PRODUCT MONOGRAPH

[Pr]MYOZYME®

alglucosidase alfa
(Recombinant human acid alpha-glucosidase)

Lyophilized Powder
50 mg vial

Enzyme Replacement Therapy

Sanofi Genzyme, a division of Sanofi-Aventis Canada Inc.
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Table of Contents

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous infusion	Sterile solution/50 mg	There are no clinically relevant nonmedicinal ingredients. For a complete listing of nonmedicinal ingredients, see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

DESCRIPTION

MYOZYME® (alglucosidase alfa) is a common form of the human enzyme acid α-glucosidase (GAA) that is produced by recombinant DNA technology in a Chinese hamster ovary cell line. Alglucosidase alfa degrades glycogen by catalyzing the hydrolysis of α-1,4- and α-1,6-glycosidic linkages of lysosomal glycogen.

INDICATIONS AND CLINICAL USE

MYOZYME® (alglucosidase alfa) is indicated for use in patients with Pompe's Disease (GAA deficiency). MYOZYME® has been shown to improve ventilator-free survival in patients with infantile-onset Pompe's Disease as compared to untreated historical controls. MYOZYME® has also been shown to stabilize % predicted forced vital capacity in patients with late-onset Pompe's Disease. Ventilation free survival was not evaluated in patients with late-onset Pompe's Disease (see CLINICAL TRIALS).

CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.

WARNINGS AND PRECAUTIONS

WARNING

RISK OF ANAPHYLAXIS

RISK OF LIFE-THREATENING ANAPHYLACTIC REACTIONS, INCLUDING ANAPHYLACTIC SHOCK, HAVE BEEN OBSERVED IN PATIENTS DURING MYOZYME® INFUSION.

BECAUSE OF THE POTENTIAL FOR SEVERE INFUSION REACTIONS, APPROPRIATE MEDICAL SUPPORT MEASURES SHOULD BE READILY AVAILABLE WHEN MYOZYME® IS ADMINISTERED.

RISK OF CARDIORESPIRATORY FAILURE
INFANTILE-ONSET PATIENTS WITH COMPROMISED CARDIAC OR RESPIRATORY FUNCTION MAY BE AT RISK OF SERIOUS ACUTE EXACERBATION OF THEIR CARDIAC OR RESPIRATORY COMPROMISE DUE TO INFUSION REACTIONS, AND REQUIRE ADDITIONAL MONITORING.

General

Based on experience in clinical studies, patients with an acute underlying illness (for example: acute febrile illness as pneumonia or sepsis, wheezing/bronchospasm, decompensated cardiac failure, etc.) at the time of MYOZYME® (alglucosidase alfa) infusion appear to be at greater risk for infusion-associated reactions. Careful consideration should be given to the patient's clinical status prior to administration of MYOZYME®.

Carcinogenesis and Mutagenesis

There are no animal or human studies to assess the carcinogenic or mutagenic potential of MYOZYME®.

A single study to address the impact of MYOZYME® on fertility in mice was not conclusive since decreased fertility was noted in all groups, including vehicle controls. (See **TOXICOLOGY**)

Cardiac Adverse Events During General Anaesthesia for Central Venous Catheter Placement

Precaution must be observed when administering general anaesthesia to patients with infantile-onset Pompe's Disease. Reports of intraoperative cardiac arrest following anaesthesia induction for invasive procedures have been reported, some of which were fatal. The presence of severe hypertrophic cardiomyopathy in infantile-onset Pompe's Disease may increase the risk of general anaesthesia complications (Ing, 2004, *Paediatr Anaesth)*.

Hypersensitivity Reactions

Significant Hypersensitivity Reactions:
In clinical trials and in the post-marketing safety experience with MYOZYME®, approximately 1% of patients developed anaphylactic shock and/or cardiac arrest during MYOZYME® infusion that required life-support measures. Some of these reactions were IgE-mediated. Additionally, in a randomized, double-blind, placebo controlled study in patients with late-onset Pompe's Disease, 5% of patients (3/60) treated with MYOZYME® experienced anaphylactic reactions, two of which were IgE-mediated.

Eight (8) of approximately 280 patients (3%) treated in clinical trials and expanded access programs with MYOZYME® experienced significant hypersensitivity reactions as of April 12, 2006. One of 59 pediatric patients (approximately 2%) experienced a life-threatening hypersensitivity reaction consisting of bronchospasm, oxygen saturation decreased, tachycardia, urticaria, and periorbital edema. Five of the 8 patients had infantile-onset Pompe's Disease and 3 had late-onset disease. Significant hypersensitivity reactions generally consisted of a constellation of signs and symptoms. Symptoms occurring in more than 1 patient included bronchospasm, oxygen saturation decreased, hypotension, and urticaria. Remaining symptoms were single occurrences of periorbital edema, swollen tongue, angioedema, chest discomfort, throat tightness, tachycardia, and rash. Reactions generally occurred within the first 3 months of initiation of treatment; all 8 patients experienced their first reaction between the first and approximately eighth infusion. Time from onset of infusion to onset of the reaction ranged between a few minutes after initiation of the infusion up to and including 20 minutes after completion of the infusion. The majority of the reactions were moderate or severe in intensity. Reactions were primarily managed with infusion rate reduction and/or interruption of the infusion and administration of antihistamines, corticosteroids, bronchodilators (including epinephrine in 2 patients) and/or oxygen. All 8 patients recovered without sequelae from the reactions. In 2 of the 8 patients, infusions were permanently discontinued as a result of the reaction. In the remaining 6 patients, MYOZYME® treatment was continued with pre-treatment medication (e.g. antihistamines, corticosteroids and/or acetaminophen) administered for infusion management in 5 patients. Two of the 8 patients experienced anaphylactic reactions of angioedema, throat tightness and chest discomfort in the double-blind, placebo-controlled study of late-onset patients. An additional third patient in the late-onset study experienced an

anaphylactic reaction of chest pain and chest discomfort.

Based on experience in clinical studies, patients with acute underlying illness (for example: acute febrile illness as pneumonia or sepsis, wheezing/bronchospasm, decompensated cardiac failure, etc.) at the time of MYOZYME® infusion appear to be at greater risk for infusion-associated reactions. Careful consideration should be given to the patient's clinical status prior to administration of MYOZYME® (see **WARNINGS AND PRECAUTIONS**, **General**). Patients with advanced Pompe's Disease may have compromised cardiac and respiratory function, which may also predispose them to a higher risk of severe complications from infusion reactions.

Patients should be closely monitored during the MYOZYME® infusion. If significant hypersensitivity reactions occur during the MYOZYME® infusion, immediate discontinuation of the MYOZYME® infusion should be considered and appropriate medical treatment should be initiated. Because of the potential for significant hypersensitivity reactions, appropriate medical support measures, including cardiopulmonary resuscitation equipment, especially for patients with cardiac hypertrophy and patients with significantly compromised respiratory function, should be readily available when MYOZYME® is administered. Patients who have experienced hypersensitivity reactions should be closely monitored when MYOZYME® is re-administered.

Infusion Reactions:
In 3 clinical studies of 59 pediatric patients receiving treatment with MYOZYME® (AGLU01602, AGLU01702, AGLU02203), 30 patients (51%) experienced infusion-associated reactions (IARs). Seventeen of the 30 patients (57%) experienced their first infusion-associated reaction within the first 3 months of initiation of treatment. In the remaining patients (43%), the first reaction occurred as late as 95 weeks after initiation of treatment. Twenty-one of the 30 patients (70%) experienced reactions with multiple infusions; the remaining 9 patients experienced reactions with a single infusion. Infusion-associated reactions that occurred in $\geq$ 5% of patients included urticaria, rash, rash maculopapular, pyrexia, rigors, oxygen saturation decreased, blood pressure decreased, blood pressure increased, heart rate increased, flushing, hypertension, cough, tachypnea, tachycardia, agitation, irritability, and vomiting (see **ADVERSE REACTIONS**). The majority of infusion-associated reactions were assessed as non-serious and mild or moderate in intensity. Two reactions (heart rate increased and pyrexia) were assessed as severe. Four patients (4/59 = 7%) experienced serious infusion-associated reactions. Serious infusion-associated reactions included rales, bronchospasm, oxygen saturation decreased, tachypnea, tachycardia, periorbital edema, urticaria, hypertension, heart rate increased and fever. Most infusion-associated reactions requiring intervention were ameliorated with slowing the infusion rate, temporarily stopping the infusion and/or administration of antipyretics, antihistamines or corticosteroids. All patients recovered without sequelae from the reactions.

In clinical trials and expanded access programs with MYOZYME®, approximately 92 of 280 (33%) patients treated with MYOZYME® have developed infusion reactions as of April 12, 2006.

Approximately 28% of the patients treated with MYOZYME® in a double-blind, placebo-controlled study in late-onset patients developed IARs, compared to 23% of placebo-treated patients. The majority of these reactions were mild to moderate and resolved spontaneously. Infusion reactions which were reported in ≥ 5% of MYOZYME®-treated patients included headache, nausea, urticaria, dizziness, chest discomfort, hyperhidrosis, flushing, blood pressure increased, and vomiting.

Based on experience in clinical studies, patients with acute underlying illness (for example: acute febrile illness as pneumonia or sepsis, wheezing/bronchospasm, decompensated cardiac failure, etc.) at the time of MYOZYME® infusion appear to be at greater risk for infusion-associated reactions. Careful consideration should be given to the patient's clinical status prior to administration of MYOZYME® (see **WARNINGS AND PRECAUTIONS**, **General**). Infusion reactions are also more likely to occur with higher infusion rates. Infantile-onset patients treated with the higher dose (40 mg/kg) generally developed a more robust antibody response and experienced more IARs. Patients with advanced Pompe's Disease may have compromised cardiac and respiratory function, which may also predispose them to a higher risk of severe complications from infusion reactions.

In clinical trials, some patients were pre-treated with antihistamines, antipyretics and/or corticosteroids. Infusion reactions occurred in some patients after receiving antipyretics, antihistamines and/or corticosteroids**.**

Patients should be closely monitored during the MYOZYME® infusion. Infusion reactions may occur at any time during, or shortly after completion of MYOZYME® infusion. If the patient experiences an infusion reaction during the MYOZYME® infusion, the patient should be managed according to general standards of care consistent with treatment of the presenting symptom(s). Regardless of pre-treatment, reduction of the infusion rate, temporarily interrupting the infusion, and/or administration of antihistamines, antipyretics and/or corticosteroids may ameliorate the symptoms. If severe infusion reactions occur, immediate discontinuation of the MYOZYME® infusion should be considered, and appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be available. Severe infusion reactions are generally managed with administration of antihistamines, corticosteroids, intravenous fluids, and/or oxygen, when clinically indicated. In some cases of anaphylactic reactions epinephrine was administered. Patients who have experienced infusion reactions should be treated with caution when they are readministered MYOZYME®.

Immunogenicity

In clinical studies, the majority of patients developed IgG antibodies to alglucosidase alfa, typically within 3 months of treatment. Thus seroconversion is expected to occur in most patients treated with MYOZYME®. Infantile-onset patients treated with higher doses of alglucosidase alfa tended to develop a more robust antibody response and experienced more IARs (see **ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions, Infantile-Onset Disease, Immunogenicity** section). It is recommended that patients be monitored for IgG antibody formation periodically. The effect of antibody development on the long term efficacy of alglucosidase alfa is not fully understood.

There is an observation that some patients who develop high and sustained IgG antibody titers, including Cross Reactive Immunologic Material (CRIM)-negative patients (i.e., patients in whom no endogenous GAA protein was detected by Western blot analysis), may experience reduced clinical treatment efficacy. The cause of a poor clinical response in some of these patients is thought to be multi-factorial.

Some IgG positive infantile-onset and late-onset patients in clinical trials who were retrospectively evaluated for the presence of inhibitory antibodies tested positive for inhibition of enzyme activity and/or uptake in *in vitro* assays. However, the clinical relevance of this *in vitro* inhibition is unclear (see **ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions, Infantile-Onset Disease, Immunogenicity; Late-Onset Disease, Immunogenicity** sections).

A small number of patients who were evaluated tested positive for alglucosidase alfa-specific IgE antibodies, some of whom experienced anaphylactic reactions. Testing was typically performed for IARs suggestive of hypersensitivity reactions. Some patients have been successfully rechallenged using slower rates and/or lower initial doses and continued to receive treatment with alglucosidase alfa under close clinical supervision.

Severe cutaneous and possibly immune-mediated reactions have been reported with MYOZYME® including ulcerative and necrotizing skin lesions. A skin biopsy in one infantile-onset 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 MYOZYME®. If immune mediated reactions occur, discontinuation of the administration of MYOZYME® should be considered, and appropriate medical treatment initiated. Patients who develop IgE antibodies to alglucosidase alfa appear to be at a higher risk for the occurrence of IARs when MYOZYME® is re-administered. The risks and benefits of re-administering MYOZYME® following an immune mediated reaction should be considered. Some patients have been successfully rechallenged and continued to receive MYOZYME® 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 Acute Cardiorespiratory Failure

Acute cardiorespiratory failure requiring intubation and inotropic support has been observed after infusion with MYOZYME® in a few infantile-onset Pompe's Disease patients with underlying cardiac hypertrophy, possibly associated with fluid overload with intravenous administration of MYOZYME®. (See **DOSAGE AND ADMINISTRATION, Administration** – Instructions for Use - for information on appropriate infusion volumes). Because of the potential for fluid overload, appropriate medical support measures should be readily available when MYOZYME® is administered.

Special Populations

Patients should be informed that a registry for patients with Pompe's Disease has been established in order to better understand the variability and progression of Pompe's Disease and to continue to monitor and evaluate treatments. Patients should be encouraged to participate and advised that their participation may involve long-term follow-up. Information regarding the registry program may be found at www.pomperegistry.com or by calling 1-800-745-4447.

Pregnant Women: Reproduction studies have been performed in pregnant mice at doses of MYOZYME® up to 40 mg/kg administered daily for 10 days with no evidence of embryo-fetal abnormality due to MYOZYME®.

There are no adequate and well-controlled studies of MYOZYME® in pregnant women. Because animal reproduction studies are not always predictive of human response, MYOZYME® should be used during pregnancy only if clearly needed.

Women of childbearing potential should be encouraged to enroll in the Pompe patient registry (see **WARNINGS AND PRECAUTIONS, Special Populations**).

Nursing Women: It is not known whether MYOZYME® is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when MYOZYME® is administered to a nursing woman. (See **WARNINGS AND PRECAUTIONS, Special Populations** regarding a registry program. Nursing women are encouraged to participate in the registry program).

Pediatrics (< 18 years of age): Pediatric patients from 1 month up to 18 years of age at time of first infusion have been treated with MYOZYME® in clinical trials.

Geriatrics (> 65 years of age): Clinical studies did not include a sufficient number of subjects aged 65 years and older.

Monitoring and Laboratory Tests

There are no marketed tests for antibodies against MYOZYME®. It is recommended that patients be monitored for IgG antibody formation periodically.

Patients who experience reactions suggestive of anaphylactic or allergic reactions may also be tested for IgE antibodies to alglucosidase alfa and other mediators of anaphylaxis. If testing is warranted, contact your local Sanofi Genzyme representative or Sanofi Genzyme Canada at 1-800-589-6215.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most serious adverse reactions reported in infantile and late-onset patients treated with MYOZYME® (alglucosidase alfa) were hypersensitivity reactions (including anaphylactic reactions), acute cardiorespiratory failure, and cardiac arrest. Acute cardiorespiratory failure, possibly associated with fluid overload, has been reported in infantile-onset Pompe disease patients with pre-existing hypertrophic cardiomyopathy (see **WARNINGS AND PRECAUTIONS, Risk of Acute Cardiorespiratory Failure** and **WARNINGS AND PRECAUTIONS boxed WARNING: RISK OF ANAPHYLAXIS**).

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

Infantile-Onset Pompe's Disease

The data described below reflect exposure of 59 pediatric patients to 20 or 40 mg/kg of MYOZYME® administered every other week in three separate clinical trials (AGLU01602, AGLU01702, AGLU02203) for a period of up to 76 weeks. These three studies included a population of patients which ranged in age from 1 month to 16 years at initiation of treatment.

Infusion Reactions

In 3 clinical studies of 59 pediatric patients receiving treatment with MYOZYME®, 30 patients (51%) experienced infusion-associated reactions. Infusion-associated reactions that occurred in $\geq$ 5% of patients included urticaria, rash, rash maculopapular, pyrexia, rigors, oxygen saturation decreased, blood pressure decreased, blood pressure increased, heart rate increased, flushing, hypertension, cough, tachypnea, tachycardia, agitation, irritability, and vomiting (see

WARNINGS AND PRECAUTIONS, Infusion Reactions).

Table 1 enumerates infusion reactions that occurred in at least 5% of the pediatric patients treated with MYOZYME® in clinical trials described above. Reported frequencies of infusion reactions have been classified by MedDRA terms.

Table 1: Summary of Infusion Reactions by System Organ Class and Preferred Term During Treatment Occurring in at Least 5% of Pediatric Patients Treated with MYOZYME® in Clinical Trials

System Organ Class Preferred Term	Number of Patients N=59 n (%)	Number of Reactions N= 271
Any Adverse Events	**30 (50.8)**	**271**
Skin and subcutaneous tissue disorders	**17 (28.8)**	**71**
Urticaria	8 (13.6)	28
Rash	6 (10.2)	12
Rash maculopapular	3 (5.1)	5
General disorders and administration site conditions	**15 (25.4)**	**43**
Pyrexia	13 (22.0)	33
Rigors	3 (5.1)	4
Investigations	**14 (23.7)**	**47**
Oxygen saturation decreased	8 (13.6)	22
Blood pressure decreased	4 (6.8)	5
Blood pressure increased	3 (5.1)	4
Heart rate increased	3 (5.1)	7
Vascular disorders	**11 (18.6)**	**29**
Flushing	7 (11.9)	19
Hypertension	4 (6.8)	5
Respiratory, thoracic and mediastinal disorders	**9 (15.3)**	**28**
Cough	5 (8.5)	17
Tachypnoea	5 (8.5)	8
Cardiac disorders	**6 (10.2)**	**18**
Tachycardia	6 (10.2)	15
Psychiatric disorders	**6 (10.2)**	**10**
Agitation	3 (5.1)	5
Irritability	3 (5.1)	3
Gastrointestinal disorders	**4 (6.8)**	**17**
Vomiting	4 (6.8)	9

Infusion associated reactions that occurred with frequency less than 5% of patients (reported in more than 1 patient) based on the MedDRA SOCs of **Skin and subcutaneous tissue disorders**

include Hyperhydrosis, Livedo reticularis, Pruritus and Rash macular; **Investigations** include Body temperature increased; **Vascular disorders** include Pallor; **Cardiac disorders** include Cyanosis; **Psychiatric disorders** include Restlessness; **Gastrointestinal disorders** include Retching and **Nervous system disorders** include Tremor.

Treatment Emergent Adverse Events
The most common treatment emergent adverse events (occurring in at least 18 of the 59 patients) (regardless of relationship) included upper respiratory tract infection, otitis media, pneumonia cough, respiratory failure, pyrexia, rash, diarrhoea, vomiting, and oxygen saturation decreased.

Table 2 enumerates **t**reatment emergent adverse events (regardless of relationship) that occurred in at least 5% of pediatric patients treated with MYOZYME® in clinical trials. Reported frequencies of adverse events have been classified by MedDRA terms.

Table 2: Summary of Adverse Events by System Organ Class and Preferred Term During Treatment Occurring in at Least 5% of Pediatric Patients Treated with MYOZYME® in Clinical Trials

System Organ Class Preferred Term	Number of Patients (N=59) n (%)	Number of Adverse Events N=2725
Any Adverse Events	**58 (98.3)**	**2725**
Infections and infestations	**54 (91.5)**	**553**
Upper respiratory tract infection	25 (42.4)	58
Otitis media	24 (40.7)	45
Pneumonia	20 (33.9)	49
Viral infection	16 (27.1)	24
Catheter related infection	14 (23.7)	22
Ear infection	14 (23.7)	26
Gastroenteritis	12 (20.3)	12
Nasopharyngitis	12 (20.3)	32
Oral candidiasis	11 (18.6)	13
Pharyngitis	11 (18.6)	19
Bronchiolitis	10 (16.9)	13
Respiratory syncytial virus infection	9 (15.3)	12
Tracheitis	9 (15.3)	31
Gastroenteritis viral	8 (13.6)	8
Influenza	8 (13.6)	17
Bacteraemia	7 (11.9)	11
Candidiasis	7 (11.9)	10
Urinary tract infection	7 (11.9)	8
Otitis media acute	6 (10.2)	11
Bronchopneumonia	5 (8.5)	7
Respiratory tract infection	5 (8.5)	5
Sinusitis	5 (8.5)	6
Bronchitis	4 (6.8)	13
Dental Caries	4 (6.8)	6
Acute tonsillitis	3 (5.1)	5
Bronchitis acute	3 (5.1)	9
Cellulitis	3 (5.1)	4
Fungal skin infection	3 (5.1)	3
Localised infection	3 (5.1)	7
Pharyngitis streptococcal	3 (5.1)	6
Sepsis	3 (5.1)	4
Tonsillitis	3 (5.1)	3
Respiratory, thoracic and mediastinal disorders	**51 (86.4)**	**423**
Cough	20 (33.9)	76
Respiratory failure	18 (30.5)	43
Respiratory distress	16 (27.1)	24
Rhinorrhoea	12 (20.3)	19
Increased bronchial secretion	11 (18.6)	24
Tachypnoea	11 (18.6)	17
Atelectasis	10 (16.9)	23
Upper respiratory tract congestion	9 (15.3)	15

Table 2: Summary of Adverse Events by System Organ Class and Preferred Term During Treatment Occurring in at Least 5% of Pediatric Patients Treated with MYOZYME® in Clinical Trials

System Organ Class Preferred Term	Number of Patients (N=59) n (%)	Number of Adverse Events N=2725
Any Adverse Events	**58 (98.3)**	**2725**
Nasal congestion	8 (13.6)	9
Pharyngolaryngeal pain	8 (13.6)	11
Pneumonia aspiration	8 (13.6)	23
Bronchospasm	6 (10.2)	12
Rhinitis	6 (10.2)	8
Wheezing	6 (10.2)	8
Asthma	5 (8.5)	10
Choking	5 (8.5)	10
Dyspnoea	5 (8.5)	7
Respiratory tract congestion	4 (6.8)	4
Tracheal disorder	4 (6.8)	5
Lung infiltration	3 (5.1)	3
Rhonchi	3 (5.1)	3
General disorders and administration site conditions	**49 (83.1)**	**369**
Pyrexia	46 (78.0)	252
Catheter related complication	10 (16.9)	22
Granuloma	7 (11.9)	11
Oedema peripheral	7 (11.9)	9
Pain	4 (6.8)	7
Asthenia	3 (5.1)	11
Hyperthermia	3 (5.1)	3
Inflammation localised	3 (5.1)	6
Lethargy	3 (5.1)	6
Oedema	3 (5.1)	3
Rigors	3 (5.1)	4
Skin and subcutaneous tissue disorders	**46 (78.0)**	**232**
Rash	18 (30.5)	46
Dermatitis diaper	17 (28.8)	40
Urticaria	12 (20.3)	32
Erythema	7 (11.9)	11
Hyperhidrosis	6 (10.2)	7
Rash macular	6 (10.2)	18
Dry skin	5 (8.5)	5
Eczema	5 (8.5)	9
Pruritus	5 (8.5)	6
Rash maculopapular	4 (6.8)	8
Rash papular	4 (6.8)	6
Skin irritation	4 (6.8)	4
Skin ulcer	4 (6.8)	4
Face oedema	3 (5.1)	4
Periorbital oedema	3 (5.1)	3
Rash erythematous	3 (5.1)	5
Gastrointestinal disorders	**44 (74.6)**	**275**

Table 2: Summary of Adverse Events by System Organ Class and Preferred Term During Treatment Occurring in at Least 5% of Pediatric Patients Treated with MYOZYME® in Clinical Trials

System Organ Class Preferred Term	Number of Patients (N=59) n (%)	Number of Adverse Events N=2725
Any Adverse Events	**58 (98.3)**	**2725**
Diarrhoea	28 (47.5)	75
Vomiting	24 (40.7)	74
Constipation	14 (23.7)	21
Gastrooesophageal reflux disease	12 (20.3)	15
Dysphagia	7 (11.9)	9
Teething	6 (10.2)	8
Loose stools	5 (8.5)	8
Abdominal distension	3 (5.1)	3
Abdominal pain	3 (5.1)	3
Nausea	3 (5.1)	4
Toothache	3 (5.1)	3
Investigations	**42 (71.2)**	**251**
Oxygen saturation decreased	21 (35.6)	57
Sputum culture positive	9 (15.3)	56
Heart rate increased	7 (11.9)	15
Blood potassium decreased	6 (10.2)	7
Blood pressure decreased	6 (10.2)	7
Blood creatine phosphokinase MB increased	5 (8.5)	5
Blood creatine phosphokinase increased	5 (8.5)	6
Blood pressure increased	5 (8.5)	6
Blood bicarbonate decreased	4 (6.8)	5
Ejection fraction decreased	4 (6.8)	4
Blood chloride decreased	3 (5.1)	3
Blood phosphorus increased	3 (5.1)	4
Blood pressure systolic increased	3 (5.1)	4
Body temperature increased	3 (5.1)	7
Haemoglobin decreased	3 (5.1)	3
Urine output decreased	3 (5.1)	3
Weight decreased	3 (5.1)	3
White blood cell count increased	3 (5.1)	3
Cardiac disorders	**34 (57.6)**	**130**
Tachycardia	12 (20.3)	42
Bradycardia	9 (15.3)	20
Cardiac failure	6 (10.2)	6
Cardio-respiratory arrest	5 (8.5)	7
Cyanosis	5 (8.5)	7
Ventricular hypertrophy	4 (6.8)	6
Arrhythmia	3 (5.1)	3
Cardiomegaly	3 (5.1)	3
Cardiomyopathy	3 (5.1)	3
Musculoskeletal and connective tissue disorders	**32 (54.2)**	**54**
Joint contracture	11 (18.6)	15
Osteopenia	10 (16.9)	10

Table 2: Summary of Adverse Events by System Organ Class and Preferred Term During Treatment Occurring in at Least 5% of Pediatric Patients Treated with MYOZYME® in Clinical Trials

System Organ Class Preferred Term	Number of Patients (N=59) n (%)	Number of Adverse Events N=2725
Any Adverse Events	**58 (98.3)**	**2725**
Arthralgia	5 (8.5)	8
Pain in extremity	4 (6.8)	4
Myopathy	3 (5.1)	6
Osteoporosis	3 (5.1)	3
Injury, poisoning and procedural complications	**30 (50.8)**	**94**
Post procedural pain	11 (18.6)	22
Medical device complication	9 (15.3)	28
Excoriation	6 (10.2)	6
Blister	4 (6.8)	4
Fall	4 (6.8)	4
Femur fracture	4 (6.8)	5
Contusion	3 (5.1)	3
Ear and labyrinth disorders	**23 (39.0)**	**37**
Hypoacusis	7 (11.9)	11
Middle ear effusion	7 (11.9)	7
Conductive deafness	3 (5.1)	4
Ear pain	3 (5.1)	3
Otorrhoea	3 (5.1)	4
Metabolism and nutrition disorders	**22 (37.3)**	**66**
Dehydration	7 (11.9)	7
Feeding disorder	5 (8.5)	6
Hypokalaemia	5 (8.5)	6
Hypoglycaemia	3 (5.1)	3
Blood and lymphatic system disorders	**21 (35.6)**	**49**
Anaemia	16 (27.1)	27
Lymphadenopathy	4 (6.8)	8
Vascular disorders	**19 (32.2)**	**48**
Flushing	8 (13.6)	20
Hypertension	8 (13.6)	10
Hypotension	5 (8.5)	11
Eye disorders	**16 (27.1)**	**20**
Conjunctivitis	7 (11.9)	8
Eye discharge	3 (5.1)	3
Psychiatric disorders	**16 (27.1)**	**31**
Insomnia	6 (10.2)	6
Agitation	5 (8.5)	8
Irritability	5 (8.5)	7
Anxiety	3 (5.1)	6
Restlessness	3 (5.1)	3
Renal and urinary disorders	**16 (27.1)**	**34**
Haematuria	4 (6.8)	7
Hypercalciuria	4 (6.8)	6
Proteinuria	3 (5.1)	3

Table 2: Summary of Adverse Events by System Organ Class and Preferred Term During Treatment Occurring in at Least 5% of Pediatric Patients Treated with MYOZYME® in Clinical Trials

System Organ Class Preferred Term	Number of Patients (N=59) n (%)	Number of Adverse Events N=2725
Any Adverse Events	**58 (98.3)**	**2725**
Renal insufficiency	3 (5.1)	3
Nervous system disorders	**13 (22.0)**	**22**
Hypotonia	3 (5.1)	4
Immune system disorders	**9 (15.3)**	**13**
Drug hypersensitivity	5 (8.5)	8
Congenital, familial and genetic disorders	**7 (11.9)**	**8**
Macroglossia	3 (5.1)	3
Reproductive system and breast disorders	**6 (10.2)**	**6**
Endocrine disorders	**4 (6.8)**	**5**

The adverse events that occurred with frequency less than 5% of patients (reported in more than 1 patient) based on the MedDRA SOCs of **Infections and infestations** include Bacteriuria, Clostridium colitis, Eye infection, Gastroenteritis rotavirus, Infection, Lower respiratory tract infection, Respiratory tract infection viral, Skin infection, Viral rash and Viral upper respiratory tract infection; **Respiratory, thoracic and mediastinal disorders** include Aspiration, Epistaxis, Hypercapnia, Hypoventilation, Hypoxia, Lung crepitation, Lung disorder, Pleural effusion, Pulmonary congestion, Respiratory acidosis, Respiratory arrest, Respiratory tract irritation, Throat secretion increased, and Tracheal pain; **General disorder and administration site conditions** include Application site reaction, Catheter site related reaction, Fatigue, Feeling hot, Infusion site reaction, and Localised oedema; **Skin and subcutaneous tissue disorders** include Decubitus ulcer, Dermatitis contact, Hair growth abnormal, Livedo reticularis, Skin disorder, and Skin lesion; **Gastrointestinal disorders** include Mouth ulceration, Regurgitation of food, Retching, and Upper gastrointestinal haemorrhage; **Investigations** include Acoustic stimulation tests abnormal, Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood calcium increased, Blood culture positive, Blood urea increased, Bone density decreased, Culture throat positive, Eosinophil count increased, Gallop rhythm present and Heart rate decreased; **Cardiac disorders** include Cardiac arrest, Hypertrophic obstructive cardiomyopathy and Supraventricular tachycardia; **Injury, poisoning and procedural complications** include Arthropod bite; **Musculoskeletal and connective tissue disorders** include Scoliosis; **Metabolism and nutrition disorders** include Electrolyte imbalance, Fluid imbalance, Hypercalcaemia, Hyperuricaemia, Hypocalcaemia, Hypochloraemia, Hypomagnesaemia and Metabolic acidosis; **Blood and lymphatic system disorders** include Eosinophilia and Lymphadenitis; **Vascular disorders** include Pallor; **Ear and labyrinth disorders**: 25 of 39 patients in the infantile-onset pooled population have been tested for hearing disorders. Of these, 15 (60%) patients had hearing loss at Baseline while 10 had normal hearing test results. Among the 10 patients with normal hearing at baseline, 5 (50%) had abnormal hearing test results at Week 26. In many patients, interpretation of hearing test results was complicated by the presence of middle ear dysfunction at Baseline and/or at subsequent time points. These findings suggest that the hearing loss in patients with Pompe's Disease is related to the disease itself and is not a complication of therapy); **Eye disorders** include Blepharitis and Keratoconjunctivitis

sicca; **Renal and urinary disorders** include Dysuria, Oliguria, and Pyuria **Nervous system disorders** include Areflexia, Headache, Hypokinesia and Tremor; **Immune System Disorders** include Hypersensitivity; **Congenital, familial and genetic disorders** include Talipes; **Reproductive system and breast disorders** include Phimosis; and **Endocrine disorders** include Hypoparathyroidism.

Immunogenicity
In the 3 pediatric clinical trials (AGLU01602, AGLU01702, AGLU02203), 49 of the 54 evaluable patients (91%) tested positive for IgG antibodies to alglucosidase alfa. The data reflect the percentage of patients whose test results were considered positive using an enzyme-linked immunosorbent assay (ELISA) and radioimmunoprecipitation (RIP) assay for alglucosidase alfa-specific IgG antibodies. The majority of patients (45 of 49 or 92%) developed IgG antibodies within the first 3 months of initiation of treatment (see **WARNINGS AND PRECAUTIONS, Immunogenicity** section).

Infusion reactions were reported in 30 of the 59 patients (51%) treated with MYOZYME® and appear to be more common in antibody-positive patients; 16 of 20 patients (80%) with high antibody titers ($\geq$ 12,800) experienced infusion reactions whereas only 1 of the 5 antibody-negative patients (20%) experienced infusion reactions. Infantile-onset patients treated with a higher dose (40 mg/kg) generally developed a more robust antibody response and experienced more infusion reactions. The effect of antibody development on the long term efficacy of MYOZYME® is not fully understood.

Patients who experience IARs suggestive of anaphylactic or allergic reactions may also be tested for IgE antibodies to alglucosidase alfa (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests** section).

In clinical trials and expanded access programs of MYOZYME®, approximately forty patients with moderate or severe or recurrent infusion reactions have been tested for MYOZYME® specific IgE antibodies. A small number of patients who were evaluated tested positive for IgE antibodies, some of whom experienced anaphylactic reactions. Testing was typically performed for IARs suggestive of hypersensitivity reactions (see **WARNINGS AND PRECAUTIONS, Significant Hypersensitivity Reactions).**

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

Late-Onset Pompe's Disease

Five additional pediatric Pompe's Disease patients were evaluated in a single-center, open-label, non-randomized, uncontrolled clinical trial. Patients were ages 5 to 15 years, ambulatory (able to walk at least 10 meters 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.

The data described below reflect exposure of 90 patients (45 male, 45 female) with late-onset Pompe's Disease, ages 10 to 70 years, to 20 mg/kg of MYOZYME® or placebo in a randomized, double-blind, placebo-controlled study. All patients were naïve to enzyme replacement therapy. Patients were randomized in a 2:1 ratio and received MYOZYME® or placebo every other week for 78 weeks (18 months).The study population included 34 males and 26 females (N=60) in the MYOZYME® group and 11 males and 19 females (N=30) in the placebo group. In the MYOZYME® treatment group, 32 patients (53%) experienced adverse reactions and 17 patients (57%) in the Placebo group. The majority of the adverse reactions were characterized as infusion reactions which included 17 patients (28%) in the MYOZYME® group and 7 patients (23%) in the Placebo group. Thirteen (22%) patients experienced serious adverse reactions in the MYOZYME® group and 6 (20%) patients in the Placebo group.

The most serious adverse reactions reported with MYOZYME® in the randomized, double-blind, placebo-controlled study were anaphylactic reactions. Reactions included non-cardiac chest discomfort/pain, throat tightness and angioedema [see **WARNINGS AND PRECAUTIONS boxed WARNING: RISK OF ANAPHYLAXIS** and **Hypersensitivity Reactions**]. Other reported serious adverse reactions included one event of supraventricular tachycardia in a single patient.

The most common adverse reactions observed were infusion reactions. In the randomized, double-blind, placebo-controlled study, infusion reactions occurred in approximately 28% of patients treated with MYOZYME®, compared to 23% of placebo-treated patients. The majority of these reactions were mild to moderate and resolved spontaneously. Infusion reactions which were reported in ≥ 5% of MYOZYME®-treated patients included headache, nausea, urticaria, dizziness, chest discomfort, hyperhidrosis, flushing, blood pressure increased, and vomiting.

Table 3: Summary of IARs Occurring in at Least 5% of Late-Onset Patients in either Treatment Group

System Organ Class Preferred Term	Myozyme Patients Number of Patients[1] (N=60) n (%)	Placebo Patients Number of Patients[1] (N=30) n (%)
Any IARs	**17 (28.3)**	**7 (23.3)**
Nervous system disorders	**9 (15.0)**	**6 (20.0)**
Headache	5 (8.3)	5 (16.7)
Dizziness	4 (6.7)	2 (6.7)
General disorders and administration site conditions	**10 (16.7)**	**2 (6.7)**
Chest discomfort	4 (6.7)	0
Gastrointestinal disorders	**8 (13.3)**	**3 (10.0)**
Nausea	5 (8.3)	3 (10.0)
Vomiting	3 (5.0)	0
Skin and subcutaneous tissue disorders	**10 (16.7)**	**0**
Urticaria	5 (8.3)	0
Hyperhidrosis	3 (5.0)	0
Vascular disorders	**3 (5.0)**	**1 (3.3)**
Flushing	3 (5.0)	0
Investigations	**3 (5.0)**	**0**
Blood pressure increased	3 (5.0)	0

[1] Percentages are based on the total number of patients treated in the study group. A patient experiencing more than 1 IAR within an SOC or preferred term is counted once within that SOC or preferred term. Events occurring in at least 5% of patients in either treatment group are presented; corresponding percentage of patients in alternate treatment group is presented which may represent less than 5% of patients.

Infusion associated reactions that occurred with frequency less than 5% in patients treated with MYOZYME® (reported in at least 1 patient) based on the MedDRA SOCs of **Nervous system disorders** include Paraesthesia, Somnolence; **General disorders and administration site conditions** include Pyrexia, Local swelling, Feeling hot, Chills, Non-cardiac chest pain, Oedema peripheral; **Gastrointestinal disorders** include Lip swelling, Oral pruritus, Dyspepsia, Epigastric discomfort, Retching, Stomach discomfort, Swollen tongue; **Skin and subcutaneous tissue disorders** include Pruritus, Rashpapular, Skin nodule, Rash macular, Cold sweat, Rash maculopapular, Erythema, Rash, Rash pruritic, Angioneurotic oedema, Subcutaneous nodule; **Investigations** include Oxygen saturation decreased; **Eye disorders** include Asthenopia, Eye pruritus; **Immune system disorders** include Hypersensitivity; **Musculoskeletal and connective tissue disorders** include Sensation of heaviness, Muscle twitching; **Respiratory, thoracic and mediastinal disorders** include Throat tightness, Wheezing; **Cardiac disorders** include sinus tachycardia; **Ear and labyrinth disorders** include Ear discomfort, Auricular swelling.

Table 4 enumerates treatment-emergent adverse reactions that occurred in at least 5% of patients

during the randomized, double-blind, placebo-controlled study. Reported adverse reactions have been classified by Medical Dictionary for Regulatory Activities (MedDRA) terminology System Organ Class and Preferred Term.

Table 4: Summary of Adverse Reactions Occurring in ≥ 5% of Late-Onset Patients by Treatment Group

System Organ Class Preferred Term	**MYOZYME®** **N=60** **n(%)**	**Placebo** **N=30** **n(%)**
Any Adverse Events	**32 (53.3)**	**17 (56.7)**
General disorders and administration site conditions	**15 (25.0)**	**7 (23.3)**
Fatigue	3 (5.0)	4 (13.3)
Chest discomfort	4 (6.7)	1 (3.3)
Asthenia	0	2 (6.7)
Nervous system disorders	**10 (16.7)**	**8 (26.7)**
Headache	5 (8.3)	6 (20.0)
Dizziness	4 (6.7)	2 (6.7)
Skin and subcutaneous tissue disorders	**13 (21.7)**	**4 (13.3)**
Urticaria	5 (8.3)	0
Hyperhidrosis	5 (8.3)	0
Gastrointestinal disorders	**9 (15.0)**	**4 (13.3)**
Nausea	5 (8.3)	3 (10.0)
Vomiting	3 (5.0)	0
Musculoskeletal and connective tissue disorders	**8 (13.3)**	**2 (6.7)**
Muscle twitching	4 (6.7)	1 (3.3)
Myalgia	3 (5.0)	1 (3.3)
Eye disorders	**6 (10.0)**	**2 (6.7)**
Cataract	4 (6.7)	1 (3.3)
Ear and labyrinth disorders	**4 (6.7)**	**2 (6.7)**
Hypoacusis	2 (3.3)	2 (6.7)
Vascular disorders	**4 (6.7)**	**2 (6.7)**
Flushing	3 (5.0)	0
Investigations	**4 (6.7)**	**0**
Blood pressure increased	3 (5.0)	0

Adverse reactions that occurred with frequency less than 5% in patients treated with MYOZYME® (reported in at least 1 patient) based on the MedDRA SOCs of **General disorders and administration site conditions** include local swelling, pyrexia, feeling hot, oedema peripheral, catheter site pain, chills, infusion site bruising, infusion site paraesthesia, malaise, non-cardiac chest pain; **Nervous system disorders** include paraesthesia, lethargy, somnolence; **Skin and subcutaneous tissue disorders** include pruritus, rash pruritic, rash, rash papular, skin

nodule, rash macular, cold sweat, rash maculopapular, erythema, angioedema, skin odour abnormal, subcutaneous nodule; **Gastrointestinal disorders** include diarrhea, lip swelling, oral pruritus, abdominal distension, dyspepsia, epigastric discomfort, retching, stomach discomfort, swollen tongue; **Musculoskeletal and connective tissue disorders** include muscle spasms, pain in extremity, sensation of heaviness; **Eye disorders** include asthenopia, eye pruritus, photophobia; **Ear and labyrinth disorders** include hypoacusis, ear discomfort, auricular swelling, tinnitus; **Vascular disorders** include hot flush; **Cardiac disorders** include bundle branch block left, bundle branch block right, sinus tachycardia, supraventricular tachycardia; **Investigations** include electrocardiogram QT corrected interval prolonged, oxygen saturation decreased; **Respiratory, thoracic and mediastinal disorders** include throat tightness, wheezing; **Renal and urinary disorders** include haematuria, urine odour abnormal; and **Immune system disorders** include hypersensitivity.

Immunogenicity
In the randomized, double-blind, placebo-controlled study, all patients with available samples treated with MYOZYME® (N=59, 100%) developed IgG antibodies to alglucosidase alfa. Patients were considered positive for antibodies to alglucosidase alfa using an enzyme-linked immunosorbent assay (ELISA) and confirmed by a radioimmunoprecipitation (RIP) assay for alglucosidase alfa-specific IgG antibodies. All patients who developed IgG antibodies did so within the first 3 months of exposure (median time to seroconversion was 4 weeks) (see **WARNINGS AND PRECAUTIONS, Immunogenicity** section).

Patients who developed IgG antibodies to alglucosidase alfa were also evaluated for inhibition of enzyme activity or cellular uptake of enzyme in *in vitro* assays. None of the 59 evaluable patients tested positive for inhibition of enzyme activity. Ten of 59 patients had antibody titers for uptake inhibition ≥40 at two consecutive time points. An additional 8 patients tested positive for uptake inhibition at least once, but did not have antibody titers for uptake inhibition ≥40 at any two consecutive time points. All other patients tested negative for inhibition of cellular uptake. Patients who were positive for uptake inhibition tended to have higher mean peak IgG titers than patients who tested negative for uptake inhibition. Among the 32 patients with evaluable pharmacokinetic (PK) samples, 5 patients tested positive for uptake inhibition at times corresponding to PK sampling times, and had higher mean clearance, lower mean AUC, and lower mean Cmax [see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**] as compared to other patients.

Ten patients in the randomized, double-blind, placebo-controlled study underwent testing for alglucosidase alfa-specific IgE antibodies. Testing was performed in patients who experienced moderate to severe or recurrent infusion reactions, for which mast-cell activation was suspected. Two of 10 patients evaluated tested positive for alglucosidase alfa-specific IgE-binding antibodies, both of whom experienced anaphylactic reactions [see **WARNINGS AND PRECAUTIONS boxed WARNING: RISK OF ANAPHYLAXIS and Hypersensitivity Reactions]**. One patient who developed IgE antibodies discontinued the study following an anaphylactic reaction. Both IgE positive patients were successfully rechallenged with MYOZYME® during or after discontinuation from the study using a slower infusion rate at lower initial doses and have continued to receive treatment under close clinical supervision. Patients who develop IgE antibodies to MYOZYME® appear to be at a higher risk for the occurrence of

infusion reactions [see **WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions**]. Therefore, these patients should be monitored more closely during administration of MYOZYME®.

Post-Market Adverse Drug Reactions

Additional IARs reported from worldwide post-marketing sources after marketing approval (including ongoing clinical programs) included: cardiac arrest, bradycardia, angioedema, pharyngeal edema, peripheral/local edema, abdominal pain, arthralgia, chest pain, chest discomfort, dyspnea, muscle spasm, fatigue, and conjunctivitis. Those IARs assessed as severe included cardiac arrest, bradycardia, chest pain, and dyspnea. Additional adverse drug reactions included proteinuria and nephrotic syndrome in patients with high IgG antibody titers (≥ 102,400).

Significant hypersensitivity reactions have been reported in both infantile- and late-onset patients treated with MYOZYME®. Some 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, edematous and/or cutaneous in nature. Reactions included bronchospasm, wheezing, respiratory arrest, respiratory distress, apnea, stridor, dyspnea, oxygen saturation decreased, brief episodes of cardiac arrest, hypotension, bradycardia, tachycardia, cyanosis, vasoconstriction, flushing, chest pain, chest discomfort, throat tightness, angioedema, face edema, peripheral edema, urticaria, and rash.

These reactions were generally managed with temporary interruption and/or discontinuation of infusion and 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 were also administered. All patients recovered from the reactions. The majority of patients continued to receive treatment with MYOZYME®, some under close clinical supervision.

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.

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.

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.

DRUG INTERACTIONS

Drug-Drug Interactions: Interactions with other drugs have not been established.

Drug-Food Interactions: Interactions with food have not been established.

Drug-Herb Interactions: Interactions with herbal products have not been established.

Drug-Laboratory Interactions: Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

MYOZYME® (alglucosidase alfa) is intended for long-term, chronic use under the guidance and supervision of a physician.

Recommended Dose and Dosage Adjustment

The recommended dosage regimen of MYOZYME® is 20 mg/kg body weight administered every 2 weeks as an intravenous infusion. There was no additional clinical benefit with doses of MYOZYME® higher than 20 mg/kg of body weight in clinical trials.

The total volume of infusion is determined by the patient's body weight and should be administered over approximately 4 hours. In the clinical trials, pre-treatment medications were used but not routinely administered to patients.

Infusions should be administered in a step-wise manner using an infusion pump. The initial infusion rate should be no more than 1 mg/kg/h. The infusion rate may be increased by 2 mg/kg/h every 30 minutes, after patient tolerance to the infusion rate is established, until a maximum rate of 7 mg/kg/h is reached. The infusion rate may be slowed and/or temporarily stopped in the event of infusion reactions.

Table 5: Recommended Administration of MYOZYME®	
1 mg/kg/h x 30 minutes	Obtain vital signs, if stable increase rate to…
3 mg/kg/h x 30 minutes	Obtain vital signs, if stable increase rate to…
5 mg/kg/h x 30 minutes	Obtain vital signs, if stable increase rate to…
7 mg/kg/h	Administer for the remainder of the infusion

Administration

Instructions for Use

Vials of MYOZYME® are stored under refrigerated conditions (at 2-8 °C). As MYOZYME® does not contain a preservative, strict aseptic techniques are to be used in the preparation of a patient's dose. Once reconstituted, vials of MYOZYME® are to be used immediately for dilution into an infusion bag. Diluted MYOZYME® into an infusion bag is also to be used immediately (within 3 hours). The reconstituted and diluted infusion solution should be protected from light. Any unused product should be discarded.

MYOZYME® should be reconstituted, diluted and administered by a health care professional. MYOZYME® treatment should be supervised by a physician who is knowledgeable in the treatment of Pompe's disease.

Use aseptic technique during preparation. Do not use filter needles during preparation.

1. Determine the number of vials to be reconstituted based on the individual patient's weight and the recommended dose of 20 mg/kg. Round up to the nearest whole vial. Remove the required number of vials from the refrigerator and allow them to reach room temperature prior to reconstitution (approximately 30 minutes).

   Patient weight (kg) x Dose (mg/kg) = Patient Dose (in mg)

   Patient dose (in mg) ÷ 50 mg/vial = number of vials to reconstitute. If the number of vials includes a fraction, round up to the next whole number.

   Example: Patient Weight (16 kg) x 20 mg/kg = Patient Dose (320 mg)
   320 mg ÷ 50 mg/vial = 6.4 vials; therefore, 7 vials should be reconstituted

2. Reconstitute each MYOZYME® vial by **slowly** injecting 10.3 mL of Sterile Water for Injection, USP to the inside wall of each vial. 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 lyophilized cake. Tilt and roll each vial gently. Do not invert, swirl or shake. Each vial will yield 5 mg/mL. The

total extractable dose per vial is 50 mg, 10 mL. The reconstituted MYOZYME® should be protected from light.

3. Visually inspect the reconstituted vials. The vials should contain a clear, colorless to pale yellow solution. The reconstituted solution may also contain a few particles in the form of thin white strands or translucent fibers. These particles have been shown to be composed of alglucosidase alfa which can be easily filtered during the infusion. Do not use vials that contain foreign matter or if discolored.

4. Slowly withdraw the reconstituted solution from each vial and further dilute with 0.9 % Sodium Chloride Injection, USP. Avoid foaming in the syringe. The final infusion solution should be prepared to a concentration of 0.5 to 4 mg/mL. Remove airspace from the infusion bag to minimize particle formation due to the sensitivity of MYOZYME® to air-liquid interface. Inject the reconstituted MYOZYME® solution directly into the sodium chloride solution rather than into the air within the infusion bag. Avoid foaming in the infusion bag. Discard any vial with unused reconstituted solution. The diluted MYOZYME® should be protected from light.

   Patient dose (in mg) ÷ 5 mg/mL = number of mL of reconstituted MYOZYME® required for patient dose.

   Example: Patient dose = 320 mg
   320 mg ÷ 5 mg/mL = 64 mL of MYOZYME®

Table 6: Recommended Total Volume

Dose (mg/kg)	Patient Weight Range (kg)	Infusion Volume (mL)
20	1 – 10	50
20	10.1 – 20	100
20	20.1 – 30	150
20	30.1 – 35	200
20	35.1 – 50	250
20	50.1 – 60	300
20	60.1 – 100	500
20	100.1 – 120	600
20	120.1 – 140	700
20	140.1 – 160	800
20	160.1 – 180	900
20	180.1 – 200	1000

5. Gently invert the infusion solution bag to mix. Avoid any vigorous shaking and agitation.

6. MYOZYME® should not be infused in the same intravenous line with other products.

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

OVERDOSAGE

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

If you think you have taken too much MYOZYME®, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Pompe's Disease is an inherited, progressive muscle disease resulting from a deficiency of the lysosomal enzyme GAA. Deficiency of GAA results in the accumulation of organelle-bound (lysosomal) and extra lysosomal glycogen. Alglucosidase alfa degrades glycogen by catalyzing the hydrolysis of α-1,4- and α-1,6- glycosidic linkages of lysosomal glycogen. Glycogen accumulation in Pompe's Disease occurs in various tissues, particularly cardiac, respiratory and skeletal muscle, leading to the development of cardiomyopathy and progressive muscle weakness, including impairment of respiratory function. MYOZYME® (alglucosidase alfa) is intended to provide an exogenous source of GAA for patients with Pompe's Disease.

Pharmacodynamics

Pharmacodynamic parameters were evaluated in two studies both of which included patients with infantile-onset Pompe's Disease. Patients in the first study were older (median age of 15.0 months at first infusion) and had signs of more advanced disease than patients in the second study (median age of 5.3 months at first infusion). Pharmacodynamics were evaluated by measuring tissue GAA activity and glycogen content in quadriceps muscle biopsies.

GAA activity in skeletal muscle was measured at baseline and week 12 in both studies and at week 52 in the first study. In both studies, muscle GAA activity increased during treatment with MYOZYME®.

Glycogen content was measured both biochemically and histomorphometrically in muscle biopsy specimens obtained from patients at baseline, week 12 (both studies), and week 52 (first study).

Table 7:
GAA Activity and Glycogen Content in Skeletal Muscle Biopsies in Study AGLU01602

Patient ID	Dose Group (mg/kg)	Visit	GAA Activity (nmol/h/g wet tissue)	Glycogen Content		Change in Glycogen Content from Baseline to Week 12	
				Biochem (mg/g tissue)[1]	Histomorph % tissue area Mean (SD)	Biochem	Histmorph
1602-301	40	Baseline	BQL	46.5	31.2 (6.19)		
		Week 12	279.5	108.2	58.5 (6.64)	Increase	Increase
1602-302	20	Baseline	8.8	11.9	8.3 (5.05)		
		Week 12	62.3	36.3	20.2 (10.26)	Increase	Stable
1602-303	40	Baseline	BQL	56.4	22.1 (6.39)		
		Week 12	225.1	43.2	25.1 (8.11)	Decrease	Stable
1602-305	20	Baseline	BQL	98.1	38.9 (8.03)		
		Week 12	22.3	99.1	59.9 (5.83)	Stable	Increase
1602-306	20	Baseline	8.5	35.2	45.5 (9.34)		
		Week 12	33.4	74.2	39.4 (6.22)	Increase	Stable
1602-307	40	Baseline	BQL	53.1	20.6 (8.04)		
		Week 12	407.9	24.0	6.6 (4.11)	Decrease	Decrease
1602-308	40	Baseline	BQL	69.7	39.1 (4.91)		
		Week 12	213.4	37.5	31.0 (7.67)	Decrease	Stable
1602-309	20	Baseline	4.6	39.4	16.7 (5.91)		
		Week 12	95.8	18.0	9.9 (3.03)	Decrease	Stable
1602-310	20	Baseline	BQL	37.1	15.7 (9.34)		
		Week 12	82.7	40.3	47.8 (6.62)	Stable	Increase
1602-311	40	Baseline	BQL	85.5	30.2 (11.78)		
		Week 12	228.8	72.3	31.3 (9.75)	Stable	Stable
1602-312	20	Baseline	BQL	96.1	32.2 (9.76)		
		Week 12	39.6	77.1	21.5 (9.21)	Stable	Stable
1602-313	40	Baseline	BQL	21.8	21.0 (4.55)		
		Week 12	638.3	10.0	5.6 (4.31)	Decrease	Decrease
1602-314	20	Baseline	BQL	48.9	17.0 (7.46)		
		Week 12	65.2	24.8	5.9 (2.36)	Decrease	Decrease
1602-315	40	Baseline	BQL	40.0	13.4 (7.38)		
		Week 12	88.6	3.4	0.01 (0.02)	Decrease	Decrease

Table 7:
GAA Activity and Glycogen Content in Skeletal Muscle Biopsies
in **Study AGLU01602** (continued)

Patient ID	Dose Group (mg/kg)	Visit	GAA Activity (nmol/h/g wet tissue)	Glycogen Content		Change in Glycogen Content from Baseline to Week 12	
				Biochem (mg/g tissue)[1]	Histomorph % tissue area Mean (SD)	Biochem	Histmorph
1602-316	20	Baseline	BQL	34.2	28.1 (6.45)		
		Week 12	79.6	20.5	16.8 (7.23)	Decrease	Stable
1602-317	40	Baseline	BQL	112.9	55.4 (12.57)		
		Week 12	197.1	68.2	51.6 (7.55)	Decrease	Stable
1602-318	40	Baseline	BQL	74.7	42.1 (8.28)		
		Week 12	799.9	47.3	27.6 (12.13)	Decrease	Stable
1602-319	20	Baseline	BQL	57.6	27.6 (5.85)		
		Week 12	428.9	45.9	29.7 (6.65)	Decrease	Stable

BQL = below quantifiable levels; Histomorph = histomorphometric
[1] To calculate the percentage of wet weight, glycogen content (mg glycogen/g tissue) is divided by 10.

Table 8:
GAA Activity and Glycogen Content in Skeletal Muscle Biopsies in Study AGLU01702

			Glycogen Content		Change in Glycogen Content from Baseline to Week 52[2]	
Patient ID	Visit	GAA Activity (nmol/h/g wet tissue)	Biochem (mg/g tissue)[1]	Histomorph % tissue area Mean (SD)	Biochem	Histomorph
1702-402	Baseline	12.1	46.9	17.41 (2.83)		
	Week 52	101.1	31.6	23.09 (10.87)	Decrease	Stable
1702-403	Baseline	NAV	NAV	53.25 (7.14)		
	Week 52	ND	ND	ND	ND	ND
1702-404	Baseline	8.9	71.4	37.71 (11.26)		
	Week 52	132.6	76.6	71.67 (4.63)	Stable	Increase
1702-405	Baseline	BQL	90.2	64.87 (5.42)		
	Week 52	D	D	D	NA	NA
1702-406	Baseline	9.3	66.9	67.25 (7.17)		
	Week 52[3]	59.6	56.6	61.63 (9.34)	Stable	Stable
1702-407	Baseline	BQL	75.8	42.08 (5.44)		
	Week 52	D	D	D	NA	NA
1702-408	Baseline	23.2	72	62.87 (10.24)		
	Week 52	105.4	43.4	57.56 (9.66)	Decrease	Stable
1702-409	Baseline	BQL	79.1	56.06 (14.98)		
	Week 52	D	D	D	NA	NA
1702-410	Baseline	19.8	98.6	58.05 (13.16)		
	Week 52	44.6	64.7	45.20 (8.02)	Decrease	Stable
1702-411	Baseline	4.8	87.9	40.60 (11.93)		
	Week 52	63.3	76.1	67.02	Stable	Increase
1702-412	Baseline	BQL	75.9	53.43 (6.85)		
	Week 52	D	D	D	NA	NA
1702-413	Baseline	BQL	46.3	24.56 (8.31)		
	Week 52	153.9	89.0	48.17 (8.36)	Increase	Increase
1702-414	Baseline	28.0	40.1	36.98 (13.25)		
	Week 52	86.5	BQL	2.59 (2.14)	Decrease	Decrease
1702-415	Baseline	16.8	63.4	30.68 (8.06)		
	Week 52	72.9	39.7	47.43 (20.71)	Decrease	Stable
1702-416	Baseline	7.2	70.9	63.62 (4.68)		
	Week 52	NAV	NAV	58.00 (12.54)	ND	Stable

Note: BQL=Below Quantifiable Level; D=deceased; NA = Not Applicable; NAV=Not Available; ND=Not Done

[1] Divide value by 10 to express glycogen content as percent of wet tissue.

[2] Results are presented only for patients who had data both at Baseline and Week 52 and for both biochemical and histomorphometric methods.

[3] Labeled as a Screening visit in the appendix.

Pharmacokinetics

The pharmacokinetics of MYOZYME® were evaluated in 13 patients with Pompe's Disease (age 1 month to 7 months) who received 20 mg/kg (as an approximate 4-hour infusion) or 40 mg/kg (as an approximate 6.5-hour infusion) of MYOZYME® every 2 weeks. The measurement of MYOZYME® plasma concentration was based on an activity assay using an artificial substrate. Systemic exposure was approximately dose proportional between the 20 and 40 mg/kg doses (see Table 9).

Table 9: Pharmacokinetic Parameters (Mean ± SD) After Single Intravenous Infusion of MYOZYME® (AGLU01602)

Pharmacokinetic Parameter	20 mg/kg (n=5)	40 mg/kg (n=8)
C_{max} (mcg/mL)	162 ± 31	276 ± 64
AUC_{∞} (mcg-h/mL)	811 ± 141	1781 ± 520
CL (mL/h/kg)	25 ± 4	24 ± 7
V_{ss} (mL/kg)	96 ± 16	119 ± 28
$t_{1/2}$ (h)	2.3 ± 0.4	2.9 ± 0.5

NOTE: With the exception of Cmax, the pharmacokinetic parameters in this table have been estimated by fitting a two-compartment model, with elimination from the central compartment, to the observed data.

The pharmacokinetics of MYOZYME® were also evaluated in a separate trial (AGLU01702) in 14 infantile-onset patients with Pompe's Disease (age from 6 months to 3.5 years) who 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 the trial of patients of age ranging from 1 month to 7 months.

Nineteen of 21 patients who received treatment with MYOZYME® in trial AGLU01602 and AGLU01702 and had pharmacokinetics and antibody titer data available at Week 12 developed antibodies to MYOZYME®. Five patients with antibody titers ≥ 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 titers < 12,800 at Week 12 had similar average clearance values at Week 1 and Week 12.

The pharmacokinetics of alglucosidase alfa were studied in a population analysis of 32 late-onset Pompe patients from the randomized, double-blind, placebo-controlled study (AGLU02704) ranging in age from 21 to 70 years old who received MYOZYME® 20 mg/kg every other week. The measurement of alglucosidase alfa plasma concentration was based on an activity assay using an artificial substrate. AUC and Cmax were similar at Week 0, 12 and 52 visits indicating alglucosidase alfa pharmacokinetics were not time-dependent (Table 10).

Table 10: Alglucosidase Alfa Pharmacokinetics After Single Dose and After 12 and 52 Weeks of Therapy (AGLU02704)

Parameter	Week 0	Week 12	Week 52
Cmax (mcg/mL)	385 ± 106	349 ± 79	370 ± 88
AUC(0-∞) (mcg*h/mL)	2672 ± 1140	2387 ± 555	2700 ± 1000
CL (mL/h)	633 ± 175	700 ± 244	645 ± 198
Vss (L)	69 ± 92	70 ± 91	70 ± 92
Effective Half-life(h)	2.4 ± 0.4	2.4 ± 0.3	2.5 ± 0.4

There was no evidence that IgG antibodies to alglucosidase alfa affected pharmacokinetics. Higher mean clearance, lower mean AUC, and lower mean Cmax were observed in 5 patients that tested positive for inhibition of cellular uptake of enzyme in the randomized, double-blind, placebo-controlled study (AGLU02704) (see **ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions, Late-Onset Pompe's Disease, Immunogenicity**).

Effects of Antibodies

Most patients who received infusions of MYOZYME® developed antibodies to alglucosidase alfa by week 12.

STORAGE AND STABILITY

Store MYOZYME® (alglucosidase alfa) under refrigeration between 2°-8°C. DO NOT FREEZE OR SHAKE. DO NOT USE MYOZYME® after the expiration date on the vial.

MYOZYME® contains no preservatives. Strict aseptic conditions are to be used for the reconstitution of vials and their dilution into the infusion bag. Reconstituted vials should be used immediately for dilution. Administration of the diluted MYOZYME® infusion bags should be initiated without delay (within 3 hours). If immediate use is not possible, MYOZYME® has been shown to be physically and chemically stable for up to 24 hours at 2°-8°C provided that aseptic technique is used throughout the procedure.

Protect reconstituted and diluted MYOZYME® from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

MYOZYME® (alglucosidase alfa) is intended for intravenous infusion. It is supplied as a sterile, nonpyrogenic, white to off-white, lyophilized cake or powder for reconstitution with 10.3 mL Sterile Water for Injection, USP. Each 50 mg vial contains 52.5 mg alglucosidase alfa, 210 mg mannitol, 0.5 mg polysorbate 80, 9.9 mg sodium phosphate dibasic heptahydrate, 31.2 mg sodium phosphate monobasic monohydrate. Following reconstitution as directed, each vial contains 10.5 mL reconstituted solution and a total extractable volume of 10 mL at 5.0 mg/mL alglucosidase alfa.

MYOZYME® does not contain preservatives; each vial is for single use only.

MYOZYME® is supplied in single-use, clear Type I glass 20 mL (cc) vials. The closure consists of a siliconized butyl stopper and an aluminum seal with a plastic royal blue flip-off cap.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Alglucosidase Alfa

Chemical name: Recombinant human acid α-glucosidase

Molecular formula and molecular mass: $C_{4490}H_{6818}N_{1197}O_{1299}S_{32}$
99,377 daltons (excluding the mass of the carbohydrates)

Physicochemical properties: Alglucosidase alfa is a glycoprotein with a calculated mass of 99,377 daltons (excluding the mass of the carbohydrates). It is identical to a commonly occurring form of human GAA in amino acid sequence. The recombinant protein contains 7 asparagine-linked glycosylation sites.

Alglucosidase alfa also contains 13 cysteine residues, 12 of which are involved in disulfide linkages. Alglucosidase alfa has a specific activity of 3-5 U/mg (one unit is defined as that amount of activity that results in the hydrolysis of 1 μmole of synthetic substrate per minute under the assay conditions).

Structural formula:

Figure 1: Structure Formula of MYOZYME®

Product Characteristics
MYOZYME® (alglucosidase alfa) is intended for intravenous infusion. It is supplied as a sterile, nonpyrogenic, white to off-white, lyophilized cake or powder for reconstitution with 10.3 mL Sterile Water for Injection, USP. Each 50 mg vial contains 52.5 mg alglucosidase alfa, 210 mg mannitol, 0.5 mg polysorbate 80, 9.9 mg sodium phosphate dibasic heptahydrate, 31.2 mg sodium phosphate monobasic monohydrate. Following reconstitution as directed, each vial contains 10.5 mL reconstituted solution and a total extractable volume of 10 mL at 5.0 mg/mL alglucosidase alfa.

MYOZYME® does not contain preservatives; each vial is for single use only.

Viral Inactivation
The viral safety of MYOZYME® is confirmed by a combination of selection and qualification of vendors, raw material testing, cell bank characterization studies, validation of the viral removal and inactivation capacity of the purification process, and routine in-process testing.

CLINICAL TRIALS

Pompe's Disease is a heterogeneous disorder that varies with respect to age at onset, rate of disease progression, and extent of organ involvement. Historically, it has been described by physicians as either infantile-onset or late-onset, depending on when the patient's signs and symptoms first appear. Of the three major trials investigating the efficacy of MYOZYME® in the treatment of Pompe's Disease two (AGLU01602 n=18 and AGLU017012 n=21) has focused on patients traditionally described as Infantile-Onset, and one (AGLU02704 n=90) focused on patients traditionally described as Late-Onset.

Study demographics and trial design

Table 11: Summary of patient demographics for clinical trials in specific indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Population: Infantile-Onset Pompe's Disease					
AGLU01602	Randomized, Open-label, Multicenter, Safety, Efficacy, Pharmacokinetic and Pharmacodynamic, Dose Ranging Study of MYOZYME®	MYOZYME®; 20 mg/kg/qow or 40 mg/kg/qow; IV; 52 weeks	18	4.6 months (1.2 to 6.1 months)	11M/7F
AGLU01702	Open-label, Multicenter, Safety, Efficacy, Pharmacokinetic and Pharmacodynamic Study of MYOZYME®	MYOZYME®; 20 mg/kg qow; IV; Patients received a minimum of 1 infusion and maximum of 85 infusions (up to 168 weeks of treatment)	21	15.7 months (3.7 to 43.1 months)	10M/11F
Population: Late-Onset Pompe's Disease					
AGLU02704	Randomized, Double-Blind, Multicenter, Multinational, Placebo-Controlled Study of the Safety, Efficacy, and Pharmacokinetics of MYOZYME®	MYOZYME® or placebo; 20 mg/kg qow; IV; 78 weeks	Myozyme: 60 Placebo: 30	45.3 years (15.9 to 70.0 years) 42.6 years (10.1 to 68.4 years)	34M/26F 11M/19F

Infantile-Onset Pompe's Disease

The safety and efficacy of MYOZYME® (alglucosidase alfa) was assessed in a pivotal, randomized, open-label, historically-controlled clinical trial (AGLU01602) of 18 infantile-onset patients aged 6 months or less at the onset of treatment. All patients were naïve to enzyme replacement therapy. Patients received either 20 mg/kg or 40 mg/kg MYOZYME® every two weeks for a period of 52 weeks.

The primary endpoint of the pivotal study was the proportion of patients alive and free of invasive ventilator support at 18 months of age as compared to survival at 18 months of age in an untreated historical cohort of patients with Pompe's Disease. After 52 weeks, patients treated with MYOZYME® demonstrated prolonged invasive ventilator-free survival (83.3% [95% CI 66.1–100]) as compared to survival in an untreated historical cohort (1.9% [95% CI 0.0–5.5]). See **Table 12** and **Figure 2**.

Table 12: Primary Efficacy Outcome in Infantile-onset Patients (AGLU01602)

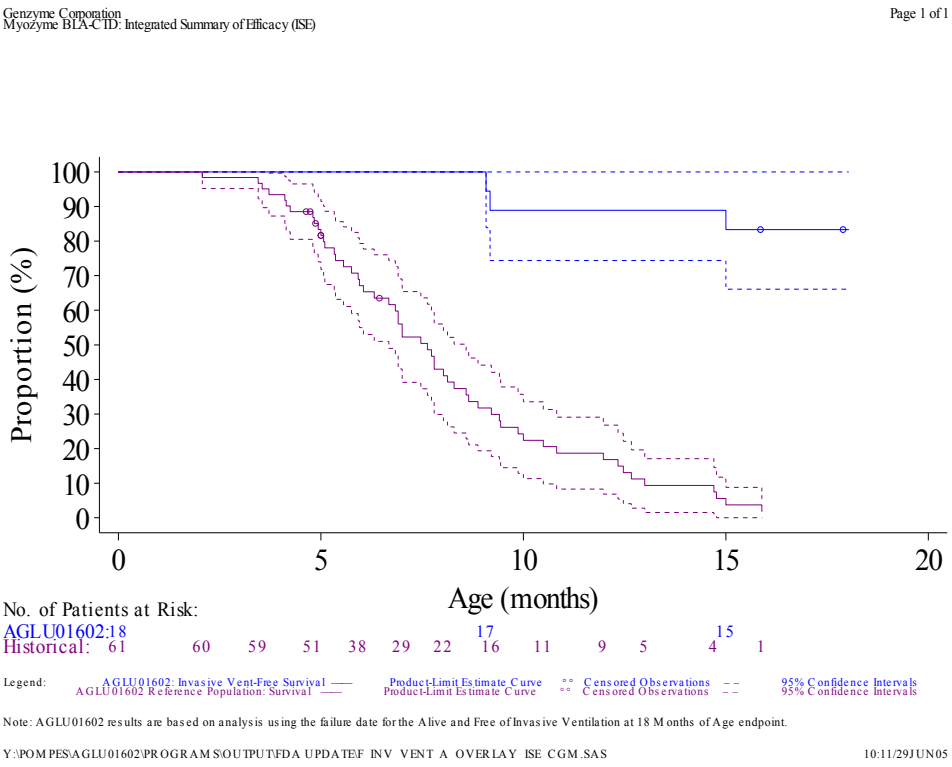
Proportion of Treated Patients Alive and Free of Invasive Ventilator Support at 18 months of Age				
Dose	**N**	**Patients Alive and Invasive Ventilator-Free**	**Patients Censored[1]**	**Proportion Estimate and 95% CI[2]**
Overall	18	13	2	83.3% (66.1, 100)
20 mg/kg	9	8	0	88.9% (68.4, 100)
40 mg/kg	9	5	2	77.8% (50.6, 100)
Proportion of Patients Alive at 18 months of Age in Historical Control				
N		**Number of Patients Alive**	**Proportion Estimate and 95% CI[3]**	
61		1	1.9% (0.0, 5.5)	

1 Patients younger than 18 months of age after 52 weeks of MYOZYME® treatment were censored in the analysis

2 Kaplan-Meier analysis of time to invasive ventilation or death

3 Kaplan-Meier analysis of time to death

Figure 2: Kaplan-Meier Estimate of Time to Invasive Ventilation or Death in Infantile-onset Patients (AGLU01602)



Hazard ratios, 95% confidence intervals for the hazard ratios, and p-values are provided in Table 13. These results provide evidence of a consistent treatment advantage (hazard ratio < 1) for

MYOZYME® treatment relative to historical control. These results include information through the end of the study.

Table 13: Results for Study AGLU01602 (Infantile-Onset Patients) using the Cox Regression Model

Treated Patients	Historical Reference Comparator	Endpoint	Treatment Effect Hazard Ratio	95% Confidence Interval	p-value
N=18	N=61	Survival	0.01	(0.00, 0.10)	<0.0001
		Invasive-ventilator-free survival	0.08	(0.03, 0.21)	<0.0001
		Ventilator-free survival	0.12	(0.05, 0.29)	<0.0001
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. The results for invasive-ventilator-free survival and ventilator free survival provide a very conservative estimate of treatment effect with MYOZYME® because only deaths are available to count as an endpoint in the untreated historical comparator group.					

A second open-label clinical trial (AGLU01702) also assessed the safety and efficacy of MYOZYME® in 21 patients with infantile-onset Pompe's Disease who ranged in age from 3.7 to 43.1 months at initiation of treatment. Patients received 20 mg/kg MYOZYME® every other week for 52 weeks. Patients received a minimum of 1 infusion and a maximum of 85 infusions (168 weeks of treatment) of MYOZYME®. The primary efficacy outcome was survival of patients over the course of MYOZYME® treatment. Fifteen patients were alive as of the time of discontinuation or end of study. None of the deaths were related to treatment with MYOZYME®. The Kaplan-Meier estimate of survival probability was 76.2% at Week 52 and 71.1% at Week 104, and the binomial estimate of survival at the end of study was 71.4%.

Table 14 summarizes the results from the Cox proportional hazards model of time to death for the 21 treated patients in AGLU01702 compared to the untreated historical control group. In this analysis, MYOZYME® was found to reduce the risk of death by 79% (hazard ratio 0.209, 95% CI: 0.083, 0.524).

Table 14: Results for Study AGLU01702 (Infantile-onset Patients) Using the Cox Regression Model

Treated Patients	Historical Reference Comparator	Endpoint	Treatment Effect Hazard Ratio	95% Confidence Interval	p-value
N=21	N=84	Survival	0.209	(0.083, 0.524)	0.0009
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.					

Clinical benefits of MYOZYME® for patients on ventilator support have not been clearly determined. Within the first 12 months of treatment, 3 of 18 MYOZYME®-treated patients in AGLU01602 required invasive ventilatory support (17%, with 95% confidence interval 4% to 41%) and there were no deaths. With continued treatment beyond 12 months, 4 additional

patients required invasive ventilatory support, after receiving between 13 and 18 months of MYOZYME® treatment; 2 of these 4 patients died after receiving 14 and 25 months of treatment, and after receiving 11 days and 7.5 months of invasive ventilatory support, respectively. Survival without invasive ventilatory support was substantially greater in the MYOZYME®-treated patients in this study than would be expected compared to the poor survival of the historical control patients. After 52 weeks of treatment with MYOZYME® in AGLU01702, the ventilator-free survival rate for 16 patients who were free of invasive ventilator support at Baseline was 62.5% (95% CI of [35.4, 84.8]). Of these patients, 4 died by Week 52 and 2 became ventilator-dependent. Over the next 52 weeks, another of these patients died, 1 became ventilator-dependent, and 1 discontinued. Thus, the ventilator-free survival rate was 46.7% at Week 104 and 43.8% at the end of the study.

Other efficacy parameters including motor function, cardiac status and growth were evaluated in studies AGLU01602 and AGLU01702. These outcome measures included unblinded assessments of motor function by the Alberta Infant Motor Scale (AIMS) (AGLU01602 and AGLU01702) and/or Peabody Development Motor Scale (PDMS-2) (AGLU01702 only). The AIMS is a measure of infant motor performance that assesses motor maturation of the infant through age 18 months and is validated for comparison to normal, healthy infants. The PDMS-2 (Folio, 2000, *Peabody Developmental Motor Scales: 2nd Edition*), which measures gross and fine motor skills from birth through 6 years, was used primarily in patients ≥ 18 months of age. Echocardiographic indices of cardiomyopathy were measured as a change in left ventricular mass (LVM). Patients were considered as maintaining or improving in growth if age and gender adjusted percentile rankings for weight and height (calculated using the CDC/NCHS growth charts; Kuczmarski, 2000, *Advance data from vital and health statistics; no. 314*) increased to and/or remained above the third percentile during treatment.

Motor function

In AGLU01602, AIMS-assessed gains in motor function occurred in 13 patients. In the majority of patients, motor function was substantially delayed compared to normal infants of comparable age. The continued effect of MYOZYME® treatment over time on motor function is unknown. Two of 9 patients who had demonstrated gains in motor function after 12 months of MYOZYME® treatment and continued to be followed regressed despite ongoing treatment. Given the wide range of ages at initiation of treatment in AGLU01702 (3.7 to 43.1 months of age), 2 instruments were used to evaluate motor function in this study. Thirteen out of 21 patients (61.9%) had measurable gains in the administered tests (AIMS and/or PDMS-2 gross and fine motor skills), as determined by increases in raw scores and age-equivalent scores from Baseline. The remaining patients (8 of 21, 38.9%) did not demonstrate measurable gains across these motor assessments.

Cardiac Status

In AGLU01602, changes from baseline to Month 12 in left ventricular mass index (LVMI), an evaluation of bioactivity, were measured by echocardiography. For the 15 patients with both baseline and Month 12 echocardiograms, all had decreases from baseline in LVMI (mean decrease 118 g/m^2, range 45 to 193 g/m^2). The magnitude of the decrease in LVMI did not

correlate with the clinical outcome measure of ventilator-free survival

Consistent with the improvements in cardiomyopathy observed in patients treated with MYOZYME® under AGLU01602, treatment with MYOZYME® under AGLU01702 resulted in marked decreases in LVMI and LVM-Z scores. Seventeen of 21 patients (81%) in AGLU01702 either improved or maintained normal LVM from first to last study evaluation. The decline in LVM and LVMI was a real change (>2 SEs) after 26 weeks of treatment. Mean LVMI declined by 42% at Week 52 and by 63% at Week 104. Interpretation of final visit results is challenging because they include variable exposure to MYOZYME®.

Growth

Fifteen of 18 patients (83.3%) in AGLU01602 maintained or improved weight for age percentiles (≥ the third percentile) during the 52-week treatment period. The 3 patients who failed to maintain normal weight had weight percentiles < 3% prior to MYOZYME® treatment. Moreover, 15 of the 16 patients (93.8%) who had body length measured at Baseline maintained normal body length-for-age percentiles during the 52-week treatment period.

Weight and length were also measured at regular intervals during the conduct of AGLU01702. Twelve of 15 patients (80.0%) with repeat evaluations up to at least Week 12 showed maintained or improved weight-for-age percentiles (≥ the third percentile) from Baseline to Week 52 (or last available assessment), while 13 of 14 patients (92.8%) showed maintained or improved length-for-age percentiles to Week 52 or last assessment. In spite of their advanced stage of disease progression at Baseline, 17 of 21 patients (81%) showed maintenance of weight-for-age values above the 3rd percentile at the last assessment *(Week 4-168)*; 19 of 21 (90%) showed maintenance of length-for-age values above the 3rd percentile at the last assessment *(Week 4-168)*.

Late-Onset Pompe's Disease

The safety and efficacy of MYOZYME® was assessed in a randomized, double-blind, placebo-controlled study (AGLU02704) of 90 patients (45 male, 45 female) with late-onset Pompe's Disease who ranged in age from 10 to 70 years at initiation of treatment. All patients were naive to enzyme replacement therapy. Patients were randomized in a 2:1 ratio and received 20 mg/kg MYOZYME® (n=60) or placebo (n=30) every other week for 78 weeks (18 months). At baseline, all patients were ambulatory (some required assistive walking devices), did not require invasive ventilator support or non-invasive ventilation while awake and sitting upright and had a forced vital capacity (FVC) between 30 and 79% of predicted in the sitting position. Patients who could not walk 40 meters in 6 minutes or were unable to perform appropriate pulmonary and muscle function testing were excluded from the study.

A total of 81 of 90 patients completed the study. Of the 9 patients who discontinued, 5 were in the MYOZYME® group and 4 were in the placebo group. Three patients discontinued the study due to an adverse event, 1 patient in the MYOZYME® group died during the study for reasons unrelated to MYOZYME®, 4 patients discontinued study participation to pursue treatment with commercial therapy and 1 patient discontinued the study for personal reasons. Of the 3 patients who discontinued due to adverse events, 2 were in the MYOZYME® treatment group and 1 was in placebo group.

The co-primary efficacy outcome assessments were distance walked (meters) in 6 minutes (6-Minute Walk Test, 6MWT) and FVC % predicted in the sitting position.

The total change from baseline over the course of the study was examined using an analysis of covariance model (ANCOVA).

After 78 weeks, patients treated with MYOZYME® showed stabilization of pulmonary function as measured by FVC % predicted and improvement in distance walked as measured by 6MWT as compared to placebo-treated patients (Table 15). The estimated mean % predicted FVC increased by 1.20% for MYOZYME® patients and decreased by 2.20% for placebo patients indicating a statistically significant MYOZYME® treatment effect of 3.40% (p=0.0055).The estimated mean distance walked in 6 minutes increased by 25.13 meters for MYOZYME® patients and decreased by 2.99 meters for placebo patients, indicating a statistically significant MYOZYME® treatment effect of 28.12 meters (p = 0.0347). However, it should be noted that in 3 of 4 MYOZYME® treated patients identified as high performers, there appeared to be a higher than expected average improvement in the 6MWT distance walked (194 meters).

Table 15: Change in Efficacy Outcomes in the Placebo-controlled Study of Late-onset Patients (AGLU02704)

		MYOZYME® (N = 60)	**Placebo (N = 30)**
Forced Vital Capacity (Percent of predicted normal)			
Pre-treatment Baseline	Mean ± s.d.	55.43 ± 14.44	53.00 ± 15.66
Week 78/Last Observation	Mean ± s.d.	56.67 ± 16.17	50.70 ± 14.88
Estimated Change from Baseline to Week 78/Last Observation (ANCOVA)	Mean (95% CI)	1.20* (-0.16, 2.57)	-2.20* (-4.12, -0.28)
Estimated Difference Between Groups in Change from Baseline to Week 78/Last Observation (ANCOVA)	Mean (95% CI) p-value	3.40* (1.03, 5.77) 0.0055	
6-Minute Walk Test Distance (meters)			
Pre-treatment Baseline	Mean ± s.d.	332.20 ± 126.69	317.93 ± 132.29
Week 78/Last Observation	Mean ± s.d.	357.85 ± 141.32	313.07 ± 144.69
Estimated Change from Baseline to Week 78/Last Observation (ANCOVA)	Mean (95% CI)	25.13* (10.07, 40.19)	-2.99* (-24.16, 18.18)
Estimated Difference Between Groups in Change from Baseline to Week 78/Last Observation (ANCOVA)	Mean (95% CI) p-value	28.12* (2.07, 54.17) 0.0347	

* Estimates are based on ANCOVA, adjusting for randomization strata and baseline observation

DETAILED PHARMACOLOGY

GAA knockout mice were used in the nonclinical program as a mouse model of Pompe's Disease. Mice homozygous for a disruption of the GAA gene lack enzyme activity and accumulate glycogen in a manner similar to the human form of Pompe's Disease**.**

The dose and dose regimen used in clinical studies was based on the pharmacodynamic data from the nonclinical program. A dose ranging study in the GAA knockout mouse model, which included weekly dosing at 0, 20 and 100 mg/kg with MYOZYME® (alglucosidase alfa), showed an effect on glycogen removal and a consistent dose-response. Higher doses of MYOZYME® removed a greater proportion of stored glycogen, particularly from the heart. Additional nonclinical studies in the same knockout mouse model at various doses indicated that every other week dosing was as effective as weekly dosing in removing stored glycogen from a wide variety of tissues including heart, diaphragm and quadriceps. While there was some variability from muscle to muscle, the similarity in response between once weekly and every other week dosing support the longer dosing interval. Two glycogen depletion/re-accumulation studies were performed in knockout mice using MYOZYME® at 100 mg/kg, one after a single dose and the other after 4 weekly doses showed persistent depletion of glycogen at 14-21 days post dose. These 2 studies indicate that a dose interval of 2 weeks intersects with the low point of substrate following the last dose. This finding suggests that repeat dosing at 2 week intervals may be optimal in maintaining depletion pressure on the substrate. This finding supports a clinical administration regimen of dosing at 14-day intervals.

A safety pharmacology study conducted in dogs to assess the effects of MYOZYME® on the cardiovascular/ pulmonary system found no test-article related, clinically relevant effects on electrocardiogram, heart rate, respiratory rate or blood pressure. Although extensive safety pharmacology studies were not conducted on all vital organ systems in the dog, the clinical experience to date has not revealed any significant concerns when MYOZYME® is administered IV. Furthermore it is unlikely that MYOZYME® would cross the blood brain and give rise to CNS effects.

TOXICOLOGY

Toxicity studies were designed to establish a maximum tolerated dose and safety profile in mice, rats, dogs and Cynomolgus monkeys. Two single dose acute toxicity studies in rats and dogs, 2 repeat dose subchronic toxicity studies in rats, 1 repeat dose subchronic toxicity study in mice and 2 repeat dose chronic toxicity studies in Cynomolgus monkeys were performed to evaluate the safety of MYOZYME® (alglucosidase alfa) administered intravenously (IV). Furthermore, 2 reproductive toxicity studies were conducted in mice to assess the effect of MYOZYME® on fertility, early embryonic development and embryo-fetal development.

Given that MYOZYME® is a recombinant human protein, and based on the therapeutic indication, risk versus benefit profile, and small patient population with significant mortality, studies to assess the effects of MYOZYME® on the mutagenic and carcinogenic potential were not performed as part of the development program.

Table 16: Overview of Toxicology Studies

Study type and duration	Route of Administration	Species	Dose (mg/kg) and Regimen	Toxicity Observed	Test Article/ Lot No.	Study Number
Single dose toxicity	IV (bolus)	Rat	1, 10 and 100 Single dose	There were no adverse toxic effects at doses up to 100 mg/kg. The no-observable-adverse-effect level (NOAEL) is >100 mg/kg.	MYOZYME® (60 L)/ Lot GW10124094	6354-134
	IV (bolus)	Dog	1, 10 and 100 Single dose	One male and 1 female administered 10 mg/kg, and 2 males and 1 female administered 100 mg/kg had tremors at 60 minutes post-injection. There were no other treatment-related effects at dose levels.	MYOZYME® (60 L)/ Lot GW10124094	6354-132
Repeat dose toxicity (4 weeks)	IV (bolus)	Rat	1, 10 and 100 1 x / week for 4 weeks	Following the third dose of 100 mg/kg of MYOZYME® on Day 15, 1 male and 1 female showed signs of anaphylactic response. Due to these anaphylactic responses, animals in all dose groups were injected with 5 mg/kg of diphenhydramine on Days 15 and 22. Anaphylactic responses were still observed after the 4th dose at all dose levels. There was a dose-related decrease in body weights and body weight changes for males administered 10 and 100 mg/kg of MYOZYME®. There were no other treatment related findings. Based on the results, the NOAEL for MYOZYME® when administered IV for 4 weekly doses to rats is >10 mg/kg.	MYOZYME® (60 L)/ Lot GW10124094	6354-133

Study type and duration	Route of Administration	Species	Dose (mg/kg) and Regimen	Toxicity Observed	Test Article/ Lot No.	Study Number
Repeat dose toxicity (4 weeks)	IV (bolus)	Rat	1, 5, 10 and 50 for MYOZYME® and Synpac rhGAA (4000 L) and 1, 10 and 25 for Synpac rhGAA (2000 L) 1 x / week for 4 weeks	Treatment-related deaths, the result of hypersensitivity reactions, were observed at doses ≥ 10 mg/kg for MYOZYME® and Synpac 2000L, and at doses ≥ 5 mg/kg for Synpac 2000L. Increased liver enzyme activities were observed for 2 out of 62 animals administered MYOZYME®. At necropsy, treatment-related stomach lesions were present in rats given MYOZYME® (all dose levels) and 2000 and 4000L Synpac rhGAA (at doses > 1 mg/kg).	MYOZYME® (30 L/60 L)/ Lot GA028 Synpac rhGAA (4000 L)/ Lot E1585AM03 Synpac rhGAA (2000 L)/ Lot 105067	6354-140
Repeat dose toxicity (4 weeks)	IV (bolus)	Mouse	1, 10 and 100 for MYOZYME®and Synpac rhGAA (4000 L) and 1, 10 and 25 for Synpac rhGAA (2000 L) 1x / week for 4 weeks	Mild lethargy was noted in 4 animals after the first or third dose. The only other finding was mildly elevated aspartate aminotransferase and alanine aminotransferase for 2 females (1 administered 100 mg/kg MYOZYME® and the other administered 100 mg/kg Synpac 4000 L rhGAA). The NOAEL for MYOZYME® administered to mice for 4 weekly IV doses is >100 mg/kg.	MYOZYME® (30 L/60 L)/ Lot GA028 Synpac rhGAA (4000 L)/ Lot E1585AM03 Synpac rhGAA (2000 L)/ Lot 105067	02009

Study type and duration	Route of Administration	Species	Dose (mg/kg) and Regimen	Toxicity Observed	Test Article/ Lot No.	Study Number
Repeat dose toxicity (6 months)	IV (infusion)	Monkey	4, 20 and 100 1x / every other week for 26 weeks	There were no unscheduled deaths in this study. The NOAEL for MYOZYME® when administered as a 6-hour IV infusion once every other week to monkeys for at least 13 doses is >100 mg/kg/dose.	MYOZYME® (160 L) / Lot 608341	6354-152
Repeat dose toxicity (3 months)	IV (infusion)	Monkey	200 1x / every other week for 13 weeks	One female monkey died on Day 5 of study. Pathologic examination indicated that the cause of death was most likely a combination of renal failure and cardiovascular collapse that was brought on by multiorgan embolic septicemia. Death was attributed to a preexisting bacterial infection and not to the test article based on pre-treatment findings. All other monkeys survived to scheduled sacrifice. The no-observable-effect level (NOEL) for MYOZYME® when administered as a 12 hour IV infusion once every other week to monkeys for a total of 7 doses is > 200 mg/kg/dose.	MYOZYME® (160 L)/ Lot 996793	6354-157

Study type and duration	Route of Administration	Species	Dose (mg/kg) and Regimen	Toxicity Observed	Test Article/ Lot No.	Study Number
Reproductive Toxicity (Segment I)	IV (bolus)	Mouse	10, 20 and 40 every other day for at least 9 weeks (males) and through GD 7-8 (females)	There were 3 unscheduled deaths during the study. A male mouse died on study Day 12 and a female mouse was found dead on GD 1. Both animals were in the 20 mg/kg dose group. The cause of death for these mice is believed to be due to an anaphylactic-type reaction resulting from repeated administration rhGAA and not direct toxicity associated with the test material. A male mouse receiving 40 mg/kg was found dead on Day 53. Since this mouse died on a non-dosing day, the death is believed to be due to undetermined factors that may have compromised the general health status of this mouse and is not attributed to an anaphylactic-type reaction observed in the other 2 unscheduled deaths. There were no indications of maternal toxicity. Based on cesarean section data, the NOEL for embryo/fetal viability is 40 mg/kg. A decreased epididymal sperm count in the 20 and 40 mg/kg dose groups and an increase in abnormal sperm morphology in the 40 mg/kg group were observed. Decreases in the fertility index across groups (including the controls) were observed and may be attributed to the vehicle or administration of diphenhydramine. The NOEL for paternal and maternal effects is <10 mg/kg based on the anaphylactic-like clinical observations seen at all dose levels.	MYOZYME® (160 L)/ Lot 608341	6354-155

Study type and duration	Route of Administration	Species	Dose (mg/kg) and Regimen	Toxicity Observed	Test Article/ Lot No.	Study Number
Reproductive Toxicity (Female Fertility)	IV (bolus)	Mouse	10, 20 and 40 every other day through GD7-8 (females only)	One female in the 40 mg/kg was found dead on Day 10 (sixth dosing day). The cause of death was undetermined. Clinical signs were only observed during gestation, ie., hyperactivity and hunched appearance, and were considered associated with DPH treatment. There were no other treatment-related findings. The NOEL for maternal fertility indices and embryo/fetal viability is 40 mg/kg.	MYOZYME® (160 L)/ Lot 1369017	6354-163
Reproductive Toxicity (Segment II)	IV (bolus)	Mouse	10, 20 and 40 mg/kg 1x / day GD 6-15	An increased mean post implantation loss was observed in the 40 mg/kg/day group, but was attributed to an anomalous pregnancy finding (unhealthy litter) and not to a general increase in early or late resorptions resulting from treatment with MYOZYME®. The NOAEL for maternal toxicity and for embryo-fetal viability, growth and fetal development (teratogenicity) in mice is 40 mg/kg/day.	MYOZYME® (160 L)/ Lot 751295	6354-153

GD = Gestation day

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

PrMYOZYME®
Alglucosidase alfa

Read this carefully before you start taking **MYOZYME®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **MYOZYME®**.

Serious Warnings and Precautions:

Do not use MYOZYME® if you are severely allergic to alglucosidase alfa or any other ingredient of MYOZYME®.

If you are treated with MYOZYME® you may experience an infusion-associated reaction. An infusion-associated reaction is defined as any related side effect occurring during the infusion or during the 2 hours following infusion. Life-threatening allergic reactions, including anaphylactic shock, have been observed in patients during MYOZYME® infusion. Because of the potential for severe infusion reactions, appropriate medical support should be readily available when MYOZYME® is administered.

Individuals with an acute underlying illness [e.g fever, pneumonia or sepsis (severe infection), wheezing/difficulty in breathing, heart failure] at the time of MYOZYME® infusion appear to be at greater risk for infusion reactions. Careful consideration should be given to your clinical status prior to administration of MYOZYME®.

Precaution must be observed when administering general anesthesia to individuals with infantile-onset Pompe's Disease. Reports of intraoperative cardiac arrest following anesthesia induction for invasive procedures have been reported, some of which were fatal. The presence of severe hypertrophic cardiomyopathy in infantile-onset Pompe's Disease may increase the risk of general anesthesia complications.

Infantile onset Pompe patients with heart or breathing problems may be at risk for increasing the seriousness of these problems as a result of MYOZYME® administration, and may require additional monitoring.

What is MYOZYME® used for?

- MYOZYME® is a medicine used for patients with Pompe's Disease (GAA deficiency). MYOZYME® is used to treat adults, children and adolescents of all ages who have a confirmed diagnosis of Pompe disease.

How does MYOZYME® work?

People with Pompe's Disease have low levels of an enzyme called alpha-glucosidase (GAA). This enzyme helps the body control levels of glycogen (a type of carbohydrate). Glycogen provides the body with energy, but in Pompe's Disease the levels can get too high. Glycogen accumulation in Pompe's Disease occurs in various tissues, particularly cardiac, respiratory and skeletal muscle, leading to the development of cardiomyopathy and progressive muscle weakness, including impairment of respiratory function.

MYOZYME® is an artificial enzyme called alglucosidase alfa – this can replace the natural enzyme which is lacking in Pompe disease.

It is postulated that MYOZYME® will restore lysosomal GAA activity resulting in stabilization or restoration of cardiac and skeletal muscle function (including respiratory muscles). Due to the blood-brain barrier effect and the enzyme's size, uptake of alglucosidase alfa in the central nervous system is unlikely.

What are the ingredients in MYOZYME®?
Medicinal ingredients: alglucosidase alfa
Non-medicinal ingredients: Mannitol, Polysorbate 80, Sodium phosphate dibasic heptahydrate, Sodium phosphate monobasic monohydrate

MYOZYME® comes in the following dosage forms:
Sterile lyophilized powder for reconstitution to be used as intravenous infusion, 50 mg

Do not use MYOZYME® if:
- You have any allergies to this drug or its ingredients or components of the container

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take MYOZYME®. Talk about any health conditions or problems you may have, including if you:
- Have an acute underlying illness
- Need general anaesthesia for central venous catheter placement
- Have had a severe hypersensitivity or anaphylactic reaction to administration of MYOZYME®
- Have experienced infusion-associated reactions
- Are at increased risk of lung infections due to the progressive effects of the disease on the lung muscles
- Have underlying heart enlargement
- Are pregnant or plan to become pregnant or are breast feeding
- Are above the age of 65

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with MYOZYME®:
No formal interaction studies have been conducted. Please inform your doctor if you are using any other medicinal products, due to the potential risk of interference with the uptake of alglucosidase alfa.

How to take MYOZYME®:
MYOZYME® will be given to you under the supervision of a doctor who is knowledgeable in the treatment of Pompe's Disease.

The dose you receive is based on your body weight. MYOZYME® should be administered as an intravenous infusion.

Infusions should be administered incrementally. It is recommended that the infusion begin at an initial rate of 1 mg/kg/h and be gradually increased by 2 mg/kg/h every 30 minutes if there are no signs of infusion associated reactions (IARs) until a maximum rate of 7 mg/kg/h is reached.

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

Overdose:
There is no experience with overdoses of MYOZYME® for doses up to 40 mg/kg of body weight.

If you think you have taken too much MYOZYME®, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you have missed a MYOZYME® infusion, please contact your doctor. It is important to have your infusion on a regular basis to avoid the accumulation of GAA. The total dose administered each month should remain substantially unchanged.

What are possible side effects from using MYOZYME®?
These are not all the possible side effects you may feel when taking MYOZYME®. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

Side effects were mainly seen while patients were being given the medicine or shortly after ("infusion related effects"). Some of these infusion related side effects became serious. Should you experience any reaction like this, please **tell your doctor immediately**. Regardless of pre-treatment, your infusion may need to be slowed or stopped and you may need to be given additional medicines to treat an allergic reaction.

The most significant infusion reactions included allergic reactions and allergic shock to MYOZYME®. Other serious infusion reactions included hives, abnormal breathing sounds, elevated heart rate, difficulty in breathing, elevated respiration, swelling around the eyes, high blood pressure, decreased oxygen concentration in blood and fever, heart attack, chest pain, abdominal pain, low blood pressure, shortness of breath.

Some patients have experienced infusion related side effects in the form of flu-like symptoms or a combination of events such as fever, chills, muscle pain, joint pain, pain or fatigue, which lasted for a few days after completion of the infusion.

In addition, patients also experienced the following non-serious events:
cough, infusion site reaction including pain and bruising, feeling unwell, itching, diarrhea, nausea, vomiting, dry heaves, constipation, stomach bloating, indigestion, inability to sleep, agitation, irritability, restlessness, tremor, headache, dizziness, tingling sensation, lack of energy, feeling sleepy, ringing in the ears and blood in the urine.

SERIOUS SIDE EFFECTS (INFUSION REACTIONS), HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM		
Symptom /effect		Talk with your doctor or pharmacist
Common (occurred in ≥ 5% of patients)	fever, decreased oxygen concentration in blood, hives, flushing, elevated heart rate, rash, shivering, low blood pressure, high blood pressure, cough, elevated respiration, agitation, irritability, vomiting, chest discomfort	yes
Uncommon (occurred in <5% of patients)	increased sweating, mottling, itching, rash, fever, pallor, cyanosis, restlessness, retching, tremor, chest pain, throat tightness, tongue swelling	yes

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

If you opt for the infusion of MYOZYME® through central catheter, discuss with your doctor potential complications related to use of such a delivery system.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store MYOZYME® in a refrigerator between 2°-8°C. DO NOT FREEZE OR SHAKE. DO NOT USE MYOZYME® after the expiration date on the vial.

It is recommended that MYOZYME® is used immediately after it has been mixed with sterile water. However it can be kept for up to 24 hours if it is kept cool (2°C – 8°C) and in the dark.

Keep out of reach and sight of children.

Pompe Registry:
Sanofi Genzyme informs all patients with Pompe's Disease that a registry has been established in order to better understand the variability and progression of Pompe's Disease and to continue to monitor and evaluate the safety and efficacy of MYOZYME® treatments. All patients are encouraged to participate and advised that their participation may involve long-term follow-up. Information regarding the registry program may be found at www.pomperegistry.com or by calling 1-800-745-4447.

If you want more information about MYOZYME®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website, or by calling 1-877-220-8918.

This leaflet was prepared by Sanofi Genzyme, a division of sanofi-aventis Canada Inc.
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