Myozyme

Powder for concentrate for solution for infusion.

1. NAME OF THE MEDICINAL PRODUCT

Myozyme
50 mg powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 50 mg of alglucosidase alfa.

After reconstitution, the solution contains 5 mg of alglucosidase alfa* per ml and after dilution, the concentration varies from 0.5 mg to 4 mg/ml.

*Human acid α-glucosidase is produced in Chinese hamster ovary cells (CHO) by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Myozyme is indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency).

The benefits of Myozyme in patients with late-onset Pompe disease have not been established.

4.2 Posology and method of administration

Myozyme treatment should be supervised by a physician experienced in the management of patients with Pompe disease or other inherited metabolic or neuromuscular diseases.

Posology
The recommended dose regimen of alglucosidase alfa is 20 mg/kg of body weight administered once every 2 weeks.

Patient response to treatment should be routinely evaluated based on a comprehensive evaluation of all clinical manifestations of the disease.

Paediatric and older people
There is no evidence for special considerations when Myozyme is administered to paediatric patients of all ages or older people.

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

Method of administration
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. IARs are described in section 4.8.

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

4.3 Contraindications

Life threatening hypersensitivity (anaphylactic reaction) to the active substance or to any of the excipients listed in section 6.1, when rechallenge was unsuccessful (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name of the administered product should be clearly recorded. It is recommended to record the batch number as well.

Hypersensitivity/Anaphylactic reactions
Serious and life-threatening anaphylactic reactions, including anaphylactic shock, have been reported in infantile- and late-onset patients during Myozyme infusions (see section 4.8). Because of the potential for severe infusion associated reactions, appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available when Myozyme is administered. If severe hypersensitivity or anaphylactic reactions occur, immediate discontinuation of Myozyme infusion should be considered and appropriate medical treatment should be initiated. The current medical standards for emergency treatment of anaphylactic reactions are to be observed.

Infusion Associated Reactions
Approximately half of the patients treated with Myozyme in infantile-onset clinical studies and 28% of the patients treated with Myozyme in a late-onset clinical study developed infusion associated reactions (IARs). IARs are defined as any related adverse event occurring during the infusion or during the hours following infusion. Some reactions were severe (see section 4.8). A tendency was observed in infantile patients treated with a higher dose (40 mg/kg) to experience more symptoms when developing IARs. Infantile onset patients who develop high IgG antibody titres appear to be at higher risk for developing more frequent IARs. However, IARs occurred regardless of antibody titres. Patients with an acute illness (e.g. pneumonia, sepsis) at the time of Myozyme infusion appear to be at greater risk for IARs. Careful consideration should be given to the patient's clinical status prior to administration of Myozyme. Patients should be closely monitored and all cases of IARs, delayed reactions and possible immunological reactions should be reported to the marketing authorisation holder.

Patients who have experienced IARs (and in particular anaphylactic reactions) should be treated with caution when re-administering Myozyme (see sections 4.3 and 4.8). Mild and transient effects may not require medical treatment or discontinuation of the infusion. Reduction of the infusion rate, temporary interruption of the infusion, or pre-treatment, generally with oral antihistamine and/or antipyretics and/or corticosteroids, has effectively managed most reactions. IARs may occur at any time during the infusion of Myozyme or generally up to 2 hours after, and are more likely with higher infusion rates.

Patients with advanced Pompe disease may have compromised cardiac and respiratory function, which may predispose them to a higher risk of severe complications from infusion associated reactions. Therefore, these patients should be monitored more closely during administration of Myozyme.

Immunogenicity
The effect of IgG antibody formation on safety and efficacy has been evaluated in clinical trials and post-marketing experience. In clinical studies, the majority of patients developed IgG antibodies to alglucosidase alfa and seroconversion typically occured within 3 months of treatment. Thus, development of IgG antibodies is expected to occur in most patients treated with Myozyme. Overall, a correlation was not observed between the onset of IARs and the time of IgG antibody formation. IARs can occur across all levels of antibody titres, however a trend was observed for more frequent IARs with higher titres of IgG antibody. The clinical impact on efficacy is multifactorial, however the development of high and sustained IgG antibody titres is a contributing factor.
With regard to IOPD, a tendency was observed for patients treated with a higher dose (40 mg/kg) to develop higher titres of IgG antibodies. Furthermore, Cross Reactive Immunologic Material (CRIM) status has been shown to be associated with immunogenicity and patients' responses to enzyme replacement therapies. Negative CRIM status, indicating no endogenous enzyme is detected, is a risk factor to develop high and sustained IgG antibody titres. This risk is higher among CRIM negative patients versus CRIM- positive patients and is a contributing factor to a poor outcome. However, high and sustained IgG antibody titres has also occurred in a limited number of CRIM-positive patients, generally with very low endogenous enzyme.

With respect to LOPD patients, the majority showed either stabilizing or decreasing antibody titres over time. The development of high and sustained IgG antibody titres is infrequent in LOPD patients. Thus, the impact of IgG antibodies is more limited for LOPD patients.

IgG antibody titres should be monitored based on clinical phenotype. Baseline serum sample collection prior to the first infusion is strongly encouraged. For IOPD patients, regular monitoring during first year of treatment (example: every 3 months) is suggested and subsequent monitoring depending on clinical outcomes and antibody titres level. For LOPD patients, antibody development should be assessed within 6 months and subsequent monitoring as clinically warranted based on safety and efficacy considerations.

Patients who experience hypersensitivity reactions may also be tested for IgE antibodies to alglucosidase alfa and other mediators of anaphylaxis. 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 (see section 4.8). Therefore, these patients should be monitored more closely during administration of Myozyme. Some IgE positive patients were successfully rechallenged with Myozyme using a slower infusion rate at lower initial doses and have continued to receive Myozyme under close clinical supervision.

Immune-mediated reactions
Severe cutaneous reactions, possibly immune-mediated, have been reported with alglucosidase alfa, including ulcerative and necrotizing skin lesions (see section 4.8). Nephrotic syndrome was observed in a few patients with Pompe disease treated with alglucosidase alfa and who had high IgG antibody titres (≥ 102,400) (see section 4.8). In these patients renal biopsy showed immune complex deposition. Patients improved following treatment interruption. It is therefore recommended to perform periodic urinalysis among patients with high IgG antibody titres.

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

Immunomodulation
Immunogenicity data from clinical trials and published literature in CRIM-negative infantile-onset patients (IOPD) suggests that the administration of immune tolerance induction (ITI) regimen given to alglucosidase alfa naive patients (prophylactic ITI) may be effective in preventing or reducing the development of High Sustained Antibody Titre (HSAT) against alglucosidase alfa. Data from a small

number of patients with HSAT, with or without inhibitory activity, showed limited ITI treatment effect. Better treatment responses were observed in younger patients with less advanced disease who received prophylactic ITI before development of HSAT, which suggests that early initiation of ITI can result in improved clinical outcomes. ITI regimens may need to be tailored to individual patient needs (see section 5.1).

Patients with Pompe disease are at increased risk of respiratory infections due to the progressive effects of the disease on the respiratory muscles. Patients with Pompe disease treated with immunosuppressive agents maybe at further increased risk of developing severe infections and vigilance is recommended. Fatal and life-threatening respiratory infections have been observed in some of these patients.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions studies have been performed. Because it is a recombinant human protein, alglucosidase alfa is an unlikely candidate for cytochrome P450 mediated drug-drug interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is limited data from the use of alglucosidase alfa in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Myozyme should not be used during pregnancy unless the clinical condition of the woman requires treatment with alglucosidase alfa.

Breast-feeding
Limited data suggest that alglucosidase alfa is excreted in breast milk in very low concentrations. No clinical effect is expected in a breastfed infant due to low breast milk transfer and poor bioavailability. Breastfeeding during treatment with Myozyme may therefore be considered. As a precautionary measure, breastfeeding interruption for the first 24 hours after treatment may be considered.
Fertility
There is too limited clinical data on the effects of alglucosidase alfa on fertility to evaluate its impact. Preclinical data did not reveal any significant adverse findings (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Because dizziness, somnolence, tremor and hypotension have been reported as an infusion associated reaction, this may affect the ability to drive and
use machines on the day of the infusion.

4.8 Undesirable effects

Summary of the safety profile

Infantile-onset Pompe disease
In clinical trials, 39 infantile-onset patients were treated with Myozyme for more than three years (168 weeks with a median of 121 weeks; see section 5.1). Adverse reactions reported in at least 2 patients are listed in Table 1 by System Organ Class. Adverse reactions were mostly mild to moderate in intensity and almost all occurred during the infusion or during the 2 hours following the infusion (infusion associated reactions, IARs). Serious infusion reactions including urticaria, rales, tachycardia, decreased oxygen saturation, bronchospasm, tachypnoea, periorbital oedema and hypertension have been reported.

Late-onset Pompe disease
In a placebo-controlled study lasting 78 weeks, 90 patients with late-onset Pompe disease, aged 10 to 70 years, were treated with Myozyme or placebo randomized in a 2:1 ratio (see section 5.1). Overall, the numbers of patients experiencing adverse reactions and serious adverse reactions were

comparable between the two groups. The most common adverse reactions observed were IARs. Slightly more patients in the Myozyme group than in the placebo group experienced IARs (28% versus 23%). The majority of these reactions were non-serious, mild to moderate in intensity and resolved spontaneously. Adverse reactions reported in at least 2 patients are listed in Table 1. Serious adverse reactions reported in 4 patients treated with Myozyme were: angioedema, chest discomfort, throat tightness, non-cardiac chest pain and supraventricular tachycardia. Reactions in 2 of these patients were IgE-mediated hypersensitivity reactions.

Tabulated list of adverse reactions

Table 1: Adverse reactions (reported in at least 2 patients) and adverse reactions reported in post-marketing setting, expanded access programs and non-controlled clinical trials, per System Organ Class, presented by frequency categories: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Due to the small patient population, an adverse reaction reported in 2 patients is classified as common. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	**Frequency**	**Adverse reaction (Preferred Term Level)**		**Additional adverse reactions[4]**
		Infantile-onset Pompe disease[1]	**Late-onset Pompe disease[2]**	**Infantile- and Late-onset Pompe disease**
Immune system disorders	common		Hypersensitivity	
Psychiatric disorders	common	Agitation		
	not known			Agitation Restlessness
Nervous system disorders	common	Tremor	Dizziness Paraesthesia Headache[3]	
	not known			Tremor Headache Somnolence
Eye disorders	not known			Conjunctivitis
Cardiac disorders	very common	Tachycardia		
	common	Cyanosis		
	not known			Cardiac arrest Bradycardia Tachycardia Cyanosis Palpitations
Vascular disorders	very common	Flushing		
	common	Hypertension Pallor	Flushing	
	not known			Hypertension Hypotension Vasoconstriction Pallor
Respiratory, thoracic and mediastinal disorders	very common	Tachypnoea Cough		
	common		Throat tightness	
	not known			Respiratory arrest

				Apnoea Respiratory distress Bronchospasm Wheezing Pharyngeal oedema Dyspnoea Tachypnoea Throat tightness Throat irritation Stridor Cough Hypoxia
Gastrointestinal disorders	very common	Vomiting		
	common	Retching Nausea	Diarrhoea Vomiting Nausea[3]	
	not known			Abdominal pain Retching Dyspepsia Dysphagia
Skin and subcutaneous tissue disorders	very common	Urticaria Rash		
	common	Erythema Rash maculopapular Rash macular Rash papular Pruritus	Urticaria Rash papular Pruritus Hyperhidrosis	
	not known			Periorbital oedema Livedo reticularis Lacrimation increased Rash Erythema Hyperhidrosis Palmar erythema Transient skin discoloration Blister
Musculoskeletal and connective tissue disorders	common		Muscle spasms Muscle twitching Myalgia	
	not known			Arthralgia
Renal and urinary disorders	not known			Nephrotic syndrome Proteinuria
General disorders and administration site conditions	very common	Pyrexia		
	common	Irritability Chills	Pyrexia Chest discomfort Peripheral oedema Local swelling Fatigue[3] Feeling hot	
	not known			Chest pain

				Face oedema Feeling hot Pyrexia Chills Chest discomfort Irritability Peripheral coldness Asthenia Malaise Feeling cold Infusion site pain Infusion site reaction Infusion site swelling Infusion site induration Infusion site extravasation Infusion site erythema Infusion site urticaria Infusion site pruritus
Investigations	very common	Oxygen saturation decreased		
	common	Heart rate increased Blood pressure increased Body temperature increased	Blood pressure increased	
	not known			Oxygen saturation decreased Heart rate increased Blood pressure decreased

[1] Reactions reported in 39 infantile-onset patients in 2 clinical trials.
[2] Reactions reported in 60 late-onset patients in a placebo-controlled clinical trial.
[3] Reactions reported more frequently in the placebo group than in the Myozyme group in late-onset patients.
[4] Additional adverse reactions from post-marketing, expanded access programs and non-controlled clinical trials.

Description of selected adverse reactions

A small number of patients (<1%) in clinical trials and in the commercial setting developed anaphylactic shock and/or cardiac arrest during Myozyme infusion that required life-support measures. Reactions generally occurred shortly after initiation of the infusion. Patients presented with a constellation of signs and symptoms, primarily respiratory, cardiovascular, oedematous and/or cutaneous in nature (see section 4.4).

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

Patients with moderate to severe or recurrent IARs have been evaluated for alglucosidase alfa specific IgE antibodies; some patients tested positive including some who experienced an anaphylactic reaction.

Nephrotic syndrome as well as severe cutaneous reactions, possibly immune-mediated, have been reported with alglucosidase alfa including ulcerative and necrotizing skin lesions (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il

4.9 Overdose

In clinical studies doses up to 40 mg/kg body weight were used. IARs are more likely to occur with higher dose or infusion rates than recommended (see section 4.4).

Symptoms and signs
IARs have been reported, which included:

- cyanosis, tachycardia, palpitations
- hypoxia, dyspnoea, cough
- dizziness, headache, dysgeusia
- hypertension, flushing
- tongue oedema, vomiting, diarrhoea, nausea
- chest pain, chest discomfort, throat tightness, pyrexia, chills, feeling cold, infusion site erythema,
- myalgia
- erythema

Management

In the event of overdose, the infusion rate should be reduced, or the infusion temporarily interrupted. There is no known specific antidote for alglucosidase alfa overdose. The patient should be monitored for any signs or symptoms of adverse reactions and, administered appropriate symptomatic treatment immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Pompe disease
Pompe disease is a rare, progressive and fatal metabolic myopathy with an estimated global incidence of 1 in 40,000 births. Other names for Pompe disease include glycogen storage disease type II (GSD-II), acid maltase deficiency (AMD) and glycogenosis type II. Pompe disease belongs to the lysosomal storage disorders as it is caused by a deficiency of a naturally occurring lysosomal hydrolase, acid α-glucosidase (GAA) that degrades lysosomal glycogen to glucose. Deficiency of this enzyme leads to glycogen accumulation in various tissues, particularly cardiac, respiratory and skeletal muscle, leading to the development of hypertrophic cardiomyopathy and progressive muscle weakness, including impairment of respiratory function.

The clinical presentation of Pompe disease can be described as a spectrum of disease which ranges from a rapidly-progressing infantile-onset form (onset of symptoms of Pompe disease typically within the first year of life and a very short, expected lifespan) to a less rapidly progressing late-onset form.

The infantile-onset form of Pompe disease is characterised by massive deposition of glycogen in the heart, and skeletal muscle always resulting in rapidly progressive cardiomyopathy, generalised muscle weakness and hypotonia. Motor development is often completely arrested, or if motor milestones are

achieved, they are subsequently lost. Death typically occurs due to cardiac and/or respiratory failure before the age of one year.

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

A non-typical, more slowly progressive form of infantile-onset Pompe disease has been described which is characterised by a less severe cardiomyopathy and consequently a more prolonged survival.

The late-onset form of Pompe disease manifests during infancy, childhood, adolescence or even adulthood and is much less rapidly progressive than the infantile-onset form. Usually, it is characterised by the presence of sufficient residual GAA activity to preclude the development of cardiomyopathy, however some cardiac involvement has been reported in up to approximately 4% of patients with late-onset Pompe disease.

Patients with late-onset Pompe disease typically present with progressive myopathy, predominantly of the proximal muscles in the pelvic and shoulder girdles, and varying degrees of respiratory involvement, ultimately progressing to profound disability and/or the need for ventilatory support. The time course of disease progression is extremely variable and not predictable, with some patients experiencing a rapid deterioration in skeletal and respiratory muscle function leading to loss of ambulation and respiratory failure, others progressing less rapidly, and yet others presenting with a dissociation in the progression of skeletal and respiratory muscle involvement.

Mechanism of action

It is postulated that Myozyme will restore lysosomal GAA activity resulting in stabilisation 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.

Clinical efficacy and safety

Infantile-onset Pompe disease; clinical trial in patients aged 6 months or less
The safety and efficacy of Myozyme was assessed in a pivotal, randomised, open-label, historically controlled clinical trial of 18 non-ventilated infantile-onset patients aged 6 months or less at the onset of treatment. The untreated historical cohort was matched to the pivotal study population and was derived from a retrospective natural history study (n=42) in patients with infantile-onset Pompe disease. Patients were randomized to receive either 20 mg/kg or 40 mg/kg once every two weeks for a period of 52 weeks. After a minimum of 52 weeks, 16 of these 18 patients were enrolled in an extension study to receive continued treatment at the same dose for a total duration of up to three years (150 weeks).

The primary endpoint was the proportion of patients who were alive and free of invasive ventilator support. However, the invasive ventilator-free survival was not recorded in the untreated historical cohort and a comparison of this endpoint is not possible. After 52 weeks of treatment, all 18 patients treated with Myozyme were alive and 15 of these 18 patients were alive and free of invasive ventilatory support whereas 1 of 42 patients in the untreated historical cohort was alive at 18 months of age. Two patients died and did not enter into the extension study. After 104 weeks of treatment, all 16 patients who enrolled in the extension study were alive and 10 of these 16 patients were free of invasive ventilatory support. At the end of the study (with individual patient treatment durations ranging from 60 to 150 weeks; mean follow-up period of 119 weeks) 14 of 16 patients were alive and 9 of 16 patients were alive and free of invasive ventilatory support. One additional patient died after study end and another one after withdrawal from the study.

Comparison of survival curves from time of diagnosis versus the untreated historical cohort was made using a Cox proportional hazards regression analysis. Patients treated with Myozyme demonstrated prolonged survival as compared to survival in an untreated historical cohort (see Table 2).

Table 2: Results for endpoint survival using the Cox regression model

Treated Patients	Historical Reference Comparator	Endpoint	Treatment Effect Hazard Ratio	95% Confidence Interval	p-value
N=18	N=42	Survival	0.05	(0.015, 0.147)	<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. Subjects were aged 6 months or less at the onset of treatment. Subjects in the untreated historical cohort were born in 1993 or later.					

Echocardiographic indices of cardiomyopathy improved as measured by a decrease in left ventricular mass (LVM). After 52 weeks of treatment, LVM decreased from baseline in all 14 patients with available data and was within normal limits in 3 of 14 patients. After the first year (64 up to 130 weeks) of treatment LVM further decreased in 8 patients. At 104 weeks of treatment LVM assessments were available for 8 patients, of which 5 decreased to within normal limits.

As measured by motor performance age-equivalent scores of the Alberta Infant Motor Scale (AIMS), seven of the 18 patients made motor development gains during the study and were walking independently by the last study assessment (with individual patient treatment durations ranging from 52 to 130 weeks; mean follow-up period of 94 weeks). An additional 4 patients made motor development gains during the study and were sitting independently by the last study assessment (with individual patient treatment durations ranging from 78 to 130 weeks; mean follow-up period of 110 weeks), although they did not have functional use of the legs. The remaining 7 patients made no clinically significant motor gains or were unable to sustain the motor gains made and had very limited motor movement by the last study assessment (with individual patient treatment durations ranging from 52 to 142 weeks; mean follow-up period of 103 weeks).

After 52 weeks of treatment 14 of 18 patients (77.8%) had maintained or improved weight-for-age percentiles (above the 3rd percentile), 14 of 15 patients (93.3%) were above the 3rd percentile for length and 12 of 15 patients (80.0%) were above the 3rd percentile for head circumference. In the second year of treatment, 15 out of 17 patients had further improved weight-for-age percentiles (with individual patient treatment durations ranging from 78 to 142 weeks; mean follow-up period of 111 weeks), 10 out of 16 patients had further improved length-for-age percentiles (with individual patient treatment durations ranging from 90 to 130 weeks; mean follow-up period of 113 weeks) and 11 out of 15 patients had further improved head circumference-for-age percentiles (with individual patient treatment durations ranging from 90 to 130 weeks; mean follow-up period of 110 weeks). At 104 weeks of treatment, all 13 patients with available data had maintained or improved weight-for-age percentiles (above the 3rd percentile), all 12 patients with available data were above the 3rd percentile for length and all 12 patients with available data were above the 3rd percentile for head circumference.

Analyses of efficacy did not reveal meaningful differences between the 2 dose groups with respect to survival, invasive ventilator-free survival, any ventilator-free survival, decrease in LVM, gains in growth parameters and acquisition of motor milestones. Based on these results the 20 mg/kg qow dose is recommended.

Infantile-onset Pompe disease; clinical trial in patients aged 6 months to 3.5 years
A second open-label clinical trial also assessed the safety and efficacy of Myozyme in 21 patients with predominantly a non-typical form of infantile-onset Pompe disease who ranged in age from 6 months to 3.5 years at initiation of treatment. Patients received 20 mg/kg Myozyme once every two weeks for 52 weeks except for 8 patients who received 40 mg/kg after at least 26 weeks of treatment. After 52 weeks all patients continued treatment for a total duration of more than 3 years (168 weeks with a median of 121 weeks).

The primary endpoint of the pivotal trial was the proportion of patients who were alive. After 52 weeks of treatment, 16 of 21 patients (76.2%) treated with Myozyme were alive. After 104 weeks of treatment, 14 of 21 patients (66.7%) were alive and 1 patient was alive but had discontinued from the study. These proportions were maintained up to the end of the study (with individual patient treatment durations ranging from 1 to 168 weeks; mean follow-up period of 109 weeks). In the untreated historical cohort 5 of 47 patients (10.6%) for whom data were available, were alive at age 30 months (2.5 years).

Survival in the treated patients was compared to survival in a similar historical cohort of untreated subjects using a Cox proportional hazards regression analysis (See Table 3).

Table 3: Results for endpoint survival using the Cox regression model

Treated Patients	Historical Reference Comparator	Endpoint	Treatment Effect Hazard Ratio	95% Confidence Interval	p-value
N=21	N=48	Survival	0.301	(0.112,0.804)	0.0166
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. Subjects ranged in age from 6 months to 3.5 years at initiation of treatment. Subjects in the untreated historical cohort were born in 1995 or later.					

Additional efficacy data showed that of 16 patients who were free of invasive-ventilator support at baseline, 7 remained so after 104 weeks of treatment. The 9 remaining patients either died (5 patients) or became invasive-ventilator dependent (4 patients). All 5 patients who were receiving invasive ventilation at baseline continued to require ventilation throughout the study (4 patients survived beyond week 104 and one patient died).

After 52 weeks of treatment, LVM decreased from baseline in all 12 patients with available data and was within normal limits in 6 of 12 patients. After the first year (58 up to 168 weeks) of treatment LVM further decreased in 9 out of 12 patients with available data. At 104 weeks of treatment LVM assessments were available for 10 patients, of which 9 decreased to within normal limits.

After 52 weeks of treatment, 3 out of 8 patients with available data made gains in motor function over baseline as measured by raw scores and age-equivalent scores from baseline in the AIMS. Six of the 11 patients with available data continued to make motor development gains beyond Week 52 (with individual patient treatment durations ranging from 58 to 168 weeks; mean follow-up period of 121 weeks), including 3 patients ambulatory and 3 patients with only functional sitting skills by the last study visit. The remaining 5 patients showed no significant change in motor development beyond Week 52 (with individual patient treatment durations ranging from 104 to 168 weeks; mean follow-up period of 140 weeks), including 4 patients with no significant motor skills in any of the positions evaluated and 1 patient with only functional sitting skills by the last study visit.

The vast majority of patients with infantile-onset Pompe disease treated with Myozyme demonstrate improvement in cardiac function as well as stabilisation or improvements in growth parameters. However, motor and respiratory responses to treatment have been more variable.
Patients with infantile-onset Pompe disease who demonstrated motor gains, had greater preservation of motor function and lower glycogen content in the quadriceps muscle at baseline. It is noteworthy that a higher proportion of patients with better motor outcomes show stability or improvement in growth parameters (weight), while the large majority of patients, regardless of their motor outcomes or baseline features, show reversal of cardiomyopathy as measured by changes in LVM Z-score.

The totality of the data suggests that early diagnosis and treatment at an early stage of disease may be critical to achieve the best outcomes in these infantile onset patients.

IOPD Immune Tolerance Induction

Use of ITI and alglucosidase alfa has been evaluated in 1 clinical trial and a retrospective chart review of patients naïve to ERT at the initiation of treatment and 1 clinical trial of patients already receiving alglucosidase alfa at time of initiating ITI.

A retrospective chart review at Duke Center identified 21 CRIM-negative IOPD patients of which 19 patients were ERT naïve at the time of ITI initiation. Of the 21 patients, 16 survived through the end of this study, with a median time from ERT initiation to last assessment of 44.6 months (range: 5.7 to 105.47); 5 patients died due to respiratory failure and disease progression, all of whom were ERT-naïve at the start of ERT+ITI treatment. Younger patients diagnosed and treated early and who received ITI concomitantly to ERT initiation had a trend towards better survival rate than patients treated with similar regimen at a later age. The study data demonstrated that prophylactic ITI prevents or reduces the occurrence of antibodies against alglucosidase alfa over time, which may maintain clinical benefit of ERT and improve survival in CRIM-negative IOPD patients.

Late-onset Pompe disease; pivotal clinical trial
The safety and efficacy of Myozyme was assessed in a randomized, double-blind, placebo-controlled study in 90 patients with late-onset Pompe disease who ranged in age from 10 to 70 years at initiation of treatment and were all 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) once every two weeks for 78 weeks (18 months).

The co-primary efficacy outcome assessments were distance walked (meters) in 6 minutes (6-Minute Walk Test, 6MWT) and FVC (Forced Vital Capacity) % predicted in the sitting position. After 78 weeks, patients treated with Myozyme showed improvement in distance walked as measured by 6MWT and stabilization of pulmonary function as measured by FVC % predicted as compared to placebo-treated patients. The distance walked in 6 minutes increased by a median of 15.0 meters for Myozyme-treated patients and decreased by a median of 7.5 meters for placebo-treated patients, indicating a statistically significant Myozyme treatment effect compared to placebo (p=0.0283). The % predicted FVC changed by a median of 0.0 for Myozyme-treated patients and decreased by a median of 3% for placebo-treated patients, indicating a statistically significant treatment effect (p=0.0026). The results are shown in Table 4.

Table 4: Change from baseline: efficacy outcomes in the placebo-controlled study

		Myozyme (N = 60)	Placebo (N = 30)
6-Minute Walk Test Distance (meters)			
Pre-treatment Baseline	Mean ± s.d. Median	332.20 ± 126.69 360.0	317.93 ± 132.29 339.0
Week 78/Last Observation	Mean ± s.d. Median	357.85 ± 141.32 367.5	313.07 ± 144.69 307.0
Change from Baseline to Week 78/Last Observation*	Mean ± s.d. Median	26.08 ± 64.41 15.0	-4.87 ± 45.24 -7.5
Wilcoxon-Mann-Whitney Test	p-value	0.0283	
Forced Vital Capacity (Percent of predicted normal)			
Pre-treatment Baseline	Mean ± s.d. Median	55.43 ± 14.44 53.5	53.00 ± 15.66 49.0
Week 78/Last Observation	Mean ± s.d. Median	56.67 ± 16.17 55.5	50.70 ± 14.88 49.0
Change from Baseline to Week 78/Last Observation*	Mean ± s.d Median	1.25 ± 5.55 0.0	-2.3 ± 4.33 -3.0
Wilcoxon-Mann-Whitney Test	p-value	0.0026	
*One patient who did not have data post baseline was excluded from the analyses.			

An open-label clinical trial assessed the safety and efficacy of Myozyme in 5 patients with late-onset Pompe disease who ranged in age from 5 to 15 years at initiation of treatment (AGLU02804). Patients received 20 mg/kg Myozyme once every two weeks for 26 weeks. All patients were freely ambulatory and all but one patient did not require any form of ventilator support (1 patient required nocturnal non-invasive ventilation). Of the 3 patients with significant pulmonary involvement at screening/baseline (percentage predicted forced vital capacity in the sitting position ranging from 58-67%), two demonstrated clinically meaningful improvements in FVC (+11.5% and +16.0%) in the sitting position by Week 26. Evaluation of motor function gave disparate results.

Ten patients with advanced late-onset Pompe disease (i.e. wheelchair-bound for 10/10 and ventilator-dependent for 9/10) aged 9-54 years were treated in expanded access programs with alglucosidase alfa 20-40 mg/kg once every two weeks for various periods of time between 6 months and 2.5 years. The pulmonary benefits observed in patients included a clinically meaningful improvement in FVC of 35% in one patient, and significant reductions in the number of hours of ventilator support needed in 2 patients. Benefits of treatment on motor function including the regaining of lost motor skills were observed in some patients. Only one patient became wheelchair-free. In this group of patients a variable response has also been seen with respect to motor function.

Pompe Registry

Medical or healthcare professionals are encouraged to register patients who are diagnosed with Pompe disease at www.registrynxt.com. Patient data will be anonymously collected in this Registry. The objectives of the “Pompe Registry” are to enhance the understanding of Pompe disease and to monitor patients and their response to enzyme replacement therapy over time, with the ultimate goal of improving clinical outcomes for these patients.

5.2 Pharmacokinetic properties

Infantile-onset Pompe disease
In a pivotal trial including 18 patients, the pharmacokinetics of alglucosidase alfa were evaluated in 15 patients with infantile-onset Pompe disease (all less than 6 months of age at treatment-onset) who

received doses of 20 mg/kg or 40 mg/kg alglucosidase alfa as an approximate 4 to 6.5-hour infusion, respectively.

Distribution and elimination
After the first and sixth infusion of Myozyme, mean maximum plasma concentrations (C_{max}) ranged from 178.2 to 263.7 μg/ml for the 20 mg/kg and 40 mg/kg dose groups respectively. The mean area under the plasma concentration-time curve (AUC_{∞}) ranged from 977.5 to 1,872.5 μg•h/ml for the 20 mg/kg and 40 mg/kg dose groups. Mean plasma clearance (CL) was 21.4 ml/h/kg and mean volume of distribution at steady state (Vss) was 66.2 ml/kg for both dose groups with small between-subject variability of 15% and 11%, respectively. Mean plasma elimination half-life ($t_{1/2}$) was 2.75 hours for the two dose groups.

Linearity/non linearity
Pharmacokinetics were dose proportional and did not change over time.

The pharmacokinetics of alglucosidase alfa were also evaluated in a separate trial in 21 patients with infantile-onset Pompe disease (all aged between 6 months and 3.5 years at treatment-onset) who received doses of 20 mg/kg of alglucosidase alfa. In 12 patients with available data the AUC_{∞} and C_{max} were approximately equivalent to those observed for the 20 mg/kg dose group in the pivotal trial. The t½ of approximately 2-3 hours was also similar in this group of patients.

Late-onset Pompe disease
The pharmacokinetics of alglucosidase alfa were evaluated in a trial in 5 patients with late-onset Pompe disease aged 6-15 years who received 20 mg/kg alglucosidase alfa once every two weeks. There was no difference in the pharmacokinetic profile of alglucosidase alfa in these juvenile late-onset patients compared to infantile-onset patients.

The pharmacokinetics of alglucosidase alfa were studied in a population analysis of 32 late-onset Pompe disease patients from the randomized, double-blind, placebo-controlled study ranging in age from 21 to 70 years who received Myozyme 20 mg/kg once every two weeks. AUC_{∞} and C_{max} were similar at week 0, 12 and 52 visits indicating alglucosidase alfa pharmacokinetics were not time-dependent (Table 5).

Distribution and elimination

Table 5: Alglucosidase alfa pharmacokinetics after a single dose and after 12 and 52 weeks of therapy

Parameter	**Week 0**	**Week 12**	**Week 52**
C_{max} (μg/ml)	385 ± 106	349 ± 79	370 ± 88
AUC_{∞} (μg•h/ml)	2672 ± 1140	2387 ± 555	2700 ± 1000
CL (ml/h/kg)	8.1 ± 1.8	8.9 ± 2.3	8.2 ± 2.4
Vss (ml/kg)	904 ± 1158	919 ± 1154	896 ± 1154
Effective half-life (h)	2.4 ± 0.4	2.4 ± 0.3	2.5 ± 0.4

There was limited evidence that IgG antibodies to alglucosidase alfa affected pharmacokinetics. Higher mean clearance, lower mean AUC_{∞}, and lower mean C_{max} were observed in 5 patients who tested positive for inhibition of cellular uptake of enzyme. However, there was no apparent association between inhibition of uptake and the co-primary efficacy endpoints (see section 4.4).

5.3 Preclinical safety data

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

Administration of 40 mg/kg Myozyme intravenously once every other day in mice with coadministration of diphenhydramine during the period of organogenesis through lactation produced an increase in mortality of offspring during the lactation period. There were no other effects on any parameter evaluated including clinical observations or body weight gain in F1 generation pups. Furthermore, no effect on sexual maturation, learning or memory, or the ability to produce another generation occurred for the F1 generation mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Sodium phosphate monobasic monohydrate
Sodium phosphate dibasic heptahydrate
Polysorbate 80

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

After dilution, an immediate use is recommended. However, chemical and physical in-use stability has been demonstrated for 24 hours at 2 to 8°C when stored under protection from light.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

50 mg of powder in a vial (Type 1 glass) with a stopper (siliconised butyl) and a seal (aluminium) with a flip-off cap (plastic). Pack sizes of 1, 10 or 25 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Myozyme has to be reconstituted with water for injections, then diluted with sodium chloride 9 mg/ml (0.9%) solution for injection and then administered by intravenous infusion. Reconstitution and dilution should be performed in accordance with good practice rules, particularly for the respect of asepsis.

Due to the proteinaceous nature of the product, particle formation may occur in the reconstituted solution and final infusion bags. Therefore, a 0.2 micron low protein binding in-line filter should be used for administration. It was demonstrated that the use of a 0.2 micron in-line filter removes visible particles and does not result in an apparent loss of protein or activity.

Determine the number of vials to be reconstituted based on the individual patient's dose regimen (mg/kg) and remove the required vials from the refrigerator in order to allow them to reach room temperature (approximately 30 minutes). Each vial of Myozyme is for single use only.

Use aseptic technique

Reconstitution

Reconstitute each 50 mg vial of Myozyme with 10.3 ml water for injections. Add the water for injections by slow drop-wise addition down the side of the vial and not directly onto the lyophilised cake. Tilt and roll each vial gently. Do not invert, swirl or shake the vial. The reconstituted volume is 10.5 ml containing 5 mg/ml, and appears as a clear, colourless to pale yellow solution which may contain particles in the form of thin white strands or translucent fibres. Perform an immediate inspection of the reconstituted vials for particulate matter and discoloration. If upon immediate inspection foreign particles other than those described above are observed, or if the solution is discoloured, do not use. The pH of the reconstituted solution is approximately 6.2.

After reconstitution, it is recommended to promptly dilute the vials (see below).

Dilution

When reconstituted as above, the reconstituted solution in the vial contains 5 mg alglucosidase alfa per ml. The reconstituted volume allows accurate withdrawal of 10.0 ml (equal to 50 mg) from each vial. This should then be further diluted as follows: Slowly withdraw the reconstituted solution from each vial until the volume for the patient's dose is obtained. The recommended final concentration of alglucosidase in the infusion bags ranges from 0.5 mg/ml to 4 mg/ml. Remove airspace within the infusion bag. Also remove an equal volume of sodium chloride 9 mg/ml (0.9%), solution for injection, that will be replaced with reconstituted Myozyme. Slowly inject the reconstituted Myozyme directly into the sodium chloride 9 mg/ml (0.9%) solution for injection. Gently invert or massage the infusion bag to mix the diluted solution. Do not shake or excessively agitate the infusion bag.

The final infusion solution should be administered as close to preparation time as possible.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 Marketing Authorisation Holder and Importer and Its Address:
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