Professional Information

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE

MYOZYME® 50 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 50 mg of alglucosidase alfa.

After reconstitution, the solution contains 5 mg/mL alglucosidase alfa (total extractable dose of 50 mg/10 mL). After dilution, the concentration varies from 0,5 mg/mL to 4 mg/mL.

Contains sugar alcohol: after reconstitution, each vial contains 20 mg/mL mannitol.

Alglucosidase alfa is a recombinant form of human acid α-glucosidase and is produced by recombinant DNA technology using Chinese hamster ovary (CHO) cell culture.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

A sterile, non-pyrogenic, white to off-white lyophilised cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MYOZYME is indicated for long-term use as an enzyme replacement therapy for the treatment of patients with a confirmed diagnosis of Pompe disease (acid alpha-glucosidase deficiency).

4.2 Posology and method of administration

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

Posology

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

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

Special populations

Paediatric patients:

The safety and efficacy of MYOZYME have been evaluated in patients with ages ranging from infancy through adulthood.

Elderly patients:

Clinical studies completed to date did not include a sufficient number of subjects aged 65 years and older in order to evaluate the safety and efficacy of MYOZYME in this population.

Renal or hepatic insufficiency:

The safety and efficacy of MYOZYME in patients with renal or hepatic insufficiency have not been evaluated and no specific dosage 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. Vital signs should be obtained at each step, prior to increasing the infusion rate. The infusion rate may be slowed and/or temporarily stopped in the event of infusion reactions.

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

4.3 Contraindications

Hypersensitivity to alglucosidase alfa or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity/anaphylactic reactions:

Serious hypersensitivity reactions, including life-threatening anaphylactic reactions, have been observed in Pompe patients during MYOZYME infusion, some of which were IgE-mediated. A small number of patients developed anaphylactic shock and/or cardiac arrest during MYOZYME infusion that required life-support measures. Reactions included bronchospasm, wheezing, respiratory arrest, respiratory distress, apnoea, stridor, dyspnoea, decreased oxygen saturation, cardiac arrest, hypotension, bradycardia, tachycardia, cyanosis, vasoconstriction, flushing, chest pain, chest discomfort, throat tightness, angioedema, pharyngeal oedema, face oedema, peripheral oedema, urticaria and rash.

If severe hypersensitivity or anaphylactic reactions occur, immediate discontinuation of the administration of MYOZYME is essential and appropriate medical treatment should be initiated. Because of the potential for severe infusion reactions, appropriate medical support measures, including cardiopulmonary resuscitation equipment especially for patients with cardiac hypertrophy and patients with significantly compromised respiratory function, should be readily available when MYOZYME is administered.

Infusion-associated reactions (IARs):

Infusion-associated reactions (IARs) occurred in approximately 50 % of patients treated with MYOZYME in two infantile-onset clinical studies for 52 weeks. In a randomised, double-blind, placebo-controlled trial of patients with late-onset Pompe disease, 28 % of patients in the alglucosidase alfa treatment group experienced IARs. IARs occur at any time during, and within a few hours after the infusion of MYOZYME, and are more likely with higher infusion rates. The majority of reactions were assessed as mild to moderate; some reactions were severe. Some patients were pretreated with antihistamines, antipyretics and/or corticosteroids. IARs may occur in patients after receiving pretreatment with antipyretics, antihistamines or corticosteroids.

If an IAR occurs, regardless of pretreatment, decreasing the infusion rate, temporarily stopping the infusion, and/or administration of antihistamines and/or antipyretics may ameliorate the symptoms. If severe infusion reactions occur, immediate discontinuation of the administration of MYOZYME should be considered, and appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be available. Patients who have experienced IARs should be treated with caution when re-administered MYOZYME.

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

General:

Patients with an acute underlying illness 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.

Immunogenicity:

In clinical studies, the majority of patients developed IgG antibodies to MYOZYME, typically within

3 months of treatment. Infantile-onset patients treated with higher doses of MYOZYME tended to develop a more robust antibody response and experienced more IARs. It is recommended that patients be monitored for IgG antibody formation periodically. The effect of antibody development on the long-term efficacy of MYOZYME is not fully understood.

There is an observation that some patients who develop high and sustained IgG antibody titres, including cross-reactive immunologic material (CRIM)-negative patients (i.e. patients in whom no endogenous GAA protein was detected by Western blot analysis and/or predicted based on the genotype), may experience reduced clinical treatment efficacy with MYOZYME. The cause of a poor clinical response in some of these patients is thought to be multi-factorial (see *Immunomodulation* below).

Some IgG-positive infantile-onset and late-onset patients in clinical trials who were retrospectively evaluated for the presence of inhibitory antibodies tested positive for inhibition of enzyme activity and/or uptake in *in vitro* assays. However, the clinical relevance of this *in vitro* inhibition is unclear.

Patients treated with higher doses of MYOZYME tended to develop a more severe antibody response and IARs. A small number (3 of 36) of IgG-positive infantile-onset patients in clinical trials who were retrospectively evaluated for the presence of inhibitory antibodies tested positive for inhibition of enzyme activity and/or uptake in *in vitro* assays.

It is recommended that patients be monitored for IgG antibody formation every 3 months. The effect of antibody development on the long-term efficacy of MYOZYME is not understood. Some patients, including those who possess 2 null mutations, may develop high and sustained anti-alglucosidase alfa antibody titres.

A small number of patients tested positive for alglucosidase alfa-specific IgE antibodies, some of whom

experienced anaphylactic reactions. Testing was typically performed for IARs, especially moderate to severe or recurrent reactions. Some patients have been successfully rechallenged using slower rates and/or lower infusion doses and continued to receive treatment with MYOZYME under close clinical supervision.

Immunomodulation:

Immunogenicity data from clinical trials and published literature in CRIM-negative infantile-onset patients (IOPD) suggest that the administration of immune tolerance induction (ITI) regimen given to MYOZYME naive patients (prophylactic ITI) may be effective in preventing or reducing the development of high sustained antibody titre (HSAT) against MYOZYME. Data from a small number of patients previously treated with HSAT, with or without inhibitory activity, showed limited 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.

Pompe patients are at increased risk of respiratory infections due to the progressive effects of the disease on the respiratory muscles. Pompe patients treated with immunosuppressive medicines may be 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.

Cardiac dysrhythmia and sudden death during general anaesthesia for central venous catheter placement:

Caution should be used when administering general anaesthesia for the placement of a central venous catheter or for other surgical procedures in infantile-onset Pompe disease patients with cardiac hypertrophy.

Cardiac dysrhythmia, including ventricular fibrillation, ventricular tachycardia and bradycardia, resulting in cardiac arrest or death, or requiring cardiac resuscitation or defibrillation have been associated with the use of general anaesthesia in infantile-onset Pompe disease patients with cardiac hypertrophy treated with MYOZYME.

Acute cardiorespiratory failure:

Acute cardiorespiratory failure requiring intubation and inotropic support has been observed after infusion with MYOZYME in a few infantile-onset patients with underlying cardiac hypertrophy, possibly associated with fluid overload with intravenous administration of MYOZYME. See section 6.6.

4.5 Interactions with other medicines and other forms of interaction

No interaction studies have been conducted with MYOZYME.

4.6 Fertility, pregnancy and lactation

Pregnancy

The limited amount of data from post-marketing reports and published case reports with the use of alglucosidase alfa in pregnant women have not identified a MYOZYME-associated risk of miscarriage, or adverse maternal or fetal outcomes. There have been reports of diaphragmatic hernia, atrial septal defect and truncus arteriosus persistent in post-marketing experience, however the relationship of MYOZYME to these events is unknown. The estimated background risk of major birth defects and miscarriage in the indicated population is unknown.

The continuation of treatment for Pompe disease during pregnancy should be individualised to the pregnant woman. Untreated Pompe disease may result in worsening disease symptoms in pregnant women.

Lactation

Alglucosidase alfa may be excreted in breast milk. However, there are no risks identified with use in the breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MYOZYME and any potential adverse effects on the breastfed child from MYOZYME or from the underlying maternal condition.

A lactating woman may consider interrupting breastfeeding, pumping and discarding breast milk during MYOZYME administration and for 24 hours thereafter in order to minimise exposure to a breastfed infant.

Fertility

The limited amount of data from clinical studies, post-marketing reports and published case reports with the use of alglucosidase alfa in male and female patients have not identified a MYOZYME-associated risk on fertility and reproductive performance.

Preclinical data did not show any effect on mating and fertility.

4.7 Effects on ability to drive and use machines

No studies on the ability to drive and handle machines have been conducted with MYOZYME. Because dizziness, somnolence, tremor and hypotension have been reported as infusion-associated reactions, these may affect the ability to drive and use machines on the day of the infusion.

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable: very common ≥ 10 %; common ≥ 1 % and < 10 %; uncommon ≥ 0,1 % and < 1 %; rare ≥ 0,01 % and < 0,1 %; very rare < 0,01 %; not known (cannot be estimated from available data).

Infantile-onset experience

The most common adverse reactions were infusion-associated reactions (IARs). IARs occurred in approximately 50 % of patients treated with MYOZYME in two infantile-onset clinical studies for 52 weeks. The majority of these reactions were mild to moderate. IARs which were reported in more than 1 patient in clinical studies and the expanded access programme, included rash, flushing, urticaria, pyrexia, cough, tachycardia, decreased oxygen saturation, vomiting, tachypnoea, agitation, increased blood pressure, cyanosis, hypertension, irritability, pallor, pruritus, retching, rigors, tremor, hypotension, bronchospasm, erythema, face oedema, feeling hot, headache, hyperhidrosis, increased lacrimation, livedo reticularis, nausea, periorbital oedema, restlessness and wheezing. Severe infusion reactions reported in more than 1 patient included pyrexia, decreased oxygen saturation, tachycardia, cyanosis and hypotension.

Most infusion-associated reactions requiring intervention were ameliorated with slowing of the infusion rate, temporarily stopping the infusion, and/or administration of antipyretics, antihistamines, or steroids. See section 4.4 – Infusion-associated reactions (IARs), for details on the management of severe IARs.

Late-onset experience

The most common adverse reactions observed in a randomised, double-blind, placebo-controlled study of 90 patients with late-onset Pompe disease (aged 10 to 70 years) were infusion reactions. Patients were treated with 20 mg/kg MYOZYME or placebo (randomised in a 2:1 ratio) once every two weeks for 78 weeks. Infusion reactions occurred in approximately 28 % of patients treated with MYOZYME, compared to 23 % of placebo-treated patients. The majority of these reactions was mild to moderate and resolved spontaneously.

Infusion reactions which were reported in ≥ 5 % of MYOZYME-treated patients included headache, nausea, dizziness, urticaria, rash, chest discomfort, anaphylaxis, vomiting, hyperhidrosis, flushing and increased blood pressure.

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 anaphylactic reactions.

Adverse reactions reported in at least 2 patients (3 %) treated with MYOZYME are listed in Table 1 below.

Table 1: Summary of treatment emergent adverse events considered related to treatment occurring in at least 3 % of MYOZYME treated patients by treatment group

System organ class Preferred term	**MYOZYME treated patients**	**Placebo patients**
	Number of patients[1] **n (%)**	**Number of patients[1]** **n (%)**
Immune system disorders		
Hypersensitivity	2 (3,3)	0
Nervous system disorders		
Headache	5 (8,3)	6 (20,0)
Dizziness	4 (6,7)	2 (6,7)
Paraesthesia	2 (3,3)	1 (3,3)
Vascular disorders		
Flushing	3 (5,0)	0
Respiratory, thoracic and mediastinal disorders		
Throat tightness	2 (3,3)	0
Gastrointestinal disorders		
Nausea	5 (8,3)	3 (10,0)

Vomiting	3 (5,0)	0
Diarrhoea	2 (3,3)	1 (3,3)
Skin and subcutaneous tissue disorders		
Urticaria	5 (8,3)	0
Hyperhidrosis	5 (8,3)	0
Pruritus	2 (3,3)	0
Papular rash	2 (3,3)	0
Musculoskeletal and connective tissue disorders		
Muscle twitching	4 (6,7)	1 (3,3)
Myalgia	4 (5,0)	1 (3,3)
Muscle spasms	2 (3,3)	1 (3,3)
General disorders and administration site conditions		
Fatigue	3 (5,0)	4 (13,3)
Chest discomfort	4 (6.7)	1 (3,3)
Local swelling	2 (3,3)	1 (3,3)
Pyrexia	2 (3,3)	1 (3,3)
Peripheral oedema	2 (3,3)	0
Feeling hot	2 (3,3)	0
Investigations		
Blood pressure increased	3 (5,0)	0

[1] Percentages are based on the total number of patients treated in the study group. A patient experiencing more than 1 adverse event within a preferred term is counted once within that preferred term.

Post-marketing experience

Significant hypersensitivity/anaphylactic reactions have been reported in patients treated with MYOZYME. Some patients experienced life-threatening anaphylactic reactions, including anaphylactic shock, some of which were IgE-mediated. Reactions generally occurred shortly after initiation of the infusion. Patients presented with a constellation of signs and symptoms, primarily respiratory, cardiovascular, oedematous and/or cutaneous in nature. Reactions included bronchospasm, wheezing, respiratory arrest, respiratory distress, apnoea, stridor, dyspnoea, decreased oxygen saturation, cardiac arrest, hypotension, bradycardia, tachycardia, cyanosis, vasoconstriction, flushing, chest pain, chest discomfort, throat tightness, angioedema, pharyngeal oedema, face oedema, peripheral oedema, urticaria and rash.

These reactions were generally managed with temporary interruption and/or discontinuation of infusion and administration of antihistamines, corticosteroids, intravenous fluids, and/or oxygen, when clinically indicated. In some cases of anaphylactic reaction and cardiac arrest, epinephrine (adrenaline) and/or cardiopulmonary resuscitation were also administered. The majority of patients continued to receive treatment with MYOZYME, some under close clinical supervision. Early detection of signs and symptoms of hypersensitivity or anaphylactic reactions may assist in effective management of patients and prevent possible significant or irreversible outcomes.

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

Recurrent reactions consisting of flu-like illness or a combination of events such as fever, chills, myalgia, arthralgia, pain, or fatigue occurring after completion of infusions and usually lasting for a few

days have been observed in some patients treated with MYOZYME. The majority of patients were successfully rechallenged with MYOZYME using lower doses and/or pretreatment with anti-inflammatory medicines and/or corticosteroids and have continued to receive treatment under close clinical supervision.

Severe cutaneous and possibly immune-mediated reactions have been reported with MYOZYME, including ulcerative and necrotising skin lesions. Skin biopsy in one patient demonstrated deposition of anti-rhGAA antibodies in the lesion. Nephrotic syndrome was observed in a few Pompe patients treated with MYOZYME and who had high IgG antibody titres (≥ 102 400). In these patients, renal biopsy was consistent with immune complex deposition. Patients improved following treatment interruption. It is therefore recommended to perform periodic urinalysis among patients with high IgG antibody titres.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of MYOZYME is important. It allows continued monitoring of the benefit/risk balance of MYOZYME. Health care providers are asked to report any suspected adverse reactions to:

- The Pharmacovigilance Unit at Sanofi: za.drugsafety@sanofi.com (email) or 011 256 3700 (tel), or
- SAHPRA via the “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

In clinical trials, patients have received doses up to 40,0 mg/kg body weight. IARs are more likely to occur with higher doses or infusion rates, than recommended. See section 4.4 – Infusion-associated reactions (IARs).

Treatment

See section 4.4 – Infusion-associated reactions (IARs).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A. 31 Enzymatic preparations.

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

ATC code: A16AB0.

Pompe disease (also known as acid maltase deficiency, glycogen storage disease type II, or glycogenosis type II) is an inherited disorder of glycogen metabolism caused by the absence or marked deficiency of the lysosomal enzyme acid α-glucosidase (GAA). Pompe disease results in intralysosomal accumulation of glycogen in various tissues, particularly cardiac and skeletal muscles, leading to the development of cardiomyopathy, progressive muscle weakness, and impairment of respiratory function.

Alglucosidase alfa provides an exogenous source of GAA. Binding to mannose 6-phosphate receptors on the cell surface has been shown to occur via carbohydrate groups on the GAA molecule, after which it is internalised and transported into lysosomes, where it undergoes proteolytic cleavage that results in increased enzymatic activity. It then exerts enzymatic activity in cleaving glycogen.

5.2 Pharmacokinetic properties

The pharmacokinetics of alglucosidase alfa were evaluated in 15 patients in pivotal Study AGLU01602 of ages ranging from 1 month to 7 months at time of first infusion, who received 20 mg/kg or 40 mg/kg (as an approximate 4 to 6,5-hour infusion) of alglucosidase alfa every 2 weeks. The measurement of alglucosidase alfa plasma concentration was based on an activity assay using an artificial substrate. Systemic exposure was less than dose proportional between the 20 mg/kg and 40 mg/kg doses. After the first and sixth infusion of alglucosidase alfa, mean maximum plasma concentrations (C_{max}) ranged from 178,2 µg/mL to 263,7 µg/mL for the 20 mg/kg and 40 mg/kg dose groups. The mean area under the plasma concentration-time curve (AUC_{∞}) ranged from 977,5 µg•h/mL to 1 872,5 µg•h/mL for the 20 mg/kg and 40 mg/kg dose groups. Mean plasma clearance (CL) was 21,9 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 2 dose groups.

The pharmacokinetics of alglucosidase alfa was also evaluated in 14 patients in supportive Study AGLU01702 who ranged in age from 6 months to 3,5 years at time of first infusion. Patients received 20 mg/kg of alglucosidase alfa as an approximate 4-hour infusion every 2 weeks. The pharmacokinetic parameters were similar to those observed for the 20 mg/kg dose group in AGLU01602 study.

The pharmacokinetics of alglucosidase alfa were evaluated in a trial in 5 patients with late-onset Pompe disease aged 5 – 15 years who received 20 mg/kg alglucosidase alfa every 2 weeks. There was no difference in the pharmacokinetic profile of alglucosidase alfa in late-onset patients compared to infantile-onset patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Polysorbate 80 (Tween 80)

Sodium phosphate dibasic heptahydrate

Sodium phosphate monobasic monohydrate.

6.2 Incompatibilities

In the absence of compatibility studies MYOZYME should not be mixed with other medicines.

6.3 Shelf life

3 years.

In-use stability:

The reconstituted and diluted solution should be administered without delay. If immediate use is not possible, the reconstituted and diluted solution is stable for up to 24 hours at 2 °C to 8 °C.

6.4 Special precautions for storage

Store in a refrigerator between 2 °C and 8 °C.

Do not use after the expiration date on the vial.

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

Storage of the reconstituted solution at room temperature is not recommended (see section 6.3).

DO NOT FREEZE OR SHAKE.

For storage conditions after reconstitution and dilution of MYOZYME, see section 6.3.

6.5 Nature and contents of container

Single-use, clear type I glass 20 mL (cc) vials. The closure consists of a siliconised butyl stopper and an aluminium seal with a plastic flip-off cap.

Pack size: 1 vial per carton.

6.6 Special precautions for disposal and other handling

- MYOZYME has to be reconstituted with water for injection, then diluted with 9 mg/mL (0,9 %)

sodium chloride solution for injection and then administered by intravenous infusion. Reconstitution and dilution should be performed in accordance with good practice rules, particularly in 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.
- Determine the number of vials to be reconstituted based on the individual patient's weight and the recommended dose of 20 mg/kg. Remove the required number of vials from the refrigerator and allow them to reach room temperature (approximately 30 minutes). As MYOZYME does not contain a preservative, each vial of MYOZYME is for single use only.
- Patient weight (kg) x dose (mg/kg) = patient dose (in mg). Patient dose (in mg) divided by 50 mg/vial = number of vials to reconstitute.

  If the number of vials includes a fraction, round up to the next whole number.

  Example: Patient weight (16 kg) x dose (20 mg/kg) = patient dose (320 mg). 320 mg divided by 50 mg/vial = 6,4 vials; therefore 7 vials should be reconstituted.

Reconstitution and dilution using aseptic technique

Reconstitution:

- Reconstitute each 50 mg vial of MYOZYME by slowly injecting 10,3 mL sterile water for injections to the inside wall of each vial. Each vial will yield 5 mg/mL. The total extractable dose per vial is 50 mg per 10 mL. Avoid forceful impact of the water for injection on the powder and avoid foaming. This is done by slow drop-wise addition of the water for injection down the inside of the vial and not directly onto the lyophilised cake. Tilt and roll each vial gently. Do not invert, swirl or shake the vial.
- Perform an immediate visual inspection of the reconstituted vials for particulate matter and discolouration. If upon immediate inspection opaque particles are observed, or if the solution is discoloured, do not use. The reconstituted solution may occasionally contain some alglucosidase alfa particles in the form of thin white strands or translucent fibres subsequent to the initial

inspection. This may also happen following dilution for infusion. These particles have been shown to contain alglucosidase alfa and may appear after the initial reconstitution step and increase over time. Studies have shown that these particles are removed via in-line filtration without having a detectable effect on the purity or strength.

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

Dilution:

- MYOZYME should be diluted in 0,9 % sodium chloride for injection, immediately after reconstitution, to a final concentration of 0,5 mg/mL to 4 mg/mL.
- Slowly withdraw the reconstituted solution from each vial. Avoid foaming in the syringe.
- Remove airspace from the infusion bag to minimise particle formation due to the sensitivity of MYOZYME to air-liquid interfaces.
- Add the reconstituted MYOZYME solution slowly and directly into the sodium chloride solution. Do not add directly into airspace that may remain within the infusion bag. Avoid foaming in the infusion bag.
- Gently invert or massage the infusion bag to mix the diluted solution. Do not shake or excessively agitate the infusion bag.
- The reconstituted and diluted infusion solution should be protected from light.
- The diluted solution should be filtered through a 0,2 µm, low protein-binding, in-line filter during administration to remove any visible particles.
- The reconstituted and diluted solution should be administered without delay.
- MYOZYME should not be infused in the same intravenous line with other products.
- MYOZYME does not contain any preservatives. Vials are single-use only. Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

Hertford Office Park, Building I, 5th Floor

90 Bekker Road, Vorna Valley

Midrand 2196

South Africa

8. REGISTRATION NUMBER

43/31/0745

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 November 2011

10. DATE OF REVISION OF THE TEXT

13 August 2025

NAMIBIA

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