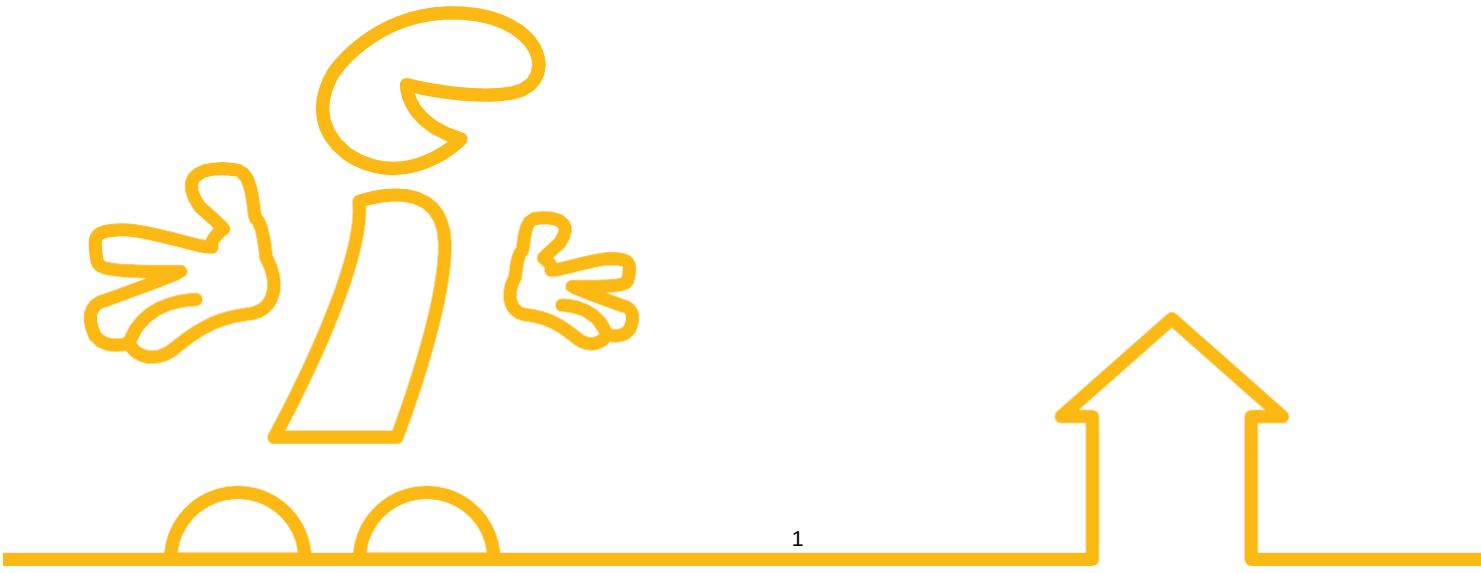
SANOFI GENZYME HOME ASSISTANCE

Myozyme Safety Information Packet

This document is approved by The Executive Directorate of Pharmacovigilance, at SFDA



SAFETY INFORMATION PACKET

Myozyme® (alglucosidase alfa)

Guidance for health care professionals on risks associated with Myozyme® administration, clinical risk management and immunology testing

You are encouraged to report any suspected adverse reactions via the national reporting system and all patients are encouraged to enroll in the Pompe Patient Registry

Update November 2020

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CONTENTS

ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CIC	Circulating-immune complex
CK	Creatine kinase
CRIM	Cross Reactive Immunologic Material
ERT	Enzyme Replacement Therapy
GAA	Acid α-glucosidase
GP	Global Pharmacovigilance
HCP	Health care professional
IAR	Infusion-associated reaction
IV	Intravenous
rhGAA	Recombinant human acid alfa-glucosidase
SIP	Safety Information Packet
SmPC	Summary of Product Characteristics

SUMMARY

Aim of the Safety Information Packet

The Myozyme (alglucosidase alfa) Safety Information Packet (SIP) is a supplementary educational material provided to physicians involved in managing patients with Pompe disease treated with Myozyme. Treating physicians may make this material available to other health care professionals (HCPs) involved in the management of the disease as required (pharmacists, non-specialist physicians, allergists, nurses). The main purpose of the SIP is to:

1. Minimize known risks associated with Myozyme treatment
2. Guide HCPs on the clinical management of these risks
3. Guide HCPs to carry out immunological testing which will help to further characterize the potential mechanism of infusion-associated reactions (IARs) and hypersensitivity reactions

The SIP also provides information on the Sanofi-Genzyme's Rare Disease Specialty Testing Program .

Myozyme and Pompe disease

Pompe disease is a lysosomal storage disorder as it is caused by a deficiency of acid α-glucosidase (GAA), an enzyme that degrades lysosomal glycogen to glucose. GAA deficiency leads to glycogen accumulation and the eventual rupture of lysosomes, resulting in cellular dysfunction in many body tissues, particularly muscle fibres.

Myozyme contains the active ingredient alglucosidase alfa (recombinant human acid α- glucosidase [rhGAA]). 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. The recommended dose regimen of Myozyme is 20 mg/kg of body weight administered once every 2 weeks.

Description of identified risks

The following risks associated with Myozyme administration have been identified (refer to section 1):

The SIP provides a full description of identified risks associated with Myozyme infusion and guidance on the clinical management of adverse reactions (refer to section 2).

Immunology testing

Genzyme has established a post-marketing immunosurveillance program for Myozyme, to determine the extent of antibody formation with Myozyme and its clinical impact, if any (refer to section 3.1.).

- Baseline serum sample collection prior to the first infusion is strongly encouraged.
- It is recommended that patients be monitored for IgG antibody regularly (refer to the Summary of Product Characteristics for more information on routine IgG monitoring).
- Treating physicians are strongly encouraged to collect samples for testing of IgE, complement activation and tryptase for patients who experience moderate to severe or recurrent IARs suggestive of hypersensitivity reactions.

The SIP provides information on the Sanofi-Genzyme's Rare Disease Specialty Testing Program. This Program provides antidrug IgG antibody and adverse event related immunogenicity testing services. These services are free of charge (refer to section 3.2.).

Please contact your local Sanofi-Genzyme contact or Sanofi-Genzyme EU Medical Services (EUMedicalServices@@sanofi.com) for information how to access Sanofi-Genzyme's Rare Disease Specialty Testing services or other test-related questions for Myozyme.

KEY CONTACTS

Please report any suspected adverse reaction to the SFDA and to the local MAH .

- **To report adverse event(s) and/or pregnancy occurring in association with the use of Myozyme:**

  For Pharmacovigilance, please contact:

  +966-544-284-797

  Ksa_pharmacovigilance@sanofi.com

- **For information how to access Sanofi-Genzyme's Rare Disease Specialty Testing services or other test-related questions for Myozyme**:
  For Medical Information, please contact: +966(12)6693318 or ksa.medicalinformation@sanofi.com

- **For medical information regarding Pompe Disease or Myozyme:**

  Please contact: +966(12)6693318 or

  ksa.medicalinformation@sanofi.com

For additional information, please visit www.pompe.com

- **In case of any drug related adverse events, please contact: The National Pharmacovigilance Centre (NPC):**
  SFDA call center : 19999
  E-mail: npc.drug@sfda.gov.sa
  Website: https://ade.sfda.gov.sa/

1. Description of risks associated with Myozyme

Identified safety risks of Myozyme (alglucosidase alfa) treatment include the development of infusion associated reactions (IARs) including hypersensitivity and life-threatening anaphylactic shock and/or cardiac arrest, immune-mediated reactions, immunologic response and acute cardiorespiratory failure associated with fluid overload.

1.1. Infusion-associated reactions including hypersensitivity and anaphylactic reactions

An IAR is defined as any adverse event (AE) occurring during the infusion or during the hours following infusion and assessed as potentially causally related to the administration of the product (Myozyme). Related events occurring after the post-infusion period may be considered IARs at the discretion of the reporter. The exact mechanism for IARs is not fully understood. Table 1 shows a list of potential mechanisms (1,2):

Table 1. Potential mechanisms of IARs, including hypersensitivity and anaphylactic reactions

- IgE mediated
- IgG mediated with complement activation
- Cytokine release with unclear mechanism
- Non-specific immunogenic mechanism
- Direct stimulation of mast cells by drug with release of histamine

In clinical trials, the occurrence of IARs was approximately 50% in infantile-onset patients treated with Myozyme (over a period of 52 weeks) and 28% in late-onset patients (over a period of 18-months). The occurrence of IARs is not unexpected given the clinical presentation of immunogenic responses to recombinant human proteins. While the majority of reactions were assessed as mild to moderate, some were severe. Some patients 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 (Table 2).

Table 2. Observed signs and symptoms of hypersensitivity/anaphylactic reactions

Respiratory	Cardiovascular	Cutaneous	Nervous system	General disorders and administration site conditions
bronchospasm wheezing respiratory arrest respiratory distress apnoea stridor dyspnoea oxygen saturation decreased throat tightness	cardiac arrest hypotension bradycardia tachycardia cyanosis vasoconstriction pallor flushing hypertension	urticaria rash erythema hyperhidrosis	dizziness restlessness headache paraesthesia.	fever nausea peripheral coldness feeling hot chest discomfort chest pain face oedema peripheral oedema angioedema

Additionally, 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 Myozyme.

Patients who have experienced IARs (and in particular anaphylactic reactions) should be treated with caution when re-administering Myozyme. For more information and guidance on infusion management, please refer to section 2. For more information on Myozyme preparation, administration and storage please refer to appendix 1, 2 and 3, respectively.

Table 3 presents a list of patients at increased risk of complication of IARs.

Table 3. Patients at increased risk of complications associated with IARs

- Patients with any acute underlying febrile illness.
- Patients with severe Pompe disease (may have compromised cardiac and respiratory function, which may predispose them to a higher risk of severe complications from infusion associated reactions).
- Patients who develop IgE antibodies to Myozyme (at a higher risk for occurrence of anaphylaxis and severe hypersensitivity reactions).
- Patients receiving Myozyme at higher infusion rates.
- Patients with infantile-onset Pompe disease who developed high IgG antibody titres.
- Patients who have experienced previous IARs.
- Patients who have temporarily interrupted Myozyme treatment (e.g. during pregnancy).

1.2. Immune mediated-reactions

Severe cutaneous and systemic immune-mediated reactions have been reported in some patients treated with Myozyme (<1/100 to ≥1/1000). The potential mechanism for immune-mediated reactions consists of the deposition of intermediate-sized circulating immune complexes in tissues and vascular endothelium leading to inflammation and resulting in a heterogeneous array of clinical signs and symptoms such as glomerulonephritis, haematuria, proteinuria, papular rash, purpura-like eruptions, arthritis, serositis, and vasculitis (3,4).

Reactions are self-limiting and usually develop within 7 to 10 days of antigen infusion, starting with some constitutional flu-like symptoms: fever, myalgia, arthralgia and rash. Clinical recovery is usually apparent after 7 to 28 days.

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

Systemic immune-mediated reactions, including possible type III immune complex-mediated reactions, have been observed with Myozyme. These reactions occurred several weeks to 3 years after initiation of Myozyme infusions.

Nephrotic syndrome was observed in a few patients with Pompe disease treated with Myozyme and who had high IgG antibody titres (≥ 102,400). In these patients renal biopsy showed immune complex deposition. Patients improved following treatment interruption.

Recommendation: It is recommended to perform periodic urinalysis among patients with high IgG antibody titres.

Patients should be monitored for the development of systemic immune–mediated reactions. 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.

1.3. Immunogenicity

As a therapeutic protein, Myozyme has the potential to trigger an immunologic response, involving the formation of antibodies against recombinant human acid α-glucosidase (anti-rhGAA IgG antibodies and anti-rhGAA IgE antibodies) (5).

1.3.1. Anti-rhGAA IgG antibodies including inhibitory antibodies

In clinical studies, the majority of infantile-onset and late-onset Pompe patients developed IgG antibodies to alglucosidase alfa, generally within 3 months of initiation of treatment (6,7). Similar proportions of patients treated in the commercial setting have developed anti-rhGAA IgG antibodies. A tendency was observed for infantile-onset patients treated with a higher dose (40 mg/kg) of Myozyme to develop higher titres of IgG antibodies and experienced more IARs.

Recommendation: Patients should be regularly monitored for IgG antibody formation.

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

Some patients treated with Myozyme in clinical trials and/or the post marketing setting were tested positive for inhibition of enzyme activity and/or uptake. The clinical relevance of in vitro inhibition is unclear. Patients with positive uptake inhibition generally had higher IgG antibody titres than patients who remained negative for uptake inhibition in infantile-onset and late-onset studies. To date, no relationship between inhibition status and the adverse events has been established. The effects of inhibitory antibody development on the long term safety and efficacy of Myozyme are not fully understood.

Please refer to section 3.1.1 for IgG and inhibitory antibody testing.

1.3.2. Anti-rhGAA IgE antibodies

Some Myozyme treated patients in clinical trials and the post-marketing setting who were evaluated, tested positive for presence of alglucosidase alfa-specific IgE antibodies, some of whom experienced anaphylaxis.

Testing was typically performed for moderate or severe or recurrent IARs suggestive of hypersensitivity reactions. Skin testing, a more sensitive measure to detect IgE antibodies, was also performed for some patients. All patients made a full recovery from the reactions. Some patients were successfully re-challenged and continued to receive treatment with Myozyme using a slower infusion rate at lower initial doses (in line with desensitisation guidelines) and continued to receive treatment under close clinical supervision. Patients who develop IgE

antibodies to alglucosidase alfa appear to be at a higher risk for the occurrence of IARs and/or anaphylactic reactions.

Recommendation: Patients who develop IgE antibodies should be monitored more closely during administration of Myozyme since they appear to be at a higher risk for the occurrence of IARs and/or anaphylactic reactions

1.4. Risks associated with concomitant immunomodulation

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

1.5. Acute cardiorespiratory failure associated with fluid overload

Infantile patients with underlying cardiac hypertrophy are at risk. Patients with an acute underlying illness at the time of Myozyme infusion may be at greater risk of acute cardiorespiratory failure. A few reports of fluid overload have been received.

Acute cardiorespiratory failure requiring intubation and inotropic support has been observed up to 72 hours after infusion with Myozyme in a few infantile-onset patients with underlying cardiac hypertrophy, possibly associated with fluid overload with intravenous administration of Myozyme.

Key points

- IARs may occur during the infusion or during the hours following infusion. Hypersensitivity/anaphylactic reactions, some of which are IgE mediated, have been reported and generally occurred during or shortly after initiation of Myozyme infusion.
- Immune-mediated reactions including severe cutaneous and systemic reactions have been reported in some cases.
- As Myozyme is a therapeutic protein there is the potential for an immunologic response. IgG antibodies to alglucosidase alfa generally develop within 3 months of treatment initiation.
- Patients should be monitored for IgG antibody formation regularly.
- Some Myozyme treated patients who were evaluated, tested positive for presence of alglucosidase alfa-specific IgE antibodies, some of whom experienced anaphylaxis.
- Patients who develop IgE antibodies should be monitored more closely during administration of Myozyme since they appear to be at a higher risk for the occurrence of IARs and/or anaphylactic reactions.

2. Clinical management of identified risks (2,8–14)

2.1. Pre-infusion stage

The complex underlying medical problems of Pompe disease must be taken into account prior to initiating ERT with Myozyme (alglucosidase alfa). 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. All patients should be clinically evaluated prior to each Myozyme infusion to rule out any acute or underlying illness.

Careful consideration should be given to the potential short and long term effects of long-term repeat use of corticosteroids, antihistamines and antipyretics especially in paediatric patients. Dosing recommendations for such treatments should be in line with individual Summaries of Product Characteristics (SmPCs).

Pre-treatment in patients with previous IgE mediated hypersensitivity reactions

- **The use of antihistamines for pre-treatment is not recommended in patients with previous IgE mediated hypersensitivity reaction**. Antihistamines can mask early symptoms of a hypersensitivity reaction (skin reaction) making it difficult for the infusion staff to recognise the initial signs of distress and the need to decrease the infusion rate and/or otherwise intervene. Additionally, in cases where significant histamine is released, antihistamines administration after release or as a premedication will not be fully effective in managing anaphylactic reactions (13).
- **Exposure to beta blockers may exacerbate anaphylactic reactions and is a relative contraindication** when a patient is at a risk of anaphylaxis. Beta-blockers are also a relative contraindication for epinephrine/adrenaline administration (10,11,14).

2.2. Myozyme infusion stage

Any recommendations should be used as guidelines only. Final decisions concerning the management of individual patients reside with the treating physician.

2.2.1. Recommended infusion rate

- It is recommended that the initial infusion rate of Myozyme be no more than 1 mg/kg/hr. The infusion rate may be increased by 2 mg/kg/hr every 30 minutes, after patient tolerance to the infusion rate is established, until the recommended maximum infusion rate of 7 mg/kg/hr is reached. Vital signs should be obtained at the end of each step. Patients who have experienced IARs should be treated with caution when re-administering Myozyme.
- If the IAR appears rate related, the following modification(s) to the infusion rate ramp schedule are suggested:
    - decrease maximum infusion rate and/or
    - prolong each infusion rate ramp step by 15-30 minutes

2.2.2. Mild or moderate reactions[1] (2,8,9)

- Slow infusion to half the rate or temporarily stop the infusion until symptoms **improve or subside.**
    - If **symptoms subside**, resume infusion rate at half the rate at which the IAR(s) occurred for 30 minutes, followed by an increase in infusion rate by 50% for 15 to 30 minutes.
    - If **symptoms do not recur**, increase the infusion rate to the rate at which the IAR(s) occurred and consider continuing to increase the rate in a stepwise manner until the maximum rate is achieved.
- If **symptoms persist** despite temporarily stopping the infusion, it is suggested that the treating physician wait at least 30 minutes more for symptoms of the IAR to clear prior to deciding to halt the infusion for the remainder of the day.

Example:

If the patient experiences mild or moderate IAR(s) at an infusion rate of 5 mg/kg/hr, reduce the infusion rate to 2.5 mg/kg/hr, or temporarily stop the infusion and wait for the symptoms to subside.

If symptoms subside, administer infusion at a rate of 2.5 mg/kg/hr for 30 minutes. If well tolerated, increase the infusion rate to 3.75 mg/kg/hr for at least 15 to 30 minutes.

If well tolerated, increase the infusion rate to 5 mg/kg/hr and administer for 15 to 30 minutes.

If well tolerated, increase the infusion rate to the maximum recommended infusion rate of 7 mg/kg/hr and administer at this rate for the remainder of the infusion as tolerated.

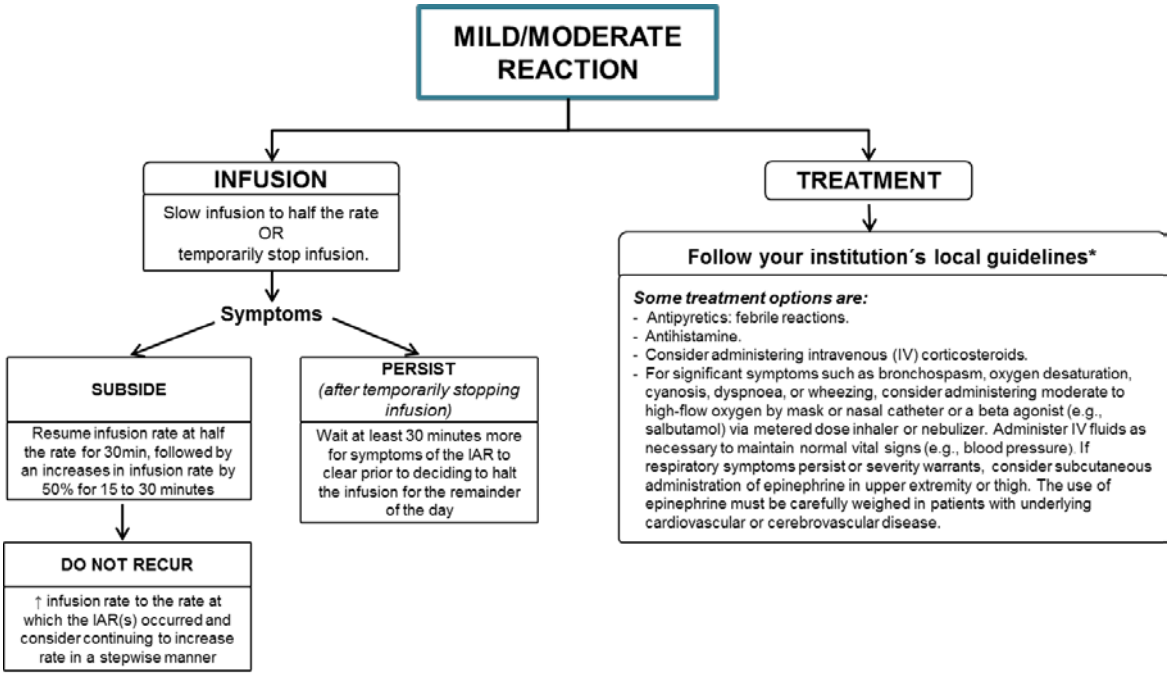
Vital signs should be obtained at the end of each step.

Treatment Recommendations for Mild to Moderate Reactions

- Administer antipyretics for febrile reactions.
- Administer age-appropriate dose of antihistamine [H1-blocker].
- Consider administering intravenous (IV) corticosteroids.
- For significant symptoms such as bronchospasm, oxygen desaturation, cyanosis, dyspnoea, or wheezing, consider administering moderate to high-flow oxygen by mask or nasal catheter or a beta agonist (e.g., salbutamol) via metered dose inhaler or nebulizer.
- If respiratory symptoms persist or severity warrants, consider subcutaneous administration of epinephrine in upper extremity or thigh. The use of epinephrine must be carefully weighed in patients with underlying cardiovascular or cerebrovascular disease.
- Administer IV fluids as necessary to maintain normal vital signs (e.g., blood pressure).

1 **These definitions serve as guidelines only based on CDSIC SDTM standard terminology v3.1.1. Overall severity assessment is at the discretion of the treating physician:**
***Mild*:** A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the research participant.

Figure 1. Clinical management of mild to moderate reactions



**Contraindications should always be weighed against the benefit or need to use epinephrine as a life-saving measure in case of life-threatening anaphylactic reactions.*

2.2.3. Severe reactions[2]: hypersensitivity/anaphylactic reactions including anaphylactic shock and IgE-mediated hypersensitivity reaction (9,10,14)

Warning: Serious hypersensitivity reactions, including life-threatening anaphylactic reactions have been observed in patients during Myozyme infusion, some of which were IgE mediated. Some patients developed anaphylactic shock and/or cardiac arrest during Myozyme infusion that required life-support measures. Medical support measures, including **cardiopulmonary resuscitation equipment** should be readily available when Myozyme is administered.

- Anaphylactic reactions are often life-threatening with acute onset within minutes to several hours following infusion initiation. Even when there are mild symptoms initially, the potential for progression to a severe and even irreversible outcome must be recognized. Because of the potential for severe hypersensitivity or anaphylactic reactions, appropriate medical support, including cardiopulmonary resuscitation equipment, should be readily available when Myozyme is administered.

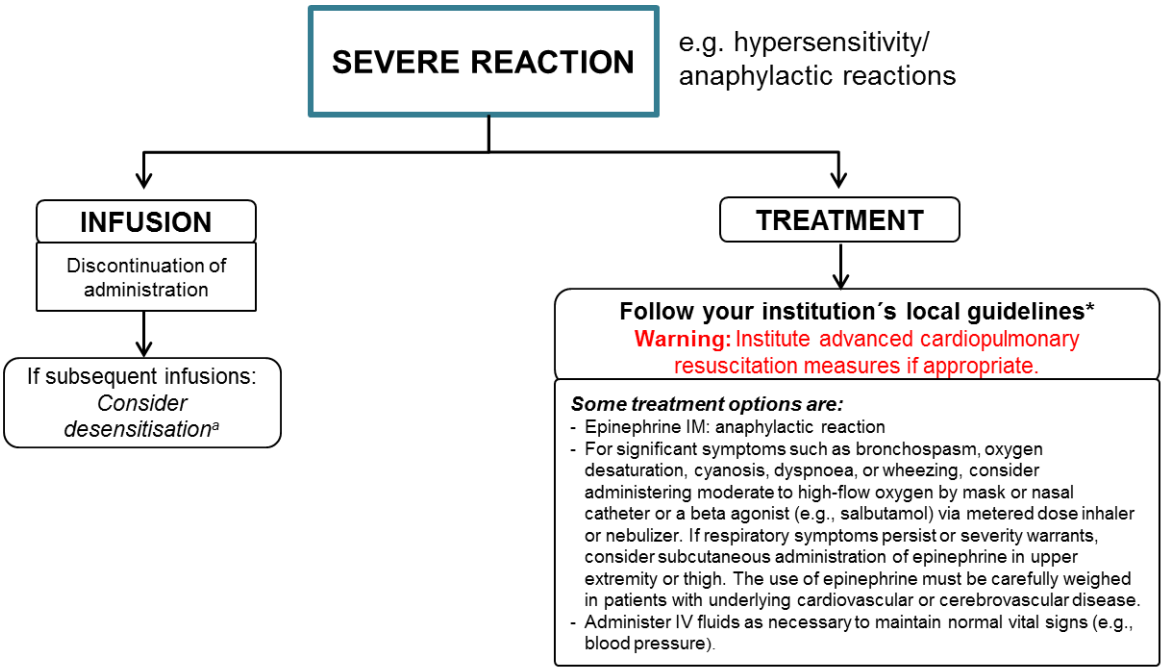
2 **This definition serves as guideline only based on CDSIC SDTM standard terminology v3.1.1. Overall severity assessment is at the discretion of the treating physician:**
Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

- 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.
- It is important to recognise the allergic phenomenon early so the infusion can be interrupted, the rate can be reduced and/or other corrective intervention can take place.
- The risks and benefits of re-administering Myozyme following an anaphylactic or severe hypersensitivity reaction should be considered. Some patients have been rechallenged and have continued to receive Myozyme under close clinical supervision. Extreme care should be exercised, with appropriate resuscitation measures available, if the decision is made to re-administer the product.

Treatment recommendations for severe reactions

- Immediate discontinuation of the administration of Myozyme should be considered, and appropriate medical treatment should be initiated, as described below.
  - Administration of epinephrine IM in upper extremity or thigh is generally indicated for life-threatening anaphylactic reactions. Although in general, careful consideration should be given to the contraindications to the use of epinephrine. Contraindications should always be weighed against the benefit or need to use epinephrine as a life-saving measure in case of life-threatening anaphylactic reactions. For detailed information please consult the SmPC of epinephrine.
  - For significant symptoms such as bronchospasm, oxygen desaturation, cyanosis, dyspnoea, or wheezing, consider administering moderate to high-flow oxygen by mask or nasal catheter or a beta agonist (e.g., salbutamol) via metered dose inhaler or nebulizer.
  - Administer IV fluids as necessary to maintain normal vital signs (e.g., blood pressure). Consider administering IV corticosteroids. Alpha-adrenergic agents and pressors with non-existent or minimal beta-adrenergic action should be considered to maximize inotropy and minimize chronotropy in patients with hypertrophic cardiomyopathy.
  - Institute advanced cardiopulmonary resuscitation measures if appropriate.
- If deemed appropriate, subsequent infusions should be initiated with a desensitisation procedure, typically without pre-treatment, in patients with previous IgE-mediated hypersensitivity reaction.
- Detailed instructions for desensitisation procedures will be made available to treating physicians upon request. Please contact Sanofi Genzyme Global Pharmacovigilance for desensitisation guidelines. Contact details are provided in ***KEY CONTACTS***.
- Recommendations for management of IgE positive patients provided herein are to be used as guidelines only. Final decisions concerning management of individual patients reside with the treating physician.

Figure 2. Clinical management of severe reactions



**Contraindications should always be weighed against the benefit or need to use epinephrine as a life-saving measure in case of life-threatening anaphylactic reactions.*

[a] *Please contact Genzyme Global Pharmacovigilance and Epidemiology* for desensitization guidelines.

2.3. Post-infusion observation

It is recommended that patients be observed for safety purposes both during and after the completion of each intravenous Myozyme infusion by appropriate medical personnel familiar with Pompe disease and potential reactions to Myozyme. In clinical trials, patients were monitored for 2 hours at the end of the Myozyme infusion. The appropriate length of post-infusion monitoring is to be determined by the treating physician based on the individual patient's clinical status and infusion history.

3. Testing

3.1. Description (table 4)

3.1.1. Immunosurveillance program: IgG antibody testing including inhibitory antibodies

In clinical studies, the majority of patients developed IgG antibodies to alglucosidase alfa, typically within 3 months of treatment (6,7,15). Thus seroconversion is expected to occur in most patients treated with Myozyme (alglucosidase alfa). The development of antibodies against recombinant protein is well recognised and has been demonstrated with other ERTs (5). A tendency was observed for infantile-onset patients treated with a higher dose 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. The effect of antibody development on the long term efficacy and safety of alglucosidase alfa is not fully understood.

In clinical studies, samples testing positive for anti-rhGAA IgG antibodies were also tested for in vitro inhibition by both enzyme activity and cellular uptake assay. Testing in the commercial setting has also occurred in patients who demonstrated clinical decline and/or became invasively ventilated. The clinical relevance of inhibitory antibody development in patients treated with Myozyme is unknown. CRIM-negative infants (patients in whom no endogenous GAA protein was detected by Western blot analysis), have shown reduced clinical effect in the presence of high sustained IgG antibody titres with inhibitory activity (16–18).

To measure inhibition of rhGAA enzymatic activity by antibody present in patient serum, patient samples that had percentage inhibition greater than 20% at any sera dilutions were considered positive by inhibitory antibody assay (enzyme activity). A flow cytometry based assay was developed to evaluate whether patient antibodies interfere with uptake of rhGAA by human fibroblast cells in culture. Samples that had enzyme uptake inhibition greater than 20% at two or more sera dilutions were considered positive at that time point by the flow cytometry cell-based assay. Patients are considered positive for uptake inhibition if they demonstrate positive activity of > 1/20 dilution at one or more time points.

As part of the general post-approval safety surveillance, Sanofi- Genzyme has initiated an immunosurveillance program for Myozyme to determine the extent of antibody formation of Myozyme to understand the clinical impact, if any. There are currently no marketed tests for antibodies against alglucosidase alfa; however, a testing service is provided by Sanofi-Genzyme. Please contact your local Sanofi-Genzyme representative or Sanofi-Genzyme Medical Services via e-mail at ksa.medicalinformation@sanofi.com for information how to access Sanofi-Genzyme's Rare Disease Specialty Testing services.

Recommendation:
- IgG antibody titres should be regularly monitored.
- Treated patients are tested for inhibition of enzyme uptake or activity if they experience a decrease in clinical benefit despite continued treatment with Myozyme.
- Baseline serum sample collection prior to the patient's first infusion is strongly encouraged.

3.1.2. Immunology testing for infusion reactions: IgE, complement activation and serum tryptase testing

Testing was typically performed for moderate or severe or recurrent IARs suggestive of hypersensitivity reactions. Some patients who were evaluated tested positive for alglucosidase alfa-specific IgE antibodies, some of whom experienced anaphylactic reactions.

Some patients have been successfully rechallenged using slower rates and/or lower initial doses and continued to receive treatment with Myozyme under close clinical supervision.

Recommendation: To further characterize the potential mechanism of IARs, samples for complement activation and serum tryptase testing must be drawn 1-3 hours after the onset of the infusion reaction. Samples for IgE testing must be drawn at least 72 hours after the infusion ends.

Please contact your local Sanofi-Genzyme representative or Sanofi-Genzyme Medical Services via e-mail at ksa.medicalinformation@sanofi.com for information how to access Sanofi-Genzyme's Rare Disease Specialty Testing services.

3.1.3. Skin testing (11,12)

Skin testing may be performed at the discretion of the treating physician in patients who experience an IAR that meets the following criteria (table 4):

- Infusion associated reaction is suggestive of an IgE-mediated reaction, with persistent symptoms such as bronchospasm, hypotension and/or urticarial requiring intervention OR any other signs or symptoms which the treating physician considers (as) relevant.
- Skin testing may be another predictor of IgE-mediated reactions and may be suggested for confirmation of the IgE results.

If the decision to perform skin testing is made, it is recommended to postpone Myozyme infusions until skin testing has been performed and the results reviewed by the treating physician.

***Note*:** Certain medications (e.g., antihistamines, adrenergic drugs) may interfere with test results. Prior to skin testing, patient's medications should be reviewed to assess whether or not they may interfere with test results.

It is recommended that skin testing is performed by a trained allergist or a medical person trained in allergy skin testing and that the testing is performed at minimum 48 hours after Myozyme infusion, and preferably > 3 weeks after an anaphylactic episode because of transient desensitisation.

The procedure only involves prick/puncture testing. If prick/puncture testing is negative, intradermal testing may be warranted. Testing includes Myozyme and positive and negative controls.

3.1.4. Circulating immune complex testing

In the event a patient exhibits signs or symptoms suggestive of systemic immune-mediated reactions involving skin and other organs while receiving alglucosidase alfa, serum samples are obtained for the evaluation of circulating immune complexes. Patients should be monitored for continuing immune complex symptomatology, and additional serum samples obtained for evaluation, as appropriate. Consideration for further evaluation of possible immune complex disease, including biopsy of suspected organs involved (e.g., skin to assess for vasculitis and kidney biopsy to assess for immune complex deposition in the glomerular basement membrane) is left to the discretion of the treating physician.

***Table 4. Clinical immunology and skin testing characteristics*.**

Test[a]	Indication for testing	Sample Type	Frequency	Collection Time[b]
Skin testing	IARs suggestive of IgE mediated reaction with persistent symptoms or for confirmation of IgE results	Prick/puncture testing	Ad hoc (after IAR)	Min. of 48h after infusion and preferably >3 weeks after anaphylactic episode
IgG[c]	Routine monitoring	Serum-Frozen Whole blood (received within 24 hours of collection)	Routine monitoring	Sample should be Pre-infusion or ≥3 days post infusion
IgG/inhibitory antibody	Decreased response to treatment or lack of effect	Serum-Frozen Whole blood (received within 24 hours of collection)	Ad hoc (as needed)	Sample should be Pre-infusion ≥3 days post infusion
IgG/IgE antibody	Moderate/severe or recurrent IARs suggestive of hypersensitivity reactions, anaphylactic reactions	Serum-Frozen Whole blood (received within 24 hours of collection)	Ad hoc (as needed)	Pre-infusion or at least ≥3 days post infusion
Serum Tryptase	Moderate/severe or recurrent IARs suggestive of hypersensitivity reactions, anaphylactic reactions	Serum-Frozen	Ad hoc (as needed)	1-3 hours post infusion reaction
Complement Activation	Moderate/severe or recurrent IARs suggestive of hypersensitivity reactions, anaphylactic reactions	EDTA Plasma-Frozen	Ad hoc (as needed)	1-3 hours post infusion reaction

[a]Sanofi-Genzyme's Rare Disease Specialty Testing Program with Labcorp offers a service free of charge for collection, , packaging and shipping of blood samples to the Labcorp central laboratory. This service applies to all tests performed as part of an IAR investigation (including IgG antibody, IgE antibody, inhibitory antibody, complement activation, and serum tryptase) and to all clinical samples for routine IgG monitoring. Skin testing is usually performed locally.

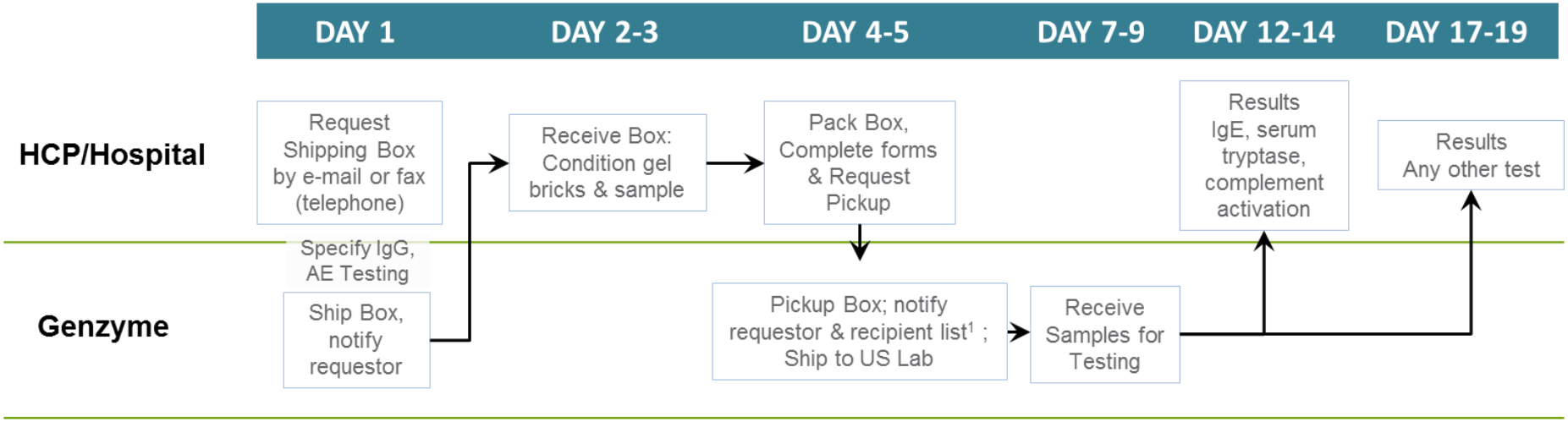
[b]Document the time and date when the sample was taken.

[c]If results show high IgG antibody titres, periodic urinalysis is recommended.

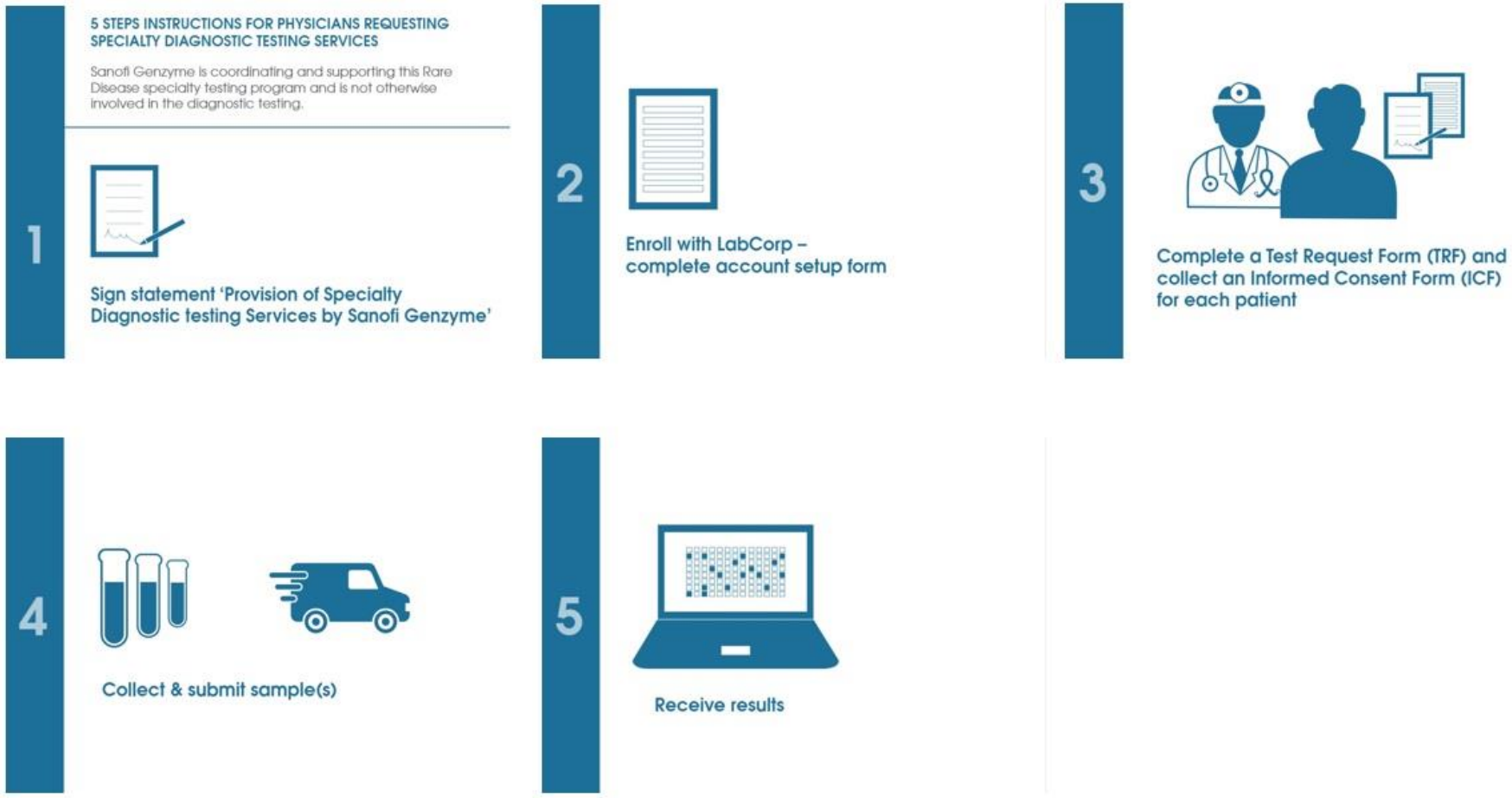
3.2. Procedure for testing

This procedure applies to all tests performed as part of an IAR investigation (including IgG antibody, IgE antibody, inhibitory antibody, complement activation, and serum tryptase) and to all clinical samples for routine post-marketing analysis and reporting (figure 3).

Figure 3. Procedure for testing and reporting adverse event related samples and samples for routine post-market antibody assessment



Estimated timelines for results reception:
5 calendar days: IgE, serum tryptase, complement activation
10 calendar days: any other test(s)



Please contact Sanofi- Genzyme E U Medical Services for collection, processing, packaging and shipping of blood samples. Contact details are provided in ***KEY CONTACTS***.

4. Reporting suspected 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 or to contact Sanofi Genzyme Pharmacovigilance department. For full contact details on reporting adverse reactions please refer to ***KEY CONTACTS***.

5. Pregnancy & breastfeeding

The use of Myozyme® (alglucosidase alfa) in pregnant women has not been investigated. The only data to evaluate reproductive risks with Myozyme are from non-clinical studies. Myozyme should not be used during pregnancy unless clearly necessary (SmPC under Section 4.6 Pregnancy and lactation).

Alglucosidase alfa may be excreted in breast milk. Because there are no data available on effects in neonates exposed to alglucosidase alfa via breast milk, it is recommended to stop breast-feeding when Myozyme is used.

Reporting information on drug exposure in pregnancy to Sanofi-Genzyme Global Pharmacovigilance is necessary to identify agents harmful to the developing foetus. Conversely, data on pregnancy exposure can also establish that the foetal toxicity of a product is limited. In order to collect, review and communicate information on safety in pregnancy, to dispose of more accurate information Sanofi-Genzyme will follow-up on all reported pregnancy cases. Sanofi-Genzyme strongly encourages physicians and other HCPs to report all pregnancies and pregnancy outcomes in patients exposed to Myozyme, regardless of the fact that such exposure is associated with an adverse event or not. For full contact details on reporting pregnancies please refer to ***KEY CONTACTS***.

6. References

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18. Genzyme, Data on file.

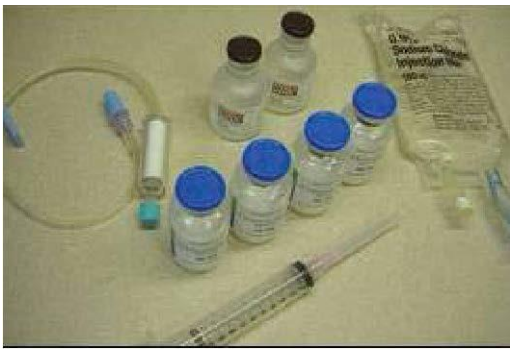
7. Appendices

Appendix 1. Preparation of Myozyme

Use aseptic technique during preparation.

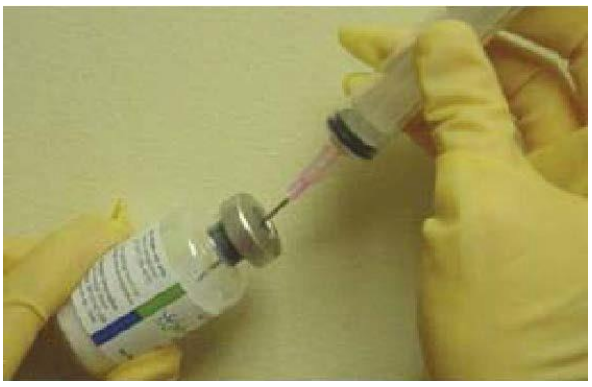
The following items are required for the preparation and administration of Myozyme® (alglucosidase alfa).

- Required quantity of Myozyme vials based on the patient's dose
- Intravenous administration set with 0.2 µm low protein-binding in-line filter
- Sterile water for injection, for reconstitution
- 9 mg/mL (0.9%) sodium chloride for injection, for dilution
- Syringes for reconstitution and dilution
- Needles with diameter not larger than 20 G for reconstitution and dilution
- Additional supplies required per institution protocol



Note: Filter needles should not be used during preparation of Myozyme.

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



Dose Calculation:

Patient weight (kg) x Dose (mg/kg) = Patient Dose (in mg)
Patient dose (in mg) ÷ 50 mg/vial=number of vials to reconstitute. If the number of vials includes a fraction, round up to the next whole number.
Examples:
A. Infantile-onset: Patient Weight (16 kg) x Dose (20mg/kg) = Patient Dose (320 mg)
320 mg ÷ 50 mg/vial=6.4 vials; therefore, 7 vials should be reconstituted
B. Adult-onset: Patient Weight (68 kg) x Dose (20mg/kg) = Patient Dose (1360 mg)
1360 mg ÷ 50 mg/vial=27.2 vials; therefore, 28 vials should be reconstituted

2. 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 G. Each vial will yield 5 mg/ml. The total extractable dose per vial is 50 mg in 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 lyophilized cake. Tilt and roll each vial gently. Do not invert, swirl or shake
3. Perform an immediate visual inspection of the reconstituted vials for particulate matter and discoloration. If upon immediate inspection opaque particles are observed or if the solution is discoloured, do not use and contact Genzyme Medical Information at + (31)35 699 1499.
   The reconstituted solution may occasionally contain some alglucosidase alfa particles (typically less than 10 in a vial) 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 using a 0.2 µm low protein-binding filter without having a detectable effect on the purity or strength.
4. Myozyme should be diluted in 9 mg/ml (0.9%) sodium chloride for injection, immediately after reconstitution, to a final Myozyme concentration of 0.5 to 4 mg/mL. See Table 1 for the recommended total infusion volume based on patient weight. Discard any vial with unused reconstituted solution.

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

   Examples:

   Patient dose = 320 mg 320 mg ÷ 5 mg/mL = 64 mL of Myozyme

Table 1. Calculation of Total Infusion Volume

Patient Weight Range(kg)	Total infusion volume	Infusion rates			
		Step 1 1 mg/kg/hr (mL/hr)	Step 2 3 mg/kg/hr (mL/hr)	Step 3 5 mg/kg/hr (mL/hr)	Step 4 7 mg/kg/hr (mL/hr) (until total volume has been infused)
1.25-10	50	3	8	13	18
10.1-20	100	5	15	25	35
20.1-30	150	8	23	38	53
30.1-35	200	10	30	50	70
35.1-50	250	13	38	63	88
50.1-60	300	15	45	75	105
60.1-100	500	25	75	125	175
100.1-120	600	30	90	150	210
120.1-140	700	35	105	175	245
140.1-160	800	40	120	200	280
160.1-180	900	45	135	225	315
180.1 -200	1000	50	150	250	350

5. Slowly withdraw the reconstituted solution from each vial using a syringe with a needle diameter not larger than 20 G. Avoid foaming in the syringe.
6. Remove airspace from the infusion bag to minimize particle formation due to the sensitivity of Myozyme to air-liquid interfaces.
7. Also remove an equal volume of sodium chloride 9 mg/ml (0.9%) solution for injection, that will be replaced with reconstituted Myozyme.
8. 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.
9. Gently invert or massage the infusion bag to mix. Do not shake.
10. Vials are single-use only. Discard any unused product.

Appendix 2. Administration of Myozyme

Note: Myozyme® (alglucosidase alfa) should not be infused in the same intravenous line with other products. The diluted solution should be filtered through a 0.2 µm, low protein-binding, in-line filter during administration to remove any visible particles. Visible particles (aggregated enzyme and degradants) are removed by the in-line filter without any detectable effect on the purity or strength of Myozyme.

Patients with an acute underlying illness at the time of Myozyme infusion appear to be at greater risk for infusion reactions. Careful consideration should be given to the patient's clinical status prior to administration of Myozyme.

1. Explain the administration procedure to the patient.
2. Obtain vital signs, including blood pressure, pulse, respiratory rate, and temperature prior to the infusion.
3. Obtain IV access. Antecubital, wrist, or hand veins may be used for access. Central access is also an option.
4. Draw any required blood work if applicable and flush line with 9 mg/mL (0.9%) sodium chloride for injection.
5. It is recommended that a primary infusion line of 9 mg/mL (0.9%) sodium chloride for injection be initiated at a rate specified by the physician, in order to maintain the patency of the IV access. If possible, use a programmable intravenous infusion pump to control this infusion rate.
6. Set up and prime the administration set with the Myozyme infusion solution. Use care to prevent the appearance of air bubbles in the tubing. In order to ensure precise control of the infusion rate, it is recommended that this infusion be performed with the use of a programmable intravenous infusion pump.
7. Connect the Myozyme solution administration set to the 0.2 µm in-line low protein-binding filter set and prime the line.
8. Connect the Myozyme solution line to the lowest additive port on the patient's primary administration set.
9. Infusions should be administered in a step-wise manner using an infusion pump.
10. When the infusion is complete, flush the tubing with 9 mg/mL (0.9%) sodium chloride for injection (at the last infusion rate) to ensure that the entire dose of Myozyme is administered to the patient.
11. Remove the administration set, and along with any unused product or waste material, discard and dispose of in accordance with local requirements.

Appendix 3. Storage of Myozyme

Unreconstituted Myozyme® (alglucosidase alfa) vials should be stored under refrigeration between 2° to 8°C. Do not use Myozyme after the expiration date on the vial.

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. Storage of the reconstituted and diluted solution at room temperature is not recommended. DO NOT FREEZE OR SHAKE.

Please see SmPC for full prescribing information

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, theconcentration varies from 0.5 mg to 4 mg/ml.

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

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 confirmeddiagnosis 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 patientswith 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 onceevery 2 weeks.

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

Paediatric and older people
There is no evidence for special considerations when Myozyme is administered to paediatric patientsof 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 beenevaluated 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 initialrate 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, seesection 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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 ofMyozyme 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 begiven 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 higherinfusion rates.

Patients with advanced Pompe disease may have compromised cardiac and respiratory function, whichmay 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 onsetof 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; patients in whom no endogenous GAA protein was detected by Western blot analysis) than among CRIM-positive patients (patients in whom endogenous GAA protein was detected by Western blot analysis). 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 Myozymeunder 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 observedin a few Pompe patients treated with alglucosidase alfa and who had high IgG antibody titres (≥ 102,400) (see section 4.8). In these patients renal biopsy showed immune complex deposition.
Patients improved following treatment interruption. It is therefore recommended to perform periodicurinalysis 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 successfullyrechallenged and continued to receive alglucosidase alfa under close clinical supervision.

Immunomodulation

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

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 are no data from the use of alglucosidase alfa in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Myozymeshould not be used during pregnancy unless clearly necessary.

Breast-feeding
Alglucosidase alfa may be excreted in breast milk. Because there are no data available on effects in neonates exposed to alglucosidase alfa via breast milk, it is recommended to stop breast-feeding whenMyozyme is used.

Fertility
There are no clinical data on the effects of alglucosidase alfa on fertility. Preclinical data did notreveal 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 has been reported as an infusion associated reaction, this may affect the ability to drive anduse 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 theinfusion (infusion associated reactions, IARs). Serious infusion reactions including urticaria, rales, tachycardia, decreased oxygen saturation, bronchospasm, tachypnea, periorbital edema 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 comparablebetween the two groups. The most common adverse reactions observed were IARs. Slightly more patients in the Myozyme group than in the placebo group experienced IARs (28% versus 23%). The majority of these reactions were non-serious, mild to moderate in intensity and resolved spontaneously. Adverse reactions reported in at least 2 patients are listed in Table 1. Serious adverse reactions reported in 4 patients treated with Myozyme were: angioedema, chest discomfort, throat tightness, non-cardiac chest pain and supraventricular tachycardia. Reactions in 2 of these patients were IgE-mediated hypersensitivity reactions.

Tabulated list of adverse reactions

Table 1: Adverse reactions (reported in at least 2 patients) and adverse reactions reported in post- marketing setting, expanded access programs and non-controlled clinical trials, per System Organ Class, presented by frequency categories: very common (≥1/10), common (≥1/100 to<1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Due to the small patient population, an adverse reactionreported 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
Eye disorders	not known			Conjunctivitis
Cardiac disorders	very common	Tachycardia		
	common	Cyanosis		
	not known			Cardiac arrest Bradycardia Tachycardia Cyanosis
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 Apnea Respiratory distress Bronchospasm Wheezing Pharyngeal oedema Dyspnoea Tachypnoea Throat tightness Stridor Cough
Gastrointestinal disorders	very common	Vomiting		
	common	Retching Nausea	Diarrhoea Vomiting Nausea[3]	
	not known			Abdominal pain Retching
Skin and subcutaneous	very common	Urticaria Rash		

tissue disorders	common	Erythema Rash maculopapular Rash macular Rash papular Pruritus	Urticaria Rash papular Pruritus Hyperhidrosis	
	not known			Periorbital edema Livedo reticularis Lacrimation increased Rash Erythema Hyperhidrosis
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 edema Feeling hot Pyrexia Chills Chest discomfort Irritability Peripheral coldness Infusion site pain Infusion site reaction Infusion site swelling Infusion site induration Infusion site extravasation
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

[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 witha constellation of signs and symptoms, primarily respiratory, cardiovascular, edematous 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, havebeen observed in some patients treated with alglucosidase alfa. The majority of patients were successfully re-challenged with alglucosidase alfa using lower doses and/or pretreatment with anti- inflammatory drugs and/or corticosteroids and have continued to receive treatment under close clinical supervision.

Patients with moderate to severe or recurrent IARs have been evaluated for alglucosidase alfa specificIgE 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:
Saudi Arabia: The National Pharmacovigilance and Drug Safety Centre (NPC)Fax: +966-11-205-7662Call NPC at +966-11-2038222, Exts: 2317-2356-2340. reporting hotline : 19999
E-mail: npc.drug@sfda.gov.sa Website: www.sfda.gov.sa/npc Sanofi-Pharmacovigilance: KSA_Pharmacovigilance@sanofi.com

4.9 Overdose

There is no experience with overdose of alglucosidase alfa. In clinical studies doses up to 40 mg/kgbody weight were used.

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, leadingto 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 withinthe first year of life and a very short expected life-span) 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 muscleweakness 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), themedian 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% ofpatients with late-onset Pompe disease.

Patients with late-onset Pompe disease typically present with progressive myopathy, predominantly ofthe 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 isunlikely.

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 onsetof 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 aperiod 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, all16 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 afterstudy end and another one after withdrawal from the study.

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

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

Treated Patients	Historical Reference Comparator	Endpoint	Treatment Effect Hazard Ratio	95% Confidence Interval	p-value
N=18	N=42	Survival	0.05	(0.015, 0.147)	<0.0001
Note: Results are from a Cox proportional hazards regression analysis which includes treatmentas a time-varying covariate, and also includes age of diagnosis and age at symptom onset. Subjects were aged 6 months or less at the onset of treatment. Subjects in the untreated historical cohort were born in 1993 or later.					

Echocardiographic indices of cardiomyopathy improved as measured by a decrease in left ventricularmass (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 LVMassessments 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 (withindividual 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 (withindividual 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 doseis 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 patientswith 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 twoweeks 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 weeksof 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 untreatedsubjects 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 treatmentas 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 andwas 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 overbaseline 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-upperiod 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 demonstrateimprovement 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 orbaseline 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 becritical to achieve the best outcomes in these infantile onset 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 initiationof treatment and were all naive to enzyme replacement therapy. Patients were randomized in a 2:1 ratio and received 20 mg/kg Myozyme (n=60) or placebo (n=30) once every two weeks for 78 weeks (18 months).

The co-primary efficacy outcome assessments were distance walked (meters) in 6 minutes (6-MinuteWalk 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 amedian 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
Three independent, open-label, single arm, investigator-initiated studies with Myozyme wereconducted:

- 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 three studies with Myozyme (with a follow up of at least 3 years in two studies and a median of23 months in the other study) suggested stabilisation or improvement of motor function and stabilisation of pulmonary function.

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 independentpatients and in those with less pronounced muscle weakness.

In two additional open-label clinical trials with Myozyme with a follow-up of 24 months, ten patientswith 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). Patientsreceived 20 mg/kg Myozyme once every two weeks for 26 weeks. All patients were freely ambulatoryand 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 alfa20-40 mg/kg once every two weeks for various periods of time between 6 months and 2.5 years. The pulmonary benefits observed in patients included a clinically meaningful improvement in FVC of 35% in one patient, and significant reductions in the number of hours of ventilator support needed in 2 patients. Benefits of treatment on motor function including the regaining of lost motor skills were observed in some patients. Only one patient became wheelchair-free. In this group of patients a variable response has also been seen with respect to motor function.

Pompe Registry

Medical or healthcare professionals are encouraged to register patients who are diagnosed with Pompedisease at www.PompeRegistry.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 monitorpatients 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) whoreceived 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}) rangedfrom 178.2 to 263.7 μg/ml for the 20 mg/kg and 40 mg/kg dose groups respectively. The mean area under the plasma concentration-time curve (AUC_{∞}) ranged from 977.5 to 1,872.5 μg•h/ml for the 20 mg/kg and 40 mg/kg dose groups. Mean plasma clearance (CL) was 21.4 ml/h/kg and mean volumeof distribution at steady state (Vss) was 66.2 ml/kg for both dose groups with small between-subject variability of 15% and 11%, respectively. Mean plasma elimination half-life ($t_{1/2}$) was 2.75 hours for the two dose groups.

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

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

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

The pharmacokinetics of alglucosidase alfa were studied in a population analysis of 32 late-onset Pompe disease patients from the randomized, double-blind, placebo-controlled study ranging in agefrom 21 to 70 years who received Myozyme 20 mg/kg once every two weeks. AUC_{∞} and C_{max} weresimilar 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 oftherapy

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

There was no evidence that IgG antibodies to alglucosidase alfa affected pharmacokinetics. Highermean 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 andearly delivery was observed. This effect was partly attributable to maternal toxicity, as a significant decrease in feed consumption and body weight gain was observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (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 medicinalproducts.

6.3 Shelf life

3 years

After dilution, an immediate use is recommended. However, chemical and physical in-use stability hasbeen 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 visibleparticles 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 roomtemperature (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 maycontain 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 localrequirements.

7. MARKETING AUTHORISATION HOLDER

Genzyme Europe B.V.
Paasheuvelweg 25
1105 BP AmsterdamThe
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 2006Date of
latest renewal: 29 March 2011

10. DATE OF REVISION OF THE TEXT 05/2019

Detailed information on this medicinal product is available on the website of the European MedicinesAgency 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 Corp. 45, 51, 76, 74 and 80 New York Avenue, Framingham, MA 01701, USA
Genzyme Flanders bvba, Cipalstraat 8, 2440 Geel, Belgium

Name and address of the manufacturers responsible for batch release

Genzyme Ltd., 37 Hollands Road, Haverhill, Suffolk CB9 8PU, United Kingdom Genzyme Ireland Ltd., IDA Industrial Park, Old Kilmeaden Road, Waterford, Ireland

The printed package leaflet of the medicinal product must state the name and address of themanufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this productin accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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 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 submittedat the same time.

SANOFI GENZYME

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This document is approved by The Executive Directorate of Pharmacovigilance, at SFDA