SAFETY INFORMATION PACKET

Myozyme® (alglucosidase alfa)

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

You are encouraged to report any adverse events via the national reporting system and all patients are encouraged to enrol in the Pompe Patient Registry

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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
HCP	Health care professional
IAR	Infusion-associated reaction
IOPD	Infantile Onset Pompe Disease
IV	Intravenous
LOPD	Late Onset Pompe Disease
PSPV	Patient Safety and Pharmacovigilance
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. Educate and minimize, when possible, the 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 Sanofi's Rare Disease Specialty Testing Program (RDSTP), for immunological testing, free of charge.

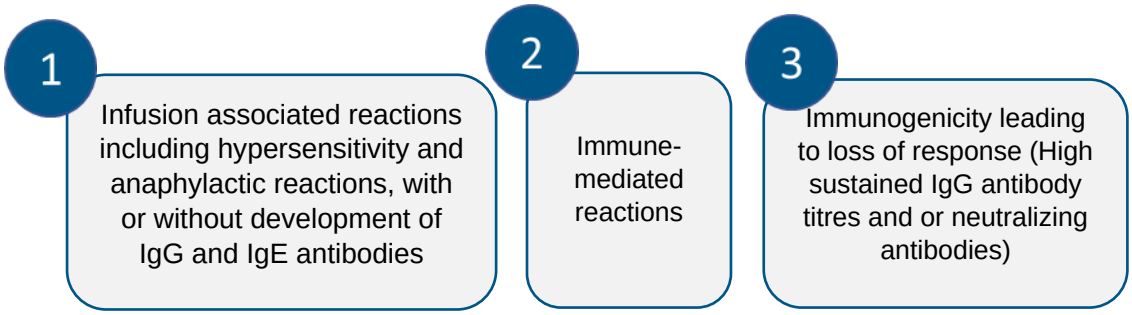
Myozyme and Pompe disease

Pompe disease is a lysosomal storage disorder 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 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 the identified risks

The following important identified 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 & Recommendations

Sanofi has established a post-marketing immunosurveillance program for Myozyme, to determine the extent of antibody formation against Myozyme and its clinical impact, if any (refer to section 3). The below summary is fully detailed in sections 1 & 3.

1) Collect baseline serum sample prior to the first infusion.

2) Monitor patients for IgG antibody formation periodically and based on their clinical phenotype.

    a. For Infantile Onset Pompe Disease (IOPD) patients, regular monitoring during first year of treatment (example: every 3 months) and subsequent monitoring dependent on clinical outcomes and antibody titer levels.

    b. For Late Onset Pompe Disease (LOPD) patients, antibody development should be assessed within 6 months after treatment start and subsequent monitoring as clinically warranted based on safety and efficacy considerations.

3) Collect samples for testing of inhibition of enzyme uptake or activity if patients experience a decrease in clinical benefit despite continued treatment with Myozyme.

4) Collect samples for testing of IgG and IgE antibodies, complement activation and tryptase for patients who experience moderate to severe or recurrent IARs suggestive of hypersensitivity reactions.

The SIP provides information on Sanofi's Rare Disease Specialty Testing Program (RDSTP). This Program provides antidrug IgG antibody and adverse event related immunogenicity testing services. These services are free of charge (refer to section 3).

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

The processes presented in this document serve as overall guidance but are subject to local medical practice and national rules and regulations.

KEY CONTACTS

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

  Please contact Local (or Global) Patient Safety and Pharmacovigilance at Sanofi:

  Local Patient Safety and Pharmacovigilance:
  Tel: +358 201 200 368
  E-mail: Pharmacovigilance.Finland@sanofi.com

  Global Patient Safety and Pharmacovigilance:
  E-mail: cl-cpv-receipt@sanofi.com

  or contact Finnish Health Authorities:
  webpage: www.fimea.fi
  Lääkealan turvallisuus- ja kehittämiskeskus Fimea
  Lääkkeiden haittavaikutusrekisteri, PL 55, 00034 FIMEA

- **For information how to access Sanofi's Rare Disease Specialty Testing services or other test-related questions for Myozyme**:

  Please contact Medical Services Department, Sanofi:

  E-mail: EUMedicalServices@sanofi.com

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

  Please contact your local Medical Information Department:

  Tel: +358 201 200 300
  E-mail: Pharmacovigilance.Finland@sanofi.com

1. Description of risks associated with Myozyme

Identified safety risks of Myozyme (alglucosidase alfa) treatment include:

- infusion associated reactions (IARs) including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies,
- immune-mediated reactions,
- immunogenicity leading to loss of response (High sustained IgG antibody titers and/or neutralizing antibodies).

1.1. Infusion-associated reactions including hypersensitivity and anaphylactic reactions with or without development of IgG and IgE antibodies

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 but knowledge has improved over the years. 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 which is not understood to date
- Direct stimulation of mast cells by drug with release of histamine
- Higher infusion rate, i.e. protein load in a shorter period

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) (3, 4, 5, 6). 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

System organ class	Sign/Symptom*
Musculoskeletal	Arthralgia Muscle spasms Myalgia
Respiratory	Apnoea Bronchospasm Cough Dyspnoea Hypoxia Pharyngeal oedema Reduced/decreased oxygen saturation Respiratory arrest Respiratory distress Stridor Tachypnoea Throat irritation Throat tightness Wheezing
Cardiovascular	Bradycardia Cardiac arrest Cyanosis Flushing Hypertension Hypotension Paleness Palpitations Tachycardia Vasoconstriction
Cutaneous	Blister Erythema Hyperhidrosis Livedo reticularis Pruritus Rash Transient skin discoloration Urticaria
Nervous system	Agitation Dizziness Headache Pain Paraesthesia Restlessness Somnolence Tremor

Gastrointestinal	Abdominal pain Diarrhoea Dyspepsia Dysphagia Nausea Retching Vomiting
Eye	Conjunctivitis Lacrimation increased Periorbital oedema
General disorders and administration site conditions	Angioedema Asthenia Chest discomfort/pain Chills Facial oedema Fatigue Feeling hot/cold Infusion site reactions (including pain, swelling, induration, extravasation, erythema, urticaria, and pruritus) Irritability Malaise Peripheral oedema Peripheral coldness Pyrexia
*Signs and symptoms are in alphabetical order and not in order of frequency.	

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.

IARs and immunogenicity

In clinical trials, the majority of the Pompe disease patients (approximately 90%) developed IgG antibodies to Myozyme, generally within 3 months of initiation of treatment (3,4,5,6). Similar proportions of patients treated in the commercial setting have developed IgG antibodies to Myozyme. A trend toward decreasing IgG antibody titers over time was observed in the majority of patients.

A correlation was not observed between the onset of IARs and the time of IgG antibody formation. IARs can occur across all levels of antibody titers, however a trend was observed for more frequent IARs with higher titers of IgG antibody (3,4,7). A tendency was observed for IOPD patients treated with a higher dose (40 mg/kg) to develop higher titers of IgG antibodies. Infantile-onset patients who develop high antibody titers appear to be at higher risk for developing more frequent IARs (5). In the LOPD study however, there was no apparent association between higher IgG titers and occurrence of IARs (3,4).

Patients who develop IgE antibodies to Myozyme appear to be at a higher risk for the occurrence of IARs and/or anaphylactic reactions when Myozyme is readministered. 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 (or desensitization procedures) and have continued to receive Myozyme under close clinical supervision (8,9).Patients with moderate to severe and recurrent IARs should be evaluated for Myozyme specific IgG and IgE antibodies, as well as skin testing, a more sensitive measure to detect IgE antibodies, which is recommended for patients who experienced significant hypersensitivity reactions (see section 3). It is unknown who will develop immediate hypersensitivity reactions (IgE positive) to Myozyme.

Patients who have experienced severe hypersensitivity reactions (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 who developed high IgG antibody titres, especially patients with infantile onset Pompe disease.
- Patients who have experienced previous IARs.

1.2. Immune mediated-reactions

Severe cutaneous and systemic immune-mediated reactions have been reported in some patients treated with Myozyme. 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 (10, 11).

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 leading to loss of response (high sustained IgG antibody titters and/or neutralizing antibodies)

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) (12).

1.3.1. Anti-rhGAA IgG antibodies including inhibitory neutralizing antibodies

The effect of IgG antibody formation on Myozyme efficacy has been evaluated in clinical trials and over years of post-marketing experience. In clinical studies, the majority of patients developed IgG antibodies to Myozyme and seroconversion typically occurred within 3 months of treatment.

The clinical impact of IgG antibodies on Myozyme efficacy is multifactorial, however the development of high and sustained IgG titers (HSAT) is a contributing factor.

1. With regards to IOPD, a tendency was observed for patients treated with a higher dose (40 mg/kg) to develop higher titers of IgG antibodies (5). The development of HSAT have been shown in Myozyme treated patients to have poor outcome. HSAT were defined as titers ≥51 200 at 2 or more timepoints after 6 months on Myozyme treatment that were at least 12 weeks apart. Furthermore, CRIM status (Cross Reactive Immunologic Material: endogenous GAA protein) is a risk factor to develop HSAT. This risk is higher among CRIM negative patients versus CRIM-positive patients and is a contributing factor to a poor outcome. Such prolonged HSAT could result in suboptimal dosing of drug to patients due to immune complex formation. HSAT has also occurred in a limited number of CRIM-positive patients (13,14,15).

2. With respect to LOPD patients, the majority showed either stabilizing or decreasing antibody titers over time. Patients with LOPD produce endogenous enzyme and are considered CRIM-positive. These patients are generally not at risk for developing HSAT and very few make high ADA titers which then decrease over time. Thus, the impact of IgG antibodies is more limited for LOPD patients (3,7).

A small number of the IgG positive patients treated with Myozyme in clinical trials and/or the post marketing setting were tested positive for inhibition of enzyme activity and/or uptake when tested

in-vitro. 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. Neutralizing antibodies, particularly those which inhibit drug cellular uptake, have developed in some IOPD patients treated with Myozyme and generally were associated with high ADA titers. CRIM-negative IOPD patients are at risk for developing HSAT and neutralizing antibodies with documented loss of clinical response (13,14,15).

Recommendation

IgG antibody titers should be monitored periodically based on clinical phenotype:

1. Collect baseline serum sample collection prior to the first infusion.
2. For IOPD patients, regular monitoring during first year of treatment (example: every 3 months) is suggested and subsequent monitoring depending on clinical outcomes and antibody titers level.
3. For LOPD patients, antibody development should be assessed within 6 months after treatment start and subsequent monitoring as clinically warranted based on efficacy considerations.
4. Collect samples for testing of inhibition of enzyme uptake or activity if patients experience a decrease in clinical benefit despite continued treatment with Myozyme.

Please refer to section 3 for IgG and neutralizing antibody testing.

1.3.2. Immunomodulation in patients with IOPD: benefits and risks

Immunogenicity data from clinical trials and published literature in CRIM-negative infantile-onset patients (IOPD) suggests that the administration of immune tolerance induction (ITI) regimen given to Myozyme naive patients (prophylactic ITI) may be effective in preventing or reducing the development of High Sustained Antibody Titer (HSAT) against Myozyme. Data from a small number of patients with HSAT, with or without neutralizing activity, showed limited ITI treatment effect. Better treatment responses were observed in younger patients with less advanced disease who received prophylactic ITI before development of HSAT, which suggests that early initiation of ITI can result in improved clinical outcomes (13,14,15). ITI regimens may need to be tailored to individual patient needs (see SmPC section 5.1).

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

Key points

- As Myozyme is a therapeutic protein there is a potential for an immunologic response. IgG antibodies to alglucosidase alfa generally develop within 3 months of treatment initiation.
- IARs, with or without the development of IgG or IgE antibodies, 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.
- 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.
- Patients treated with Myozyme should be monitored for IgG antibody formation periodically based on clinical phenotype and in case of clinical decline.
- Immune-mediated reactions including severe cutaneous and systemic reactions have been reported in some cases.

2. Clinical management of identified risks (2,16–22)

2.1. Pre-infusion stage

The complex underlying medical problems of Pompe disease must be taken into account prior to initiating ERT with Myozyme. 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 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).

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 (18,19,22).

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 (21).

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. 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* (2,16,17)

- 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.

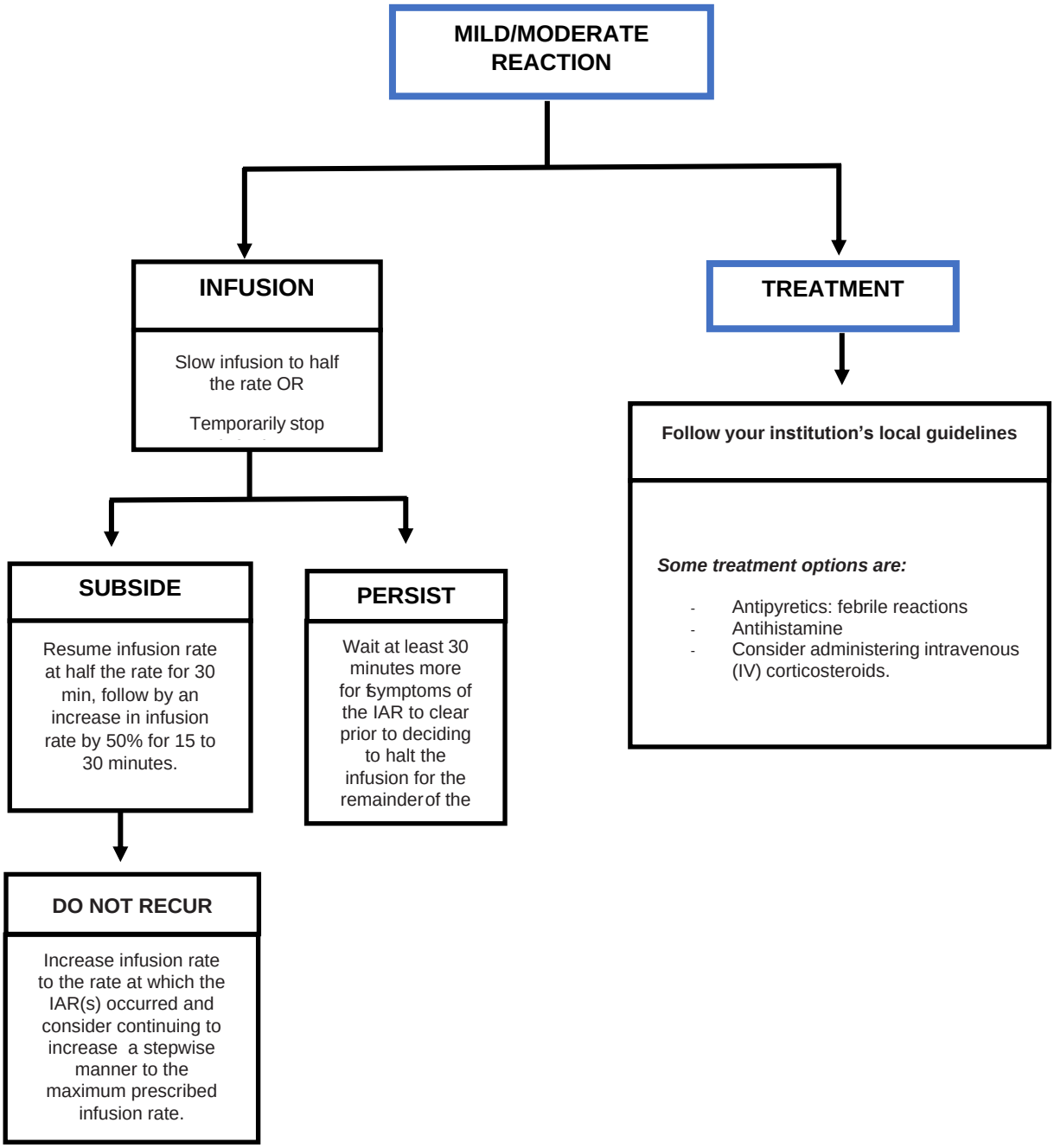
Vital signs should be obtained at the end of each step.

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.
- Administer IV fluids as necessary to maintain normal vital signs (e.g., blood pressure).

*
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



2.2.3. Severe reactions*: hypersensitivity/anaphylactic reactions including anaphylactic shock and IgE-mediated hypersensitivity reaction [17, 18, 22]

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.
- 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.

* **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.

Treatment recommendations for severe reactions

- The administration of Myozyme should be immediately discontinued and appropriate medical treatment should be initiated, as described below.

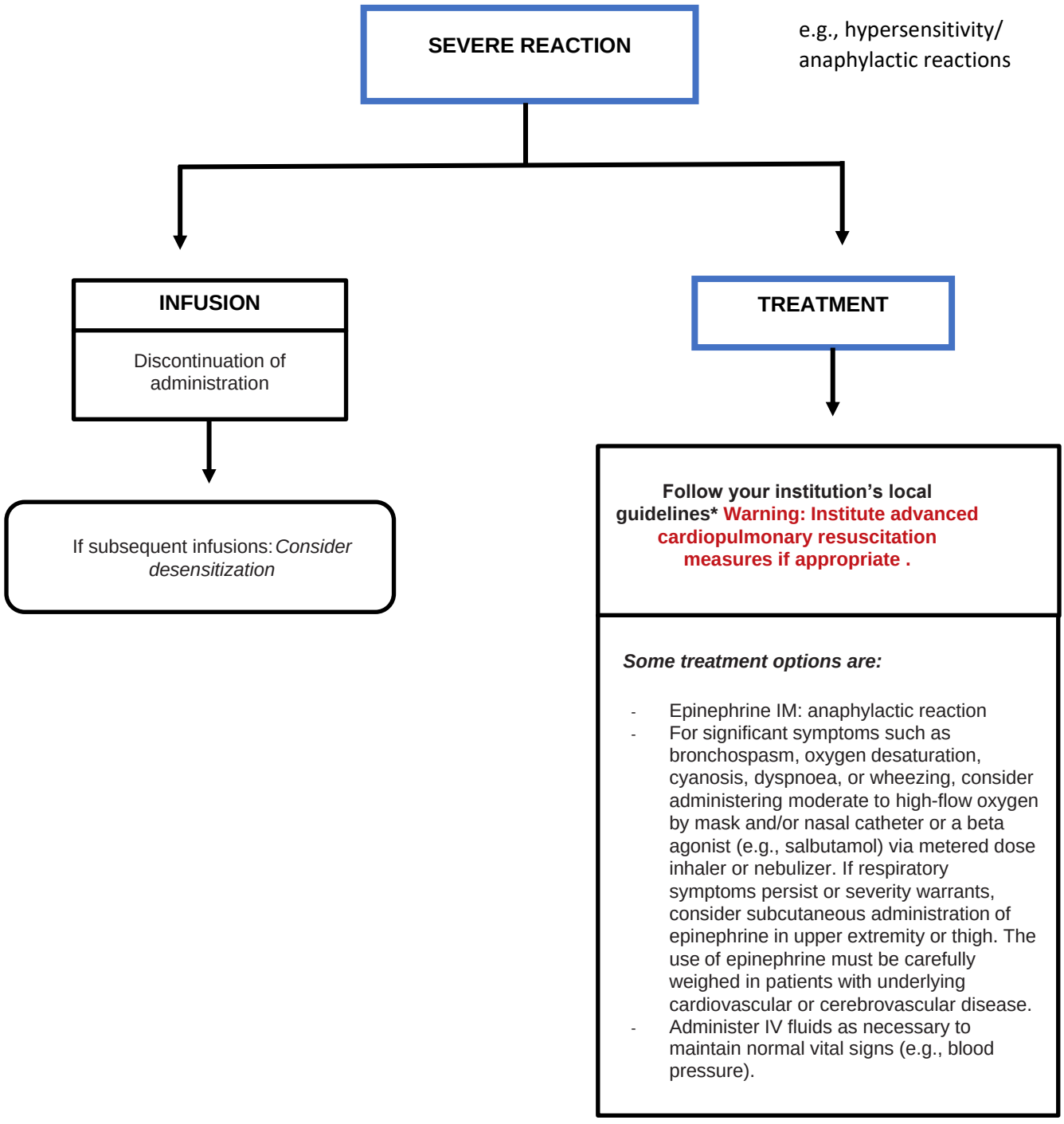
  - Administration of epinephrine IM in upper extremity or thigh is generally indicated for life-threatening anaphylactic reactions. Although in general, careful consideration should be given to the contraindications to the use of epinephrine. Contraindications should always be weighed against the benefit 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.

- Please contact the Medical Information department of Sanofi for bibliography on 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.*

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. Immunology Testing

3.1. Description

As part of the general post-approval safety surveillance, Sanofi has initiated an immunosurveillance program for Myozyme to determine the extent of antibody formation against Myozyme to understand the clinical impact, if any. There are currently no marketed tests for antibodies against Myozyme; however, a free testing service is provided by Sanofi (see Table 4). Please contact your local Sanofi- representative or Sanofi- Medical Services via e-mail at EUMedicalServices@sanofi.com for information how to access Sanofi-'s RDSTP.

3.1.1. Immunosurveillance program: IgG antibody testing including neutralizing antibodies

As described in section 1, development of IgG may be linked to IARs in some patients and development of HSAT has been associated to poor efficacy outcomes, especially for the patients with infantile onset. Thus, the below recommendations for IgG testing are suggested.

Recommendation

1) Baseline serum sample collection prior to the first infusion.

2) Periodic monitoring for IgG antibody formation based on patients' clinical phenotype.

   a) For IOPD patients, regular monitoring during first year of treatment (example: every 3 months) and subsequent monitoring dependent on clinical outcomes and antibody titer levels.

   b) For LOPD patients, antibody development within 6 months after treatment start and subsequent monitoring as clinically warranted based on safety and efficacy considerations.

3) Testing for inhibition of enzyme uptake or activity if patients experience a decrease in clinical benefit despite continued treatment with Myozyme.

3.1.2. Immunology testing for moderate/severe infusion associated reactions: IgG, IgE, complement activation and serum tryptase testing

Testing for IgG and IgE antibodies is typically performed for moderate or severe or recurrent IARs suggestive of hypersensitivity reactions. Some patients who were evaluated tested positive for Myozyme-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, collect samples for testing for IG and IgE antibodies, complement activation and tryptase for patients who experience moderate to severe or recurrent IARs suggestive of hypersensitivity reactions.
- 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. Samples for IgG ideally should be collected at trough, so before the next infusion.

3.1.3. Skin testing [19, 20]

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):

A. IAR 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.
B. 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 Myozyme, 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.

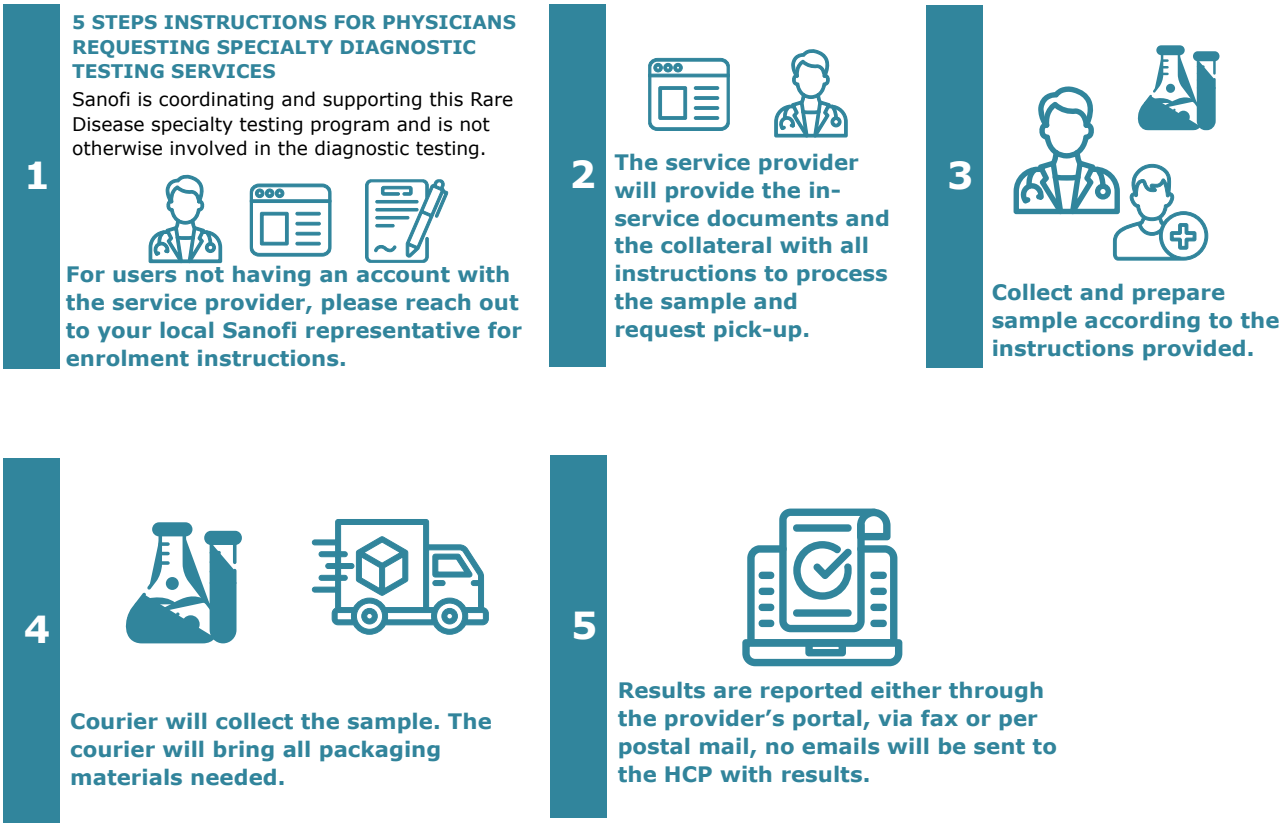
Test[a]	Indication for testing	Sample Type	Frequency	Collection Time[b]
Skin testing	IARs suggestive of IgE mediated reaction with persistent symptoms or for confirmation of IgE results	Prick/puncture testing	Ad hoc (after IAR)	Min. of 48h after infusion and preferably >3 weeks after anaphylactic episode
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/ neutralizing 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'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, neutralizing 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 titers, 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, neutralizing 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



Please contact Sanofi EU Medical Services for collection, packaging, and shipping of blood samples. Contact details are provided in ***KEY CONTACTS***.

4. Reporting adverse events

Reporting adverse events 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 adverse events via the national reporting system or to contact Sanofi Patient Safety and Pharmacovigilance (PSPV) Local (or Global) department. For full contact details on reporting adverse reactions please refer to ***KEY CONTACTS***.

5. Pregnancy & breastfeeding

There is limited data from the use of Myozyme in pregnant women. Studies in animals have shown reproductive toxicity (SmPC section 5.3). Myozyme should not be used during pregnancy unless the clinical condition of the woman requires treatment with Myozyme (SmPC section 4.6).

Limited data suggest that Myozyme is excreted in breast milk in very low concentrations. No clinical effect is expected in a breastfed infant due to low breast milk transfer and poor bioavailability. Breastfeeding during treatment with Myozyme may therefore be considered. As a precautionary measure, breastfeeding interruption for the first 24 hours after treatment may be considered.

Reporting information on drug exposure in pregnancy to Sanofi Patient Safety and 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 will follow-up on all reported pregnancy cases. Sanofi 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. Pompe Registry

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

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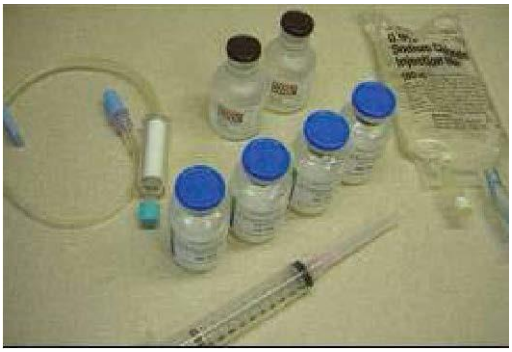
8. Appendices

Appendix 1. Preparation of Myozyme

Use aseptic technique during preparation.

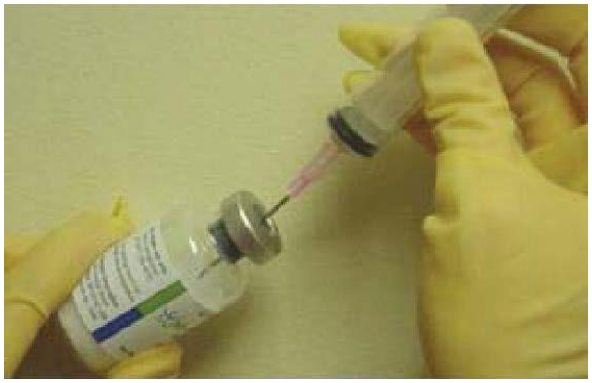
The following items are required for the preparation and administration of Myozyme® (alglucosidase alfa).

1. Required quantity of Myozyme vials based on the patient's dose.
2. Intravenous administration set with 0.2 µm low protein-binding in-line filter.
3. Sterile water for injection, for reconstitution.
4. 9 mg/mL (0.9%) sodium chloride for injection, for dilution
5. Syringes for reconstitution and dilution.
6. Needles with diameter not larger than 20 G for reconstitution and dilution.
7. Additional supplies required per institution protocol.



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

A. 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:

1. **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

2. **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

B. 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

C. 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 Medical Information.
   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.

D. 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

E. 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.
F. Remove airspace from the infusion bag to minimize particle formation due to the sensitivity of Myozyme to air-liquid interfaces.
G. Also remove an equal volume of sodium chloride 9 mg/ml (0.9%) solution for injection, that will be replaced with reconstituted Myozyme.
H. 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.
I. Gently invert or massage the infusion bag to mix. Do not shake.
J. 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.

A. Explain the administration procedure to the patient.
B. Obtain vital signs, including blood pressure, pulse, respiratory rate, and temperature prior to the infusion.
C. Obtain IV access. Antecubital, wrist, or hand veins may be used for access. Central access is also an option.
D. Draw any required blood work if applicable and flush line with 9 mg/mL (0.9%) sodium chloride for injection.
E. 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.
F. 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.
G. Connect the Myozyme solution administration set to the 0.2 µm in-line low protein- binding filter set and prime the line.
H. Connect the Myozyme solution line to the lowest additive port on the patient's primary administration set.
I. Infusions should be administered in a step-wise manner using an infusion pump.
J. 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.
K. 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.