NEW ZEALAND DATA SHEET

1. SYNAGIS® palivizumab (rmc) solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SYNAGIS 50 mg*: Each vial contains 50 mg/0.5 mL palivizumab.

SYNAGIS 100 mg: Each vial contains 100 mg/mL palivizumab.

Palivizumab is produced by DNA technology in recombinant mouse myeloma cells (rmc).

For a full list of excipients, see section 6.1.

* This presentation is not currently available in New Zealand.

3. PHARMACEUTICAL FORM

The solution is clear or slightly opalescent.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Synagis (palivizumab) is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in children at high risk of RSV disease. Safety and efficacy were established in children with bronchopulmonary dysplasia (BPD), infants with a history of prematurity (gestational age less than or equal to 35 weeks at birth) and children with haemodynamically significant congenital heart disease (CHD), see section 5.1 - Clinical Efficacy and Safety.

4.2 Dose and Method of Administration

Palivizumab is to be administered by intramuscular injection only.

Each palivizumab vial is for use in one patient on one occasion only. To prevent the transmission of infectious diseases, sterile disposable syringes and needles should be used. Do not reuse syringes and needles.

Dose

The recommended dose of palivizumab is 15 mg/kg of body weight, given once a month during anticipated periods of RSV risk in the community. Where possible, the first dose should be administered prior to commencement of the RSV season and subsequent doses should be administered monthly throughout the RSV season. To avoid risk of reinfection, it is recommended that children receiving palivizumab who become infected with RSV continue to receive monthly doses of palivizumab for the duration of the RSV season.

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

Method of Administration

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

For instructions on the preparation of the medicine before administration, see section 6.6.

4.3 Contraindications

Synagis is contraindicated in patients with known hypersensitivity to Synagis or to any of its excipients listed in section 6.1. It is also contraindicated in patients with known hypersensitivity to other humanised monoclonal antibodies.

4.4 Special Warnings and Precautions for Use

Allergic reactions including very rare anaphylaxis and anaphylactic shock have been reported following palivizumab administration. In some cases, fatalities have been reported (see section 4.8 Undesirable Effects - Post-Marketing Experience).

Medications for the treatment of severe hypersensitivity reactions, including anaphylaxis and anaphylactic shock should be available for immediate use following administration of palivizumab. If a severe hypersensitivity reaction occurs, therapy with palivizumab should be discontinued. As with other agents administered to this population, if milder hypersensitivity reactions occur, caution should be used on re-administration of palivizumab.

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

The single-use vial of palivizumab does not contain a preservative.

A moderate to severe acute infection or febrile illness may warrant delaying the use of palivizumab, unless, in the opinion of the physician, withholding palivizumab entails a greater risk. A mild febrile illness, such as a mild upper respiratory infection, is not usually reason to defer administration of palivizumab.

4.5 Interactions with Other Medicines and Other Forms of Interactions

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

Since the monoclonal antibody is specific for RSV, palivizumab is not expected to interfere with the immune response to vaccines, including live viral vaccines.

Laboratory Test Interactions

Palivizumab may interfere with immune-based RSV diagnostic tests, such as some antigen detection-based assays. In addition, palivizumab inhibits virus replication in cell culture and, therefore, may also interfere with viral culture assays. Palivizumab does not interfere with reverse transcriptase polymerase chain reaction-based assays. Assay interference could lead to false-negative RSV diagnostic test results. Therefore, diagnostic test results, when obtained, should be used in conjunction with clinical findings to guide medical decisions.

4.6 Fertility, Pregnancy and Lactation

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

4.7 Effects on Ability to Drive and Use Machines

Not relevant.

4.8 Undesirable Effects

Summary of the Safety Profile

In the combined paediatric prophylaxis studies, the proportions of subjects in the placebo and palivizumab groups who experienced any adverse event or any serious adverse event were similar. The majority of adverse events were transient, and mild to moderate in severity. In the study of premature infants and children with bronchopulmonary dysplasia, no medically important differences in adverse events by body system or in subgroups of children categorised by gender, age, gestational age, country, ethnicity or quartile serum palivizumab concentration were observed. No significant difference in safety profile was observed between children without active RSV infection and those hospitalised for RSV. Permanent discontinuation of palivizumab because of adverse events was rare (0.2%). Deaths were balanced between the placebo and palivizumab treatment groups, and were not drug-related.

Tabulated Summary of Adverse Reactions

As shown in Table 1, very common (≥ 10%) adverse events reported with Synagis include upper respiratory infection, otitis media, rhinitis, fever, rash, cough, diarrhoea and wheeze. Table 6 also provides a listing and incidence of all common (≥ 1%) adverse events when compared to placebo.

Table 1: Summary of Adverse Events Reported in More Than 1.0% of Synagis Group, Paediatric Prophylaxis Studies

Adverse Event Code	SYNAGIS [n = 1168] No. of Patients		Placebo [n = 520] No. of Patients	
URI	573	(49.1%)	253	(48.7%)
Otitis Media	449	(38.4%)	209	(40.2%)
Rhinitis	348	(29.8%)	130	(25.0%)
Fever	301	(25.8%)	144	(27.7%)
Rash	295	(25.3%)	116	(22.3%)
Cough	213	(18.2%)	95	(18.3%)
Diarrhoea	179	(15.3%)	96	(18.5%)
Wheeze	154	(13.2%)	72	(13.8%)
Nervousness	114	(9.8%)	54	(10.4%)
Vomiting	109	(9.3%)	51	(9.8%)
Bronchiolitis	107	(9.2%)	52	(10.0%)
Conjunctivitis	105	(9.0%)	56	(10.8%)
Pain	94	(8.0%)	35	(6.7%)
Pneumonia	89	(7.6%)	45	(8.7%)
Oral Moniliasis	87	(7.4%)	47	(9.0%)
Gastroenteritis	85	(7.3%)	49	(9.4%)
Infection, Viral	83	(7.1%)	38	(7.3%)
Hernia	71	(6.1%)	30	(5.8%)
AST Increased	70	(6.0%)	19	(3.7%)
Anaemia	66	(5.7%)	10	(1.9%)
Respiratory Disorder	64	(5.5%)	36	(6.9%)
Gastrointestinal Disorder	62	(5.3%)	30	(5.8%)
Constipation	59	(5.1%)	35	(6.7%)
Fungal Dermatitis	52	(4.5%)	26	(5.0%)
ALT Increased	35	(3.0%)	14	(2.7%)

Adverse Event Code	SYNAGIS [n = 1168] No. of Patients		Placebo [n = 520] No. of Patients	
Accidental Injury	34	(2.9%)	17	(3.3%)
Dyspnoea	30	(2.6%)	12	(2.3%)
Eczema	29	(2.5%)	15	(2.9%)
Injection Site Reaction, Other	28	(2.4%)	11	(2.1%)
Pharyngitis	28	(2.4%)	7	(1.3%)
Study Drug Injection Site Reaction	27	(2.3%)	9	(1.7%)
Flu Syndrome	25	(2.1%)	19	(3.7%)
Bronchitis	22	(1.9%)	13	(2.5%)
Miscellaneous Procedure	22	(1.9%)	12	(2.3%)
RSV	22	(1.9%)	21	(4.0%)
Apnoea	20	(1.7%)	13	(2.5%)
Flatulence	20	(1.7%)	10	(1.9%)
Sinusitis	19	(1.6%)	12	(2.3%)
Ear Disorder	18	(1.5%)	10	(1.9%)
Urinary Tract Infection	18	(1.5%)	7	(1.3%)
Asthma	17	(1.5%)	10	(1.9%)
Failure to Thrive	16	(1.4%)	5	(1.0%)
Seborrhoea	16	(1.4%)	7	(1.3%)
Injection Site Reaction	15	(1.3%)	1	(0.2%)
BUN Increased	13	(1.1%)	4	(0.8%)
Croup	13	(1.1%)	9	(1.7%)
Feeding Abnormal	13	(1.1%)	17	(3.3%)
Liver Function Tests Abnormal	13	(1.1%)	5	(1.0%)
Ecchymosis	12	(1.0%)	4	(0.8%)
Hypertonia	12	(1.0%)	1	(0.2%)

CHD Study

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

Adverse events that occurred in more than 1% of patients receiving palivizumab and for which the incidence was 1% greater in the palivizumab group than in the placebo group are shown in Table 2.

Table 2: Adverse Events by Body System (Total Population)

BODY SYSTEM	Palivizumab	Placebo	p-value
Total number of events	4169	4518	
Total number of children with one or more events	611 (95.6%)	625 (96.5%)	0.477
Haemic and lymphatic system	52 (8.1%)	70 (10.8%)	0.107
Endocrine system	5 (0.8%)	3 (0.5%)	0.504
Metabolic and nutritional disorders	48 (7.5%)	72 (11.1%)	0.028
Nervous system	89 (13.9%)	106 (16.4%)	0.244
Special senses	237 (37.1%)	250 (38.6%)	0.605
Cardiovascular system	286 (44.8%)	315 (48.6%)	0.180
Respiratory system	525 (82.2%)	547 (84.4%)	0.296
Digestive system	323 (50.5%)	344 (53.1%)	0.372
Skin and Appendages	197 (30.8%)	224 (34.6%)	0.154
Musculoskeletal	3 (0.5%)	5 (0.8%)	0.726
Urogenital system	41 (6.4%)	54 (8.3%)	0.202
Body as a whole	342 (53.5%)	332 (51.2%)	0.435

Other adverse events reported in 1% or more of the palivizumab group included:

BODY SYSTEM	Adverse Event
Metabolic and Nutritional Disorders	Anaemia, failure to thrive
Nervous System	Nervousness, somnolence
Cardiovascular System	Coagulation disorder, haemorrhage, hypokalemia, congestive heart failure, thrombocytopenia, heart failure, cardiovascular disorder, pericardial effusion, tachycardia, bradycardia
Respiratory System	Otitis media, rhinitis, cough, wheeze, bronchiolitis, pneumonia, respiratory disorders, dyspnoea, pharyngitis, pleural effusion, hyperventilation, stridor, pulmonary hypertension, lung oedema, atelectasis, pneumothorax, hypoxia, bronchitis, RSV, apnoea, sinusitis, ear disorder, croup
Digestive System	Diarrhoea, vomiting, oral moniliasis, gastroenteritis, gastrointestinal disorder, constipation, flatulence, feeding abnormalities
Skin and Appendages	Rash, fungal dermatitis, eczema
Urogenital System	Urinary tract infection
Body as a Whole	Pain (primarily teething), viral infection, accidental injury, oedema, bacterial infection, fungal infection, sepsis, flu syndrome

Extended Dose Study

No reported adverse events were considered related to palivizumab and no deaths were recorded.

Solution for Injection Studies

Two clinical studies were conducted to directly compare the solution for injection and lyophilised powder for injection* presentations of palivizumab. In the first study, all 153 premature infants received both palivizumab presentations in different sequences. In the second study, 211 and 202 premature infants or children with chronic lung disease received both palivizumab presentations, respectively. In two additional studies, palivizumab solution for injection was used as an active control (3918 paediatric subjects) to evaluate an investigational monoclonal antibody for prophylaxis of serious RSV disease in premature infants or children with BPD or haemodynamically significant CHD. The overall rate and pattern of adverse events, study medication discontinuation due to AEs, and the number of deaths reported in these clinical studies were consistent with those observed during the clinical development programs for the lyophilised formulation. No deaths were considered related to palivizumab and no new ADRs were identified in these studies.

(* Powder for injection presentation has been discontinued)

Immunogenicity

In the IMpact-RSV trial, the incidence of anti-palivizumab antibody following the fourth injection was 1.1% in the placebo group and 0.7% in the palivizumab group. In paediatric patients receiving palivizumab for a second season, one of the fifty-six patients had transient, low titre reactivity. This reactivity was not associated with adverse events or alteration in palivizumab serum concentrations. Immunogenicity was not assessed in the CHD Study.

Antibody to palivizumab was also evaluated in four additional studies in 4337 palivizumab-treated patients (children born at 35 weeks of gestation or less and 6 months of age or less, or < 24 months of age with bronchopulmonary dysplasia or with haemodynamically significant congenital heart disease were included in these studies), and was observed in 0% - 1.5% of patients at different study time points. There was no association observed between the presence of antibody and adverse events. Therefore, anti-drug antibody (ADA) responses appear to be of no clinical relevance.

In one infant in the Extended Dose Study (n=18), after the second dose of palivizumab, transient low levels of anti-palivizumab antibody, dropping to undetectable levels at the fifth and seventh dose, were observed.

A trial of high-risk preterm children less than or equal to 24 months of age was conducted to evaluate the immunogenicity of the lyophilised formulation of Synagis and the liquid formulation of Synagis. Three hundred seventy-nine children contributed to the 4 to 6 months post-final dose analysis. The rate of anti-palivizumab antibodies at this time point was low in both formulation groups (anti-palivizumab antibodies were not detected in any subject in the liquid formulation group and were detected in one subject in the lyophilised group (0.5%), with an overall rate of 0.3% for both treatment groups combined).

These data reflect the percentage of children whose test results were considered positive for antibodies to palivizumab in an enzyme-linked immunosorbent assay (ELISA) and are highly dependent on the sensitivity and specificity of the assay.

The ELISA has substantial limitations in detecting anti-palivizumab antibodies in the presence of palivizumab. Immunogenicity samples tested with the ELISA assay likely contained palivizumab at levels that may interfere with the detection of anti-palivizumab antibodies.

An electrochemical luminescence (ECL) based immunogenicity assay, with a higher tolerance for palivizumab presence compared to the ELISA, was used to evaluate the presence of anti-palivizumab antibodies in subject samples from two additional clinical trials. The rates of anti-palivizumab antibody positive results in these trials were 1.1% and 1.5%.

Post-Marketing Experience

The following adverse reactions have been reported with palivizumab therapy. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to palivizumab exposure (see section 4.4)

Blood and the lymphatic system disorders: Thrombocytopenia.

Immune system disorders: Allergic manifestations to palivizumab (including immediate hypersensitivity reactions such as anaphylaxis, anaphylactic shock, angioedema, dyspnoea, asthma, bronchospasm and pruritus). In some cases, fatalities have been reported.

Nervous system disorders: Convulsions.

Respiratory, thoracic and mediastinal disorders: Apnoea.

Skin and subcutaneous tissue disorders: Urticaria.

A compliance registry (REACH program) of nearly 20,000 palivizumab-treated infants obtained treatment schedules and spontaneously reported adverse events. 1250 enrolled infants received 6 injections, 183 infants received 7 injections and 27 infants received either 8 or 9 injections. From this registry and from routine post-marketing reports, adverse events observed in patients following a sixth or greater dose were similar in character and frequency to those after the initial five doses.

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

From post-marketing experience, overdoses with doses up to 85 mg/kg have been reported and, in some cases, adverse reactions were reported which did not differ from those observed with 15 mg/kg dose (see section 4.8 Undesirable effects). In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: immune sera immunoglobulins, specific immunoglobulins; ATC Code**:** J06BB16.

CAS Number: 188039-54-5.

Palivizumab is a humanised IgG1 monoclonal antibody directed to an epitope in the A antigenic site of the fusion protein of respiratory syncytial virus (RSV). This humanised monoclonal antibody is composed of 95% human and 5% murine amino acid sequences. Palivizumab is composed of two heavy chains and two light chains having a molecular weight of approximately 148,000 Daltons.

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

The *in vivo* neutralising activity of the active ingredient in palivizumab was assessed in a randomised, placebo-controlled study of 35 paediatric patients tracheally intubated because of RSV disease. A total

of 17 of the 35 children enrolled received intravenous infusions of palivizumab at a dose of 15 mg/kg. For patients with both a day 0 and day 1 result the mean decline in RSV log pfu (plaque forming units) from day 0 to day 1, measured in tracheal aspirates was 0.6 in patients given placebo and 1.7 in patients given palivizumab (p = 0.004, Wilcoxon rank sum test). There was no statistically significant difference between placebo and palivizumab in the reduction of RSV replication in nasal washings. Mean serum palivizumab levels were 131.3 micrograms/mL (range: 33.4 to 198.4) on day 1 and 105.5 micrograms/mL (range: 23.3 to 204.1) on day 2.

Microbiology

Antiviral Activity

The antiviral activity of palivizumab was assessed in a micro-neutralisation assay in which increasing concentrations of antibody were incubated with RSV prior to addition of the human epithelial cells HEp-2. After incubation for 4 - 5 days, RSV antigen was measured in an enzyme-linked immunosorbent assay (ELISA). The neutralisation titre (50% effective concentration [EC_{50}]) is expressed as the antibody concentration required to reduce detection of RSV antigen by 50% compared with untreated virus-infected cells. Palivizumab exhibited median EC_{50} values of 0.65 micrograms/mL (mean [standard deviation] = 0.75 [0.53] micrograms/mL; n = 69, range 0.07 - 2.89 micrograms/mL) and 0.28 micrograms/mL (mean [standard deviation] = 0.35 [0.23] micrograms/mL; n = 35, range 0.03 - 0.88 micrograms/mL) against clinical RSV A and RSV B isolates, respectively. The majority of clinical RSV isolates tested (n = 96) were collected from subjects in the United States with the remainder from Japan (n = 1), Australia (n = 5) and Israel (n = 2). These isolates encoded the most common RSV F sequence polymorphisms found among clinical isolates worldwide.

Resistance

Palivizumab binds a highly conserved region on the extracellular domain of mature RSV F protein, referred to as antigenic site II or A antigenic site, which encompasses amino acids 262 to 275. All RSV mutants that exhibit resistance to palivizumab have been shown to contain amino acid changes in this region on the F protein. No known polymorphic or non-polymorphic sequence variations outside of the A antigenic site on RSV F protein have been demonstrated to render RSV resistant to neutralisation by palivizumab. At least one of the palivizumab resistance-associated substitutions, N262D, K272E/Q, or S275F/L, was identified in 8 of 126 clinical RSV isolates from subjects who failed immunoprophylaxis, resulting in a combined resistance-associated mutation frequency of 6.3%. A review of clinical findings revealed no association between A antigenic site sequence changes and RSV disease severity among children receiving palivizumab immunoprophylaxis who develop RSV lower respiratory tract disease. Analysis of 254 clinical RSV isolates, collected from immunoprophylaxis-naïve subjects, revealed palivizumab resistance-associated substitutions in 2 (1 with N262D and 1 with S275F), resulting in a resistance associated mutation frequency of 0.79%.

Clinical Efficacy and Safety

The safety and efficacy of palivizumab were assessed in a randomised, double-blind, placebo-controlled trial (IMpact-RSV Trial) of RSV disease prophylaxis among children with premature birth and children with bronchopulmonary dysplasia, and in a randomised double-blind, placebo-controlled trial of RSV disease prophylaxis among children with haemodynamically significant congenital heart disease (CHD Study). Additional clinical studies conducted following the initial approval of palivizumab have provided further data on the safety and effectiveness of palivizumab prophylaxis for the prevention of RSV-related diseases among the similar paediatric populations.

Studies using Powder for Injection*

(* Powder for injection presentation has been discontinued)

IMpact-RSV Trial

This trial, conducted at 139 centres in the United States, Canada and the United Kingdom, studied patients less than or equal to 24 months of age with bronchopulmonary dysplasia (BPD) and patients with premature birth (less than or equal to 35 weeks gestation) who were less than or equal to 6 months of age at study entry. Patients with uncorrected congenital heart disease were excluded from enrolment. In this trial, 500 patients were randomised to receive five monthly placebo injections and 1,002 patients were

randomised to receive five monthly injections of 15 mg/kg of lyophilised palivizumab. Subjects were randomised into the study and were followed for safety and efficacy for 150 days. Ninety-nine percent of all subjects completed the study and 93% received all five injections. The primary endpoint was the incidence of RSV hospitalisation.

The incidence of RSV related hospitalisation was 10.6% in the placebo group and 4.8% in the palivizumab group, a relative reduction of 54.8% ($p < 0.001$). There was also a statistically significant reduction in RSV hospitalisation for the subgroups of children with BPD (38.5% relative reduction, $p = 0.038$) and those with prematurity (78.1% relative reduction for children with gestation $\leq$ 35 weeks, $p < 0.001$, and 54% relative reduction for children with gestation $\leq$ 32 weeks, $p < 0.05$). The smallest relative risk reductions and therefore the least benefit occurred in children with the most severe BPD - those requiring ongoing oxygen (94% relative risk) or oxygen in the last 6 months (70% relative risk). Children receiving ongoing steroids who were treated with palivizumab had a higher rate of hospitalisation for RSV infection than did those receiving ongoing steroids who were not treated with palivizumab (relative risk 139%). No statistical significance levels are available for the BPD subgroups.

Among secondary endpoints, the incidence of ICU admission during hospitalisation for RSV infection was lower among subjects receiving palivizumab (1.3%) than among those receiving placebo (3.0%) but there was no difference in the mean duration of ICU care between the two groups for patients requiring ICU care. Overall, the data do not suggest that RSV illness was less severe among patients who received palivizumab and who required hospitalisation due to RSV infection than among placebo patients who required hospitalisation due to RSV infection. Palivizumab did not alter the incidence and mean duration of hospitalisation of non-RSV respiratory illness or the incidence of otitis media.

Table 3: Secondary Efficacy Endpoints from IMpact-RSV Trial

	Placebo	**SYNAGIS 15 mg/kg**	**p-value[1]**
Number of Children	n = 500	n = 1002	---
Days of RSV Hospitalisation			< 0.001
Total Days	313.1	364.6	
Total Days/100 Children[2]	62.6	36.4	
ICU Admitted:			0.03
No	485 (97.0%)	989 (98.7%)	
Yes	15 (3.0%)	13 (1.3%)	
Days of ICU Stay			0.02
Total Days	63.5	133.6	
Total Days/100 Children[2]	12.7	13.3	
Mechanical Ventilation Required:			0.28
No	499 (99.8%)	995 (99.3%)	
Yes	1 (0.2%)	7 (0.7%)	
Days of Mechanical Ventilation			0.21
Total Days	8.3	83.7	
Total Days/100 Children[2]	1.7	8.4	
Hospital Days of Increased Supplemental O_2 Therapy[3]			< 0.001
Total Days	253.0	304.0	
Total Days/100 Children[2]	50.6	30.3	
RSV Hospital Days with LRI Score $\geq$ 3			< 0.001
Total Days	237.0	297.0	
Total Days/100 Children[2]	47.4	29.6	

1. p-values for total days of RSV hospitalisation/100 children, ICU stay/100 children, mechanical ventilation/100 children, increased supplemental oxygen/100 children and RSV hospital days with LRI score $\geq$ 3/100 children were obtained from Wilcoxon Rank Sum Test. p-values for incidence of ICU stay and incidence of mechanical ventilation were obtained from Fisher's exact test.
2. The total days divided by the total number of children randomised and multiplied by 100.
3. For O_2 supplementation above pre-illness value.

Table 4: Incidence of RSV Hospitalisation by Stratum for Study MI-CP048

	Palivizumab	Placebo	% Reduction	p-value
Cyanotic Stratum	n = 339	n = 343	29%	0.285
RSV hospitalisation*	19 (5.6%)	27 (7.9%)		
No SRV hospitalisation	320 (94.4%)	316 (92.1%)		
Other Stratum	n = 300	n = 305	58%	0.003
RSV hospitalisation	15 (5.0%)	36 (11.8%)		
No RSV hospitalisation	285 (95.0%)	269 (88.2%)		

* children with >1 hospitalisation were counted only once

p-value obtained from Fisher's exact test

Table 5: Secondary Efficacy Endpoints for Study MI-CP048

	Palivizumab	Placebo	% Reduction	p-value
Days RSV hospitalisation				
Total Days	367	836	56%	0.003
Days/100 children	57.4	129.0		
RSV hospital days of ↑ supplemented oxygen				
Total Days	178	658	73%	0.014
Days/100 children	27.9	101.5		
RSV associated ICU admission				
Yes	13 (2.0%)	24 (3.7%)	46%	0.094
Total Days	101	461		0.80
Days/100 children	15.9	71.2	78%	
RSV associated Mechanical ventilation				
Yes	8 (1.3%)	14 (2.2%)	41%	0.282
Total Days	42	354		0224
Days/100 children	6.5	54.7		

p-values for total days were obtained from the Wilcoxon test; p-values for incidence were obtained from Fisher's exact test.

CHD Study

This trial, conducted at 76 centres in the United States, Canada, France, Germany, Poland, Sweden and the United Kingdom, studied patients less than or equal to 24 months of age with haemodynamically significant CHD. In this trial, 648 patients were randomised to receive five monthly placebo injections and 639 patients were randomised to receive five monthly injections of 15 mg/kg of lyophilised palivizumab. The trial was conducted during four consecutive RSV seasons. Subjects were stratified by

cardiac lesion (cyanotic vs. other) and were followed for safety and efficacy for 150 days. Ninety-six percent (96%) of all subjects completed the study and 92% received all five injections. The primary endpoint was the incidence of RSV hospitalisation.

RSV hospitalisations occurred among 63 of 648 (9.7%) patients in the placebo group and 34 of 639 (5.3%) patients in the palivizumab group, a 45% reduction (p = 0.003). The reduction of RSV hospitalisation was consistent over time, across geographic regions, across stratification by anatomic cardiac lesion (cyanotic vs. other) and within subgroups of children defined by gender, age, weight, race and presence of RSV neutralising antibody at entry. The secondary efficacy endpoints that showed significant reductions in the palivizumab group compared to placebo included total days of RSV hospitalisation (56% reduction, p = 0.003) and total RSV days with increased supplemental oxygen (73% reduction, p = 0.014).

Studies using Solution for Injection

Pre-term Infants and Children with CLD of Prematurity (CLDP)

This trial, conducted at 347 centres in the North America, European Union and 10 other countries, studied patients less than or equal to 24 months of age with CLDP and patients with premature birth (less than or equal to 35 weeks gestation) who were less than or equal to 6 months of age at study entry. Patients with haemodynamically significant congenital heart disease were excluded from enrolment in this study and were studied in a separate study. In this trial, patients were randomised to receive 5 monthly injections of 15 mg/kg of liquid palivizumab (n = 3306) used as active control for an investigational monoclonal antibody (n = 3329). Subjects were followed for safety and efficacy for 150 days. Ninety-eight percent of all subjects receiving palivizumab completed the study and 97% received all five injections. The primary endpoint was the incidence of RSV hospitalisation.

RSV hospitalisations occurred among 62 of 3306 (1.9%) patients in the palivizumab group. The RSV hospitalisation rate observed in patients enrolled with a diagnosis of CLDP was 28/723 (3.9%) and in patients enrolled with a diagnosis of prematurity without CLDP was 34/2583 (1.3%).

CHD Study 2

This trial, conducted at 162 centres in North America, European Union and four other countries over two RSV seasons, studied patients less than or equal to 24 months of age with haemodynamically significant CHD. In this trial, patients were randomised to receive 5 monthly injections of 15 mg/kg of palivizumab solution for injection (n = 612) used as active control for an investigational monoclonal antibody (n = 624). Subjects were stratified by cardiac lesion (cyanotic vs. other) and were followed for safety and efficacy for 150 days. Ninety-seven percent of all subjects receiving palivizumab completed the study and 95% receive all five injections. The primary endpoint was a summary of adverse events and serious adverse events, and the secondary endpoint was the incidence of RSV hospitalisation. The incidence of RSV hospitalisation was 16 of 612 (2.6%) in the palivizumab group.

Extended Dose Study

An open label, prospective safety and pharmacokinetics study examined the safety, tolerance and pharmacokinetics of palivizumab when administered for up to 7 months in Saudi Arabia, a subtropical region where the reported RSV season is frequently longer than in temperate countries. Eighteen preterm infants (less than 34 weeks gestation), ranging in age from newborn to 29 weeks, with or without chronic lung disease (CLD), judged to be at risk for RSV infection, and palivizumab-naïve, were included in the study. Lyophilised palivizumab 15 mg/kg was injected once per month, for up to 7 months during the RSV season.

Palivizumab levels in the extended dose study were comparable to those achieved in the Impact- RSV trial. No significant elevations of anti-palivizumab antibody titre were observed.

5.2 Pharmacokinetic Properties

Solution for Injection

The pharmacokinetics and safety of palivizumab solution for injection and lyophilised powder for injection, following 15 mg per kg intramuscular administration, were compared in a cross-over trial of 153 infants less than or equal to 6 months of age with a history of prematurity (less than or equal to 35 weeks gestational age). The results of this trial indicated that the trough serum concentrations of palivizumab were similar between both presentations, i.e. solution for injection and lyophilised powder for injection, and bioequivalence between both presentations was demonstrated.

*Powder for Injection**

(* Powder for injection presentation has been discontinued)

Two formulations were studied in the clinical development of palivizumab. Early studies used a liquid phosphate-buffered saline formulation with a concentration of 10 mg palivizumab/mL. All other studies used the commercial lyophilised formulation. In all studies, the collection of multiple serum samples from children was intentionally limited to reduce the number of blood draws in these patients. Therefore, a complete assessment of the pharmacokinetics on the commercial formulation by intramuscular administration could only be obtained from a study performed in adult volunteers. Given the volume constraints for intramuscular dosing, the maximum dose that could be studied in adults was 3 mg/kg. Repeat single 3 mg/kg intramuscular doses were studied in four healthy adults with the results as follows:

Table 6: Pharmacokinetics in Healthy Adults (n = 4) at 3 mg/kg Dose by Intramuscular Administration

Dose Period	**C_{max} (µg/mL)**	**t_{max} (days)**	**$AUC_{0-\infty}$ (µg/day/mL)**	**$t_{1/2}$ (days)**
1 (Days 0-30)	28.2 ± 6.48	4.50 ± 1.732	906 ± 195.0	20.7 ± 8.24
2 (Days 30-60)	33.6 ± 4.62	5.50 ± 1.732	812 ± 214.7	12.6 ± 2.59

There have been three studies in paediatric patients using the commercial formulation intramuscularly including the IMpact-RSV trial. The overall mean 30-day serum trough levels and ranges are given below:

Table 7: Mean Serum Trough Concentrations Paediatric Prophylaxis Studies at 15 mg/kg Dose by Intramuscular Administration

15 mg/kg Dose	Arithmetic Mean (µg/mL)
30 Day Post-Injection 1	n = 414
Mean	41.7
Range	0.0 - 172.8
30 Day Post-Injection 2	n = 382
Mean	62.0
Range	0.0 - 377.5
30 Day Post-Injection 3	n = 366
Mean	72.9
Range	0.0 - 590.0
30 Day Post-Injection 4	n = 959
Mean	74.0
Range	0.0 - 839.5
30 Day Post-Injection 5	n = 55
Mean	99.3
Range	39.6 - 217.0
n = number of patients in which serum level was determined 30 days after the injection	

The pharmacokinetics of palivizumab appear to show a linear relationship between dose and mean area under the serum concentration time curve. Metabolism has not been assessed.

The 30 days post dose mean serum concentration was > 30 micrograms/mL, which is the level associated in preclinical studies with a 2-log reduction in pulmonary RSV titres. There is considerable individual variation in palivizumab serum concentration at any timepoint and some individuals will be below 30 micrograms/mL at 30 days post dose.

In a phase III/IV, multicentre evaluation of the immunogenicity of palivizumab in children who previously received palivizumab prophylaxis and children receiving the drug for the first time (W99-310), the mean serum concentrations following the first and fourth injections were approximately 60 and 90 micrograms/mL.

In paediatric patients less than or equal to 24 months of age with haemodynamically significant congenital heart disease (CHD) who received palivizumab, underwent cardiopulmonary bypass for open-heart surgery, and were assessed for palivizumab serum concentrations pre and post cardiac bypass surgery (N=139), the mean serum palivizumab concentration was approximately 100 micrograms/mL pre-cardiac bypass and declined to approximately 40 micrograms/mL after bypass.

A prospective, phase II, open-label trial, designed to evaluate pharmacokinetics, safety and immunogenicity after administration of 7 doses of palivizumab within a single RSV season was conducted in 18 preterm infants born at less than 34 weeks gestation. Results indicated that adequate mean palivizumab levels were achieved in all 18 participants.

5.3 Preclinical Safety Data

In a human tissue cross-reactivity study, biotinylated palivizumab did not stain in a specific fashion to the more than 30 human adult and neonatal tissues studied.

Acute toxicity studies in three species, the Sprague Dawley rat, the cynomolgus monkey and the NZW rabbit demonstrated tolerance at the site of injection as well as lack of specific systemic toxicity.

In the cotton rat model, pre-treatment with palivizumab was shown to reduce mean pulmonary viral titres (replication) by a mean of 99% at serum concentrations of approximately 30 micrograms/mL. At no concentration was increased viral replication seen, nor was there an increase in pulmonary inflammation or histopathology at any palivizumab concentration examined. No RSV mutants escaped therapy and reinfection with RSV after palivizumab exposure did not enhance RSV viral titres (replication) or the resultant pulmonary histopathology.

Carcinogenesis, mutagenesis and reproductive toxicity studies have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Histidine

Glycine

Water for injections

6.2 Incompatibilities

This medicine should not be mixed with other medicines.

6.3 Shelf-life

36 months

Administer solution immediately after drawing the dose into the syringe.

6.4 Special Precautions for Storage

Store at 2°C to 8°C (Refrigerate, do not freeze).

Store in the original container.

Do not use beyond the expiration date.

6.5 Nature and Contents of Container

Palivizumab is supplied as a sterile solution for intramuscular injection.

- Palivizumab single-use vial*: 3 mL capacity, clear, colourless Type I glass vial with stopper and flip-off seal containing 0.5 mL palivizumab solution for injection with a concentration of 100 mg/mL (50 mg/0.5 mL).
- Palivizumab single-use vial: 3mL capacity, clear, colourless Type I glass vial with stopper and flip-off seal containing 1 mL palivizumab solution for injection with a concentration of 100 mg/mL.

* This presentation is not currently available in New Zealand.

6.6 Special Precautions for Disposal and Other Handling

Palivizumab solution for injection should not be mixed with any medications or diluents.

Administration Instructions

Both the 0.5 mL and 1 mL vials contain an overfill to allow the withdrawal of 50 mg or 100 mg palivizumab, respectively.

- **DO NOT DILUTE THE PRODUCT.**
- **DO NOT SHAKE VIAL**.
- To administer, remove the tab portion of the vial cap and clean the stopper with 70% ethanol of equivalent. Insert the needle into the vial and withdraw an appropriate volume of solution into the syringe.
- Palivizumab injection does not contain a preservative and should be administered immediately after drawing the dose into the syringe.
- The product is for single use in one patient only. Do not re-enter the vial after withdrawal of drug. Discard unused contents.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

AbbVie Limited
6th Floor, 156-158 Victoria Street
Wellington, 6011
New Zealand

Phone No.: 0800 900 030

9. DATE OF FIRST APPROVAL

*Powder for Injection**

(* Powder for injection presentation has been discontinued)

23 September 1999

Solution for Injection

28 July 2016

10. DATE OF REVISION OF THE TEXT

9 December 2019

Version 19

SUMMARY TABLE OF CHANGES

Sections changed	Summary of new information
1. Trade name 2. Qualitative and quantitative information 3. Pharmaceutical form 4. Clinical particulars 5. Pharmacological properties 6. Pharmaceutical particulars 9. Date of first approval	Lyophilised powder for injection presentation has been discontinued. Asterisks and comments relating to the discontinuation of the powder for injection included, where appropriate.
Throughout document	Minor spelling corrections and formatting changes.