SAFETY INFORMATION PACKET

Myozyme® (alglucosidase alfa)

Ireland

Risk Minimisation Information for Healthcare Professionals.
This educational material is part of the marketing authorisation and has been approved by the Health Products Regulatory Authority (HPRA)

Guidance for healthcare professionals on risks associated with alglucosidase alfa administration, clinical risk management and immunology testing

Essential Non-Promotional Information

Do not discard

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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	Healthcare Professional
IAR	Infusion-Associated Reaction
IOPD	Infantile Onset Pompe Disease
IV	Intravenous
LOPD	Late Onset Pompe Disease
rhGAA	Recombinant human acid alfa-glucosidase
SIP	Safety Information Packet
SmPC	Summary of Product Characteristics

SUMMARY

Aim of the Safety Information Packet

The alglucosidase alfa Safety Information Packet (SIP) is a supplementary educational material provided to physicians involved in managing patients with Pompe disease treated with alglucosidase alfa. Treating physicians may make this material available to other healthcare 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 minimise, when possible, the known risks associated with alglucosidase alfa treatment.
2. Guide HCPs on the clinical management of these risks.
3. Guide HCPs to carry out immunological testing which will help to further characterise the potential mechanism of infusion-associated reactions (IARs) and hypersensitivity reactions.

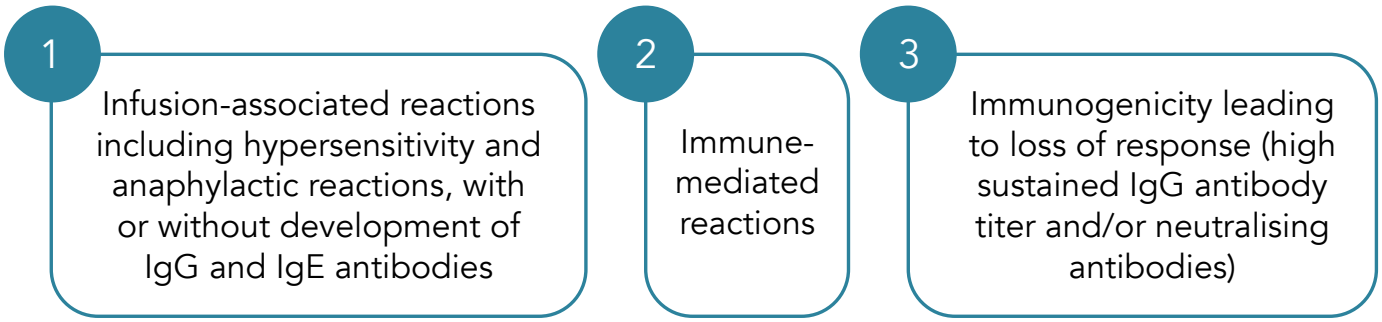
Alglucosidase alfa and Pompe disease

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.

Alglucosidase alfa contains the active ingredient alglucosidase alfa (recombinant human acid α-glucosidase [rhGAA]). Alglucosidase alfa is indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency). Alglucosidase alfa is indicated in adults and paediatric patients of all ages. The recommended dose regimen of alglucosidase alfa is 20 mg/kg of body weight administered once every 2 weeks.

Description of identified risks

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



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

Immunology testing & Recommendations

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

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 titre level.
   b) For Late Onset Pompe Disease (LOPD) patients, antibody development assessment within 6 months of 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 alglucosidase alfa.
4) Collect samples for testing of IgG and IgE antibodies, for patients who experience moderate to severe or recurrent IARs suggestive of hypersensitivity reactions.

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

For further information in relation to any aspect of alglucosidase alfa treatment and its associated procedures:

Please contact the Sanofi Medical Information Department. Telephone: 01 403 5600

Email: IEmedinfo@sanofi.com

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

1. Description of risks associated with alglucosidase alfa

Identified safety risks of 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 neutralising 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 (alglucosidase alfa). 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 alglucosidase alfa (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 post-marketing setting developed anaphylactic shock and/or cardiac arrest during alglucosidase alfa 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. Please refer to section 4.8 of the SmPC for complete information on the safety profile of alglucosidase alfa.

IARs and immunogenicity

In clinical trials, the majority of the Pompe disease patients (approximately 90%) developed IgG antibodies to alglucosidase alfa, generally within 3 months of initiation of treatment (3,4,5,6). Similar proportions of patients treated in the post-marketing setting have developed IgG antibodies to alglucosidase alfa. 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 alglucosidase alfa appear to be at a higher risk for the occurrence of IARs and/or anaphylactic reactions when alglucosidase alfa is re-administered. Therefore, these patients should be monitored more closely during administration of alglucosidase alfa. Some IgE-positive patients were successfully rechallenged with alglucosidase alfa using a slower infusion rate at lower initial doses (or desensitisation procedures) and have continued to receive alglucosidase alfa under close clinical supervision (8,9). Patients with moderate to severe and recurrent IARs should be evaluated for alglucosidase alfa-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. It is unknown who will develop immediate hypersensitivity reactions (IgE-positive) to alglucosidase alfa.

Patients who have experienced severe hypersensitivity reactions (and in particular anaphylactic reactions) should be treated with caution when re-administering alglucosidase alfa. For more information and guidance on infusion management, please refer to section 2.

Table 2 presents a list of patients at increased risk of complication of IARs.

Table 2. Patients at increased risk of complications associated with IARs.

- Patients with any acute underlying febrile illness.
- Patients with advanced stage 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 alglucosidase alfa (at a higher risk for occurrence of anaphylaxis and severe hypersensitivity reactions).
- Patients receiving alglucosidase alfa at higher infusion rates.
- Patients with infantile-onset Pompe disease who developed high IgG antibody titers.
- Patients who have experienced previous IARs.
- Patients who have temporarily interrupted alglucosidase alfa 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 alglucosidase alfa. 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 necrotising skin lesions, possibly immune-mediated, have been reported with alglucosidase alfa. A 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 alglucosidase alfa. These reactions occurred several weeks to 3 years after initiation of alglucosidase alfa infusions.

Nephrotic syndrome was observed in a few patients with Pompe disease treated with alglucosidase alfa and who had high IgG antibody titers (≥ 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 titers.

Patients should be monitored for the development of systemic immune–mediated reactions. If immune-mediated reactions occur, discontinuation of the administration of alglucosidase alfa should be considered, and appropriate medical treatment initiated. The risks and benefits of re-administering alglucosidase alfa following an immune-mediated reaction should be considered.

Some patients have been successfully rechallenged and continued to receive alglucosidase alfa under close clinical supervision.

1.3. Immunogenicity leading to loss of response (high sustained IgG antibody titers and/or neutralising antibodies)

As a therapeutic protein, alglucosidase alfa 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 neutralising antibodies

The effect of IgG antibody formation on alglucosidase alfa 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 alglucosidase alfa and seroconversion typically occurred within 3 months of treatment.

The clinical impact of IgG antibodies on alglucosidase alfa 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 to have a poor outcome in alglucosidase alfa-treated patients. HSAT were defined as titers ≥51,200 at 2 or more timepoints after 6 months on alglucosidase alfa 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 stabilising 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 alglucosidase alfa 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 titers than patients who remained negative for uptake inhibition in infantile-onset and late-onset studies. Neutralising antibodies, particularly those which inhibit drug cellular uptake, have developed in some IOPD patients treated with alglucosidase alfa and generally were associated with high ADA titers. CRIM-negative IOPD patients are at risk for developing HSAT and neutralising 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 titer levels.
3. For LOPD patients, antibody development should be assessed within 6 months of 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 alglucosidase alfa.

Please refer to section 3 for IgG and neutralising 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 alglucosidase alfa naive patients (prophylactic ITI) may be effective in preventing or reducing the development of High Sustained Antibody Titers (HSAT) against alglucosidase alfa. Data from a small number of patients with HSAT, with or without neutralising 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 may be at further increased risk of developing severe infections and vigilance is recommended. Fatal and life-threatening respiratory infections have been observed in some of these patients.

Key points

- As alglucosidase alfa 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 alglucosidase alfa infusion.
- Patients who develop IgE antibodies should be monitored more closely during administration of alglucosidase alfa since they appear to be at a higher risk for the occurrence of IARs and/or anaphylactic reactions.
- Patients treated with alglucosidase alfa 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[2,16-21]

2.1. Pre-infusion stage

The complex underlying medical problems of Pompe disease must be taken into account prior to initiating ERT with alglucosidase alfa. Patients with an acute underlying illness at the time of alglucosidase alfa infusion appear to be at greater risk for IARs. Careful consideration should be given to the patient's clinical status prior to administration of alglucosidase alfa. All patients should be clinically evaluated prior to each alglucosidase alfa infusion to rule out any acute or underlying illness.

Careful consideration should be given to the potential short and long-term effects of antihistamines, antipyretics and long-term repeat use of corticosteroids, especially in paediatric patients. Dosing recommendations for such treatments should be in line with individual Summaries of Product Characteristics (SmPCs). Please refer to www.medicines.ie or www.hpra.ie for the full prescribing information. Electronic versions of this Safety Information Packet can be found on www.hpra.ie, enter "Myozyme" in the search box and then click "EdM" next to the medicine.

2.1.1. 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 (20).
- 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 (18,19,21).

2.2. Alglucosidase alfa 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 alglucosidase alfa 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 alglucosidase alfa.
- 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**, consider continuing to increase rate in a stepwise manner to the maximum prescribed infusion rate.
- 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).
- Please see Figure 1 for further details.

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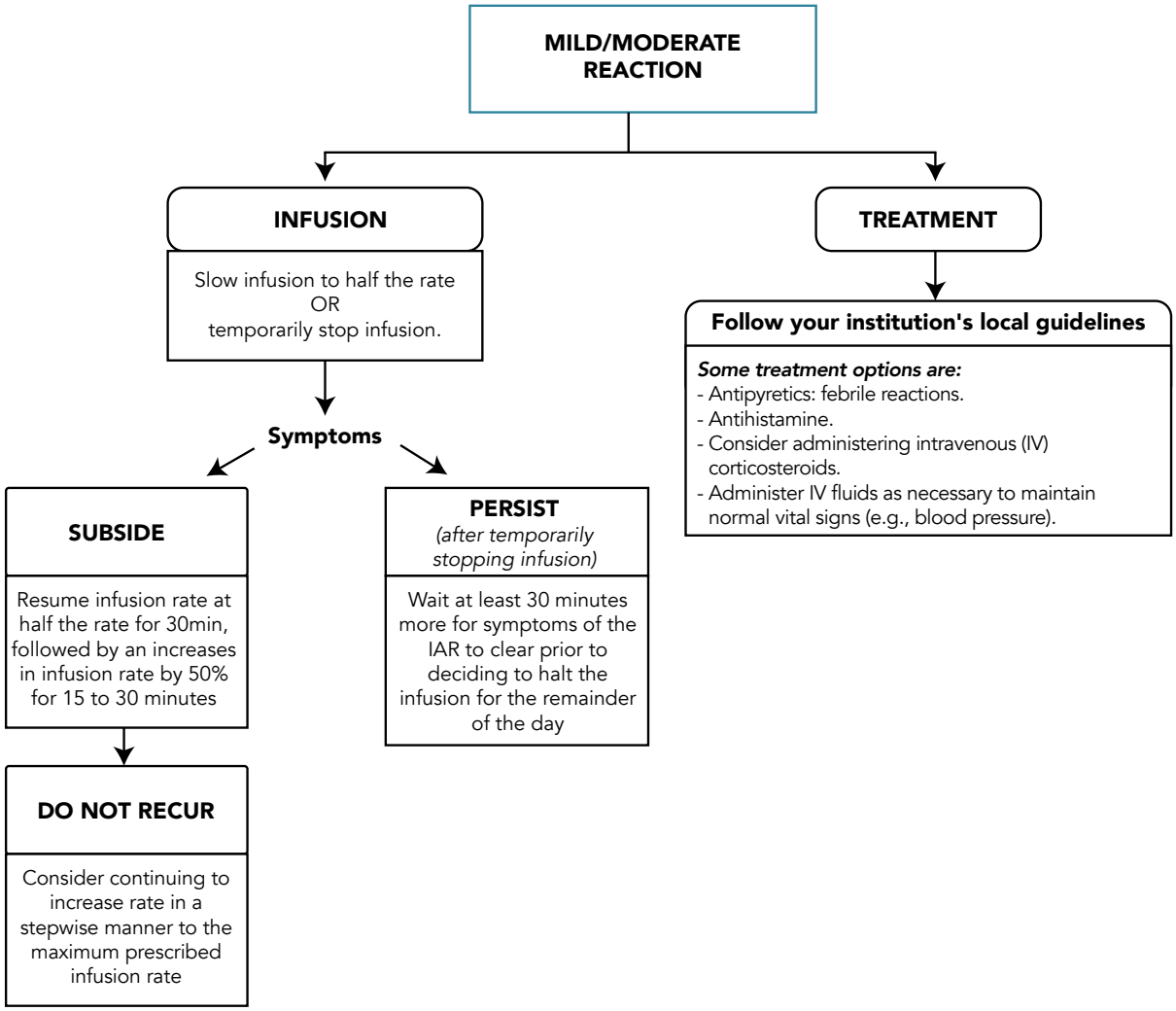
* **These definitions serve as guidelines only based on CDSIC SDTM standard terminology v3.1.1. Overall severity assessment is at the discretion of the treating physician:**
Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does 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[17,18,21]

Warning: Serious hypersensitivity reactions, including life-threatening anaphylactic reactions have been observed in patients during alglucosidase alfa infusion, some of which were IgE-mediated. Some patients developed anaphylactic shock and/or cardiac arrest during alglucosidase alfa infusion that required life-support measures. Medical support measures, including **cardiopulmonary resuscitation equipment,** should be readily available when alglucosidase alfa 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 recognised. Because of the potential for severe hypersensitivity or anaphylactic reactions, appropriate medical support, including cardiopulmonary resuscitation equipment, should be readily available when alglucosidase alfa 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.

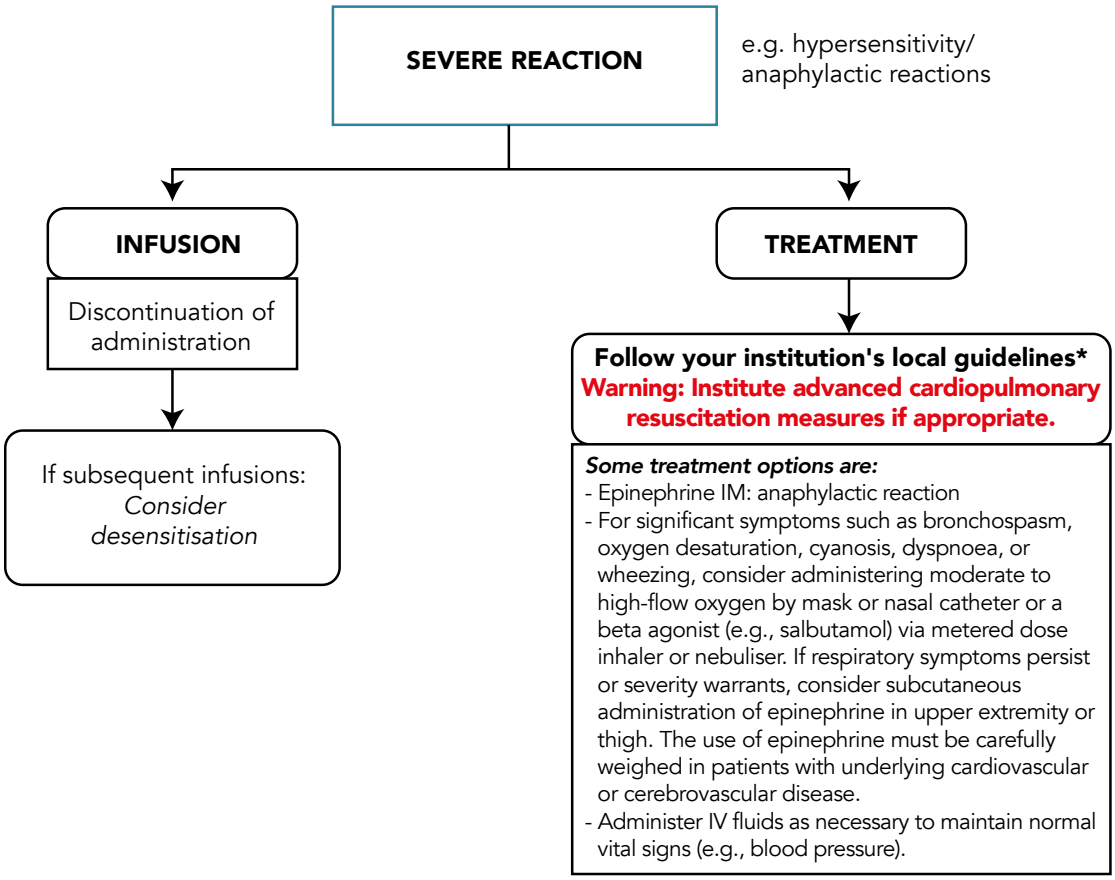
** **This definition serves as guideline only based on CDSIC SDTM standard terminology v3.1.1. Overall severity assessment is at the discretion of the treating physician:**
Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require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

- The risks and benefits of re-administering alglucosidase alfa following an anaphylactic or severe hypersensitivity reaction should be considered. Some patients have been rechallenged and have continued to receive alglucosidase alfa 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

- The administration of alglucosidase alfa 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 nebuliser.
  - 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 maximise inotropy and minimise 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 reactions.
- 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 alglucosidase alfa infusion by appropriate medical personnel familiar with Pompe disease and potential reactions to alglucosidase alfa. In clinical trials, patients were monitored for 2 hours at the end of the alglucosidase alfa 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

3.1.1. Immunosurveillance programme: IgG antibody testing including neutralising antibodies

As described in section 1, development of IgG may be linked to IARs in some patients and development of HSAT has been associated with poor efficacy outcomes, especially for infantile-onset patients. 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 of 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 alglucosidase alfa.

3.1.2. Circulating immune complex testing

In the event a patient exhibits signs or symptoms suggestive of systemic immune-mediated reactions 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.

Table 4. Clinical immunology testing characteristics.

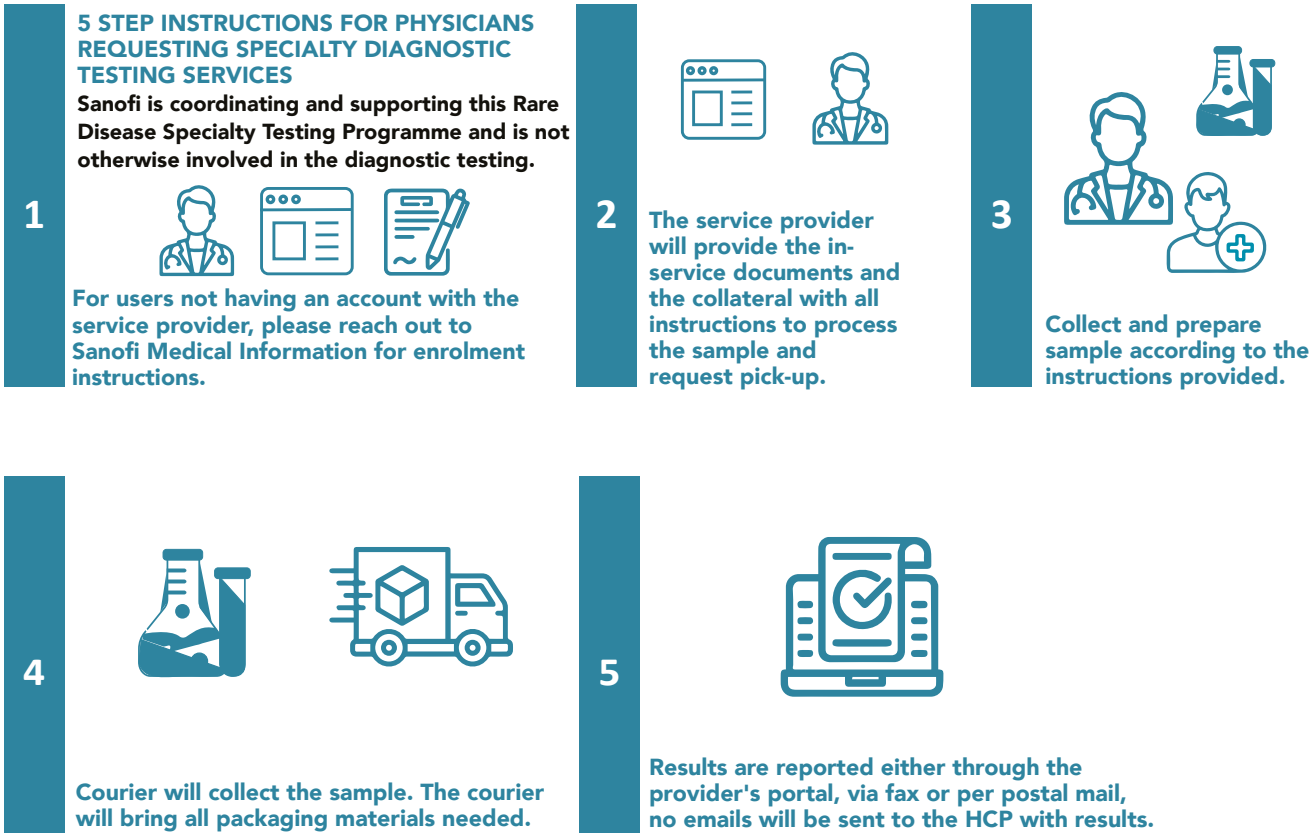
Test[a]	Indication for testing	Sample Type	Frequency	Collection Time[b]
IgG[c]	Routine monitoring	Serum-Frozen Whole blood (received within 24 hours of collection)	Routine monitoring	Sample should be pre-infusion or ≥3 days post-infusion
IgG/inhibitory antibody	Decreased response to treatment or lack of effect	Serum-Frozen Whole blood (received within 24 hours of collection)	Ad hoc (as needed)	Sample should be pre-infusion or ≥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

[a] Sanofi - Rare Disease Specialty Testing Programme with Labcorp offers a service free of charge for collection, packaging and shipping of blood samples to their Labcorp central laboratory. This service applies to all tests performed as part of an IAR investigation (including IgG antibody, IgE antibody, inhibitory antibody) and to all clinical samples for routine IgG monitoring.
[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, and inhibitory antibody) and to all clinical samples for routine post-marketing analysis and reporting (figure 3)

Figure 3. Procedure for testing.



Please contact Sanofi Medical Information department for collection, processing, packaging and shipping of blood samples.

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 appropriate national reporting system and contact Sanofi.

Please report suspected adverse drug reactions (ADRs) to the HPRA via the website: www.hpra.ie

Suspected adverse reactions should also be reported to Sanofi:

Tel: 01 403 5600. Email: IEPharmacovigilance@sanofi.com

For further information in relation to any aspect of alglucosidase alfa treatment and its associated procedures.

Please contact the Sanofi Medical Information Department. Telephone: 01 403 5600

Email: IEmedinfo@sanofi.com

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