DATA SHEET

1 MYOZYME 50 MG/10 ML POWDER FOR INFUSION CONCENTRATE

MYOZYME 50 mg/10 mL powder for concentrate for solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 50 mg vial contains 52.5 mg alglucosidase alfa.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

MYOZYME is indicated for the long-term treatment of patients with a confirmed diagnosis of Pompe disease (acid alfa-glucosidase deficiency).

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose

The recommended dosage regimen of MYOZYME is 20 mg/kg of body weight administered once every 2 weeks as an intravenous infusion.

Elderly population

Clinical studies did not include any subjects aged 65 years and older. It is not known whether they respond differently than younger subjects.

Paediatric population

There is no evidence for special considerations when MYOZYME is administered to paediatric patients of all ages.

Method of administration

Each reconstituted vial must be diluted prior to administration in 0.9% sodium chloride for injection.

For instructions on reconstitution and dilution of the medicine before administration, see section 6.6.

MYOZYME should be administered at an initial infusion rate of no more than 1 mg/kg/hr. The infusion rate may be increased by 2 mg/kg/hr every 30 minutes, after patient tolerance to the infusion rate is established, until a maximum rate of 7 mg/kg/hr is reached. Appropriate medical support measures should be readily available when MYOZYME is administered because of the potential for severe infusion reactions. The infusion rate may be slowed and/or temporarily stopped in the event of Infusion Associated Reactions (IARs).

4.3 CONTRAINDICATIONS

Hypersensitivity (anaphylactic reaction) to the active substance or to any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Risk of Hypersensitivity Reactions

Serious hypersensitivity reactions, including life-threatening anaphylactic reactions, have been observed in infantile and late-onset Pompe patients during MYOZYME infusion, some of which were IgE-mediated. A small number of patients (<1%) in clinical trials and in the commercial setting developed anaphylactic shock and/or cardiac arrest during MYOZYME infusion that required life-support measures.

If severe hypersensitivity or anaphylactic reactions occur, immediate discontinuation of the administration of MYOZYME should be considered and appropriate medical treatment should be initiated. Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available when MYOZYME is administered because of the potential for severe infusion reactions.

In clinical trials and expanded access programs with MYOZYME, 38 of 280 (approximately 14%) patients treated with MYOZYME have developed infusion reactions that involved at least 2 of 3 body systems: cutaneous, respiratory or cardiovascular systems. These events included: Cardiovascular: hypotension, cyanosis, hypertension, tachycardia, ventricular extrasystoles, bradycardia, pallor, flushing, nodal rhythm, peripheral coldness; Respiratory: tachypnoea,

wheezing/bronchospasm, rales, throat tightness, hypoxia, dyspnoea, cough, respiratory tract irritation, oxygen saturation decreased; Cutaneous: angioneurotic oedema, urticaria, rash, erythema, periorbital oedema, pruritus, hyperhidrosis, cold sweat, livedo reticularis (see section 4.8). Of these cases, 8 patients experienced severe or significant hypersensitivity reactions.

Additional IARs reported from worldwide post-marketing sources after marketing approval (including ongoing clinical programs) included: cardiac arrest, bradycardia, angioneurotic oedema, pharyngeal oedema, oedema peripheral, chest pain, chest discomfort, dyspnoea, muscle spasm, fatigue and conjunctivitis. Those IARs assessed as severe included cardiac arrest, bradycardia, chest pain, and dyspnoea.

Immunogenicity

There are no marketed tests for antibodies against alglucosidase alfa. It is recommended that patients be monitored for IgG antibody formation every 3 months. If testing is warranted, contact Sanofi Genzyme at 1800 818 806 for information on testing and to obtain a sample collection box.

In clinical studies, the majority of patients i.e. 89% (34/38) developed IgG antibodies to alglucosidase alfa, typically within 3 months of treatment. Patients treated with higher doses of MYOZYME tended to develop a more robust antibody response and experienced more IARs. There does not appear to be a correlation between the onset of IARs and the time of antibody formation. A small number of patients who were IgG positive also tested positive for inhibition of enzyme effects in an in vitro assay. There is evidence to suggest that patients developing sustained titres $\geq$ 12,800 of anti-alglucosidase alfa antibodies may have a poorer clinical response to treatment, or may lose motor function as antibody titres increase. Treated patients who experience a decrease in motor function should be tested for neutralisation of enzyme uptake or activity.

A small number of patients tested positive for alglucosidase alfa - specific IgE antibodies, 1 of whom experienced an anaphylactic reaction. Testing was typically performed for IARs, especially moderate to severe or recurrent reactions.

The effect of antibody development on the long - term efficacy of MYOZYME is not fully understood. There is an observation that some patients who develop high and sustained anti-alglucosidase alfa antibody titres, including those who possess 2 null mutations, have a poorer clinical response. The cause of a poorer clinical response in some of these patients is thought to be multi - factorial.

Some IgG-positive patients in clinical trials and on commercial therapy who were evaluated for the presence of inhibitory antibodies tested positive for inhibition of enzyme activity and/or uptake in in vitro assays.

Infusion reactions were reported in 20 of 39 patients (51%) treated with MYOZYME in clinical studies and appear to be more common in antibody-positive patients: 8 of 15 patients with high antibody titres experienced infusion reactions whereas none of 3 antibody-negative patients experienced infusion reactions.

Patients in clinical trials, expanded access programs and on commercial therapy have undergone testing for MYOZYME-specific IgE antibodies. Testing was performed for infusion reactions, especially moderate to severe or recurrent reactions, for which mast - cell activation was suspected. A small number of these patients tested positive for MYOZYME specific IgE binding antibodies, some of whom experienced an anaphylactic reaction (see section 4.4: Hypersensitivity Reactions).

Some patients have been successfully rechallenged using a slower infusion rate at lower initial doses and have continued to receive treatment with MYOZYME under close clinical supervision.

Severe cutaneous and possibly immune-mediated reactions have been reported with alglucosidase alfa including ulcerative and necrotizing skin lesions. Skin biopsy in one patient demonstrated deposition of anti-rhGAA antibodies in the lesion.

Nephrotic syndrome was observed in a few Pompe patients treated with alglucosidase alfa and who had high IgG antibody titers (≥ 102, 400). In these patients renal biopsy was consistent with immune complex deposition. Patients improved following treatment interruption. It is therefore recommended to perform periodic urinalysis among patients with high IgG antibody titers.

Patients should be monitored for signs and symptoms of systemic immune complex-mediated reactions involving skin and other organs while receiving alglucosidase alfa. If immune mediated reactions occur, discontinuation of the administration of alglucosidase alfa should be considered, and appropriate medical treatment initiated. The risks and benefits of re-administering alglucosidase alfa following an immune mediated reaction should be considered. Some patients have been successfully rechallenged and continued to receive alglucosidase alfa under close clinical supervision.

Immunomodulation

Pompe patients are at increased risk of respiratory infections due to the progressive effects of the disease on the respiratory muscles. Immunosuppressive agents have been administered in a small number of patients, in an attempt to reduce or prevent the development of antibodies to alglucosidase alfa. Fatal and life-threatening respiratory infections have been observed in some of these patients. Therefore, Pompe patients treated with immunosuppressive agents may be at further increased risk of developing severe infections and vigilance is recommended.

Risk of Cardiac Arrhythmia and Sudden Cardiac Death During General Anaesthesia for Central Venous Catheter Placement

Cardiac arrhythmia, including ventricular fibrillation, ventricular tachycardia and bradycardia, resulting in cardiac arrest or death, or requiring cardiac resuscitation or defibrillation have been observed in infantile-onset Pompe disease patients with cardiac hypertrophy, associated with the use of general anaesthesia for the placement of a central venous catheter intended for MYOZYME infusion. Caution should be used when administering general anaesthesia for the placement of a central venous catheter in infantile-onset Pompe disease patients with cardiac hypertrophy.

Risk of Acute Cardiorespiratory Failure

Acute cardiorespiratory failure requiring intubation and inotropic support has been observed after infusion with MYOZYME in 1 infantile-onset Pompe disease patient with underlying cardiac hypertrophy, possibly associated with fluid overload with intravenous administration of MYOZYME. (See section 6.6.)

Infusion Associated Reactions (IARs)

Infusion associated reactions (IARs) occurred in 51% (20/39) of patients treated with MYOZYME in two infantile - onset clinical studies for 52 weeks. IARs occur at any time during and mostly up to 2 hours after the infusion of MYOZYME. They are more likely to occur with higher infusion rates. The majority of reactions were assessed as mild to moderate, some reactions were severe. Some patients were pre-treated with antihistamines, antipyretics and/or steroids. IARs may occur in patients after receiving antipyretics, antihistamines or steroids. If an IAR occurs, regardless of pre-treatment, decreasing the infusion rate, temporarily stopping the infusion and/or administration of antihistamines and/or antipyretics may ameliorate the symptoms. If severe infusion reactions occur, immediate discontinuation of the administration of MYOZYME should be considered and appropriate medical treatment should be initiated. Severe reactions are generally managed with administration of antihistamines, corticosteroids, intravenous fluids, and/or oxygen, when clinically indicated. In some cases of anaphylactic reaction and cardiac arrest, epinephrine and/or cardiopulmonary resuscitation measures have been administered. Early detection of signs and symptoms of hypersensitivity or anaphylactic reactions may assist in effective management of patients and prevent possible significant or irreversible outcomes. Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available when MYOZYME is administered because of the potential for severe hypersensitivity reactions. Patients who have experienced IARs should be treated with caution when re-administered MYOZYME.

Severe infusion reactions reported in more than 1 patient in clinical studies and the expanded access program included pyrexia, decreased oxygen saturation, tachycardia, cyanosis, and hypotension. Other infusion reactions reported in more than 1 patient in clinical studies and the expanded access program included rash, flushing, urticaria, pyrexia, cough, tachycardia, decreased oxygen saturation, vomiting, tachypnoea, agitation, increased blood pressure, cyanosis, hypertension, irritability, pallor, pruritus, retching, rigors, tremor, hypotension, bronchospasm, erythema, face oedema, feeling hot, headache, hyperhidrosis, lacrimation increased, livedo reticularis, nausea, periorbital oedema, restlessness, and wheezing.

Patients with advanced Pompe disease may have compromised cardiac and respiratory function, which may predispose them to a higher risk of severe complications from infusion reactions. These patients should be monitored more closely when administering MYOZYME.

There were no differences between the 20mg/kg and 40mg/kg doses in any of the studied endpoints; however there was an increase in infusion related reaction with the 40 mg/kg dose (see section 4.8).

Paediatric Use

Paediatric patients from 1 month up to 3.5 years of age at time of first infusion have been treated with MYOZYME in clinical trials. Other open-label clinical trials of MYOZYME have been performed in older paediatric patients ranging from 2 to 16 years at the initiation of treatment. There has been very limited study of the safety and efficacy of MYOZYME in the treatment of juvenile-onset Pompe patients; however additional studies of MYOZYME in the juvenile-onset patients are currently ongoing.

Use in the Elderly

Clinical studies did not include any subjects aged 65 years and older. It is not known whether they respond differently than younger subjects.

Use in Renal/Hepatic Impaired Patients

The safety and efficacy of MYOZYME in patients with renal or hepatic impairment have not been evaluated and no specific dose regimen can be recommended for these patients.

Genotoxicity

No studies have been conducted to assess the genotoxic potential of MYOZYME.

Carcinogenicity

No studies have been conducted to assess the carcinogenic potential of MYOZYME.

Effects on Laboratory tests

Overall, there were few clinically significant abnormal clinical laboratory evaluations in patients treated with MYOZYME. However, assessment of clinical significance varied across investigators based upon individual standards of clinical practice. In general, changes in laboratory parameters during the conduct of the studies of patients treated with MYOZYME were consistent with the evolving clinical status of individual patients and were not considered treatment related.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

No drug interaction studies have been conducted with MYOZYME.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Category B1

There are no adequate and well-controlled studies of MYOZYME in pregnant women. Animal developmental toxicity studies are not always predictive of the human response, therefore MYOZYME should be given to a pregnant woman only when clearly needed and after a careful risk/benefit analysis has been conducted for both the mother and foetus.

Developmental studies have been performed in mice and rabbits at doses of MYOZYME up to 40 mg/kg/day (9.5 and 13 times the expected human exposure, based on AUC values) administered daily for 10 days with no evidence of embryo-foetal abnormality. In the rabbit embryo–foetal study, a few cases of abortion and early delivery were observed (4.3% and 3.2% total incidence respectively).

Breast-feeding

It is not known whether MYOZYME is secreted in human milk. In a pre- and post-natal study in mice, survival of the offspring was reduced during days 15-21 of lactation at the highest dose evaluated (5 times the expected human exposure based on AUC values). However, the relationship of this finding to MYOZYME was unclear since this observation was not dose or time dependant, and there were no other effects on any other parameter evaluated in the high dose group. Furthermore, when the data was analysed on a per litter basis, the litter loss was not significantly different between the control group and the highest dose tested. MYOZYME should be given to a breastfeeding woman only if clearly needed and after a careful risk/benefit analysis has been conducted for both the mother and child.

Fertility

MYOZYME treatment of male and female mice had no effect on fertility up to exposures 5 times the expected human exposure, based on AUC values.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the ability to drive and handle machines have been conducted with alglucosidase alfa. Because dizziness has been reported as an infusion associated reaction, this may affect the ability to drive and use machines on the day of the infusion.

4.8 UNDESIRABLE EFFECTS

Adverse events

The most common serious treatment-emergent adverse events (regardless of relationship) observed in clinical studies with MYOZYME were pneumonia, respiratory failure, respiratory distress, catheter related infection, respiratory syncytial virus infection, gastroenteritis, and fever. The most common treatment-emergent adverse events (regardless of relationship) were fever, diarrhoea, rash, vomiting, cough, pneumonia, otitis media, upper respiratory tract infection, gastroenteritis and decreased oxygen saturation.

Table 1 - enumerates treatment - emergent adverse events (regardless of relationship) that occurred in at least 20% of patients treated with MYOZYME® in clinical trials described above. Reported frequencies of adverse events have been classified by MedDRA terms.

System Organ Class	Number of Patients	Number of
Preferred Term	(N=39)	Adverse Events
	n (%)	n
Any Adverse Events =	39 (100)	1859
General disorders and administration site conditions	38 (97)	
Pyrexia	36 (92)	169
Respiratory, thoracic and mediastinal disorders	38 (97)	
Cough	18 (46)	69
Respiratory distress	13 (33)	18
Respiratory failure	12 (31)	24
Rhinorrhoea	11 (28)	16
Tachypnoea	9 (23)	15
Infections and infestations	37 (95)	
Pneumonia	18 (46)	43
Otitis media	17 (44)	35
Upper respiratory tract infection	17 (44)	39
Gastroenteritis	16 (41)	17
Pharyngitis	14 (36)	26
Ear Infection	13 (33)	23
Oral candidiasis	12 (31)	20
Catheter related infection	11 (28)	15
Bronchiolitis	9 (23)	10
Nasopharyngitis	9 (23)	25
Gastrointestinal disorders	32 (82)	
Diarrhoea	24 (62)	62
Vomiting	19 (49)	62
Gastroesophageal reflux disease	10 (26)	13
Constipation	9 (23)	14
Skin and subcutaneous tissue disorders	32 (82)	
Rash	21 (54)	72
Diaper dermatitis	14 (36)	34
Urticaria	8 (21)	25
Investigations	28 (72)	
Oxygen saturation decreased	16 (41)	44

System Organ Class	Number of Patients	Number of
Cardiac disorders	24 (62)	
Tachycardia	9 (23)	31
Bradycardia	8 (21)	18
Injury, poisoning and procedural complications	22 (56)	
Post procedural pain	10 (26)	20
Blood and lymphatic system disorders	17 (44)	
Anaemia	12 (31)	23
Vascular disorders	14 (36)	
Flushing	8 (21)	15

Five additional juvenile-onset Pompe disease patients were evaluated in a single-centre, open label, non-randomised, uncontrolled clinical trial. Patients were aged 5 to 15 years, ambulatory (able to walk at least 10 metres in 6 minutes), and not receiving invasive ventilatory support at study entry. All 5 patients received treatment with 20 mg/kg MYOZYME for 26 weeks. The most common treatment-emergent adverse events (regardless of causality) observed with MYOZYME treatment in this study were headache, pharyngitis, upper abdominal pain, malaise, and rhinitis.

Significant hypersensitivity reactions have been reported from worldwide post-marketing sources in patients treated with MYOZYME. Some of these patients experienced life-threatening anaphylactic reactions, including anaphylactic shock, some of which were IgE-mediated. Reactions generally occurred shortly after initiation of the infusion. Patients presented with a constellation of signs and symptoms, primarily respiratory, cardiovascular, oedematous and/or cutaneous in nature.

Infusion-associated reactions (IARs) reported from worldwide post-marketing sources have included cardiac arrest, bradycardia, angioneurotic oedema, pharyngeal oedema, oedema peripheral, chest pain, chest discomfort, dyspnoea, muscle spasm, fatigue, respiratory distress, throat tightness and conjunctivitis. Those IARs assessed as severe included cardiac arrest, bradycardia, chest pain, and dyspnoea. The majority of patients continued to receive treatment with MYOZYME, some under close clinical supervision.

Significant skin lesions (necrotising inflammation) were reported in 1 patient following MYOZYME treatment in a post-marketing setting. After temporary discontinuation of MYOZYME treatment, lesions resolved and the patient was able to continue on therapy.

Paediatric Population

Adverse Drug Reactions

The most common adverse drug reactions (ADRs) were infusion associated reactions (IARs). Infusion reactions occurred in approximately 50% of patients treated with MYOZYME in two infantile-onset clinical studies for 52 weeks. The majority of these reactions were mild to

moderate. IARs which were reported in more than 1 patient in clinical studies and the expanded access program included rash, flushing, urticaria, pyrexia, cough, tachycardia, decreased oxygen saturation, vomiting, tachypnoea, agitation, increased blood pressure, cyanosis, hypertension, irritability, pallor, pruritus, retching, rigors, tremor, hypotension, bronchospasm, erythema, face oedema, feeling hot, headache, hyperhidrosis, lacrimation increased, livedo reticularis, nausea, periorbital oedema, restlessness and wheezing. Severe infusion reactions reported in more than 1 patient included pyrexia, decreased oxygen saturation, tachycardia, cyanosis and hypotension.

If severe infusion reactions occur, immediate discontinuation of the administration of MYOZYME should be considered, and appropriate medical treatment should be initiated. Because of the potential for severe infusion reactions, appropriate medical support measures should be readily available when MYOZYME is administered. Most infusion related reactions requiring intervention were ameliorated with slowing of the infusion rate, temporarily stopping the infusion and/or administration of antipyretics, antihistamines or steroids.

Other ADRs reported in clinical trials that were not assessed as IARs and occurred in more than 1 patient included increased blood creatine phosphokinase MB.

All ADRs are summarised in Table 2.

Table 2 - Summary of ADRs – Infantile-onset Pooled Population (AGLU01602 and AGLU01702)

System Organ Class Preferred Term	Number of Patients[1] (N=39) n (%)	Number of Adverse Events[2] n (%)
Any Adverse Events	24 (61.5)	222 (100.0)
Skin and subcutaneous tissue disorders	12 (30.8)	65 (29.3)
Urticaria	6 (15.4)	23 (10.4)
Rash	5 (12.8)	11 (5.0)
Rash maculo-papular	3 (7.7)	5 (2.3)
Rash macular	2 (5.1)	13 (5.9)
Rash papular	2 (5.1)	3 (1.4)
Erythema	2 (5.1)	2 (0.9)
Pruritus	2 (5.1)	2 (0.9)
Rash erythematous	1 (2.6)	2 (0.9)
Hyperhidrosis	1 (2.6)	1 (0.5)
Livedo reticularis	1 (2.6)	1 (0.5)
Palmar erythema	1 (2.6)	1 (0.5)
Periorbital oedema	1 (2.6)	1 (0.5)
Investigations	13 (33.3)	38 (17.1)
Oxygen saturation decreased	7 (17.9)	21 (9.5)

System Organ Class Preferred Term	Number of Patients[1] (N=39) n (%)	Number of Adverse Events[2] n (%)
Blood creatine phosphokinase MB increased	2 (5.1)	2 (0.9)
Blood pressure increased	2 (5.1)	2 (0.9)
Heart rate decreased	1 (2.6)	2 (0.9)
Alanine aminotransferase increased	1 (2.6)	1 (0.5)
Aspartate aminotransferase increased	1 (2.6)	1 (0.5)
Blood calcium increased	1 (2.6)	1 (0.5)
Blood creatine phosphokinase increased	1 (2.6)	1 (0.5)
Blood pressure decreased	1 (2.6)	1 (0.5)
Blood urea increased	1 (2.6)	1 (0.5)
Body temperature increased	1 (2.6)	1 (0.5)
Haemoglobin decreased	1 (2.6)	1 (0.5)
Heart rate increased	1 (2.6)	1 (0.5)
Platelet count decreased	1 (2.6)	1 (0.5)
Respiratory rate increased	1 (2.6)	1 (0.5)
General disorders and administration site conditions	11 (28.2)	33 (14.9)
Pyrexia	10 (25.6)	28 (12.6)
Rigors	2 (5.1)	3 (1.4)
Infusion site reaction	1 (2.6)	1 (0.5)
Lethargy	1 (2.6)	1 (0.5)
Respiratory, thoracic and mediastinal disorders	8 (20.5)	27 (12.2)
Cough	5 (12.8)	17 (7.7)
Tachypnoea	5 (12.8)	8 (3.6)
Bronchospasm	1 (2.6)	1 (0.5)
Rales	1 (2.6)	1 (0.5)
Vascular disorders	8 (20.5)	20 (9.0)
Flushing	5 (12.8)	11 (5.0)
Hypertension	3 (7.7)	4 (1.8)
Pallor	2 (5.1)	3 (1.4)
Hypotension	1 (2.6)	2 (0.9)
Gastrointestinal disorders	4 (10.3)	17 (7.7)
Vomiting	3 (7.7)	8 (3.6)
Retching	2 (5.1)	7 (3.2)

System Organ Class Preferred Term	Number of Patients[1] (N=39) n (%)	Number of Adverse Events[2] n (%)
Constipation	1 (2.6)	1 (0.5)
Gastrooesophageal reflux disease	1 (2.6)	1 (0.5)
Cardiac disorders	4 (10.3)	10 (4.5)
Tachycardia	4 (10.3)	7 (3.2)
Cyanosis	2 (5.1)	3 (1.4)
Psychiatric disorders	5 (12.8)	8 (3.6)
Agitation	2 (5.1)	4 (1.8)
Irritability	2 (5.1)	2 (0.9)
Insomnia	1 (2.6)	1 (0.5)
Restlessness	1 (2.6)	1 (0.5)
Nervous system disorders	2 (5.1)	3 (1.4)
Tremor	2 (5.1)	3 (1.4)
Injury, poisoning and procedural complications	1 (2.6)	1 (0.5)
Hypothermia	1 (2.6)	1 (0.5)

[1] Percentages are based on the total number of patients treated in the studies. A patient experiencing more than 1 AE within an SOC or preferred term is counted once within that SOC or preferred term.

[2] Percentages are based on the total number of AEs considered possibly, probably or definitely related to treatment.

Serious Adverse Drug Reactions

Of the serious ADRs reported with MYOZYME, the most significant were cardiorespiratory failure, anaphylactic reactions and cardiac arrest. Cardiorespiratory failure, possibly associated with fluid overload, was reported in 1 infantile - onset Pompe disease patient and pre - existing cardiac hypertrophy likely contributed to the severity of the reaction (see section 4.4: Risk of Acute Cardiorespiratory Failure).

Post-Marketing Experience

A review of the safety information revealed a total of 5 patient experienced significant infusion associated reactions. In addition, a patient who experienced non-serious recurrent generalised urticaria was IgE positive. In total, 11 patients treated in either clinical studies or with commercial MYOZYME have tested positive for IgE antibodies. In total, (up until March 2008) 178 patients treated with MYOZYME in clinical trials and/or the commercial setting were evaluated for *in vitro* inhibition of enzyme activity. Of these, 137 patients were also evaluated for inhibition of uptake. A total of 32 of 178 (18.0%) patients tested positive for *in vitro* inhibition by inhibition of enzyme activity and/or inhibition of uptake assay at one or more time points.

Four of the 32 patients tested for inhibition of enzyme activity and all 32 patients tested positive for inhibition of uptake at one or more time points. Nineteen of the 32 (59%) patients were classified as positive for uptake inhibition and 13 (41%) patients were classified as borderline. The majority of infantile-onset patients who developed inhibitory antibodies were Cross Reactive Immunologic Material (CRIM) negative, developed peak antibody titers ≥ 102,400 and showed signs of clinical decline. In late-onset patients who tested positive for inhibition of cellular uptake in study AGLU02704 there was no clear effect of IgG antibodies or inhibitory antibodies on safety or efficacy endpoints at study conclusion.

The majority of adverse reactions received during the current reporting period were consistent with the manifestation of the underlying Pompe disease or disease progression.

Physicians should monitor hypersensitivity reactions, drug–induced skin reactions, clinical decline or plateau of treatment and consider the risks and benefits of continued treatment.

Additional Infusion Associated Reactions reported from worldwide post-marketing sources after marketing approval (including ongoing clinical programs) included: cardiac arrest, bradycardia, angioneurotic oedema, pharyngeal oedema, oedema peripheral, chest pain, chest discomfort, dyspnoea, muscle spasm, fatigue and conjunctivitis. Those IARs assessed as severe included cardiac arrest, bradycardia, chest pain, and dyspnoea.

In addition to infusion reactions reported in clinical trials and expanded access program, the following infusion reactions have been reported from worldwide sources after marketing approval, including ongoing clinical programs: peripheral/local edema, abdominal pain and arthralgia. Additional adverse drug reactions included proteinuria and nephrotic syndrome in patients with high IgG antibody titers (≥ 102,400).

Recurrent reactions consisting of flu-like illness or a combination of events such as fever, chills, myalgia, arthralgia, pain, or fatigue occurring after completion of infusions and lasting usually for a few days have been observed in some patients treated with alglucosidase alfa. The majority of patients were successfully rechallenged with alglucosidase alfa using lower doses and/or pretreatment with anti-inflammatory drugs and/or corticosteroids and have continued to receive treatment under close clinical supervision.

Severe cutaneous and possibly immune-mediated reactions have been reported with alglucosidase alfa including ulcerative and necrotizing skin lesions. Skin biopsy in one patient demonstrated deposition of anti-rhGAA antibodies in the lesion.

Nephrotic syndrome was observed in a few Pompe patients treated with alglucosidase alfa and who had high IgG antibody titers (≥ 102,400). In these patients renal biopsy was consistent with immune complex deposition. Patients improved following treatment interruption. It is therefore recommended to perform periodic urinalysis among patients with high IgG antibody titers.

Hypersensitivity

In approximately 280 patients treated with MYOZYME, some patients experienced severe or significant hypersensitivity reactions, including a life-threatening anaphylactic shock (see section

4.4: Risk of Hypersensitivity Reactions). One patient developed an anaphylactic shock, which consisted of bronchoconstriction, hypotension, cyanosis, hypoxia, pallor and oxygen desaturation, during MYOZYME infusion that required life-support measures.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems (Australia) or https://nzphvc.otago.ac.nz/reporting/ (New Zealand).

4.9 OVERDOSE

There have been no reports of overdose with MYOZYME. In clinical trials, patients received doses up to 40 mg/kg of body weight.

For general advice on management of overdose, contact the Australian Poisons Information Centre (telephone 13 11 26), or the New Zealand National Poisons Information Centre (telephone 0800 POISON or 0800 764 766) for advice on management.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other alimentary tract and metabolism products, enzymes, ATC code: A16AB07.

MYOZYME is a purified form of the lysosomal enzyme acid alfa - glucosidase (GAA). Alglucosidase alfa - rch is produced by recombinant DNA technology in a Chinese hamster ovary cell line. Alglucosidase alfa - rch is a 896 amino acid glycoprotein with 7 asparagine - linked glycosylation sites that are occupied by a mixture of complex, oligomannose and phosphorylated oligomannose structures. Alglucosidase alfa - rch has a molecular weight of approximately 110 kD.

Mechanism of Action

Pompe disease (glycogen storage disease type II, GSD II, glycogenosis type II, acid maltase deficiency) is a rare autosomal recessive disease caused by the deficiency of lysosomal acid alfa-glucosidase (GAA). GAA degrades lysosomal glycogen by catalysing the hydrolysis of the α-1, 4- and α-1,6-glycosidic linkages. Pompe disease results in intralysosomal accumulation of glycogen in various tissues, particularly cardiac and skeletal muscles, leading to the development of cardiomyopathy, progressive muscle weakness, and impairment of respiratory function.

Treatment of Pompe disease with MYOZYME provides an exogenous source of GAA.

Intracellular trafficking of the 110 kD form of rhGAA to the lysosome occurs via a cation independent mannose-6-phosphate receptor dependent mechanism. This receptor is present on the surface of many cell types and may play a role in uptake of exogenous lysosomal enzymes. During internalisation and trafficking to the lysosome, rhGAA undergoes proteolytic and N-glycan processing resulting in the formation of a mature form, which degrades lysosomal glycogen at low pH.

Clinical efficacy and safety

The efficacy of MYOZYME has been evaluated in 3 clinical trials of patient's naïve to enzyme replacement therapy (ERT) at the initiation of treatment and are detailed below. In addition, several other studies and expanded access programs were conducted. Other supportive studies and expanded access programmes have been conducted.

In a retrospective natural history study in patients with infantile-onset Pompe disease (n=168), the median age at onset of symptoms was 2.0 months and the median age of death was 9.0 months. Kaplan-Meier survival rates at 12, 24 and 36 months of age were 26%, 9% and 7%, respectively.

Paediatric Population

Infantile - Onset Pompe Disease

The pivotal study, AGLU01602, was an international, multicentre, historically - controlled clinical trial of 18 non-ventilated infantile-onset Pompe disease patients aged 7 months or less at first infusion.

Patients were randomised equally to receive either 20 mg/kg or 40 mg/kg MYOZYME every 2 weeks for the duration of the study. The primary endpoint was the proportion of patients alive and/or free of invasive ventilation at 18 months of age (time to event). An untreated historical cohort (n = 42), derived from a retrospective natural history study discussed above, served as a comparator group for assessment of the primary endpoint. Given the limited data on invasive ventilator use in the historical population, a comparison to overall survival in the historical cohort was made.

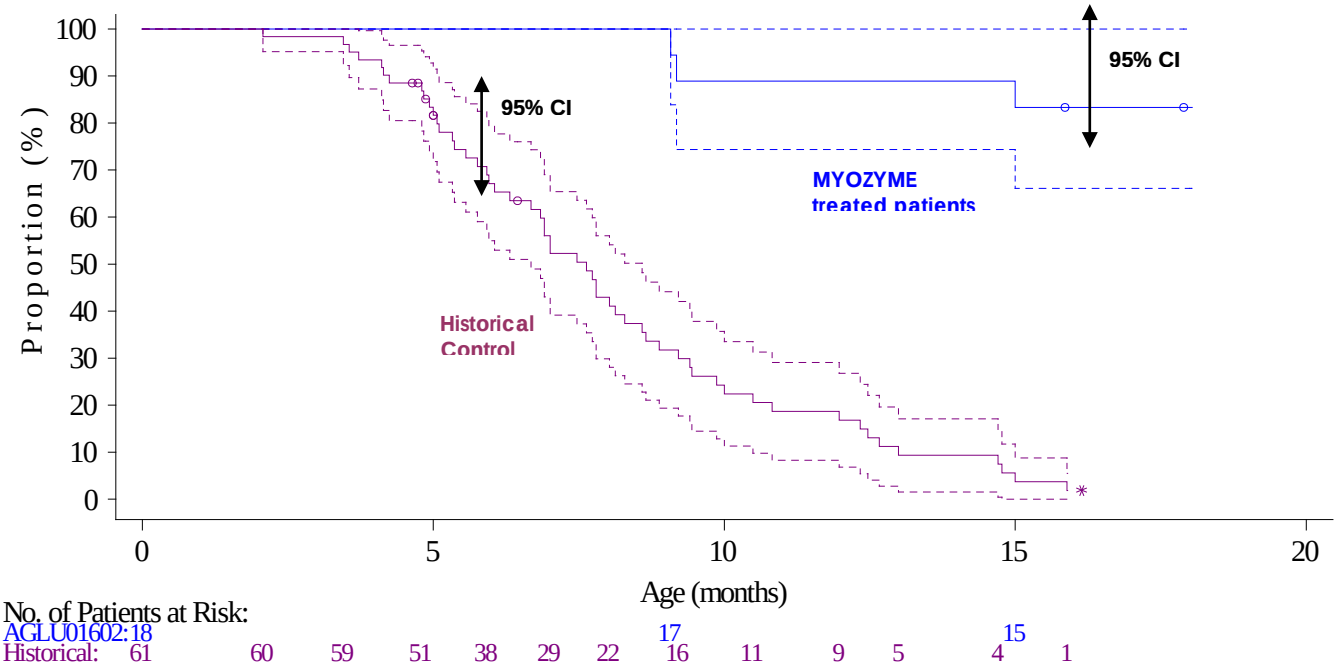
The primary efficacy endpoint for pivotal study AGLU01602 was achieved. At the 18-month milestone, 13 of the 18 patients in AGLU01602 were alive and invasive ventilator-free, 3 were receiving invasive ventilator support, and 2 patients who had not reached the age of 18 months by the end of the study were censored from the analysis, though they were alive and free of invasive ventilator support at that time. By contrast only one of 42 patients in the historical cohort group was alive at 18 months of age. Comparison of survival curves from time of diagnosis versus the historical control population was made using a Cox proportional hazards regression analysis. After 52 weeks, patients treated with MYOZYME demonstrated prolonged survival as compared to survival in an untreated historical cohort (see Table 3). Results from the Cox analysis indicate that in this study MYOZYME reduced the risk of death and/or allowed the patient to be free of invasive ventilation at 18 months of age by 99% (hazard ratio 0.01), which is also highly significant. Results for the primary endpoint are detailed in Table 3 and Figure 1.

Table 3 - Results for study endpoints using the Cox regression model

Treated patients	Historical Reference Comparator	Endpoint	Treatment Effect Hazard ratio	95% Confidence Interval	p-value
N=18	N=42	Survival	0.01	(0.00, 0.10)	<0.0001

Note: Results are from a Cox proportional hazards regression analysis which includes me-varying covariate, and also includes age of diagnosis and age at symptom onset. Subjects in the historical reference group were born in 1993 or later.

Figure 1 - Kaplan - Meier Estimate of Time to Invasive Ventilation or Death from Date of Birth to 18 Months of Age (Comparison to Historical Control Subgroup): AGLU01602



For primary endpoint of Kaplan-Meier Estimate, for the untreated historical cohort n=61

Treatment with MYOZYME greatly increased patient survival as assessed at 18 months of age.

Cardiac status and motor function were assessed as secondary endpoints.

Changes from baseline to Month 12 in left ventricular mass index (LVMI) were measured by echocardiography. For the 14 patients with both baseline and Month 12 echocardiograms, all had decreases from baseline in LVMI (mean decrease 118 g/m2, range 45 to 193 g/m2). 13 patients (72%, 13/18) made gains in motor function over baseline as measured by motor performance age-equivalent scores of the Alberta Infant Motor Scale (AIMS).

There were no differences between the 20mg/kg and 40mg/kg doses in any of the studied endpoints; however there was an increase in infusion related reactions with the 40mg/kg dose (see section 4.8).

Study AGLU01702 was an international, multicentre, open-label clinical trial of 21 infantile-onset patients who were 3 months to 3.5 years old at first treatment. All patients received 20 mg/kg MYOZYME every other week for up to 104 weeks. Five of 21 patients were receiving invasive ventilatory support at the time of first infusion.

The primary outcome measure was the proportion of patients alive at the conclusion of treatment. At the 52-week interim analysis, 16 of 21 patients were alive, yielding a 52-week survival rate of 76%. The effect of MYOZYME treatment on survival was further assessed using a Cox proportional hazards model to fit time-to-event from time of disease diagnosis. Survival data were compared firstly to these observed in a subgroup of the Natural History study population (called the Historical Reference Sub-group) (n = 86) and secondly to a subset of 16 patients belonging to the Historical Reference Sub-group who had survived past 15 months. Results from the Cox analysis (Table 4) indicate that in this study MYOZYME reduced the risk of death by 78% (hazard ratio 0.22), which is also highly significant.

Table 4 - Survival Results for Study AGLU01702 using the Cox Regression Model

Treated Patients	Historical Reference Comparator	Endpoint	Treatment Effect Hazard Ratio	95% Confidence Interval	p-value
N=21	N=86	Survival	0.22	(0.08, 0.57)	0.002

Note: Results are from a Cox proportional hazards regression analysis which includes treatment as a time-varying covariate, and also includes age of diagnosis and age at symptom onset. Data are updated through 15 September 2005.

16 patients were free of invasive ventilatory support at the time of first infusion: of these, 4 died, 2 required invasive ventilatory support, and 10 were free of invasive ventilatory support after 52 weeks of treatment. For the 5 patients who were receiving invasive ventilatory support at baseline, 1 died, and 4 remained on invasive ventilatory support at week 52.

Follow up data after 52 weeks of treatment with MYOZYME (n-15), showed the survival rate was 73% (95%CI: 44.9%, 92.2%) compared to the corresponding survival figure of 37.5% % (95%CI: 13.8%, 61.2%) in the subset of 16 patients belonging to the Historical Reference Sub-group who had survived 15 months.

After 52 weeks of treatment with MYZOYME, 5 of the extra 6 patients not included in the interim analysis were alive and all those alive were free of invasive ventilation. The single death was assessed as not treatment-related.

13 of 15 patients (87%) with follow up data showed improvement in cardiomyopathy as measured by a decrease in left ventricular mass. 6 patients (40%) had measurable gains in motor function as determined by increases in age-equivalent scores from baseline in the AIMS and/or Peabody Development Motor Scale.

The status of patients at week 52 overlapped with that of an untreated historical group of patients, and no effect of MYOZYME treatment could be determined.

Late - Onset Pompe Disease

There has been very limited study of the safety and efficacy of MYOZYME in patients with later onset forms of Pompe disease and the risk/benefits of MYOZYME treatment have not been fully elucidated in these patients; however additional studies of MYOZYME in these patients are currently ongoing. Patient with later onset forms of Pompe disease may be treated with MYOZYME when clearly needed and after a careful risk/benefit analysis has been conducted by the physician.

AGLU02804 was a single-centre, open-label clinical trial which assessed the efficacy of MYOZYME in 5 patients with late-onset Pompe disease who ranged in age from 5 to 15 years at initiation of treatment. Patients received 20 mg/kg MYOZYME every other week for 26 weeks. All patients were freely ambulatory and all but 1 patient did not require any form of ventilator support. Of the 3 patients with significant pulmonary involvement at baseline (percentage predicted forced vital capacity (FVC) in the sitting position ranging from 58 - 67%), 2 demonstrated clinically meaningful improvements in FVC (+11.5 and +16%) in the sitting position by week 26. Motor function was evaluated using the 6 - Minute Walk Test (6MWT). Three of the patients demonstrated a clinically meaningful improvement (ranging from 41-118 m) in 6MWT at fast speed by week 26. 1 patient experienced a clinically meaningful improvement in the 6MWT at comfortable speed.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetic profile of MYOZYME was evaluated in studies AGLU01602 and AGLU01702 as part of the clinical development program. In both studies, plasma GAA levels obtained before and after MYOZYME infusions on day 0 and week 12 were evaluated via a GAA activity assay and these data were used to determine various pharmacokinetic parameters. The pharmacokinetic profile of MYOZYME was also evaluated in AGLU02804 on day 0 and at weeks 12 and 26. Pharmacokinetic parameters from these 3 clinical studies are summarised in Table 5.

Pharmacokinetic data were available from 15 of the 18 patients with infantile-onset Pompe disease treated with MYOZYME in study AGLU01602 at a dosage of 20 mg/kg or 40 mg/kg every 2 weeks. the 20 mg/kg dose was infused over a period of approximately 4 hours and the 40 mg/kg dose was infused over approximately 6.5 hours. The pharmacokinetics of rhGAA were dose proportional and did not change over time.

The pharmacokinetics of MYOZYME were also evaluated in 12 patients with infantile - onset Pompe disease in Study AGLU01702 at a dosage of 20 mg/kg. Patients received 20 mg/kg of MYOZYME as an approximate 4-hour infusion every 2 weeks. The pharmacokinetic parameters were similar to those observed for the 20 mg/kg dose group in AGLU01602 study (see Table 5).

The pharmacokinetics of MYOZYME were evaluated in clinical study AGLU02804 in 5 patients with late-onset Pompe disease who received 20 mg/kg MYOZYME every 2 weeks. There was no difference in the pharmacokinetic profile of MYOZYME in late-onset patients compared to infantile onset patients (see Table 5).

Table 5 - Summary of Pharmacokinetic Parameters after IV Infusion of MYOZYME® 20 mg/kg in Studies AGLU01602, AGLU01702, and AGLU02804

		Study AGLU01602 (N=18)		Study AGLU01702 (N=15)		Study AGLU02804 (N=5)		
Parameter		Day 0 (N=151)	Week 12 (N=151)	Day 0 (N=14)	Week 12 (N=12)	Day 0 (N=4)	Week 12 (N=5)	Week 26 (N=5)
Cmax (ng/mL)		160,910 ± 27,598	195,540 ± 73,190	188,112 ± 83, 402	208, 239 ± 58,612	306,921 ± 104,801	368,904 ± 63,629	310,883 ± 65,866
AUC∞(hr*ng/mL)		937,896 ±199,381	1,017,118 ± 262,278	901,074 ± 313,911	1,103,327 ± 277,549	1,435,034 ± 182,983	1,689,479 ± 252,296	1,471,771 ± 230,970
T½ β (hr)		2.71 ± 0.58	2.80 ± 0.57	2.05 ± 0.49	2.72 ± 0.64	2.71 ± 0.36	2.88 ± 0.61	2.59 ± 0.23
CL	(mL/hr/kg)	22.1 ± 4.2	21.8 ± 5.4	26.1 ± 14.2	19.5 ± 6.24	14.1 ± 1.66	12.1 ± 1.89	13.9 ± 2.30
	(mL/hr)	133 ± 41	154 ± 51	286 ± 248	204 ± 83.3	554 ± 197	455 ± 126	541 ± 160
Vss	(mL/kg)	66.9 ± 10.3	67.0 ± 9.8	84.8 ± 29.6	75.8 ± 20.8	56.0 ± 12.2	47.2 ± 9.66	53.8 ± 10.7
	(mL)	404 ± 116	469 ± 100	914 ± 592	795 ± 304	2,251 ± 1,066	1,774 ± 526	2,111 ± 715

19 of 21 patients who received treatment with MYOZYME and had pharmacokinetics and antibody titre data available at week 12 developed antibodies to alglucosidase alfa. 5 patients with antibody titres ≥ 12,800 at Week 12 had an average increase in clearance of 50% (range 5% to 90%) from week 1 to week 12. The other 14 patients with antibody titres < 12,800 at week 12 had similar average clearance values at week 1 and week 12.

5.3 PRECLINICAL SAFETY DATA

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity. No significant adverse findings on embryo-foetal development were observed in a mouse and a rabbit embryo-foetal study and no significant adverse findings were observed in a mouse fertility and early embryonic development study. In the rabbit embryo-foetal development study, following administration of MYOZYME (10-40 mg/kg/day) with co-administration of diphenhydramine, a treatment-related increase in the incidence of abortions and early delivery was observed. This effect was partly attributable to maternal toxicity, as a significant decrease in feed consumption and body weight gain was observed.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mannitol

Polysorbate 80

Dibasic sodium phosphate heptahydrate

Monobasic sodium phosphate monohydrate

6.2 INCOMPATIBILITIES

MYOZYME SHOULD NOT BE INFUSED IN THE SAME INTRAVENOUS LINE WITH OTHER PRODUCTS.

6.3 SHELF LIFE

3 years.

IF STORAGE IS NECESSARY AFTER RECONSTITUTION HOLD AT 2°C - 8°C FOR NO MORE THAN 24 HOURS.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store MYOZYME under refrigeration at 2°C - 8°C. DO NOT FREEZE OR SHAKE. Do not use MYOZYME after the expiration date on the vial.

This product contains no preservatives. To reduce microbial hazard, use as soon as practicable after dilution. For storage conditions after dilution of the medicinal product, see section 6.3.

The reconstituted and diluted infusion solution should be protected from light.

6.5 NATURE AND CONTENTS OF CONTAINER

It is supplied in single-use, clear Type I glass 20 mL vials. The closure consists of a siliconised butyl stopper and an aluminium seal with a plastic flip-off cap.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Preparation and Administration Instructions: Use Aseptic Techniques

1. Determine the number of vials to be reconstituted based on the individual patient's weight and the recommended dose of 20 mg/kg.

   Patient weight (kg) x dose (mg/kg) = patient dose (in mg).

   Patient dose (in mg) divided by 50 mg/vial = number of vials to reconstitute. If the number of vials includes a fraction, round up to the next whole number for vials needed to withdraw the calculated volume of MYOZYME required.

   Patient dose (in mg) ÷ 5 mg/mL = total number of mL required of reconstitution MYOZYME solution.

   Example:

   Patient weight (16 kg) x dose (20 mg/kg) = patient dose (320 mg). 320 mg divided by 50 mg/vial = 6.4 vials therefore, 7 vials should be reconstituted.

2. Remove the required number of vials from the refrigerator and allow them to reach room temperature prior to reconstitution (approximately 30 minutes). Reconstitute each vial by slowly injecting 10.3 mL of sterile water for injection to the inside wall of each vial. Each vial will yield 5 mg/mL. The total extractable dose per vial is 50 mg per 10 mL. Avoid forceful impact of the water for injection on the powder and avoid foaming. This is done by slow drop-wise addition of the water for injection down the inside of the vial and not directly onto the lyophilised cake. Tilt and roll each vial gently. Do not invert, swirl, or shake.
3. The reconstituted MYOZYME solution should be protected from light.
4. Perform an immediate visual inspection on the reconstituted vials for particulate matter and discolouration. If upon immediate inspection opaque particles are observed or if the solution is discoloured do not use. The reconstituted solution may occasionally contain some alglucosidase alfa rch particles in the form of thin white strands or translucent fibres subsequent to the initial inspection. This may also happen following dilution for infusion. These particles have been shown to contain alglucosidase alfa rch and may appear after the initial reconstitution step and increase over time. Studies have shown that these particles are removed via in-line filtration without having a detectable effect on the purity or strength.
5. Withdraw the calculated volume of MYOZYME from the appropriate number of vials
6. MYOZYME should be diluted in 0.9% sodium chloride for injection immediately after reconstitution to a final concentration of 0.5 to 4 mg/mL.
7. Slowly withdraw the reconstituted solution from each vial. Avoid foaming in the syringe.
8. Remove airspace from the infusion bag to minimise particle formation due to the sensitivity of MYOZYME to air - liquid interfaces.

9. Add the reconstituted MYOZYME solution slowly and directly into the sodium chloride solution. Do not add directly into airspace that may remain within the infusion bag. Avoid foaming in the infusion bag.
10. Gently invert or massage the infusion bag to mix. Do not shake. To reduce microbial hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2°C - 8°C for no more than 24 hours. Protect from light.

The diluted solution should be filtered through a 0.2 µm, low protein - binding, in - line filter during administration to remove any visible particles.

After reconstitution: **MYOZYME IS FOR SINGLE USE IN ONE PATIENT ONLY.** Remaining MYOZYME left in a vial after withdrawing the patient's calculated dose should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine

8 SPONSOR

AUSTRALIA

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9 DATE OF FIRST APPROVAL

16 April 2009

10 DATE OF REVISION OF THE TEXT

3 July 2018

Summary of changes

Section changed	Summary of new information
All	Align with the Medsafe data sheet format including minor additions of text to meet requirements