319 (0.1%)	407 (0.2%)	507 (0.2%)	683 (0.3%)	565 (0.2%)	621 (0.3%)	798 (0.6%)	4,396 (0.2%)
Worldwide Total[c]	4,861	79,415	112,763	138,026	183,160	218,192	233,805	254,210	252,678	267,429	267,592	255,697	239,934	237,811	126,359	2,871,932

a. Estimate based on ex-US sale data from AbbVie and US sale data from MedImmune, Inc.

b. Percentages are based on column total for each specific year.

c. Worldwide totals are not additive as region of sale could not be determined in some cases.

SV.3 Post-Authorisation Use in Populations Not Studied in Clinical Trials

There have been no post-authorization clinical studies of palivizumab in patient populations involving paediatric patients older than 2 years of age, elderly, and patients with hepatic or renal impairment, Down syndrome (except a few cases in Japan Study M12-420), neuromuscular disorders, sub-populations carrying known polymorphisms, or patients of different racial and/or ethnic origin. Pregnant or lactating women and patients with differences of disease severity are not applicable as palivizumab is indicated for prophylaxis in paediatric patients < 2 years of age. Therefore, no post-authorization data is available for these populations.

There have been 2 post-authorization clinical studies conducted in children ≤ 2 years of age in patient populations not studied in clinical trials for the approved indication. One study (Study MI-MA001) evaluated the safety and tolerance of palivizumab, compared with placebo, in children with cystic fibrosis (Table 33). The second study (Study M12-420) assessed the pharmacokinetics, efficacy, safety, and tolerability of palivizumab in young Japanese children with immunocompromised medical conditions (ICC) (Table 34).

Table 33. Children with Cystic Fibrosis

Estimated Use	Number	Comment on Any Variation in Benefit or Risk from Overall Target Population
Children with Cystic Fibrosis	92	The benefit-risk profile is similar to what has been demonstrated in the overall target population.
Data Source: Study MI-MA001		
Method of Calculation: Actual Number of Patients Received Palivizumab Prophylaxis		

Table 34. Children with Immunocompromised Medical Conditions (ICC)

Estimated Use	Number	Comment on Any Variation in Benefit or Risk from Overall Target Population
Children with ICC	28	The benefit-risk profile is similar to what has been demonstrated in the overall target population.
Data Source: Study M12-420		
Method of Calculation: Actual Number of Patients Received Palivizumab Prophylaxis		

SV.4 Post-Authorisation Off-Label Use

No clinical trial has been conducted in the EU for the off-label use of palivizumab.

SV.5 Epidemiological Study Exposure

Table 35. Listing of Epidemiological Studies Conducted to Clarify Safety or Efficacy Issues, Study Drug Utilisation, or to Measure Effectiveness of Risk Minimisation Measures

Study Title and Study Type	Objectives	Population Studied	Duration	Number of Persons and Person Time	Comment
Risk of autoimmune and allergic diseases in Danish and Swedish children who received passive respiratory syncytial virus prophylaxis: a population-based, retrospective, cohort study.	The objective is to examine the potential long-term risk of development of chronic autoimmune and/or allergic diseases in children following prophylaxis with palivizumab in early childhood.	Premature children, children with BPD or CHD, or all live born children in Denmark and Sweden.	Danish Cohort: (1999 – 2010) Swedish Cohort: (July 1, 2005 to 2010)	Denmark: Premature cohort-160 BPD-103 CHD-42 All live born-264 Sweden: Premature cohort-547 BPD-419 CHD-242 All live birth-912	Final data analysis is on-going. Final report due Dec 2013.
Retrospective Palivizumab Outcomes Survey 1998 – 1999; a retrospective, cohort study.	The purpose of this retrospective survey was to evaluate clinical outcomes following administration of palivizumab during its first two seasons of use.	The 1998/1999 season in 9 US sites and the 1999/2000 season in 12 sites in US.	1998 – 2000 RSV season	4723 participants	The overall RSV hospitalization rates were 2.3% for 1998 – 1999 season and 2.4%, for 1999 – 2000 season

Table 35. Listing of Epidemiological Studies Conducted to Clarify Safety or Efficacy Issues, Study Drug Utilisation, or to Measure Effectiveness of Risk Minimisation Measures (Continued)

Study Title and Study Type	Objectives	Population Studied	Duration	Number of Persons and Person Time	Comment
Palivizumab outcome: prospective observational registry (Frogel 2008).	The objective of this study was to collect data on the demographics, clinical characteristics and clinical outcomes of infants and young children who received palivizumab as prophylaxis for RSV.	The registry included data from the 2000 – 2001 through 2003 – 2004 RSV seasons, in multiple US sites.	2000 – 2004 RSV season	19548 infants	An analysis of the combined 4-year experience of the overall RSV hospitalization rate was 1.3% (virology confirmed RSV).
REACH Program: prospective cohort study.	The major objective of this study was to assess safety and compliance after palivizumab administration.	A telephone survey of palivizumab users in 1 US site.	1998 – 1999 RSV season	7013 children	Among these children, 105 (1.5%) were re-hospitalized with RSV lower respiratory tract infection
The German Palivizumab registry, postmarketing observational study (Simon 2011).	The purpose of this registry was to provide data on drug administration, patient risk factors, hospitalization, and compliance after palivizumab prophylaxis for RSV.	A registry study in Germany.	RSV seasons (2002/2003 to 2006/2007)	10686 patients	The hospitalization rate related to RSV infection was 2.5%.

Table 35. Listing of Epidemiological Studies Conducted to Clarify Safety or Efficacy Issues, Study Drug Utilisation, or to Measure Effectiveness of Risk Minimisation Measures (Continued)

Study Title and Study Type	Objectives	Population Studied	Duration	Number of Persons and Person Time	Comment
The Canadian Synagis registry, prospective, observational registry (Mitchell 2011, Paes 2012).	The purpose of this study was to document the utilization, compliance, and health outcomes of infants receiving palivizumab prophylaxis in the hospital and community settings.	Enrolled at 27 sites in Canada.	2005/2006 to 2010/2011 RSV seasons	10,092 patients	The overall RSV hospitalization rate was 1.47%.

Module SVI Additional EU Requirements for the Safety Specification

SVI.1 Potential for Harm from Overdose

Palivizumab is administered at a dose of 15 mg/kg of body weight, given once a month during anticipated periods of RSV risk in the community. In clinical studies, children receiving an overdose, up to 22.27 mg/kg, reported no medical consequences. From postmarketing experience, the use of palivizumab up to 70 mg/kg has been reported. In some cases, adverse events (AEs) were reported with an undetermined causal relationship to palivizumab overdose. These same AEs have also been reported in patients receiving the indicated dosage. None of these AEs reported in any of the cases with either overdosage or indicated dosage has been described to cause life-threatening or fatal outcome.

SVI.2 Potential for Transmission of Infectious Agents

Transmission of infectious agents in both the lyophilised and liquid formulations of palivizumab is controlled throughout the manufacturing process. This includes routine monitoring and control of raw materials, processing conditions, and the processing environment.

The palivizumab manufacturing process uses bovine-derived raw materials. These materials pose a theoretical risk for transmission of infectious agents. This potential risk is controlled through 3 mechanisms: first, we are in compliance with the Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products, EMEA/410/01Rev 3 for bovine derived raw materials; second, the palivizumab manufacturing purification process contains orthogonal steps for virus inactivation and removal including nanofiltration, a low pH treatment step, and removal of viruses through column chromatography steps; third, palivizumab drug product is manufactured and distributed as a sterile lyophilised powder or solution.

Based on these risk mitigations, and the control and monitoring of the manufacturing process and environment, the potential for transmission of infectious agents is regarded as very low. No clinical symptoms or laboratory findings indicating transmission of an infectious agent have ever been reported.

SVI.3 Potential for Misuse for Illegal Purposes

It is unlikely that palivizumab will be used as a recreational drug or for any illegal purposes. No data from the palivizumab clinical studies, or data from the postmarketing safety database have been reported that are relevant to misuse of palivizumab for illegal purposes.

SVI.4 Potential for Medication Errors

SVI.4.1 Description of Medication Errors During the Clinical Trial Programme

Table 36. Medication Errors Reported During Clinical Trials

Medication Errors During Clinical Trial Programme				
Product Name(s):				
Description of Error	**Number of Occurrences**	**Analysis of Cause**	**Steps Taken to Prevent**	**Comment**
Overdose	6	Four of the patients received a dose greater than assigned; however, the dose was less than 15 mg/kg. Two of the patients received a dose up to 22.7 mg/kg due to miscalculation.	No step was taken, e.g., protocol amendment.	No health consequence was reported for these overdose cases.
Injection site extravasation	1	Unknown	No step was taken.	No health consequence was reported.

Note: Clinical trials presented in Section SIII.2 are included for the search of medication errors.

SVI.4.2 Preventive Measures for the Final Product(s) Being Marketed

Palivizumab is almost exclusively prescribed by paediatricians and is administered by healthcare professionals. These healthcare professionals have the experience and training to reconstitute and administer palivizumab in the target populations. The palivizumab prescribing information contains a detailed description of the dosage, dose calculation, route and frequency of administration for palivizumab to minimize the risk of medication errors. The prescribing information details the reconstitution procedure for the lyophilised formulation.

The Incompatibilities section of the SmPC provides healthcare providers the information that palivizumab should not be mixed with any medicinal products or, for the lyophilised formulation, diluents other than water for injections.

The SmPC and patient leaflet provided for liquid palivizumab contain administration information that lyophilised and liquid palivizumab cannot be mixed for injection.

SVI.4.3 Effect of Device Failure

Not applicable.

SVI.4.4 Reports of Medication Errors with the Marketed Product(s)

It is well recognized that the postmarketing spontaneous AEs are under reported and the analysis of postmarketing AEs has limitations due to the lack of details in these reports. Such factors may complicate the ability to derive a true incidence of AEs from postmarketing data or, in the case of medication errors, to determine the true causes that led to the error occurrence. The most frequently reported medication errors (MedDRA PTs) for palivizumab from the postmarketing reporting source since IBD to 31 December 2012 are presented in Table 40.

Table 37. Reports of Medication Errors with Marketed Product(s)

Reports of Medication Errors with Marketed Product(s)				
Product Name(s): Palivizumab				
Description of Error	**Number of Occurrences[a]**	**Analysis of Cause**	**Steps Taken to Prevent**	**Comment**
Overdose	60	Calculation/human error	Addition to labeling of how to calculate dosage for a patient	As discussed in SVI.1, dosage up to 70 mg/kg has been reported and in some cases, AEs have been reported with undetermined causality to palivizumab overdose. None of these AEs was reported to cause life-threatening or fatal events.
Incorrect dose administered	58	Calculation/human error	Addition to labeling of how to calculate dosage for a patient	Incorrect dose included both overdose and underdose. No reports with untoward medical events or consequences.
Inappropriate schedule of drug administration	54	Human error	Labeling has instruction of once a month administration	No reports with untoward medical events or consequences.
Medication error	31	Unknown	None	Non-specific term describing other types of medication errors. No untoward medical events or consequences.
Product reconstitution issue	19	User skill in reconstituting lyophilised formulation	Formulation conversion from lyophilised to liquid; no need to reconstitute	No untoward medical events or consequences. The conversion should eliminate this medication error.
Expired drug administered	18	Human error	None	No untoward medical events or consequences. Vial label has expiry date.

Table 37. Reports of Medication Errors with Marketed Product(s) (Continued)

Reports of Medication Errors with Marketed Product(s)				
Product Name(s): Palivizumab				
Description of Error	**Number of Occurrences[a]**	**Analysis of Cause**	**Steps Taken to Prevent**	**Comment**
Wrong technique in drug usage process	18	User skill	None	No untoward medical events or consequences.
Accidental overdose	14	Calculation/human error	None	No untoward medical events or consequences.

a. Number of individual medication errors.

Of the many types of postmarketing medication errors reported for palivizumab, the evaluation of the potential for harm from overdose is presented in Section SVI.1. One of the medication errors for lyophilised palivizumab is the "product reconstitution issue" (MedDRA term). However, this issue will no longer be a concern when the conversion of lyophilised formulation to liquid formulation in the market is complete. Other types of medication errors are not unique to palivizumab, such as incorrect route or schedule of administration, use of expired drug, wrong technique in drug usage, drug dose omission, and off-label use. The number of reports for each of these medication errors is low in context of approximately 3 million seasonal courses of therapy for palivizumab exposure. The majority of these medication errors are nonserious and had reported no associated AEs. There have been no reports of medication errors for palivizumab that directly caused life-threatening events or death. The causes for these medication errors were primarily due to oversight or inexperience of the product users in preparing and administering palivizumab. The causes for these medication errors are not related to the product quality and usually can be avoided if the approved prescribing instruction is strictly followed.

There have been no reports indicative of drug name confusion, spoken or written, in the postmarketing database for palivizumab.

After the approval of liquid palivizumab formulation and before the complete market withdrawal of lyophilised palivizumab, both formulations will be coexisting in the market. Thus, there is a potential risk of mixing lyophilised and liquid palivizumab before injection. Additionally, there will be a very low chance that the liquid palivizumab could be diluted before use. Of note, because the 2 formulations contain the same active substance and are used with the same posology and administration, it is not expected to be a safety concern if a patient receives both lyophilised and liquid palivizumab (without mixing before administration) at the same time. The potential safety risk of the above medication errors, if they do occur, is deemed to be very minimal. However, the safety risk of mixing 2 formulations before injection is unknown. There have been no reports of mixing 2 formulations or dilution of liquid palivizumab in the US and Japan market during the time when both formulations were available.

SVI.5 Potential for Off-Label Use

Refer to Section SVI.6.2 for relevant information.

SVI.6 Specific Paediatric Issues

SVI.6.1 Issues Identified in Paediatric Investigation Plans

The Paediatric Committee adopted the liquid palivizumab PIP (May 2013) for prevention of serious lower respiratory tract disease requiring hospitalization caused by RSV in children at high risk for RSV disease within the approved indication for the paediatric subset aged 0 to 2 years. A waiver was granted for the paediatric population from 2 to 18 years due to lack of therapeutic benefit. No issues were identified.

SVI.6.2 Potential for Paediatric Off-Label Use

Palivizumab is indicated for the prevention of serious lower respiratory tract disease caused by RSV in paediatric patients < 2 years of age at high risk of RSV infection, including premature infants (≤ 35 weeks of gestation and < 6 months of age), children < 2 years of age with BPD/CLD, and children < 2 years of age with HSCHD. However, it is acknowledged that the potential always exists for any medicinal product to be used

outside of its licensed indications through the exercise of the physician's right to invoke clinical judgment in the best interests of the patient. Although data are limited, there are literature and spontaneous reports of palivizumab off-label use in patient populations, such as paediatric patients with Down syndrome, cystic fibrosis, immunocompromised medical conditions, use in patients older than 2 years of age, and in the treatment of RSV (Paes 2012, Hu 2010, Malley 1998). In the randomized, placebo-controlled, double-blind, Phase 4 study (Study MI-MA001) of the safety of palivizumab for prophylaxis of serious RSV disease in children with cystic fibrosis, it was found that palivizumab was safe and well tolerated. The overall incidence of AEs was similar between the palivizumab and placebo groups. The clinical study (Study M12-420) conducted in Japan of palivizumab prophylaxis for serious RSV disease in newborns, infants, and children $\leq$ 2 years of age with various immunocompromised medical conditions confirmed a similar pharmacokinetic and safety profile of palivizumab in this patient population compared with the indicated populations. The review of these off-label use data and the spontaneous reports from the company safety database did not identify any new safety concerns that have already been described in the well-characterized safety profile of palivizumab used for the approved indication.

The off-label uses of palivizumab will continue to be monitored in order to identify any potential risks they may cause.

SVI.7 Conclusions

There is a potential for mixing reconstituted lyophilised and liquid palivizumab before administration when both formulations are available on the market. However, information on whether the injection of this mixture would cause a safety risk to the patients is unknown. A proper description of the 2 formulations of palivizumab will be made in the prescribing information and to avoid such occurrences.

No other significant potential safety risks have been identified from the review of relevant data for the topics discussed in this module, and none is anticipated based on the available

clinical data, the mechanism of action, the manufacturing processes, and the indicated patient population for palivizumab.

Module SVII Identified and Potential Risks

SVII.1 Newly Identified Safety Concerns (since this module was last submitted)

This section is not relevant because this document is the first European Union Risk Management Plan (EU-RMP) to be submitted for palivizumab.

SVII.2 Recent Study Reports with Implications for Safety Concerns

There are no study reports with implications for identified safety concerns.

SVII.3 Details of Important Identified and Potential Risks from Clinical Development and Post-Authorisation Experience (including newly identified)

Anaphylaxis and anaphylactic shock, and hypersensitivity have been reported in clinical studies and/or postmarketing spontaneous reports. These identified risks of palivizumab are presented in Table 38 and Table 39.

Table 38. Anaphylaxis and Anaphylactic Shock

Identified Risk	**Anaphylaxis and Anaphylactic Shock**
Frequency with 95 % CI	There have been no reports of anaphylaxis and anaphylactic shock in clinical trials for palivizumab. There were 14 postmarketing, spontaneous reports describing anaphylactic or anaphylactoid reactions among approximately 3 million patients coincidently with palivizumab administration as of 31 December 2012.
Seriousness/outcomes	Anaphylactic reactions led to hospitalization for the majority of the 14 patients in the 14 postmarketing, spontaneous reports. No death was reported directly due to the event of anaphylaxis or anaphylactic shock.
Severity and nature of risk	The risk severity ranges from mild to severe including death.
Background incidence/prevalence	In the general population, the incidence of anaphylaxis is 4 – 5 per 100,000 persons per year (Lee 2011). Worldwide, the lifetime risk (prevalence) of anaphylaxis is estimated to be 0.05% to 2% and the rates appear to be increasing (Simons 2010). However, the incidence and prevalence of anaphylaxis is not known for the unexposed paediatric populations that are indicated for palivizumab prophylaxis.

Table 38. Anaphylaxis and Anaphylactic Shock (Continued)

Identified Risk	Anaphylaxis and Anaphylactic Shock
Risk groups or risk factors	Patient history of prior hypersensitivity to palivizumab, any of its excipients, or other monoclonal antibodies may be a risk factor for anaphylaxis or anaphylactic shock with palivizumab administration. There are no other known risk factors identified within the indicated patient populations in relation to palivizumab.
Potential mechanisms	The development of anaphylaxis is due to the release of inflammatory mediators and cytokines from master cells and basophils. Typically anaphylaxis occurs through an immunologic reaction but can also develop due to non-immunologic mechanisms. The immunologic mechanism involves IgE binding to antigen. The antigen bound IgE activates the target cells leading to the release of inflammatory mediators such as histamine. These mediators then cause all the anaphylactic symptoms (e.g., bronchial muscle contraction, vasodilation, fluid leakage from blood vessels) (Khan 2011). Palivizumab is a monoclonal antibody of 95% human and 5% murine components. When injected in a patient, palivizumab could act as a foreign antigen and trigger the cascade of immunologic responses leading to an anaphylactic reaction. However, there are no data available demonstrating palivizumab causes anaphylaxis through this pathway.
Preventability	Palivizumab is contraindicated in patients with known hypersensitivity to the active substance or to any of the excipients, or other humanized monoclonal antibodies. Medicinal products for the treatment of severe hypersensitivity reactions, including anaphylaxis and anaphylactic shock, should be available for immediate use following administration of palivizumab.
Impact on individual patient	Anaphylactic shock can cause death to a patient.
Potential public health impact of safety concern	Anaphylaxis occurs on an individual basis and is very rare in patients who have received palivizumab; therefore, there is no potential public health impact.
Evidence source	Clinical trial data, postmarketing safety data and literature publication.
MedDRA terms	Anaphylactic reactions SMQ

Table 39. Hypersensitivity

Identified Risk	Hypersensitivity
Frequency with 95 % CI	There were a total of 10 reports of hypersensitivity among 6682 patients who participated and received palivizumab in the clinical trials, which translates to an incidence of 0.15% with 95% CI: 0.072 – 0.275.
Seriousness/outcomes	Of the 10 reports of hypersensitivity, none of these reported cases were considered serious. The event of hypersensitivity in 8 of the 10 reports completely recovered while in the remaining 2 reports, the event had not resolved.
Severity and nature of risk	The safety concern refers to Type I hypersensitivity or allergic reactions. The severity of the risk ranges from mild such as itching, rash, red eyes to life-threatening or fatal anaphylactic shock.
Background incidence/prevalence	The incidence and prevalence of allergic reactions vary significantly depending on the allergic conditions. However, the incidence and prevalence of hypersensitivity is not known for the unexposed paediatric populations that are indicated for palivizumab prophylaxis.
Risk groups or risk factors	Risk factors include host and environmental factors, of which hereditary is the most significant by far (Grammatikos 2008). Allergic reactions can occur acutely or in a late-phase response. It is impossible to identify risk groups among patients receiving palivizumab.
Potential mechanisms	Hypersensitivity, as identified for palivizumab, refers to a Type 1 reaction involving IgE and IgG4, presenting commonly as urticaria and/or eczema. The production of IgE is in response to a certain antigen (allergen). IgE activates mast cells and basophils, which release inflammatory mediators and cytokines causing various systemic effects (Janeway 2001). Palivizumab is a monoclonal antibody of 95% human and 5% murine components. When being injected in a patient, it could act as a foreign antigen and trigger the cascade of immunologic responses. However, there are no data available demonstrating palivizumab causes hypersensitivity through this pathway.

Table 39. Hypersensitivity (Continued)

Identified Risk	Hypersensitivity
Preventability	Palivizumab is contraindicated in patients with known hypersensitivity to the active substance or to any of the excipients, or other humanized monoclonal antibodies. Medicinal products for the treatment of severe hypersensitivity reactions, including anaphylaxis and anaphylactic shock, should be available for immediate use following administration of palivizumab.
Impact on individual patient	Hypersensitivity can be life-threatening or fatal to a patient.
Potential public health impact of safety concern	Hypersensitivity due to allergy to palivizumab occurs on an individual basis. Therefore, there is no potential public health impact.
Evidence source	Clinical trial data, post-marketing safety data and literature publications (see references cited).
MedDRA terms	Hypersensitivity SMQ

SVII.4 Identified and Potential Interactions

SVII.4.1 Overview of Potential for Interactions

Palivizumab is a monoclonal antibody directly binding to the conserved F protein of RSV to inhibit the viral replication and transmission. It has a pharmacokinetic profile similar to a natural human IgG1 antibody. There are no mechanisms of action known that indicate palivizumab can interact with other medicinal products or food. In the case of vaccines, none of the current paediatric vaccines are specific to RSV. Therefore, no interaction of RSV-specific monoclonal antibodies with any vaccine is expected. However, no formal drug-drug interaction studies were conducted. In Study MI-CP018, the proportions of children in the placebo and Synagis groups who received routine childhood vaccines, influenza vaccine, bronchodilators, or corticosteroids were similar and no incremental increase in adverse reactions was observed among children receiving these agents.

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. Nonetheless, in most cases of RSV-induced bronchiolitis or pneumonia, routine laboratory tests are of minimal diagnostic use and the diagnosis of RSV infection relies on the age of the children, the clinical presentations, and the patterns of the local RSV strains present for that season in the community. Furthermore, the management of children who have been diagnosed specifically with a viral lower respiratory tract infection, including RSV, is typically not any different from if a viral diagnosis was not made. Thus, the RSV diagnostic test interference by palivizumab has very minimal risk to patients' health.

SVII.4.2 Important Identified and Potential Interactions

No important interactions have been described to date.

SVII.5 Pharmacological Class Effects

SVII.5.1 Pharmacological Class Risks Already Included as Important Identified or Potential Risks

Palivizumab is the only product available used for the prophylaxis of serious RSV disease. Since it is a monoclonal antibody, it has the potential of causing similar effects as other IgG type monoclonal antibody products, such as hypersensitivity reactions including anaphylaxis.

SVII.5.2 Important Pharmacological Class Effects Not Discussed Above

Palivizumab is a monoclonal antibody containing the framework of human IgG while retaining some murine variable regions of palivizumab to maintain RSV F glycoprotein binding specificity. As such, immune responses could occur that result in an immune complex-mediated disease, such as serum sickness, arthralgias, and vasculitis, or result in

altered palivizumab serum levels or activity. However, there have been no reports of immune complex-mediated adverse events that were caused by the administration of palivizumab in both clinical trials and postmarketing experience.

Module SVIII Summary of the Safety Concerns

The review of safety information as presented in Modules SII, SIV, SVI, and SVII 2, resulted in the conclusion that there are 2 important identified risks for palivizumab, anaphylaxis/anaphylactic shock and hypersensitivity; both of these risks are described in the SmPC. Additionally, 1 safety concern with missing information has been identified as an unknown risk, which is the potential mixture of lyophilised and liquid formulations of palivizumab before injection when both formulations of palivizumab are available in the market. There are no other risks identified from the review of available safety information on palivizumab. The safety concerns categorized as important identified risks and missing information are as follows:

Summary of Safety Concerns	
Important identified risks	Anaphylaxis and anaphylactic shock Hypersensitivity
Important potential risks	None
Missing information	Medication error of mixing lyophilised and liquid paliviziumab before injection.[a]

a. Only possible when both formulations are available in the market.

Part III Pharmacovigilance Plan

III.1 Safety Concerns and Overview of Planned Pharmacovigilance Actions

Routine pharmacovigilance activities are outlined in the MAHs Pharmacovigilance (PV) Master File.

Details of the planned pharmacovigilance actions to address the important identified risks are described in Table 40.

Table 40. Summary of the Planned Pharmacovigilance Actions Beyond Routine Pharmacovigilance Action for the Important Identified Risks

Areas Requiring Confirmation or Further Investigation	Proposed Routine and Additional PhV Activities	Objectives
Safety Concern 1: Anaphylaxis and anaphylactic shock		
None	Routine pharmacovigilance surveillance is being performed.	NA
Safety Concern 2: Hypersensitivity		
None	Routine pharmacovigilance surveillance is being performed.	NA

Table 41. Summary of the Planned Pharmacovigilance Actions Beyond Routine Pharmacovigilance Action for the Missing Information

Areas Requiring Confirmation or Further Investigation	Proposed Routine and Additional PhV Activities	Objectives
Safety Concern 1: Medication error of mixing lyophilised and liquid palivizumab before injection		
Unknown risk	Routine Pharmacovigilance activities.	Relevant postmarketing reports will be monitored and evaluated when received to determine the safety impact of the mixture.

III.2 Additional Pharmacovigilance Activities to Assess Effectiveness of Risk Minimisation Measures

The risk minimization measures rely on the approved Product Information. No activities to assess the effectiveness of Product Information are proposed.

III.3 Studies and Other Activities Completed Since Last Update of Pharmacovigilance Plan

Not applicable.

III.4 Details of Outstanding Additional Pharmacovigilance Activities

III.4.1 Imposed Mandatory Additional Pharmacovigilance Activity (Key to Benefit Risk)

Not applicable.

III.4.2 Mandatory Additional Pharmacovigilance Activity (Being a Specific Obligation)

Not applicable.

III.4.3 Required Additional Pharmacovigilance Activities to Address Specific Safety Concerns or to Measure Effectiveness of Risk Minimisation Measures

Not applicable.

III.4.4 Stated Additional Pharmacovigilance Activities

The completed or ongoing studies of Studies MI-CP116, M03-681, and A11-632 (Table 42) were initiated before the EU PV regulation was in place, when no RMP was required for palivizumab. Therefore, these studies are not part of this PV plan but are listed here for transparency purposes. To note that Study A11-632 was recently re-classified by the Committee for Medicinal Products as a recommendation post approval measure (EMA/CHMP/742393/2012 letter dated 21 November 2012) because this

follow-up measure (FU2 032.4) was not considered key to the benefit/risk balance and no RMP for palivizumab was deemed necessary at any stage post approval until now.

Table 42. Stated Additional Pharmacovigilance Activities

Description of Activity (or study title if known)	Expected Date of Report
Activity 1: Study MI-CP116: A Phase 4, Randomized, Double-Blind Study to Assess the Immune Reactivity of the Liquid and Lyophilised Formulations of Palivizumab (MEDI-493, palivizumab) in Children at High Risk for the Development of Serious RSV Disease.	Study had been completed (02 October 2007) and the final study report is included with the liquid palivizumab marketing authorization application October 2013.
Activity 2: Study M03-681: Palivizumab (Synagis®) Postmarketing Surveillance Cohort Study in Children < 24 Months of Age with Hemodynamically Significant Congenital Heart Disease. Study assessed specific AEs of arrhythmia, infection, and death.	Study had been completed (29 January 2010) and final study report was submitted on 09 February 2011.
Study A11-632: Risk of Autoimmune and Allergic Diseases in Danish and Swedish Children who Received Passive Respiratory Syncytial Virus Prophylaxis: A Population-based Cohort Study.	Study report will be submitted in December 2013.

III.5 Summary of the Pharmacovigilance Plan

III.5.1 Table of On-Going and Planned Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan

There are no on-going and planned additional Pharmacovigilance activities as described in Part III.4.1 through Part III.4.3.

III.5.2 Table of Completed Studies/Activities from the Pharmacovigilance Plan

There are no completed studies for the Pharmacovigilance activities described in Part III.4.1 through Part III.4.3.

Part IV Plans for Post-Authorisation Efficacy Studies

No studies are planned.

Part V Risk Minimisation Measures

V.1 Risk Minimisation Measures by Safety Concern

There are 2 identified safety risks, anaphylaxis/anaphylactic shock and hypersensitivity that have been described for palivizumab. The safety risk of mixing lyophilised and liquid palivizumab before injection is unknown. The risk minimization measures for these safety concerns are presented in the following tables.

Table 43. Identified Risk: Anaphylaxis and Anaphylactic Shock

Safety Concerns: Anaphylaxis and Anaphylactic Shock	
Objective(s) of the risk minimisation measures	Avoid the use of palivizumab in patients allergic to the active substance or to any of the excipients, or other humanized monoclonal antibodies.
Routine risk minimisation measures	Text in SmPC: **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. **4.8 Undesirable effects** Anaphylaxis/anaphylactic shock (in some cases, fatalities have been reported.).
	Comment: None
	Other routine risk minimisation measures: Prescription only medicine.
Additional risk minimisation measure(s)	Objective and justification of why needed: None proposed
	Proposed actions/components and rationale: NA
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	NA
Criteria for judging the success of the proposed risk minimisation measures	NA
Planned dates for assessment	NA
Results of effectiveness measurement	NA
Impact of risk minimisation	NA
Comment	Anaphylactic reaction occurs on an individual and random basis. The SmPC description of this reaction should provide awareness to prescribers of its potential occurrences.

Table 44. Identified Risk: Hypersensitivity

Safety Concern: Hypersensitivity	
Objective(s) of the risk minimisation measures	Avoid the use of palivizumab in patients allergic to the drug and any of its excipients.
Routine risk minimisation measures	Text in SmPC: **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. **4.8 Undesirable effects** Anaphylaxis/anaphylactic shock (in some cases, fatalities have been reported).
	Comment (e.g., on any differences between SmPCs): None
	Other routine risk minimisation measures: Prescription only medicine.
Additional risk minimisation measure(s)	Objective and justification of why needed: None proposed
	Proposed actions/components and rationale: NA
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	NA
Criteria for judging the success of the proposed risk minimisation measures	NA
Planned dates for assessment	NA
Results of effectiveness measurement	NA

Table 44. Identified Risk: Hypersensitivity (Continued)

Safety Concern: Hypersensitivity	
Effectiveness of Risk Minimisation Measures (continued)	
Impact of risk minimisation	NA
Comment	The safety risk of hypersensitivity refers to the immediate allergic reaction to palivizumab or any of its excipients. It occurs on an individual basis. The SmPC description of this reaction including the most serious anaphylaxis and fatal anaphylactic reactions should provide awareness to prescribers of its potential occurrences.

Table 45. Missing Information: Mixing Lyophilised and Liquid Palivizumab Before Injection

Safety Concern: Mixing lyophilised and liquid palivizumab before injection	
Objective(s) of the risk minimisation measures	Avoid the mixing of 2 palivizumab formulations before injection.
Routine risk minimisation measures	Text in proposed liquid formulation SmPC: **4.2 Posology and method of administration** Palivizumab should not be mixed with any medications or diluents. Synagis solution for injection is a ready to use formulation see section 6.6 for special handling requirements. **6.6 Special precautions for disposal and other handling** Do not mix the liquid and the lyophilised formulations. Do not dilute the product.
	Comment (e.g., on any differences between SmPCs): None
	Other routine risk minimisation measures: None
Additional risk minimisation measure(s)	Objective and justification of why needed: None proposed
	Proposed actions/components and rationale: NA
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	NA
Criteria for judging the success of the proposed risk minimisation measures	NA
Planned dates for assessment	NA
Results of effectiveness measurement	NA
Impact of risk minimisation	NA
Comment	Information on this potential safety concern is missing. Wording describing not to mix the 2 formulations before injection is proposed in the SmPC.

V.2 Risk Minimisation Measure Failure

Not applicable.

V.2.1 Analysis of Risk Minimisation Measure(s) Failure

Not applicable.

V.2.2 Revised Proposal for Risk Minimisation

Not applicable.

V.3 Summary Table of Risk Minimisation Measures

Adequate information for the safe and effective use of palivizumab is based upon clinical trial data, epidemiological studies, and more than 14 years of post-marketing experience.

Minimization of the identified safety risks (anaphylaxis/anaphylactic shock and hypersensitivity), as well as the unknown risk of mixing lyophilised and liquid formulations, consists of appropiate wording in the SmPC and patient leaflet. No additional risk minimization measures are proposed.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Anaphylaxis and anaphylactic shock	Text in SmPC: **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 SmPC). Medicinal products for the treatment of severe hypersensitivity reactions, including anaphylaxis and anaphylactic shock, should be available for immediate use following administration of palivizumab. **4.8 Undesirable effects** Anaphylaxis/anaphylactic shock (in some cases, fatalities have been reported).	None proposed

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Hypersensitivity	Text in SmPC: **4.3 Contraindications** Known hypersensitivity to the active substance or to any of the excipients (see Section 6.1 of SmPC), 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 of SmPC). Medicinal products for the treatment of severe hypersensitivity reactions, including anaphylaxis and anaphylactic shock, should be available for immediate use following administration of palivizumab. **4.8 Undesirable effects** Anaphylaxis/anaphylactic shock (in some cases, fatalities have been reported).	None proposed
Mixing of lyophilised and liquid palivizumab before injection	Text in proposed liquid formulation SmPC: **4.2 Posology and method of administration** Palivizumab should not be mixed with any medications or diluents. Synagis solution for injection is a ready to use formulation see section 6.6 for special handling requirements. **6.6 Special precautions for disposal and other handling** Do not mix the liquid and the lyophilised formulations. Do not dilute the product.	None proposed

Part VI Summary of Activities in the Risk Management Plan by Product

VI.1 Elements for Summary Tables in the European Public Assessment Report (EPAR)

VI.1.1 Summary Table of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Anaphylaxis and anaphylactic shock Hypersensitivity
Important potential risks	None
Missing information	Mixing of lyophilised and liquid Synagis before injection

VI.1.2 Table of On-Going and Planned Studies in the Post-Authorization Pharmacogivilance Development Plan

There are no on-going and planned additional Pharmacovigilance activities as described in Part III.4.1 through Part III.4.3.

VI.1.3 Summary of Post-Authorisation Efficacy Development Plan

No studies are planned.

VI.1.4 Summary Table of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Anaphylaxis and anaphylactic shock	Known hypersensitivity to the active substance or to any of the excipients (ingredients), or other humanised monoclonal antibodies is listed in the contraindications section (Section 4.3 of the SmPC). Warnings for anaphylaxis and anaphylactic shock are in the Special warnings and precautions for use in Section 4.4 of the SmPC. Products for the treatment of severe hypersensitivity reactions, including anaphylaxis and anaphylactic shock, should be available for immediate use following administration of palivizumab. Anaphylaxis/anaphylactic shock is listed as an adverse reaction in Section 4.8 of the SmPC.	None proposed.
Hypersensitivity	Contraindications for known hypersensitivity to the active substance (palivizumab) or to any of the excipients (other ingredients), or to humanised monoclonal antibodies (a monoclonal antibody is a type of protein that has been designed to recognise and attach to a specific structure called an antigen) are included in Section 4.3 of the SmPC. Warnings for anaphylaxis and anaphylactic shock are in the Special warnings and precautions for use in Section 4.4 of the SmPC. Products for the treatment of severe hypersensitivity reactions, including anaphylaxis and anaphylactic shock, should be available for immediate use following administration of palivizumab. Anaphylaxis/anaphylactic shock (in some cases, fatalities have been reported.) is listed in the Adverse Drug Reaction table in Section 4.8 with a frequency of "Not known."	None proposed.
Mixing of lyophilised and liquid palivizumab before injection	Information is provided in Sections 4.2 and 6.6 of SmPC that no mixing of liquid palivizumab with any medications, diluents, or lyophilised palivizumab should be done.	None proposed.

VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

- Respiratory syncytial virus (RSV) is a virus that infects lungs and respiratory tract. It is a major cause of respiratory illness in young children that results in an estimated 33.8 million new episodes yearly worldwide in children younger than 5 years of age. RSV disease also results into high mortality among premature children (approximately 8.1%).
- Up to 69% of children are infected with RSV during their first year of life and up to 99% are infected by 2 years of age.
- Infants aged 6 weeks to 6 months have the highest rates of RSV infection.
- Among infants, RSV has been estimated to cause up to 90% of all hospitalizations resulting from bronchiolitis (inflammation of the smallest air passages of the lung) and up to 50% of all pneumonia admissions.
- RSV-related hospitalization and deaths are higher in pre-term infants and children with bronchopulmonary dysplasia (a type of chronic lung disease of infancy) or congenital heart disease (heart defect at birth) than in full-term and healthy children.

VI.2.2 Summary of Treatment Benefits

Synagis is the only available drug approved for preventing serious RSV disease. It is a drug that includes a man-made, disease-fighting protein called an antibody that works directly against RSV. Synagis is given as an injection, usually in the thigh muscle, by a healthcare provider. Two large clinical studies of Synagis were conducted for the prevention of serious lung disease caused by RSV in children at high risk for RSV infection.

- Study 1: Children with prematurity and/or bronchopulmonary dysplasia (a type of chronic lung disease of infancy) received Synagis (1002 children) or placebo containing no Synagis (500 children) as comparative groups. A dose of 15 mg/kg Synagis once a month for 5 months decreased the frequency of RSV-related hospitalization by 55% compared with the placebo group; this result was statistically significant.
- Study 2: Children with congenital heart disease (heart defect at birth) received Synagis (639 children) or placebo containing no Synagis (648 children) as comparative groups. A dose of 15 mg/kg once a month for 5 months reduced the frequency of RSV-related hospitalization by 45% compared with the placebo group; this result was statistically significant.
- The occurrence of side effects was low in these 2 studies and the reported side effects were not significantly different between Synagis and placebo groups.

VI.2.3 Unknowns Relating to Treatment Benefits

The main and supporting Synagis studies were conducted in many countries or regions around the world. These studies included patients from various ethnic and cultural backgrounds who were younger than 2 years of age at high risk for RSV infection. There is no evidence to suggest that there are differences in efficacy or safety between patient populations of whites versus non-whites, Hispanics versus non-Hispanics, or males versus females.

VI.2.4 Summary of Safety Concerns

In general, the sources used to describe what is known about the identified risks described in the table below were taken from the Synagis Patient Information Leaflet, the National Health Service website homepage (http://www.nhs.uk/Pages/HomePage.aspx as accessed on 01 July 2013), and the Mayo Clinic website homepage (http://www.mayoclinic.com/ as accessed on 01 July 2013).

Important Identified Risks

Risk	What Is Known	Preventability
Life-threatening allergic reactions or allergic shock (Anaphylaxis and anaphylactic shock)	Anaphylaxis is a serious allergic reaction that may cause death. It can occur within seconds or minutes of exposure to substances that you are allergic to. However, it can also occur a half hour or longer after exposure. The symptoms include hives, itching, rash, wheezing or trouble breathing, nausea, vomiting, diarrhea, dizziness or fainting. Anaphylaxis requires immediate emergency management. Anaphylaxis can occur at any time to any person for various reasons. The occurrence of anaphylaxis in patients who received Synagis is very rare. Patients with any history of allergy to Synagis, any of its ingredients, or other types of human antibodies have a higher chance to experience this reaction.	The reaction can be prevented by avoiding Synagis injection if you are allergic to Synagis, any of its ingredients, or other human antibodies. Seeking emergency medical care when symptoms are noticed will allow the allergic reactions to be managed early and prevent the potential very rare occurrence of death.
Allergic reaction (Hypersensitivity)	Hypersensitivity is an allergic disorder of your immune system (the system that helps protect the body against diseases). Allergic reactions can be mild or severe. Mild hypersensitivities, such as itching and rash, are very common among people. Severe reactions can be life-threatening or cause death, such as anaphylaxis. The onset of allergy symptoms is usually rapid. Mild allergic reactions can go away (resolve) without special treatment; however, serious allergic reactions require immediate emergency attention. Hypersensitivity has been reported as occurring in few patients who have received Synagis. Patients with any history of allergy to Synagis, any of the ingredients in Synagis, or other types of human antibodies, have a higher chance of experiencing these reactions.	The reaction can be prevented by avoiding Synagis injection if you are allergic to Synagis, any of its ingredients, or other human antibodies. Seeking emergency medical care when symptoms are noticed will allow the allergic reactions to be managed early and prevent the potential very rare occurrence of death.

Missing Information

Risk	What Is Known
Mixing of lyophilised and liquid Synagis before injection	Synagis has 2 forms – freeze-dried and liquid. The freeze-dried form needs water to make it a liquid before injection. Besides Synagis antibody, the 2 forms contain different additives and, therefore, it is not recommended to mix them for injection. It is not known whether the mixture of the 2 forms of Synagis before injection can cause any health problems to patients.

VI.2.5 Summary of Additional Risk Minimisation Measures by Safety Concern

All medicines have a Summary of Product Characteristics (SmPC), which provides physicians, pharmacists, and other healthcare professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimization measures.

The SmPC and the PL for Synagis can be found in the Synagis EPAR page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned Post-Authorisation Development Plan

List of Studies in Post-Authorisation Development Plan

None.

Studies Which Are a Condition of the Marketing Authorisation

No studies are conditions of the marketing authorization.

VI.2.7 Summary of Changes to the Risk Management Plan Over Time

This is not applicable as this is the first edition of the Risk Management Plan.

Annex 7. Specific Adverse Event Follow-Up Forms

None.

Annex 10. Details of Proposed Additional Risk Minimisation Measures

Not applicable.