SAFETY INFORMATION PACKET

Myozyme® (alglucosidase alfa)

Ireland

Risk Minimisation Information for Healthcare Professionals

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
CRIM	Cross Reactive Immunologic Material
ERT	Enzyme Replacement Therapy
GAA	Acid α-glucosidase
HCP	Healthcare 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 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. Minimise 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 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

Sanofi-Genzyme 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.).

- 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 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.).

Please contact the Sanofi-Genzyme Medical Information Department for information on how to access the Rare Disease Specialty Testing services or other test-related questions for alglucosidase alfa. Contact details are provided on page 7.

KEY CONTACTS

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-Genzyme.

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-Genzyme:

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-Genzyme Medical Information Department.
Telephone: 01 403 5600
Email: IEmedinfo@sanofi.com

1. Description of risks associated with Alglucosidase alfa

Identified safety risks of 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 (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. 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 alglucosidase alfa (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 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 (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 alglucosidase alfa.

Patients who have experienced IARs (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. For more information on alglucosidase alfa 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 alglucosidase alfa (at a higher risk for occurrence of anaphylaxis and severe hypersensitivity reactions).
- Patients receiving alglucosidase alfa at higher than recommended 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 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 (<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 alglucosidase alfa. 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 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 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

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) (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 alglucosidase alfa 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 titres, 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 alglucosidase alfa. The cause of a poor clinical response in these patients is thought to be multi-factorial.

Some 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. 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 alglucosidase alfa 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 alglucosidase alfa 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 alglucosidase alfa using a slower infusion rate at lower initial doses (in line with desensitisation recommendations) 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 alglucosidase alfa 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 alglucosidase alfa 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 alglucosidase alfa in a few infantile-onset patients with underlying cardiac hypertrophy, possibly associated with fluid overload with intravenous administration of alglucosidase alfa.

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 alglucosidase alfa infusion.
- Immune-mediated reactions including severe cutaneous and systemic reactions have been reported in some cases.
- As alglucosidase alfa 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 alglucosidase alfa 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 alglucosidase alfa 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 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.

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. 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[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.

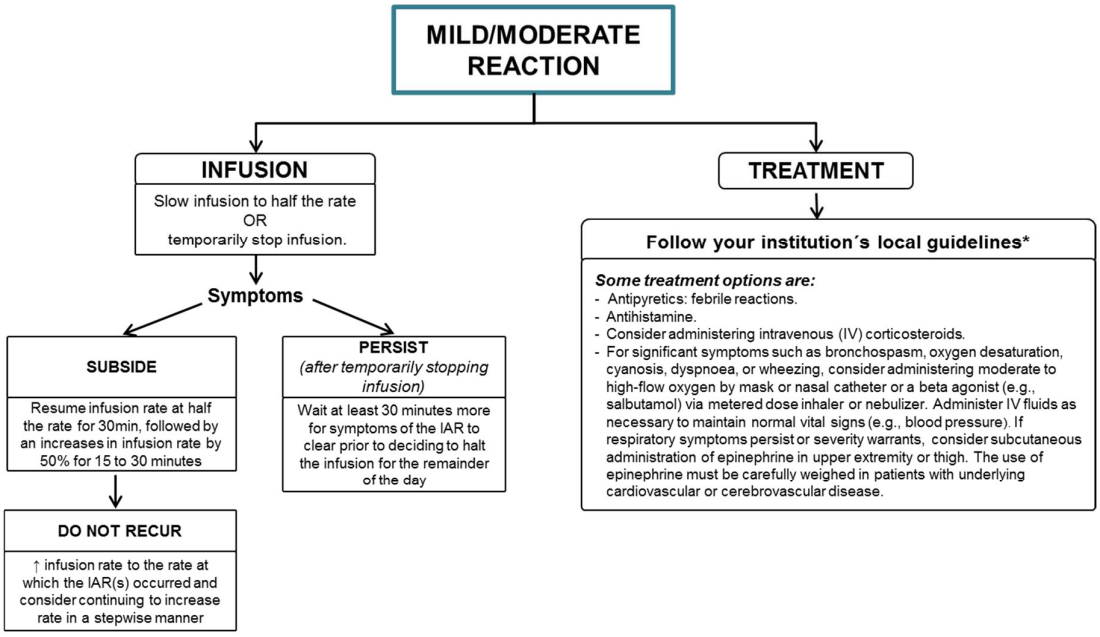
Vital signs should be obtained at the end of each step.

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 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.

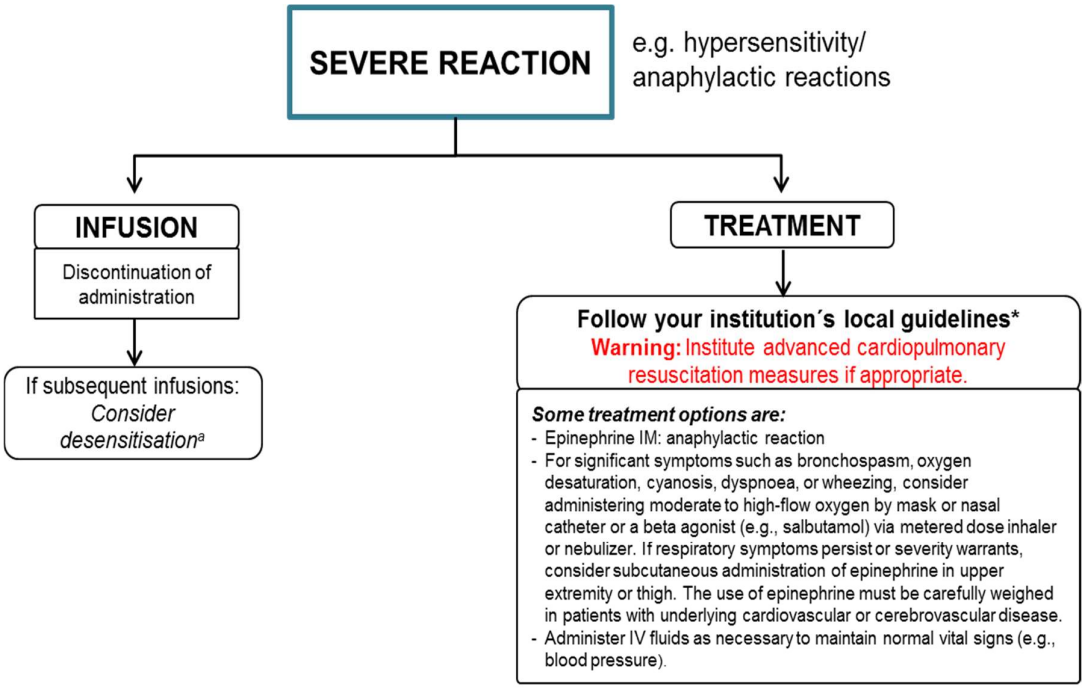
[2] **This definition serves as guideline only based on CDSIC SDTM standard terminology v3.1.1. Overall severity assessment is at the discretion of the treating physician:**
Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require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

- 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

- Immediate discontinuation of the administration of alglucosidase alfa 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 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 reaction.
- Detailed recommendations for desensitisation procedures will be made available to treating physicians upon request. Please contact Sanofi-Genzyme Medical Information Department for desensitisation recommendations. Contact details are provided on page 7**.**
- 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 Sanofi-Genzyme Global Pharmacovigilance for desensitisation recommendations.*

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. Testing

3.1. Description (table 4)

3.1.1. Immunosurveillance programme: 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 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 alglucosidase alfa 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 programme for alglucosidase alfa to determine the extent of antibody formation of alglucosidase alfa 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 the Sanofi-Genzyme Medical Information Department for information on how to access the Rare Disease Specialty Testing services. Contact details are provided on page 7.

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 alglucosidase alfa.
- 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 alglucosidase alfa under close clinical supervision.

Recommendation: To further characterise 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 the Sanofi-Genzyme Medical Information Department for information on how to access Sanofi-Genzyme's Rare Disease Specialty Testing services. Contact details are provided on page 7.

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 alglucosidase alfa 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 alglucosidase alfa 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 alglucosidase alfa 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.

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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 their 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.

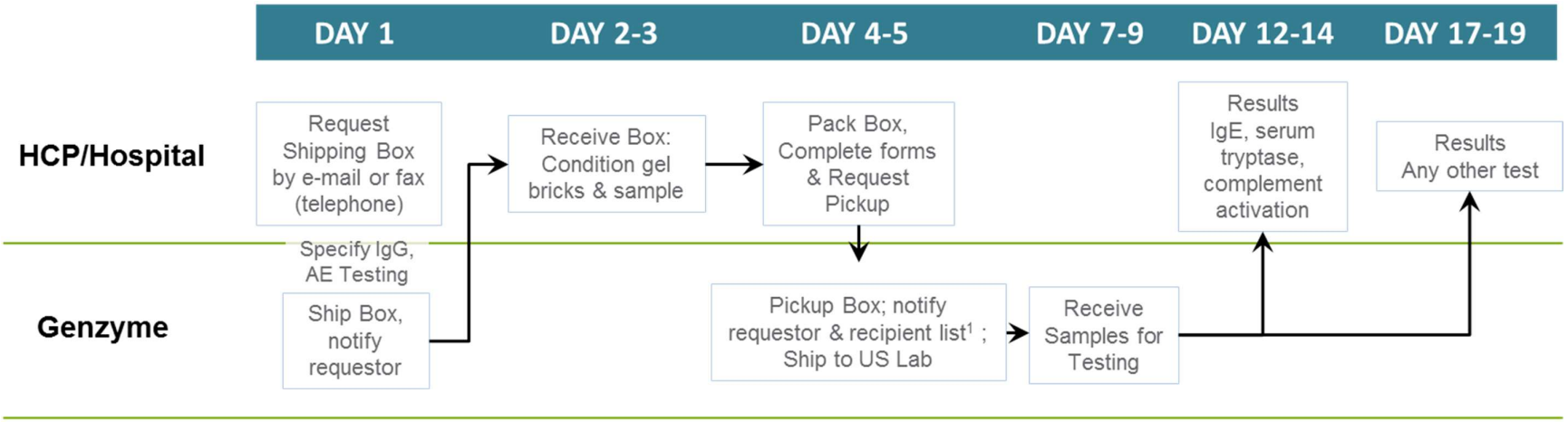
[b]Document the time and date when the sample was taken.

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

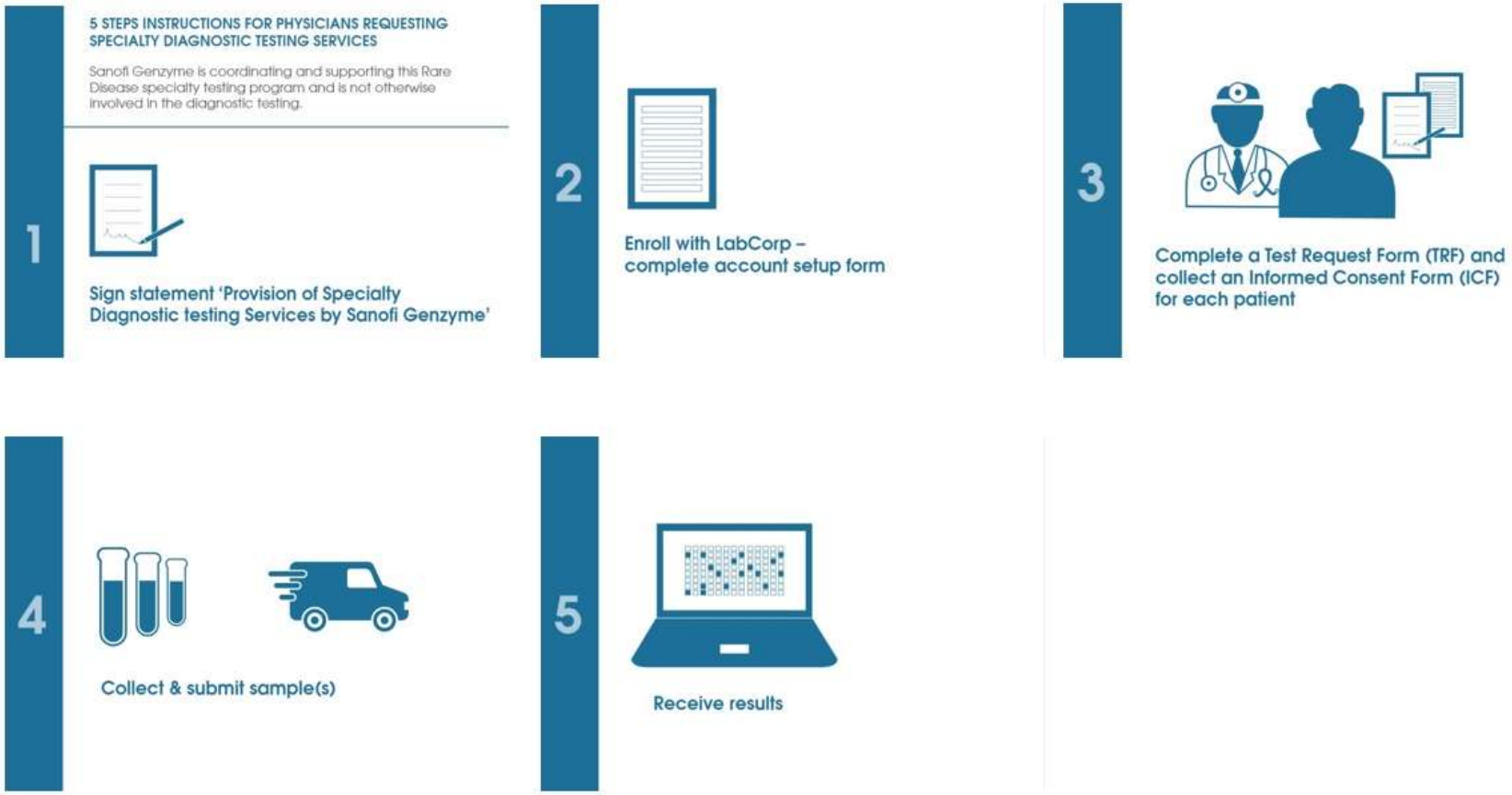
3.2. Procedure for testing

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 Medical Information department for collection, processing, packaging and shipping of blood samples. Contact details are provided *on page 7.*

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-Genzyme.

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-Genzyme:

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

5. Pregnancy & breastfeeding

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

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 alglucosidase alfa is used.

Reporting information on drug exposure in pregnancy to Sanofi-Genzyme 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 alglucosidase alfa, 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 page 7.

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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18. Sanofi-Genzyme, Data on file.

8. Appendices

Appendix 1. Preparation of Alglucosidase alfa

Use aseptic technique during preparation.

The following items are required for the preparation and administration of alglucosidase alfa.

- Required quantity of alglucosidase alfa 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 alglucosidase alfa.

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 alglucosidase alfa 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 lyophilised 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 Sanofi-Genzyme Medical Information department. Contact details are provided on page 7. 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. alglucosidase alfa should be diluted in 9 mg/ml (0.9%) sodium chloride for injection, immediately after reconstitution, to a final alglucosidase alfa 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 alglucosidase alfa required for patient dose.

   Examples:

   Patient dose = 320 mg 320 mg ÷ 5 mg/mL = 64 mL of alglucosidase alfa

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 minimise particle formation due to the sensitivity of alglucosidase alfa 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 alglucosidase alfa.
8. Add the reconstituted alglucosidase alfa 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 Alglucosidase alfa

Note: 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 alglucosidase alfa.

Patients with an acute underlying illness at the time of alglucosidase alfa 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 alglucosidase alfa.

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 alglucosidase alfa 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 alglucosidase alfa solution administration set to the 0.2 µm in-line low protein-binding filter set and prime the line.
8. Connect the alglucosidase alfa 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 alglucosidase alfa 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 Alglucosidase alfa

Unreconstituted alglucosidase alfa vials should be stored under refrigeration between 2° to 8°C. Do not use alglucosidase alfa 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 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.