SANOFI GENZYME HOME ASSISTANCE

CEREZYME Home Infusion HCP Guide

This additional risk minimization activity are approved by SFDA

V2-JAN 2021

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Cerezyme® Home Infusion: A Guide for Healthcare Professionals Treating Patients with Gaucher Disease



1. OBJECTIVES AND GOALS

The objective of this document is to provide guidance to healthcare professionals for the management of patients receiving Cerezyme® at home. The process (described in detail below) will start with patient evaluation and selection, and discussion of requirements for home infusion. This is followed by the organisation of home infusion and training.

The goal is to offer home infusion to patients as an alternative to hospital infusion in order to improve quality of life (Hughes, 2007; Milligan, 2006).

Offering home infusion of Cerezyme will make it possible for patients to do the following:

- Receive treatment within his or her own living environment.
- Increase flexibility of infusion timing.
- Avoid spending time travelling to and from the hospital and being hospitalised.
- Follow a normal schooling programme.
- Organise social and professional activities more easily.
- Facilitate arranging treatment around family and friends.

2. PATIENT EVALUATION AND SELECTION

Cerezyme infusions are generally tolerated well (Starzyk, 2007) and patients may prefer to be given their infusions at home. The choice to commence home treatment can be made by the patient and/or caregiver and the treating physician after a period of several months of hospital treatment to ensure satisfactory tolerance (Belmatoug, 2009; Hughes, 2007).
It is important to ensure that the patient and/or caregiver understand the nature of the home infusion. Other factors to consider for patient evaluation and selection include:

- Is the home situation safe and adequate?
- Is the patient and/or caregiver able to safely, efficiently, and reliably deliver the Cerezyme infusion?
- Is rapid and reliable communication possible if problems occur?
- Is the patient and/or caregiver aware of the risks of home infusion?

A homecare nurse, with the appropriate training, will assist the patient to ensure optimal treatment.

3. REQUIREMENTS FOR HOME INFUSION

The decision to administer Cerezyme in the home setting is that of the treating physician, in consultation with the patient and/or caregiver. The following information identifies clinical and logistical issues that should be considered prior and subsequent to homecare transition (National Healthcare Protocol for Gaucher Disease, HAS, 2007):

Patient Assessment by Treating Physician

- Patients should be considered medically stable. An evaluation should be completed prior to transition.
- Patients should have received Cerezyme infusions in a controlled setting for several months until there is a documented pattern of well tolerated infusions with no infusion associated reactions (IARs) or mild IARs that have been controlled with pre-medication.
- Patients should have a history of adherence to the prescribed infusion schedule.
- Regular disease monitoring of the home-infused patient is the responsibility of the treating physician.

Home Conditions

- The home environment must be conducive for home infusion therapy including a clean environment with electricity, water, telephone access, refrigeration, and physical space to support storage of Cerezyme and other infusion supplies.
- The infusion rate of Cerezyme that was tolerated by the patient in a more controlled setting (e.g., in the hospital or outpatient setting) should not be changed in the home setting unless necessary due to safety considerations.
- Appropriate scheduling and monitoring of the infusion is the responsibility of the treating physician/homecare nurse.
- A resource contact list should be completed and available at home, in the Logbook, (Appendix 11.2) for the patient and/or care giver and the nurse.

Available pre-treatment and emergency treatment

- Appropriate pre-treatment should be provided based on the patient-specific prescription. Treatment administered in the hospital/clinic setting should not be altered in the home setting unless medically warranted.
- Medications must be available to respond to an emergency situation if necessary. Proper education on the use of emergency medications must be provided to the patient and/or caregiver (see Logbook, Appendix 11.2).

- In the event the patient experiences an adverse event during the infusion, the patient/caregiver should discontinue the infusion immediately and phone the treating physician or homecare nurse to seek advice. Subsequent infusions may need to occur in a clinical setting.

4. TRAINING IN ADMINISTERING CEREZYME

In principle, the initial instructions will be given in the hospital and the level of support required from the homecare nurse will be discussed and agreed by the treating physician and the patient and/or caregiver.

Should the patient prefer full support when having their infusion at home, the homecare nurse will carry out the entire procedure for the patient.

Should the patient prefer to carry out the procedure him/herself or with the assistance of a caregiver, the patient and/or caregiver will receive training from the homecare nurse while the infusion is being prepared and administered. The homecare nurse will explain and demonstrate the complete infusion procedure to the patient and/or caregiver.

At subsequent visits, the homecare nurse will be present to assist if required, but the patient and/or caregiver will gradually transition to performing more of the administration under the homecare nurse's supervision until they feel confident with the entire infusion procedure.

While reconstituting and administering Cerezyme, the procedure described in the Summary of Product Characteristics must be closely observed (Saudi SPC, see Appendix 11.1).

A homecare agency, care provider, or hospital will provide equipment required to administer the home infusion.

Genzyme will provide the patient care team with home infusion training and educational material.

5. ORGANISATION OF HOME INFUSION

The following information is intended to provide information and guidance to all persons involved in the procedures for organizing home infusion of Cerezyme.

Patient

General

- The patient and/or caregiver, and/or homecare agency have been informed by the treating physician about the treatment to be provided at home, the associated risks, the possible

complications, and the provision of medical assistance at home.

- The patient and/or caregiver have an understanding of the illness and are able to recognise adverse events and understand the procedure to be followed should these occur. The patient and/or caregiver must agree to the treatment at home.
- The patient and/or caregiver have been adequately trained in the procedures of Cerezyme reconstitution and infusion.
- The home environment must be conducive to home infusion therapy including a clean environment with electricity, water, telephone access, refrigeration, and physical space to support storage of Cerezyme and other infusion supplies.
- In case the patient carries out the procedure him/herself
    - The patient/caregiver will strictly follow the prescribed method of administration of Cerezyme as stated in the Patient Manual and Reconstitution guide.
    - The patient/caregiver records each administration of Cerezyme in the Logbook.
    - In the event the patient experiences an adverse event effect during the infusion, the patient/caregiver should discontinue the infusion immediately and phone the treating physician or home nurse to seek advice.

Medical

- The patient must be physically and mentally able to undergo the infusions at home. The treating physician is responsible for the recommendation to receive Cerezyme infusions at home.
- The patient has venous access or a central venous access device that allows for adequate infusion.

Treating physician

- The treating physician is responsible for the initiation of all necessary administrative actions, allowing other stakeholders (pharmacy, nurse, patient, caregiver) to proceed.
- The treating physician is responsible for the dose and the infusion rate. Any changes in Cerezyme administration must be clearly communicated to the patient and described in the Logbook).
- The patient should be regularly monitored for IARs and maintenance of therapeutic goals as per the published guidelines for children (Charrow, 2004) and adults (Weinreb, 2004).

Hospital/Pharmacy

- The hospital/pharmacy arranges the provision of the patient's medication for each prescription and the equipment/materials required.

Homecare Nurse

- The homecare nurse is qualified to give intravenous (IV) infusions.
- The homecare nurse has been trained on Cerezyme and is aware of the possible adverse events and the actions to be taken should they occur.
- The homecare nurse will establish with the patient and/or caregiver the level of support necessary.
- The homecare nurse will strictly follow the prescribed method of administration of Cerezyme as stated in the Logbook.
- For each patient, the homecare nurse will have a coordinating task vis-à-vis treating physician and patient/care giver in organizing the treatment at home.
- The homecare nurse records each administration of Cerezyme in the Logbook.
- In the event of an IAR, the homecare nurse should discontinue the infusion and phone the treating physician and/or the country-specific national emergency number described in the Logbook.

Third Person/Caregiver

It is preferable that a caregiver/third party be present during home infusion.

The Logbook (Appendix 11.2

- The Logbook serves as a means of communication for everyone involved in administering Cerezyme in the home setting.
- The Logbook should be kept at the patient's home and will be kept updated by the homecare nurse/patient/caregiver each time Cerezyme is administered.
- The patient/caregiver must take the Logbook along to the hospital at each appointment for a check-up and bring it home afterwards.
- In the Logbook, the treating physician clearly states the dose and the infusion rate, as well as any changes to the dosing regimen.
- The homecare nurse records the findings and actions from the initial interview in the Logbook. The homecare nurse, patient and/or caregiver records all relevant information from

subsequent visits in the Logbook.

- In the Logbook, the treating physician clearly states what has to be done and which medications are to be administered in the event of an IAR.

6. ADMINISTRATION OF CEREZYME

6.1 Prescription

The Cerezyme dose, infusion rate as well as any changes will be determined by the treating physician.

6.2 Ancillary Supplies

The medicinal products and equipment required for home treatment include the following:

- Vials of Cerezyme
  - Must be stored at a temperature of between +2°C and +8°C.
  - Supplied by the hospital/pharmacy to the patient or to a third party with the appropriate prescription.
- Infusion materials
  - Infusion lines, syringes, needles, compresses, antiseptics, etc. (supplied by the hospital/pharmacy to the patient or delivered by the homecare agency in case of care provided by a homecare nurse).
  - NaCl 0.9% solution and sterile water (supplied by the local pharmacy to the patient or to a third party with the appropriate prescription).

6.3 Preparation of the Cerezyme infusion for intravenous use

<u>Requisites</u>

Supplied by the hospital/pharmacy to the patient or to a third party with the appropriate prescription.

- Vials of Cerezyme (400 U per vial);
  Must be stored at a temperature of between +2°C and +8°C.
- Sterile water for injections to reconstitute Cerezyme
- NaCl 0.9% solution, 2 x 100 ml or 1 x 250 ml for IV administration



- NaCl 0.9% solution, 2 x 50 ml to flush infusion line pre- and post-infusion
- Chlorhexidine 0.5% in alcohol 70% (antiseptic solution)
- Appropriate number of 10 ml and 50 ml syringes depending upon dose of Cerezyme
- 3 x sterile hypodermic needles (1.1 x 40 mm)
- 1 x butterfly needle
- In-line low protein-binding 0.2 micron filter
- Hypodermic needle tray
- Micropore tape
- Mediswabs
- Sharps bin
- Hand wash
- Additional requisites if using a venous access device
    - Heparin
    - Needles for heparin
    - Dressing pack
    - Sterile gloves
- Emergency medication (antihistamines and/or corticosteroids)

Preparations

1. Prepare a clean work area and lay out the requisites.

2. The vials with Cerezyme should be removed from the refrigerator to reach room temperature approximately 30 minutes before preparation
3. Check the expiry date printed on the bottom of the vial pack (do not use Cerezyme after the expiry date).
4. Verify if the number of vials received is correct.
5. Prepare only the number of vials required for 1 infusion (*Note:* Cerezyme may not be stored in reconstituted or diluted form for later use).

Reconstituting Cerezyme

1. Remove the flip-off cap from the Cerezyme vial.
2. Disinfect the rubber stopper of the Cerezyme vial with chlorhexidine and allow to air dry.
3. Open the sterile water for injections.
4. Draw the required number of ml of sterile water into the syringe.
    - For 400 U vials, reconstitute each vial with 10.2 ml water for injections; the reconstituted volume is 10.6 ml.
5. Inject the water gently into a vial of Cerezyme.
6. Repeat the process for more Cerezyme vials if required.
7. Carefully swirl the vial(s) to mix the solution (avoid forceful shaking during the reconstitution process to avoid foaming of the solution).
8. Small bubbles may appear after the mixing.
9. Let the solution settle for a few minutes to allow any bubbles present to disappear and to ensure that the powder is properly reconstituted.
10. After reconstitution, Cerezyme should be inspected visually before use. Because this is a protein solution, slight flocculation (described as thin translucent fibres) occurs occasionally after dilution. The reconstituted solution must be a clear, colourless liquid, free from foreign matter
11. If you notice foreign matter in or discolouration of the liquid, do not use the product and contact the home nurse.

Dilution

1. Disinfect the cap/opening of 1 or 2 bags of NaCl 0.9% solution using chlorhexidine and allow to air dry.
2. Calculate the quantity of reconstituted Cerezyme solution present in the vials and draw the same quantity from the bag of NaCl 0.9% solution, thus creating enough space to add the reconstituted Cerezyme solution.
   For instance, if the prescribed quantity is 3 vials of Cerezyme of 400 units each, remove 30 ml (=3 x 10 ml) of NaCl solution from the bag of NaCl solution. Never remove more than half the content of the bag of NaCl to ensure that at least half the diluted solution consists of NaCl.
3. Using one or more 50 ml syringes, draw 10 ml for the 400 U vials so as to minimise the number of operations. At the point when these quantities are drawn, the reconstituted product should not contain any foam.
4. Then gently inject the total volume of the reconstituted Cerezyme solution into the bag of NaCl 0.9% solution.
5. Carefully mix this Cerezyme solution.
6. The diluted solution should be filtered through an in-line low protein-binding 0.2 micron filter during administration.

Filling the Infusion Line

1. Remove the infusion system from the package and close it using the roller clamp.
2. Connect the spike in the NaCl 0.9% bag and fill the infusion system by holding the drip chamber upside down and opening the clamp.
3. Fill the entire system, remove any air bubbles that may be present and close the roller clamp.
4. Connect the infusion bag containing Cerezyme to the y-system.

Inserting the Needle in the Vein

1. Ensure that some strips of sticking plaster are hanging ready for use and that the start of the infusion system is within reach. Place the chlorhexidine close by along with some gauzes.
2. Remove the butterfly needle from the packaging.
3. Have the patient sit down and rest one arm on the table (preferably on the clean cloth).



4. Apply the tourniquet and disinfect the area where the needle is to be inserted and allow it to dry.
5. Pull the skin tight and insert the needle (with its eye facing upward) at a slight angle through the skin and into the vein. When the needle has entered the vein, a 'flash' of blood will be visible at the start of the tubing.
6. Insert the needle approximately 0.5 cm in the vein to ensure that it does not immediately pop out again. Tape the butterfly needle into place using a plaster.
7. Loosen the tourniquet and remove the cap from the tube. The tube will now fill up with blood. If this does not happen, the needle is not positioned correctly in the vein. The process must then be repeated.
8. Attach the prepared infusion bag to the drip stand and open the valve.

Administration

The reconstituted solution must be administered as prescribed within 3 hours of having been prepared. The product diluted in NaCl 0.9% solution will retain chemical stability if stored up to 24 hours at a temperature between 2°C and 8°C away from light.

The Cerezyme dose, infusion rate as well as any changes will be determined by the treating physician.

After the Cerezyme infusion has been completed, the system is flushed with NaCl 0.9% solution at the same rate and the needle removed.

6.4 Preparation of the Cerezyme infusion in case of venous access device

When the patient has a venous access device for the delivery of Cerezyme, the patient and/or caregiver will be shown how to care for the device.

Proper home care of a venous access device involves regular irrigation with heparin to prevent clotting and attention to a sterile technique to keep the device free of infectious agents. The patient and/or caregiver will be informed of the following necessary steps:

- When in use, cover site with transparent occlusive dressing. No dressing required when not in use.
- Flush with 5 mL saline before and after each use.
- Flush with 5 mL heparin (100 U/mL) after each use.

7. CEREZYME SAFETY INFORMATION

Approximately 15% of patients treated with Cerezyme develop immunoglobulin G (IgG) antibodies to imiglucerase during the first year of therapy. Patients who develop IgG antibody are most likely to do so within 6 months of treatment and will rarely develop antibodies to Cerezyme after 12 months of therapy. Patients with antibody to imiglucerase have a higher risk of hypersensitivity reactions. Conversely, not all patients with symptoms of hypersensitivity have detectable IgG antibody. If a patient experiences a reaction suggestive of hypersensitivity, subsequent testing for imiglucerase antibodies is advised.

Treatment with Cerezyme should be approached with caution in patients who have exhibited symptoms of hypersensitivity to the product. Symptoms suggestive of hypersensitivity occurring during, or shortly after, infusions included pruritis, flushing, urticaria, angioedema, chest discomfort, tachycardia, cyanosis, respiratory symptoms, paraesthesia, backache and hypotension. **The infusion should be discontinued immediately if these symptoms occur.** Most patients have successfully continued therapy after a reduction in rate of infusion and pre-treatment with antihistamines and/or corticosteroids.

Adverse drug reactions are listed by system organ class and frequency (common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥1/10,000 to <1/1,000)) in Table 5-1 below. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

Table 5-1: Common and Uncommon Adverse Events

Nervous system disorders	Uncommon:	Dizziness, headache, paraesthesia*
Cardiac disorders	Uncommon:	Tachycardia*, cyanosis*
Vascular disorders	Uncommon:	Flushing*, hypotension*
Respiratory, thoracic and mediastinal disorders	Common:	Dyspnoea*, coughing*
Gastrointestinal disorders	Uncommon:	Vomiting, nausea, abdominal cramping, diarrhoea
Immune system disorders	Common:	Hypersensitivity reactions
	Rare :	Anaphylactoid reactions
Skin and subcutaneous tissue disorders	Common:	Urticaria/angioedema*, pruritus*, rash*
Musculoskeletal and connective tissue disorders	Uncommon:	Arthralgia, backache*
General disorders and administration site conditions	Uncommon:	Infusion site discomfort, infusion site burning, infusion site swelling, injection site sterile abscess, chest discomfort*, fever, rigors, fatigue

* Symptoms suggestive of hypersensitivity
Source: Summary of Product Characteristics (SmPC), October 2010

8. SAFETY REPORTING

An adverse event (AE) is defined as any untoward medical occurrence in a patient administered a medicinal product which does not necessarily have to have a causal relationship with this treatment. A serious adverse event (SAE) involves an occurrence defined as having at least one of the following outcomes or characteristics:

- Results in death
- Is life-threatening (any event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Required inpatient hospitalisation or prolongation of an existing hospitalisation
- Results in persistent or significant disability/incapacity (any adverse event that resulted in a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is an important medical event (any event that, based upon appropriate medical judgement, may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above)

In case of any drug related adverse events, please contact:

The National Pharmacovigilance Center (NPC)
Fax: +966-11-205-7662
Call Center: 19999

E-mail:npc.drug@sfda.gov.sa

Website: https://ade.sfda.gov.sa/
For Pharmacovigilance, please contact Sanofi:

Mobile: +966-544-284-797
E-mail: Ksa_pharmacovigilance@sanofi.com

9. FURTHER INFORMATION

Please refer to the Summary of Product Characteristic (Appendix 11.1) for complete indication statements and further information about the approved use of Cerezyme (imiglucerase).

10. REFERENCES

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11. APPENDICES

11.1 Summary of Product Characteristics

11.2 Logbook



ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS



1. NAME OF THE MEDICINAL PRODUCT

Cerezyme 200 Units Powder for concentrate for solution for infusion
Cerezyme 400 Units Powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cerezyme 200 Units powder for concentrate for solution for infusion
Each vial contains 200 units* of imiglucerase**.

After reconstitution, the solution contains 40 units (approximately 1.0 mg) of imiglucerase per ml (200 U/5 ml).

Cerezyme 400 Units powder for concentrate for solution for infusion
Each vial contains 400 units* of imiglucerase**.

After reconstitution, the solution contains 40 units (approximately 1.0 mg) of imiglucerase per ml (400 U/10 ml).

* An enzyme unit (U) is defined as the amount of enzyme that catalyses the hydrolysis of one micromole of the synthetic substrate para-nitrophenyl β-D-glucopyranoside (pNP-Glc) per minute at 37°C.
** Imiglucerase is a modified form of human acid β-glucosidase and is produced by recombinant DNA technology using a mammalian Chinese Hamster Ovary (CHO) cell culture, with mannose modification for targeting macrophages.

Excipients:
For the full list of excipients, see section 6.1.

Cerezyme 200 Units powder for concentrate for solution for infusion
This medicinal product contains sodium and is administered in 0.9% sodium chloride intravenous solution (see section 6.6). After reconstitution, the solution contains 0.62 mmol sodium (200 U/5 mL). To be taken into consideration by patients on a controlled sodium diet.

Cerezyme 400 Units powder for concentrate for solution for infusion
This medicinal product contains sodium and is administered in 0.9% sodium chloride intravenous solution (see section 6.6). After reconstitution, the solution contains 1.24 mmol sodium (400 U/10 mL). To be taken into consideration by patients on a controlled sodium diet.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.
Cerezyme is a white to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cerezyme (imiglucerase) is indicated for use as long-term enzyme replacement therapy in patients with a confirmed diagnosis of non-neuronopathic (Type 1) or chronic neuronopathic (Type 3) Gaucher disease who exhibit clinically significant non-neurological manifestations of the disease.

The non-neurological manifestations of Gaucher disease include one or more of the following conditions:

- anaemia after exclusion of other causes, such as iron deficiency
- thrombocytopenia
- bone disease after exclusion of other causes such as Vitamin D deficiency
- hepatomegaly or splenomegaly

4.2 Posology and method of administration

Disease management should be directed by physicians knowledgeable in the treatment of Gaucher disease.

Posology

Due to the heterogeneity and the multi-systemic nature of Gaucher disease, dosage should be individualised for each patient based on a comprehensive evaluation of all clinical manifestations of the disease. Once individual patient response for all relevant clinical manifestations is well-established, dosages and frequency of administration may be adjusted with the goal to either maintain already reached optimal parameters for all clinical manifestations or further improve those clinical parameters which have not yet been normalised.

A range of dosage regimens has proven effective towards some or all of the non-neurological manifestations of the disease. Initial doses of 60 U/kg of body weight once every 2 weeks have shown improvement in haematological and visceral parameters within 6 months of therapy and continued use has either stopped progression of or improved bone disease. Administration of doses as low as 15 U/kg of body weight once every 2 weeks has been shown to improve haematological parameters and organomegaly, but not bone parameters. The usual frequency of infusion is once every 2 weeks; this is the frequency of infusion for which the most data are available.

Paediatric population

No dose adjustment is necessary for the paediatric population.

The efficacy of Cerezyme on neurological symptoms of chronic neuronopathic Gaucher patients has not been established and no special dosage regimen can be recommended for these manifestations (see section 5.1).

Method of administration

After reconstitution and dilution, the preparation is administered by intravenous infusion. At initial infusions, Cerezyme should be administered at a rate not exceeding 0.5 unit per kg body weight per minute. At subsequent administrations, infusion rate may be increased but should not exceed 1 unit per kg body weight per minute. Infusion rate increases should occur under supervision of a health care professional.

Infusion of Cerezyme at home may be considered for patients who are tolerating their infusions well for several months.. Decision to have patient move to home infusion should be made after evaluation and recommendation by the treating physician. Infusion of Cerezyme by the patient or caregiver at home requires training by a health care professional in a clinical setting. The patient or caregiver will be instructed in infusion technique and the keeping of a treatment diary. Patients experiencing adverse events during the infusion need to immediately **stop the infusion process and** seek the attention of a healthcare professional. Subsequent infusions may need to occur in a clinical setting. Dose and infusion rate should remain constant while at home, and not be changed without supervision of a health care professional.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

Medical or healthcare professionals are encouraged to register Gaucher patients, including those with chronic neuronopathic manifestations of the disease, in the "ICGG Gaucher Registry" (see section 5.1).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity
Current data using a screening ELISA followed by a confirmatory radioimmunoprecipitation assay, suggest that, during the first year of therapy, IgG antibodies to imiglucerase are formed in approximately 15% of the treated patients. It appears that patients who will develop IgG antibody are most likely to do so within 6 months of treatment and will rarely develop antibodies to Cerezyme after 12 months of therapy. It is suggested that patients suspected of a decreased response to the treatment be monitored periodically for IgG antibody formation to imiglucerase.

Patients with antibody to imiglucerase have a higher risk of hypersensitivity reactions (see section 4.8). If a patient experiences a reaction suggestive of hypersensitivity, subsequent testing for imiglucerase antibodies is advised. As with any intravenous protein product, severe allergic-type hypersensitivity reactions are possible, but occur uncommonly. If these reactions occur, immediate discontinuation of the Cerezyme infusion is recommended and appropriate medical treatment should be initiated. The current medical standards for emergency treatment are to be observed.

Patients who have developed antibodies or symptoms of hypersensitivity to Ceredase (alglucerase) should be treated with caution when administering Cerezyme (imiglucerase).

Sodium
This medicinal product contains sodium and is administered in 0.9% sodium chloride intravenous solution (see section 6.6). To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy
Limited experience from 150 pregnancy outcomes (primarily based on spontaneous reporting and literature review) is available suggesting that use of Cerezyme is beneficial to control the underlying Gaucher disease in pregnancy. Furthermore, these data indicate no malformative toxicity for the foetus by Cerezyme, although the statistical evidence is low. Foetal demise has been reported rarely, although it is not clear whether this related to the use of Cerezyme or to the underlying Gaucher disease.

No animal studies have been carried out with respect to assessing the effects of Cerezyme on pregnancy, embryonal/foetal development, parturition and postnatal development. It is not known whether Cerezyme passes via the placenta to the developing foetus.

In pregnant Gaucher patients and those intending to become pregnant, a risk-benefit treatment assessment is required for each pregnancy. Patients who have Gaucher disease and become pregnant may experience a period of increased disease activity during pregnancy and the puerperium. This includes an increased risk of skeletal manifestations, exacerbation of cytopenia, haemorrhage, and an increased need for transfusion. Both pregnancy and lactation are known to stress maternal calcium

homeostasis and to accelerate bone turnover. This may contribute to skeletal disease burden in Gaucher disease.

Treatment naïve women should be advised to consider commencing therapy prior to conception in order to attain optimal health. In women receiving Cerezyme treatment continuation throughout pregnancy should be considered. Close monitoring of the pregnancy and clinical manifestations of Gaucher disease is necessary for the individualization of dose according to the patient's needs and therapeutic response.

Breast-feeding
It is not known whether this active substance is excreted in human milk, however, the enzyme is likely to be digested in the child's gastrointestinal tract

4.7 Effects on ability to drive and use machines

Cerezyme has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Tabulated list of adverse reactions
Adverse reactions are listed by system organ class and frequency (common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥1/10,000 to <1/1,000)) in the table below. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA System Organ Class	Common	Uncommon	Rare
Nervous system disorders		Dizziness, headache, paraesthesia*	
Cardiac disorders		Tachycardia*, cyanosis*	
Vascular disorders		Flushing*, hypotension*	
Respiratory, thoracic and mediastinal disorders	Dyspnoea*, coughing*		
Gastrointestinal disorders		Vomiting, nausea, abdominal cramping, diarrhoea	
Immune system disorders	Hypersensitivity reactions		Anaphylactoid reactions
Skin and subcutaneous tissue disorders	Urticaria/angioedema*, pruritus*, rash*		
Musculoskeletal and connective tissue disorders		Arthralgia, backache*	
General disorders and administration site conditions		Infusion site discomfort, infusion site burning, infusion site swelling, injection site sterile abscess, chest discomfort*, fever, rigors, fatigue	

Symptoms suggestive of hypersensitivity (* marked in the table above) have been noted, overall in approximately 3% of the patients. Onset of such symptoms has occurred during or shortly after

infusions. These symptoms generally respond to treatment with antihistamines and/or corticosteroids. Patients should be advised to discontinue infusion of the product and contact their physician if these symptoms occur.

To report any side effect(s):
• Saudi Arabia:

- Please contact: The National Pharmacovigilance Center (NPC)
  - Fax: +966-11-205-7662
  - Call Center: 19999
  - E-mail: npc.drug@sfda.gov.sa
  - Website: https://ade.sfda.gov.sa/
- For SANOFI Pharmacovigilance center, please contact: +966-544-284-797
  - E-mail: Ksa_pharmacovigilance@sanofi.com

4.9 Overdose

No case of overdose has been reported. In patients dosages up to 240 U/kg body weight once every two weeks have been used.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Enzymes-Imiglucerase (recombinant macrophage targeted β-glucocerebrosidase), ATC code: A16AB02.

Mechanism of action
Gaucher disease is a rare recessively inherited metabolic disorder that results from a deficiency of the lysosomal enzyme acid β-glucosidase. This enzyme breaks down glucosylceramide, a key component of the lipid structure of cell membranes, into glucose and ceramide. In individuals with Gaucher disease, glucosylceramide degradation is insufficient, leading to accumulation of large quantities of this substrate within the lysosomes of macrophages (termed 'Gaucher cells'), leading to widespread secondary pathology.

Gaucher cells are typically found in liver, spleen and bone marrow and occasionally in lung, kidney and intestine. Clinically, Gaucher disease is a heterogeneous phenotypic spectrum. The most frequent disease manifestations are hepatosplenomegaly, thrombocytopenia, anaemia, and skeletal pathology, The skeletal abnormalities are frequently the most debilitating and disabling features of Gaucher disease. These skeletal manifestations include bone marrow infiltration, osteonecrosis, bone pain and bone crises, osteopenia and osteoporosis, pathological fractures, and growth impairment. Gaucher disease is associated with increased glucose production and increased resting energy expenditure rate, which may contribute to fatigue and cachexia. Patients with Gaucher disease may also have a low grade inflammatory profile. In addition, Gaucher disease has been associated with an increased risk of immunoglobulin abnormalities such as hyperimmunoglobulinemia, polyclonal gammopathy, monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma. The natural history of Gaucher disease usually shows progression, with the risk of irreversible complications arising in various organs over time. The clinical manifestations of Gaucher disease can adversely affect quality of life. Gaucher disease is associated with increased morbidity and early mortality. Signs and symptoms presenting in childhood typically represent more severe Gaucher disease. In children, Gaucher disease can lead to growth retardation and delayed puberty.

Pulmonary hypertension is a known complication of Gaucher disease. Patients who have undergone a splenectomy have an increased risk of pulmonary hypertension. Cerezyme therapy reduces the requirement for splenectomy in most cases and early treatment with Cerezyme has been associated

with a reduced risk of pulmonary hypertension. Routine evaluation to detect the presence of pulmonary hypertension after diagnosis of Gaucher disease and over time is recommended. Patients diagnosed with pulmonary hypertension, in particular, should receive adequate doses of Cerezyme to ensure control of underlying Gaucher disease as well as be evaluated for the need of additional pulmonary hypertension specific treatments.

Pharmacodynamic effects

Imiglucerase (recombinant macrophage targeted acid ß-glucosidase) replaces the deficient enzyme activity, hydrolysing glucosylceramide, thus correcting initial pathophysiology and preventing secondary pathology. Cerezyme reduces spleen and liver size, improves or normalises thrombocytopenia and anaemia, improves or normalises bone mineral density and bone marrow burden, and reduces or eliminates bone pain and bone crises. Cerezyme reduces resting energy expenditure rate. Cerezyme has been shown to improve both mental and physical aspects in the quality of life of Gaucher disease. Cerezyme decreases chitotriosidase, a biomarker for glucosylceramide accumulation in macrophages and response to treatment. In children, Cerezyme has been shown to enable normal pubertal development, and to induce catch-up growth, leading to normal height and bone mineral density in adulthood.

Clinical efficacy and safety

The rate and extent of response to Cerezyme treatment is dose-dependent. Generally, improvements in organ systems with a faster turnover rate, such as the haematological, can be noted far more rapidly than in those with a slower turnover, such as the bone.
In an ICGG Gaucher Registry analysis of a large cohort of patients (n=528) with Gaucher disease type 1, a time- and dose-dependent effect for Cerezyme was observed for haematological and visceral parameters (platelet count, haemoglobin concentration, spleen and liver volume) within the dose range of 15, 30 and 60 U/kg body weight once every 2 weeks. Patients treated with 60 U/kg body weight every 2 weeks showed a faster improvement and a greater maximum treatment effect as compared to patients receiving the lower doses.

Similarly, in an ICGG Gaucher Registry analysis of bone mineral density using dual-energy X-ray absorptiometry (DXA) in 342 patients, after 8 years of treatment normal bone mineral density was achieved with a Cerezyme dose of 60 U/kg body weight once every 2 weeks, but not with lower doses of 15 and 30 U/kg body weight once every 2 weeks (Wenstrup et al, 2007).

In a study investigating 2 cohorts of patients treated with a median dose of 80 U/kg body weight every 4 weeks and a median dose of 30 U/kg body weight every 4 weeks, among the patients with bone marrow burden score ≥ 6, more patients in the higher dose cohort (33%; n=22) achieved a decrease in the score of 2 points after 24 months of Cerezyme treatment compared with patients in the lower dose cohort (10%; n=13) (de Fost et al, 2006).

Treatment with Cerezyme at a dose of 60 U/kg body weight once every 2 weeks, showed improvement in bone pain as early as 3 months, decrease in bone crises within 12 months, and improvement in bone mineral density after 24 months of treatment (Sims et al, 2008).

The usual frequency of infusion is once every 2 weeks (see section 4.2). Maintenance therapy every 4 weeks (Q4) at the same cumulative dose as the bi-weekly (Q2) dose has been studied in adult patients with stable residual Gaucher disease type 1. Changes from baseline in hemoglobin, platelets, liver and spleen volumes, bone crisis, and bone disease comprised a predefined composite endpoint; achievement or maintenance of established Gaucher disease therapeutic goals for the hematologic and visceral parameters comprised an additional endpoint. Sixty-three percent of Q4- and 81% of Q2-treated patients met the composite endpoint at Month 24; the difference was not statistically significant based on the 95% CI (-0.357, 0.058). Eighty-nine percent of Q4- and 100% of Q2-treated patients met the therapeutic goals-based endpoint; the difference was not statistically significant based on the 95% CI (-0.231, 0.060). A Q4 infusion regimen may be a therapeutic option for some adult patients with stable residual Gaucher disease type 1, but clinical data are limited.

No controlled clinical studies have been conducted on the efficacy of Cerezyme on neurological manifestations of the disease. Therefore no conclusions on the effect of enzyme replacement therapy on the neurological manifestations of the disease can be drawn.

Medical or healthcare professionals are encouraged to register Gaucher patients, including those with chronic neuronopathic manifestations of the disease, in the "ICGG Gaucher Registry". Patient data will be anonymously collected in this Registry. The objectives of the "ICGG Gaucher Registry" are to enhance the understanding of Gaucher disease and to evaluate the effectiveness of enzyme replacement therapy, ultimately leading to improvement in the safe and efficacious use of Cerezyme.

5.2 Pharmacokinetic properties

During 1 hour intravenous infusions of 4 doses (7.5, 15, 30, 60 U/kg) of imiglucerase, steady-state enzymatic activity was achieved by 30 minutes. Following infusion, plasma enzymatic activity declined rapidly with a half-life ranging from 3.6 to 10.4 minutes. Plasma clearance ranged from 9.8 to 20.3 ml/min/kg, (mean ± S.D, 14.5 ± 4.0 ml/min/kg). The volume of distribution corrected for weight ranged from 0.09 to 0.15 l/kg (mean ± S.D 0.12 ± 0.02 l/kg). These variables do not appear to be influenced by dose or duration of infusion, however, only 1 or 2 patients were studied at each dose level and infusion rate.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity and genotoxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol,
sodium citrate (to adjust pH),
citric acid monohydrate (to adjust pH),
polysorbate 80.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

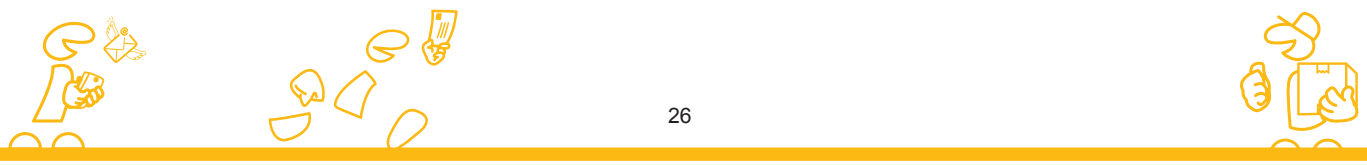
6.3 Shelf life

Unopened vials:
Cerezyme 200 Units powder for concentrate for solution for infusion
2 years

Cerezyme 400 Units powder for concentrate for solution for infusion
3 years

Diluted solution:
From a microbiological safety point of view, the product should be used immediately. If not used immediately, in-use storage and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C - 8°C under protection from light.

6.4 Special precautions for storage



Store in a refrigerator (2°C – 8°C).

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Cerezyme is supplied in type I borosilicate (clear) glass 20 ml vials. The closure consists of a siliconised butyl stopper with a tamper proof flip-off cap.

Cerezyme 200 Units powder for concentrate for solution for infusion
To provide sufficient volume to allow accurate dispensing, each vial is formulated to contain an overfill of 0.3 ml.

Pack sizes: 1 or 25 vials per carton.
Not all pack sizes may be marketed.

Cerezyme 400 Units powder for concentrate for solution for infusion
To provide sufficient volume to allow accurate dispensing, each vial is formulated to contain an overfill of 0.6 ml.

Pack sizes: 1, 5 or 25 vials per carton.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Each vial of Cerezyme is for single use only.

The powder for concentrate for solution for infusion has to be reconstituted with water for injections, diluted with 0.9% sodium chloride intravenous solution and then administered by intravenous infusion.

Determine the number of vials to be reconstituted based on the individual patient's dosage regimen and remove the vials from the refrigerator.

Occasionally, small dosage adjustments may be made to avoid discarding partially used vials. Dosages may be rounded to the nearest full vial, as long as the monthly administered dosage remains substantially unaltered.

Use Aseptic Technique

Reconstitution
Cerezyme 200 Units powder for concentrate for solution for infusion
Reconstitute each vial with 5.1 ml water for injections; avoid forceful impact of water for injections on the powder and, by mixing gently, avoid foaming of the solution. The reconstituted volume is 5.3 ml. The pH of the reconstituted solution is approximately 6.1.

Cerezyme 400 Units powder for concentrate for solution for infusion
Reconstitute each vial with 10.2 ml water for injections; avoid forceful impact of water for injections on the powder and, by mixing gently, avoid foaming of the solution. The reconstituted volume is 10.6 ml. The pH of the reconstituted solution is approximately 6.1.

After reconstitution it is a clear, colourless liquid, free from foreign matter. The reconstituted solution must be further diluted. Before further dilution, visually inspect the reconstituted solution in each vial for foreign particles and discoloration. Do not use vials exhibiting foreign particles or discoloration. After reconstitution, promptly dilute vials and do not store for subsequent use.

Dilution
Cerezyme 200 Units powder for concentrate for solution for infusion
The reconstituted solution contains 40 units imiglucerase per ml. The reconstituted volume allows accurate withdrawal of 5.0 ml (equal to 200 units) from each vial. Withdraw 5.0 ml reconstituted solution from each vial and combine the withdrawn volumes. Then dilute the combined volumes with 0.9% sodium chloride intravenous solution to a total volume of 100 to 200 ml. Mix the infusion solution gently.

Cerezyme 400 Units powder for concentrate for solution for infusion
The reconstituted solution contains 40 units imiglucerase per ml. The reconstituted volume allows accurate withdrawal of 10.0 ml (equal to 400 units) from each vial. Withdraw 10.0 ml reconstituted solution from each vial and combine the withdrawn volumes. Then dilute the combined volumes with 0.9% sodium chloride intravenous solution to a total volume of 100 to 200 ml. Mix the infusion solution gently.

Administration
It is recommended to administer the diluted solution through an in-line low protein-binding 0.2 µm filter to remove any protein particles. This will not lead to any loss of imiglucerase activity. It is recommended that the diluted solution be administered within 3 hours. The product diluted in 0.9% sodium chloride intravenous solution will retain chemical stability if stored up to 24 hours at 2°C and 8°C under protection from light; but microbiological safety will depend on the reconstitution and dilution having been performed aseptically.

Cerezyme contains no preservatives. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Genzyme Europe BV
Paasheuvelweg 25, 1105 BP Amsterdam, The Netherlands

8. MARKETING AUTHORISATION NUMBERS

8-832-16

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2016
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

20-Dec-18.

Logbook for Cerezyme® Home Infusion

General data

Patient	Name:	
	Address:	
	City:	
	Telephone:	
Nurse	Name:	
	Organisation:	
	Telephone:	
Treating physician	Name:	
	Hospital:	
	Address:	
	City:	
	Telephone:	
Pharmacy	Name:	
	Address:	
	City:	
	Telephone:	
National emergency number	Telephone:	997

Administration details (to be completed by treating physician)

Cerezyme administered since	Date (dd-mmm-yyyy):
First infusion at home	Date (dd-mmm-yyyy):
Reasons for Cerezyme infusion at home	
Please indicate support to be provided by nurse	
Cerezyme dosing regimen (dose, frequency, and rate of infusion)	

Emergency treatment details (to be completed by treating physician)

Necessary actions in the event of a serious infusion associated reaction:

1. Stop the infusion
2. Call KSA Ambulance emergency number: 997
3. Call the physician

Infusion data (to be completed by homecare nurse)

Date of infusion	Date (dd-mmm-yyyy):
Patient's general health condition: specific problems/ remarks	
Dose of infusion	
Number of vials used	400 U vials: ……
Duration of administration	
Rate of administration	
Problems/Remarks (related to infusion, e.g. side effects)	

Date of infusion	Date (dd-mmm-yyyy):
Patient's general health condition: specific problems/ remarks	
Dose of infusion	
Number of vials used	400 U vials: ……
Duration of administration	
Rate of administration	
Problems/Remarks (related to infusion, e.g. side effects)	



Date of infusion	Date (dd-mmm-yyyy):
Patient's general health condition: specific problems/ remarks	
Dose of infusion	
Number of vials used	400 U vials: ……
Duration of administration	
Rate of administration	
Problems/Remarks (related to infusion, e.g. side effects)	

Date of infusion	Date (dd-mmm-yyyy):
Patient's general health condition: specific problems/ remarks	
Dose of infusion	
Number of vials used	400 U vials: ……
Duration of administration	
Rate of administration	
Problems/Remarks (related to infusion, e.g. side effects)	

For Medical Information, please contact: +966-12-6693318
E-mail: ksa.medicalinformation@sanofi.com
In case of any drug related adverse events, please contact: The National Pharmacovigilance Center (NPC)
Call Center: 19999
E-mail: npc.drug@sfda.gov.sa
Website: https://ade.sfda.gov.sa/
For SANOFI Pharmacovigilance center, please contact: +966-544-284-797
E-mail: Ksa_pharmacovigilance@sanofi.com
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