

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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).

Myozyme is indicated in adults and paediatric patients of all ages.

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 and the batch number of the administered product should be clearly recorded.

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. 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

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. A tendency was observed for infantile-onset patients treated with a higher dose (40 mg/kg) to develop higher titres of IgG antibodies. There does not appear to be a correlation between the onset of IARs and the time of IgG antibody formation. A limited number of the IgG positive patients evaluated tested positive for inhibitory effects on *in vitro* testing. Due to the rarity of the condition and the limited experience to date, the effect of IgG antibody formation on safety and efficacy is currently not fully established. The probability of a poor outcome and of developing high and sustained IgG antibody titres appears higher among CRIM-negative patients (Cross Reactive Immunologic Material-negative patients in whom no endogenous GAA protein was detected by Western blot analysis) than among CRIM-positive patients in whom endogenous GAA protein was detected by Western blot analysis and/or predicted based on genotype. However, high and sustained IgG antibody titres also occur in some CRIM-positive patients. The cause of a poor clinical outcome and of developing high and sustained IgG antibody titres is thought to be multi-factorial. IgG antibody titres should be regularly monitored.

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 ($\geq 102,400$) (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 Titer (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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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
<p>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.</p> <p>Subjects in the untreated historical cohort were born in 1993 or later.</p>					

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 naïve 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.			

Late-onset Pompe disease; other clinical trials and analyses

Four independent, open-label, single arm, investigator-initiated studies with Myozyme were conducted:

- One study in the Netherlands enrolled 102 late-onset patients with a median follow up of 5 years (60 months)
- One study in Italy enrolled 74 late-onset patients with up to 48 months follow up.
- One study in Germany enrolled 38 late-onset patients with 36 months follow up.
- One study in the Netherlands enrolled 69 late-onset patients with a median follow-up of 23 months.

These four studies with Myozyme suggested stabilisation or improvement of motor function and stabilisation of pulmonary function, for up to 5 years in the study conducted in the Netherlands with 102 late-onset patients.

In the above described study in 69 late-onset patients in the Netherlands, Myozyme showed an improvement in muscle strength. However, muscle function only improved in wheelchair independent patients and in those with less pronounced muscle weakness.

The improvement in muscle strength was confirmed up to 5 years in the study conducted in the Netherlands with 102 late-onset patients.

In two additional open-label clinical trials with Myozyme with a follow-up of 24 months, ten patients with severe late-onset Pompe disease (moderate to severe motor impairment and assisted ventilation) showed a variable response on measures of motor and respiratory functions, mostly in the form of a modest improvement (AGLU03105, AGLU04107).

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.

Late-onset Pompe disease; patient reported outcomes

An International Pompe Association (IPA)/Erasmus Medical Center (Netherlands) Pompe survey evaluated the impact of Myozyme on different patient outcomes collected annually:

- Myozyme significantly reduced the risk of becoming wheelchair dependent: at any point during follow-up, wheelchair dependency was less likely in LOPD treated patients than untreated patients (hazard ratio: 0.36; 95% CI: 0.17, 0.75 in a study of 198 eligible patients with a median follow-up of 5 years). No effect on respiratory support was demonstrated in this study.
- After 3 years of treatment with Myozyme in 163 adult patients, the mean Fatigue Severity Scale (FSS) score improved significantly by 0.13 score points per year ($p < 0.001$), indicating treatment helped to reduce fatigue in this study. Before treatment with Myozyme (median follow up of 4 years), the mean FSS score was stable at approximately 5.3 score points.
- Myozyme provided improvements and stabilisation in health-related quality of life and participation in 174 adult patients with a median follow-up period of 4 years (range 0.5-8) both before and during treatment.
 - After declining before treatment (-0.73 score points per year (sp/y); 95% CI: -1.07, -0.39), the Physical Component Summary measure of the SF36 patient reported survey improved in the first 2 years of Myozyme treatment (1.49 sp/y; 95% CI: 0.76, 2.21) and remained stable thereafter.
 - After declining before treatment (-0.49 sp/year; 95% CI: -0.64, -0.34), the Rotterdam Handicap Scale (RHS) stabilised under Myozyme (-0.02 sp/year; 95% CI: -0.17, 0.13).

Finally, in the 5-year prospective study conducted in the Netherlands with 102 adult patients with LOPD, the impact of treatment with Myozyme on daily life activities was measured by the Rasch-Built Pompe-Specific Activity (R-PACT) scale. Compared to baseline, the R-PACT score improved by 3.6 percentage points ($p = 0.004$) at 5 years of treatment, showing a benefit of Myozyme in these patients.

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 $\mu\text{g/ml}$ 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 $\mu\text{g}\cdot\text{h/ml}$ 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 (V_{ss}) 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 $t_{1/2}$ 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} ($\mu\text{g/ml}$)	385 ± 106	349 ± 79	370 ± 88
AUC_{∞} ($\mu\text{g}\cdot\text{h/ml}$)	2672 ± 1140	2387 ± 555	2700 ± 1000
CL (ml/h/kg)	8.1 ± 1.8	8.9 ± 2.3	8.2 ± 2.4
V_{ss} (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 no 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 (E421)
Sodium dihydrogen phosphate monohydrate (E339)
Disodium phosphate heptahydrate (E339)
Polysorbate 80 (E433)

6.2 Incompatibilities

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

6.3 Shelf life

3 years

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

Sanofi B.V.
Paasheuvelweg 25
1105 BP Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/333/001-003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 March 2006

Date of latest renewal: 21 February 2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE
SUBSTANCE AND MANUFACTURERS RESPONSIBLE
FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY
AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE
MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO
THE SAFE AND EFFECTIVE USE OF THE MEDICINAL
PRODUCT**

**A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND
MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturers of the biological active substance

Genzyme Corporation 45, 51, 76, 74 and 80 New York Avenue, Framingham, MA 01701, United States

Genzyme Flanders, Cipalstraat 8, 2440 Geel, Belgium

Name and address of the manufacturers responsible for batch release

Genzyme Ireland Limited, IDA Industrial Park, Old Kilmeaden Road, Waterford, Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING
AUTHORISATION**

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND
EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Myozyme 50 mg powder for concentrate for solution for infusion
Alglucosidase alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 50 mg of alglucosidase alfa.

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

3. LIST OF EXCIPIENTS

Excipients:

Mannitol (E421)

Sodium dihydrogen phosphate monohydrate (E339)

Disodium phosphate heptahydrate (E339)

Polysorbate 80 (E433)

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial

powder for concentrate for solution for infusion.

10 vials

powder for concentrate for solution for infusion.

25 vials

powder for concentrate for solution for infusion.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only

Read the package leaflet before use.

Intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

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.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (at 2°C-8°C).

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused product should be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi B.V.
Paasheuvelweg 25
1105 BP Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/333/001

EU/1/06/333/002

EU/1/06/333/003

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC:

SN:

NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS VIAL LABEL
--

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
--

Myozyme 50 mg powder for concentrate for solution for infusion
Aglucosidase alfa
Intravenous use after reconstitution and dilution

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
--

50 mg

6. OTHER

Store in a refrigerator (at 2°C-8°C).
Sanofi B.V.-NL

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Myozyme 50 mg powder for concentrate for solution for infusion

Alglucosidase alfa

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4

What is in this leaflet

1. What Myozyme is and what it is used for
2. What you need to know before you are given Myozyme
3. How Myozyme is given
4. Possible side effects
5. How to store Myozyme
6. Contents of the pack and other information

1. What Myozyme is and what it is used for

Myozyme is used to treat adults, children and adolescents of all ages who have a confirmed diagnosis of Pompe disease.

People with Pompe disease have low levels of an enzyme called alpha-glucosidase. This enzyme helps the body control levels of glycogen (a type of carbohydrate). Glycogen provides the body with energy, but in Pompe disease the levels of glycogen can get too high.

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

2. What you need to know before you are given Myozyme

Do not use Myozyme:

If you have experienced life-threatening allergic (hypersensitive) reactions to alglucosidase alfa or any of the other ingredients of this medicine (listed in section 6) and re-administration of the medicine was not successful. Symptoms of life-threatening allergic reactions include, but are not limited to, low blood pressure, very fast heart rate, difficulty breathing, vomiting, facial swelling, hives or rash.

Warnings and Precautions

If you are treated with Myozyme, you may experience an infusion-associated reaction while you are being given the medicine or during the hours following the infusion. Such a reaction comprises different symptoms like low blood pressure, chest discomfort, throat tightness, face, lips or tongue swelling (angioedema), hives (urticaria), dizziness, rash, itchy skin, nausea, vomiting, cough and bronchospasm (see section 4 for an overview of all infusion-associated reactions). An infusion-associated reaction can sometimes be very severe. If you experience a reaction like this, you should **tell your doctor immediately**. You may need to be given pre-treatment medicines to prevent an allergic reaction (e.g. antihistamines and/or corticosteroids) or to reduce fever (antipyretics).

In studies doctors have used medicines to suppress the immune system to reduce the production of antibodies. Because you have Pompe disease, there is a risk that you get a severe infection of your airways or lungs. Using these medicines to suppress the immune system may further increase this risk. If you experience severe ulcerative lesions of your skin, please inform your doctor. If you experience swelling of your lower limbs or generalized swelling, please inform your doctor. Your doctor should

consider discontinuation of the administration of Myozyme and initiate appropriate medical treatment. Your doctor should consider the risks and benefits of re-administering Myozyme.

Other medicines and Myozyme

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding and fertility

There is limited experience of the use of Myozyme in pregnant women. You should not be using Myozyme during pregnancy unless clearly necessary. Tell your doctor if you are breastfeeding. There is limited experience suggesting that Myozyme passes into human breast milk in very small amounts. No effects on the breastfeed infant is expected. Therefore breastfeeding during the treatment may be considered. However, you can discuss with your doctor whether to interrupt breastfeeding as a precautionary measure for the first 24 hours after each dose of Myozyme. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

Take care when driving or using any tools or machines shortly after infusion of Myozyme, since you may experience dizziness, sleepiness, shaking, and/or low blood pressure.

Myozyme contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially 'sodium free'.

3. How Myozyme is given

Myozyme will be given to you under the supervision of a doctor who is experienced in the treatment of Pompe disease.

The dose you receive is based on your body weight. The recommended dosage of Myozyme is 20 mg per kg of body weight. It will be given to you once every 2 weeks.

Use in children and adolescents

The recommended dosage of Myozyme in children and adolescents is the same as in adults.

Instructions for proper use

Myozyme is given through a drip into a vein (by intravenous infusion). It is supplied as a powder which will be mixed with sterile water before it is given.

If you are given more Myozyme than you should

If you are given Myozyme at a higher dose or infusion rate than recommended, you may experience infusion associated reactions. Such a reaction may include symptoms like :

- skin and lips turning blue because of a lack of oxygen in body tissues, increased heart rate, palpitations
- difficulty in breathing, cough
- dizziness, headache, taste disturbance
- high blood pressure, hot flush
- tongue swelling, vomiting, diarrhoea, feeling sick (nausea)
- chest pain, chest discomfort, throat tightness, fever, chills, feeling cold, redness at the infusion site
- muscle pain
- reddening of the skin

If you experience a reaction like this, you should tell your doctor immediately (see section 2). The rate of your infusion will be reduced or the infusion will be interrupted, and, as appropriate, you may receive a corrective treatment.

If you forget to use Myozyme

If you have missed an infusion, please contact your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

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 were serious or life-threatening. Life threatening reactions, including very severe generalised allergic reactions and anaphylactic shock, have been reported in some patients. Symptoms of such reactions include low blood pressure, very fast heart rate, difficulty breathing, vomiting, facial, lip or tongue swelling, hives or rash. Some patients have experienced infusion related side effects in the form of flu-like symptoms, which lasted for a few days after completion of the infusion.

Should you experience any reaction like this, please **tell your doctor immediately**. You may need to be given pre-treatment medicines to prevent an allergic reaction (e.g. antihistamines and/or corticosteroids) or to reduce fever (antipyretics).

Very common: may affect more than 1 in 10 people

- Hives
- Rash
- Increased heart rate
- (Facial) flushing
- Fever or increased body temperature
- Cough
- Increased breathing rate
- Vomiting
- Low level of oxygen in the blood

Common: may affect up to 1 in 10 people

- Paleness
- Increased or high blood pressure
- Bluish discolouration of the skin
- Chills
- Agitation
- Tremor
- Headache
- Tingling
- Pain or local reaction at the site of the drip
- Dizziness
- Irritability
- Itchy skin
- Retching
- Swelling of the face, swelling of the throat or severe combined swelling of the face, throat and tongue due to a severe allergic reaction
- Swelling of the arms and legs
- Nausea
- Chest discomfort

- Throat tightness
- Diarrhoea
- Tiredness
- Muscle pain
- Muscle spasms
- Severe ulcerative lesions of the skin
- Redness of the skin

Not known: frequency cannot be estimated from the available data

- Swelling around the eyes
- Abnormal breathing sounds, including a whistling sound
- Difficulty in breathing (including shortness of breath)
- Cold extremities (e.g. hands, feet)
- Decreased or low blood pressure
- Narrowing of the blood vessels causing blood flow to be decreased
- Sudden constriction of bronchi restricting air going in and out the lungs (bronchospasm)
- Feeling hot
- Feeling cold
- Feeling generally unwell (malaise)
- Feeling weak
- Sleepiness
- Increased sweating
- Eyes tearing
- Mottled skin
- Restlessness
- Wheezing
- Throat irritation
- Lack of oxygen in body tissues
- Decreased heart rate
- Heart stopping
- A forceful heartbeat that may be rapid or irregular (palpitations)
- Chest pain (not in the heart)
- Inflammation of membrane that covers eyeball and eyelid
- Abdominal pain
- Indigestion
- Difficulty in swallowing
- Joint pain
- Temporary suspension or sudden cessation of breathing
- Protein loss in urine
- Nephrotic Syndrome: swelling of lower limbs, generalized swelling and protein loss in urine
- Swelling and thickening of the skin at infusion site in case of leakage of the product outside blood vessels
- Redness of the palms
- Transient skin discoloration
- Redness at the infusion site
- Hives (rash) at the infusion site
- Itching at the infusion site
- Blister

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine

5. How to store Myozyme

Keep this medicine out of the sight and reach of children

Do not use this medicine after the expiry date which is stated on the label after 'EXP'. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).

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.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Myozyme contains

-The active substance is alglucosidase alfa. 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.

-The other ingredients are

- mannitol (E421),
- sodium dihydrogen phosphate monohydrate (E339)
- disodium phosphate heptahydrate (E339)
- polysorbate 80 (E433).

What Myozyme looks like and contents of the pack

Myozyme is a powder for concentrate for solution for infusion in a vial (50 mg/vial). Each pack contains 1, 10 or 25 vials. Not all pack sizes may be marketed.

The powder is white to off-white. After reconstitution it is a clear, colourless to pale yellow solution, which may contain particles. The reconstituted solution must be further diluted.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

Sanofi B.V.
Paasheuvelweg 25
1105 BP Amsterdam
The Netherlands

Manufacturer

Genzyme Ireland Limited, IDA Industrial Park, Old Kilmeaden Road, Waterford, Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>. There are also links to other websites about rare diseases and treatments.

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The following information is intended for healthcare professionals only:

Instructions for use – reconstitution, dilution and administration

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 using a syringe with a needle diameter not larger than 20 gauge. 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 enzyme/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 using a syringe with a needle diameter not larger than 20 gauge. 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 product or waste material should be disposed of in accordance with local requirements.

- **Administration**

It is recommended to start the administration of the diluted solution within three hours. The total time between reconstitution and completion of the infusion should not exceed 24 hours.

The recommended dose regimen of Myozyme is 20 mg/kg of body weight administered once every 2 weeks 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 IARs (Infusion Associated Reactions) until a maximum rate of 7 mg/kg/h is reached.