Cerezyme®
imiglucerase

CEREZYME® 400 HOME INFUSION:

A guide for Healthcare Professionals treating Patients with Gaucher Disease

South Africa/Namibia **Version 1:** June 2024

For full prescribing information refer to the professional information approved by the medicines regulatory authority.
SOUTH AFRICA: S4 **CEREZYME® 400** (powder for concentrate for solution for infusion).
QUALITATIVE AND QUANTITATIVE COMPOSITION: Each reconstituted vial contains 400 units imiglucerase per 10 mL (40 U/mL). **REGISTRATION NUMBER:** 36/31/0179.
NAMIBIA: NS2 **CEREZYME® 400** (powder for concentrate for solution for infusion).
QUALITATIVE AND QUANTITATIVE COMPOSITION: Each reconstituted vial contains 400 units imiglucerase per 10 mL (40 U/mL). **REGISTRATION NUMBER:** 14/31/0064.
HOLDER OF CERTIFICATE OF REGISTRATION: sanofi-aventis south africa (pty) ltd., Reg. no.: 1996/010381/07, Floor 5, Building I, Hertford Office Park,
90 Bekker Road, Midrand, 2196. Tel: (011) 256 3700.
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1. OBJECTIVES AND GOALS

The objective of this document is to provide guidance to health care providers for the management of patients receiving Cerezyme® 400 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 program, if applicable.
- 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 health care provider 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 home care nurse, with the appropriate training, may assist the patient to ensure optimal treatment. The treating health care provider is responsible for the appointment and training of a home care nurse, where required

3. REQUIREMENTS FOR HOME INFUSION

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

Patient assessment by treating health care provider

- 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 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 health care provider.

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 healthcare provider and the patient and/or caregiver.
- 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.
- Patients experiencing adverse events need to immediately seek the attention of the treating health care provider or nurse and 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 home care nurse will be decided upon and communicated by the treating health care provider, and discussed and agreed upon with the patient and/or caregiver.

Should the patient prefer full support when having their infusion at home, the home care 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 home care nurse while the infusion is being prepared. The home care nurse will explain and demonstrate the complete infusion procedure to the patient and/or caregiver.

At subsequent visits, the home care 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 home care nurse's supervision until they feel confident with the entire infusion procedure.

While reconstituting and administering Cerezyme®, the procedure described in the approved Professional Information must be closely observed.

A care provider, or hospital can provide equipment required to administer the home infusion.

5. ORGANISATION OF HOME INFUSION

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

PATIENT GENERAL

- The patient and/or caregiver, have been informed by the treating health care provider 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 by the treating health care provider 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 logbook.
  - The patient/caregiver records each administration of Cerezyme® in the logbook.
  - In the event of an infusion associated reaction, the patient/caregiver should discontinue the infusion immediately and phone the treating health care provider and/or emergency number described in the logbook.

MEDICAL

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

TREATING HEALTH CARE PROVIDER

- The treating health care provider is responsible for ensuring the adequate training of the patient/caregiver prior to home infusions being started
- The treating health care provider is responsible for the appointment and training of a home care nurse, where required
- The treating health care provider is responsible for the initiation of all necessary administrative actions, allowing all stakeholders (pharmacy, nurse, patient, caregiver) to proceed.
- The treating health care provider 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 (Appendix 11.2).
- The patient should be regularly monitored for infusion associated reactions and maintenance of therapeutic goals as per the published guidelines for children (Charrow, 2004) and adults (Weinreb, 2004).
- In case of non-serious and serious adverse events, please complete an Adverse event (AE) form (Appendix 11.1) and send it to the Sanofi Pharmacovigilance Department at ZA.Drugsafety@sanofi.com or call +27 11 256 3700. Adverse events considered serious must be reported to Sanofi as soon as possible and at the latest within one business day

HOSPITAL/PHARMACY

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

HOME CARE NURSE

- The treating health care provider is responsible for the appointment and training of a home care nurse, where required
- The home care nurse is qualified to give IV infusions.
- The home care nurse has been trained on Cerezyme® and is aware of the possible side effects and the actions to be taken should they occur.
- The home care nurse will establish with the patient and/or caregiver the level of support necessary.
- The home care nurse will strictly follow the prescribed method of administration of Cerezyme® as stated in the logbook.
- For each patient, the home care nurse will have a coordinating task vis-à-vis treating health care provider and patient/caregiver in organizing the treatment at home.
- The home care nurse records each administration of Cerezyme® in the logbook.
- In the event of an infusion associated reaction, the home care nurse should discontinue the infusion immediately and phone the treating health care provider and/or the emergency number described in the logbook, or follow the infusion guide.

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 home care nurse/patient/caregiver each time Cerezyme® is administered.
- The patient 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 health care provider clearly states the dose, the infusion rate, as well as any changes.
- The home care nurse/patient/caregiver records the findings and actions from the initial interview and all relevant information from subsequent visits in the logbook. In the logbook, the treating health care provider clearly states what must be done and which medications are to be administered in the event of an infusion-associated reaction.

6. ADMINISTRATION OF CEREZYME®

6.1 Prescription

The Cerezyme® dose, infusion rate as well as any changes will be determined by the treating health care provider.

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).
  - NaCl 0.9% intravenous solution and water for injection (supplied by the hospital/pharmacy to the patient or to a third party with the appropriate prescription).

6.3 Preparation of the Cerezyme® infusion for intravenous use

Requisites

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

- Vials of Cerezyme® 400 (400 U per vial);
  - Must be stored at a temperature of between +2°C and +8°C.
- Sterile water for injections (10.2 mL per vial) is required to reconstitute Cerezyme®
- NaCl 0.9% solution, 100 - 200 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, 20mL 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

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 one 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, and reconstitute each vial with 10.2 mL water for injections; the reconstituted volume is 10.6 mL**.
5. Inject the water gently to the inside wall of each vial of Cerezyme® (avoid forceful impact of water for injections on the powder).
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 gentle 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. **The reconstituted volume of each vial allows accurate withdrawal of 10,0 mL (equal to 400 units) from each vial.**
11. After reconstitution, Cerezyme® should be inspected visually before use. The reconstituted solution must be a clear, colourless liquid, free from foreign matter
12. If you notice foreign matter in or discolouration of the liquid, do not use the product and contact the home nurse/healthcare provider.

Dilution

1. Disinfect the cap/opening of the NaCl 0.9% solution bag 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 7 vials of Cerezyme® of 400 units each, remove 70 mL (=7 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 20 or 50 mL syringes, withdraw 10 mL from each of the reconstituted Cerezyme® vials and combine the withdrawn volumes. At the point when these quantities are withdrawn, 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. Gently rotate, invert or massage the infusion bag.
6. Do not shake the solution.
7. The appropriate amount of Cerezyme® for each patient is diluted with 0,9 % sodium chloride injection solution, to a final volume of 100 – 200 mL

8. Because this is a protein solution, slight flocculation (described as thin translucent fibres) occurs occasionally after dilution. 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 a 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 (refer to the infusion rate specified by the treating health care provider in the Logbook).

Administration

Do not infuse Cerezyme® in the same IV line with other products.

The reconstituted and diluted solution is administered by intravenous infusion over 1-2 hours, and should be administered 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. Monitor vital signs at 15 minutes, 60 minutes and at the completion of the infusion or as directed by the treating health care provider.

The Cerezyme® dose, infusion rate as well as any changes will be determined by the treating health care provider.

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 infection. 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 and tested to date have developed IgG antibody to Cerezyme® during the first year of therapy. Patients who developed IgG antibody largely did so within 6 months of treatment and rarely developed antibodies to Cerezyme® after 12 months of therapy. Approximately 46 % of patients with detectable IgG antibodies experienced symptoms of hypersensitivity. Patients with antibodies to Cerezyme® have a higher risk of hypersensitivity reaction. Conversely, not all patients with symptoms of hypersensitivity have detectable IgG antibody. It is suggested that patients be monitored periodically for IgG antibody formation during the first year of treatment.

Treatment with Cerezyme® should be approached with caution in patients who have exhibited symptoms of hypersensitivity to the product.

Anaphylactoid reaction has been reported in less than 1% of the patient population. Further treatment with imiglucerase should be conducted with caution. Most patients have successfully continued therapy after a reduction in rate of infusion and pre-treatment with antihistamines and/or corticosteroids.

Adverse reactions are listed by system organ class and frequency: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000), not known (cannot be estimated from the available data) in Table 1 below.

TABLE 1. COMMON AND UNCOMMON ADVERSE EVENTS

System organ class	Common	Uncommon	Not known
Immune system disorders	Hypersensitivity, anaphylactoid reactions		
Nervous system disorders	Fatigue, dizziness, headache		
Cardiac disorders	Cyanosis, tachycardia		
Vascular disorders	Hypotension, flushing		
Respiratory, thoracic and mediastinal disorders	Chest discomfort, dyspnoea, coughing		
Gastrointestinal disorders	Nausea, vomiting, abdominal pain, diarrhoea		
Skin and subcutaneous tissue disorders	Angioedema, urticaria, pruritus, rash		Transient peripheral oedema
General disorders and administration site conditions	Backache, fever, chills	Infusion site discomfort, pruritus, burning, swelling or sterile abscess at the site of venipuncture	

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 non-serious and serious adverse events, please complete an AE form (Appendix 11.1) and contact the Sanofi Pharmacovigilance Department at ZA.Drugsafety@sanofi.com or call +27 11 256 3700. Adverse events considered serious must be reported to Sanofi as soon as possible and at the latest within one business day.

9. FURTHER INFORMATION

Please refer to the attached approved Professional Information (Appendix 11.3) for complete indication statements and the full details of the prescribing information for Cerezyme® 400 (imiglucerase).

10. REFERENCES

1. Belmatoug, N. and S. Mamine. Traitement à domicile de la maladie de Gaucher. *Presse Med* 2009;38: 2546-2549. **2.** Charrow J, Andersson HC, Kaplan P, Kolodny EH, Mistry P, Pastores G, et al. Enzyme replacement therapy and monitoring for children with type 1 Gaucher disease: Consensus recommendations. *J Pediatr* 2004;144:112-20. **3.** Hughes, D.A., A. MLilligan and A. Mehta. Home therapy for lysosomal storage disorders. *Br J Nurs* 2007;16(22): 1384, 1386-9. **4.** Milligan, A., D. Hughes, S. Goodwin, L. Richfield and A. Mehta. Intravenous enzyme replacement therapy: better in home or hospital? *Br J Nurs* 2006;15(6): 330-3. **5.** Starzyk, K., S. Richards, J. Yee, S.E. Smith and W. Kingma. The long-term international safety experience of imiglucerase therapy for Gaucher disease. *Mol Genet Metab* 2007;90(2): 157-63. **6.** Weinreb N, Aggio MC, Andersson HC, Andria G, Charrow J, Clarke JT, et al. Gaucher disease type 1: revised recommendations on evaluations and monitoring for adult patients. *Semin Hematol* 2004;41(4 Suppl 5):15-22. **7.** National Healthcare Protocol for Gaucher Disease, Haute Autorité de Santé, 2007 – www.has-sante.fr

11. APPENDICES

- Adverse Event Form
- Logbook
- Approved Professional Information

11.1 ADVERSE EVENT FORM

Enzyme Replacement Therapies Adverse Event Reporting Form		
SANOFI ERT Adverse Event Report Form		
Report Date: DD-MMM-YYYY		
Report Type: [ ] Initial [ ] Follow-up		
Registry ID (if applicable):		
Patient Initials:		
Drug/Biologic: (select ONE) [ ] Cerezyme [ ] NONE Reason:		
Lot Number & Expiration Date:		
Reporter Name, Institution, Address:		
Age:		
Gender: [ ] Male [ ] Female		
Indication: Gaucher Phenotype: [ ] Type 1 [ ] Type 2 [ ] Type 3 Pompe Phenotype: [ ] Infantile-onset [ ] Late-onset		
Country:		
Dose:	Units:	Frequency:
Date of Birth: DD-MMM-YYYY		
Administration schedule (including rate ramp schedule):		
Reporter's Telephone Number:		
Height: [ ] cm [ ] in		
Weight: [ ] kg [ ] lb		
Route: [ ] I.V. [ ] Other		
Reporter's Fax Number:		
Pregnant? [ ] Yes [ ] No [ ] NA If yes, please complete pregnancy forms		
Therapy Start Date: DD-MMM-YYYY		
Please provide the patient's medical history.		
Date of Last Dose (prior to event): DD-MMM-YYYY		
Therapy Stop Date: DD-MMM-YYYY [ ] continuing		

Event term(s): (List one term per column) Provide Diagnosis, if known	Event #1	Event #2	Event #3	Event #4
	Event Start Date & Time: DD-MMM-YYYY	Event Start Date & Time: DD-MMM-YYYY	Event Start Date & Time: DD-MMM-YYYY	Event Start Date & Time: DD-MMM-YYYY
	Event Stop Date & Time: DD-MMM-YYYY [ ] Ongoing	Event Stop Date & Time: DD-MMM-YYYY [ ] Ongoing	Event Stop Date & Time: DD-MMM-YYYY [ ] Ongoing	Event Stop Date & Time: DD-MMM-YYYY [ ] Ongoing
Event Serious:	[ ] YES [ ] NO	[ ] YES [ ] NO	[ ] YES [ ] NO	[ ] YES [ ] NO
Infusion Associated Reaction?: If yes, please include time to onset	[ ] YES [ ] NO Time to onset:	[ ] YES [ ] NO Time to onset:	[ ] YES [ ] NO Time to onset:	[ ] YES [ ] NO Time to onset:
Severity:	[ ] Mild [ ] Moderate [ ] Severe	[ ] Mild [ ] Moderate [ ] Severe	[ ] Mild [ ] Moderate [ ] Severe	[ ] Mild [ ] Moderate [ ] Severe
Outcome of the Event:	[ ] Recovered [ ] Recovered with sequelae Specify: [ ] Recovering [ ] Not recovered [ ] Fatal Cause of death: [ ] Unknown	[ ] Recovered [ ] Recovered with sequelae Specify: [ ] Recovering [ ] Not recovered [ ] Fatal Cause of death: [ ] Unknown	[ ] Recovered [ ] Recovered with sequelae Specify: [ ] Recovering [ ] Not recovered [ ] Fatal Cause of death: [ ] Unknown	[ ] Recovered [ ] Recovered with sequelae Specify: [ ] Recovering [ ] Not recovered [ ] Fatal Cause of death: [ ] Unknown
Serious Criteria:	[ ] Not applicable (non-serious) [ ] Life-threatening [ ] Fatal [ ] Inpatient/ prolonged hospitalization [ ] Persistent or significant disability/ incapacity [ ] Important medical event [ ] Congenital anomaly/birth defect	[ ] Not applicable (non-serious) [ ] Life-threatening [ ] Fatal [ ] Inpatient/ prolonged hospitalization [ ] Persistent or significant disability/ incapacity [ ] Important medical event [ ] Congenital anomaly/birth defect	[ ] Not applicable (non-serious) [ ] Life-threatening [ ] Fatal [ ] Inpatient/ prolonged hospitalization [ ] Persistent or significant disability/ incapacity [ ] Important medical event [ ] Congenital anomaly/birth defect	[ ] Not applicable (non-serious) [ ] Life-threatening [ ] Fatal [ ] Inpatient/ prolonged hospitalization [ ] Persistent or significant disability/ incapacity [ ] Important medical event [ ] Congenital anomaly/birth defect

Action Taken with Suspect Drug:	Event #1	Event #2	Event #3	Event #4
	[ ] Discontinued [ ] Dose changed Specify: [ ] None Did event abate after drug was stopped or dose changed? [ ] Yes [ ] No [ ] Unknown Date Stopped: DD-MMM-YYYY Did event reoccur after drug was restarted? [ ] Yes [ ] No [ ] NA [ ] Unknown Date Re-started: DD-MMM-YYYY	[ ] Discontinued [ ] Dose changed Specify: [ ] None Did event abate after drug was stopped or dose changed? [ ] Yes [ ] No [ ] Unknown Date Stopped: DD-MMM-YYYY Did event reoccur after drug was restarted? [ ] Yes [ ] No [ ] NA [ ] Unknown Date Re-started: DD-MMM-YYYY	[ ] Discontinued [ ] Dose changed Specify: [ ] None Did event abate after drug was stopped or dose changed? [ ] Yes [ ] No [ ] Unknown Date Stopped: DD-MMM-YYYY Did event reoccur after drug was restarted? [ ] Yes [ ] No [ ] NA [ ] Unknown Date Re-started: DD-MMM-YYYY	[ ] Discontinued [ ] Dose changed Specify: [ ] None Did event abate after drug was stopped or dose changed? [ ] Yes [ ] No [ ] Unknown Date Stopped: DD-MMM-YYYY Did event reoccur after drug was restarted? [ ] Yes [ ] No [ ] NA [ ] Unknown Date Re-started: DD-MMM-YYYY
Was Treatment Administered? If yes, please specify.:	[ ] YES Specify: [ ] NO	[ ] YES Specify: [ ] NO	[ ] YES Specify: [ ] NO	[ ] YES Specify: [ ] NO

If Fatal, date of death: DD-MMM-YYYY Autopsy: [ ] Yes [ ] No If Yes, please attach Cause of Death:	Was a 0.2 micron inline filter used during the administration? [ ] Yes [ ] No

HOME INFUSION INFORMATION

Did the patient receive the infusion associated with this event in a home setting?
[ ] Yes [ ] No [ ] Unknown

Who administered the home infusion associated with this event?

On what date did the patient begin home infusions? DD-MMM-YYYY

Please approximate the number of home infusions the patient has received to date:

Has the patient reported similar events during infusion that occurred in a hospital setting?
[ ] Yes [ ] No [ ] Unknown

Did you notice a medication error that may explain the occurrence of the event(s)?
[ ] Yes [ ] No If yes, please explain:

If the patient experienced an IAR, were samples for immunology testing obtained?
If so, please provide date and timing of sample draw as well as test type.

Type Sample date	IgE Yes [ ] No [ ] DD-MMM-YYYY	Complement Yes [ ] No [ ] DD-MMM-YYYY	Tryptase Yes [ ] No [ ] DD-MMM-YYYY	Other DD-MMM-YYYY

PRE-TREATMENT MEDICATIONS

Medication	Dose, Schedule or Total Daily Dose (units)	Start Date	Stop Date	Indication
		DD-MMM-YYYY	DD-MMM-YYYY [ ] continuing	
		DD-MMM-YYYY	DD-MMM-YYYY [ ] continuing	
		DD-MMM-YYYY	DD-MMM-YYYY [ ] continuing	
		DD-MMM-YYYY	DD-MMM-YYYY [ ] continuing	

CONCOMITANT MEDICATIONS

Medication	Dose, Schedule or Total Daily Dose (units)	Start Date	Stop Date	Indication
		DD-MMM-YYYY	DD-MMM-YYYY [ ] continuing	
		DD-MMM-YYYY	DD-MMM-YYYY [ ] continuing	
		DD-MMM-YYYY	DD-MMM-YYYY [ ] continuing	
		DD-MMM-YYYY	DD-MMM-YYYY [ ] continuing	

Adverse Event Description: Diagnosis (if known). Also describe signs, symptoms, severity, time course, relevant medical history, and relevant laboratory data. Include results of confirmatory procedures if any. Indicate any medication required to treat the event.

Physician
(Printed Name)

Physician Signature
(Signed Name)

DD-MMM-YYYY

11.2: LOG BOOK

General Data		
Patient	Name:	
	Address:	
	Postal Code:	
	Telephone:	
Nurse	Name:	
	Organisation:	
	Telephone:	
Treating Health Care provider	Name:	
	Hospital	
	Address:	
	Telephone:	
Pharmacy	Name:	
	Place:	
	Telephone:	
Emergency number	Telephone:	

Administration details and dosing regimen (To be completed by treating health care provider)	
Dose:	
Frequency:	
Rate of infusion:	
Required reconstituted volume (mL)	
Total volume in infusion bag (mL)	
Pre-treatment medication (if applicable):	
Findings and actions from initial interview	
Cerezyme® administered since	Date (dd-mmm-yyyy):
First infusion at home	Date (dd-mmm-yyyy):
Reasons for Cerezyme® infusion at home	
Indicate support to be provided by infusion nurse at home	

Infusion data	
Date of infusion	Date (dd-mmm-yyyy):
Clinical status	
Dose	
Number of vials used	
Duration of administration	
Rate of administration	
Problems/Remarks	

Date of infusion	Date (dd-mmm-yyyy):
Clinical status	
Dose	
Number of vials used	
Duration of administration	
Rate of administration	
Problems/Remarks	

Date of infusion	Date (dd-mmm-yyyy):
Clinical status	
Dose	
Number of vials used	
Duration of administration	
Rate of administration	
Problems/Remarks	

Date of infusion	Date (dd-mmm-yyyy):
Clinical status	
Dose	
Number of vials used	
Duration of administration	
Rate of administration	
Problems/Remarks	

11.3 APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CEREZYME® 400 powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each reconstituted vial contains 400 units imiglucerase per 10 mL (40 U/mL).
Contains sugar alcohol: each reconstituted vial contains 320 mg mannitol per 10 mL.

An enzyme unit (U) is defined as the amount of enzyme that catalyses the hydrolysis of 1 micromole of the synthetic substrate para-nitrophenyl-ß-D-glucopyranoside (pNP-Glc) per minute at 37 °C.

Imiglucerase is a modified form of human acid ß-glucosidase and is produced by recombinant DNA technology using a mammalian Chinese hamster ovary (CHO) cell culture, with mannose modification for targeting macrophages.

Excipient with known effect:
CEREZYME contains sodium (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.
CEREZYME is supplied as a sterile, non-pyrogenic, white to off-white lyophilised cake of powder.
The reconstituted powder is a clear, colourless liquid, free from foreign matter.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

CEREZYME is indicated for long-term enzyme replacement therapy for paediatric and adult patients with a confirmed diagnosis of non-neuronopathic (Type I) 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:

a. anaemia after exclusion of other causes, such as iron deficiency,

b. thrombocytopenia,

c. bone disease after exclusion of other causes, such as vitamin D deficiency, and

d. hepatomegaly or splenomegaly.

4.2. Posology and method of administration

Therapy with CEREZYME should be directed by health care providers knowledgeable in the management of patients with Gaucher disease.

Posology

CEREZYME is administered by intravenous infusion over 1 – 2 hours.
Dosage should be individualised to each patient. 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).
Disease severity may dictate that treatment be initiated at a relatively high dose or relatively frequent administration.
Dosage adjustments should be made on an individual basis, and may increase or decrease, based on achievement of therapeutic goals as assessed by routine comprehensive evaluations of the patient's clinical manifestations.

Paediatric population:

No dose adjustment is necessary for the paediatric population.

Chronic neuronopathic Gaucher patients:

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.

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 U/kg/min. At subsequent administrations, infusion rate may be increased, but should not exceed 1 U/kg/min. Infusion rate increases should occur under supervision of a health care provider.

Home infusion:

Infusion of CEREZYME at home may be considered for patients who have tolerated their infusions well for several months.
The decision to have the patient move to home infusion should be made after evaluation and recommendation by the treating health care provider. Infusion of CEREZYME by the patient or caregiver at home requires training by a health care provider 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 contact a health care provider. 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 provider.

For instructions on reconstitution and dilution of CEREZYME before administration, see section 6.6.

4.3. Contraindications

Hypersensitivity to the active ingredient, imiglucerase, or to any other inactive ingredients listed in section 6.1.

4.4. Special warnings and precautions for use

Approximately 15 % of patients treated and tested to date have developed IgG antibodies to CEREZYME during the first year of therapy. Patients who developed IgG antibodies largely did so within 6 months of treatment and rarely developed antibodies to CEREZYME after 12 months of therapy. Approximately 46 % of patients with detectable IgG antibodies experienced symptoms of hypersensitivity.

Patients with antibodies to CEREZYME have a higher risk of hypersensitivity reaction. Conversely, not all patients with symptoms of hypersensitivity have detectable IgG antibodies. It is suggested that patients be monitored periodically for IgG antibody formation during the first year of treatment.

Treatment with CEREZYME should be approached with caution in patients who have exhibited symptoms of hypersensitivity to the product.
Anaphylactoid reaction has been reported in less than 1 % of the patient population. Further treatment with imiglucerase should be conducted with caution. Most patients have successfully continued therapy after a reduction in rate of infusion and pretreatment with antihistamines and/or corticosteroids.
In less than 1 % of the patient population, pulmonary hypertension and pneumonia have also been observed during treatment with CEREZYME. Pulmonary hypertension and pneumonia are known complications of Gaucher disease, and have been observed both in patients receiving and not receiving CEREZYME. No causal relationship with CEREZYME has been established. Patients with respiratory symptoms in the absence of fever should be evaluated for the presence of pulmonary hypertension.

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.

Caution may be advisable in administration of CEREZYME to patients previously treated with placenta-derived glucocerebrosidase and who have exhibited symptoms of hypersensitivity or developed antibody to placenta-derived glucocerebrosidase.

Paediatric use:

The safety and effectiveness of CEREZYME have been established in patients between 2 and 16 years of age. Use of CEREZYME in this age group is supported by evidence from adequate and well-controlled studies of CEREZYME and CEREDASE® (alglucerase injection) in adult and paediatric patients, with additional data obtained from the medical literature and from long-term post-marketing experience. CEREZYME has been administered to patients younger than 2 years of age, however, the safety and effectiveness in patients younger than 2 years have not been established.

Sodium:
CEREZYME contains approximately 34 mg sodium per reconstituted vial (i.e 3,4 mg/mL), equivalent to 1,7 % of the WHO recommended maximum daily intake of 2 g sodium for an adult. Additionally, CEREZYME is administered in 0,9 % sodium chloride intravenous solution (see section 6.6). To be taken into consideration by patients on a sodium-controlled diet.

4.5. Interaction with other medicines and other forms of interaction
Data regarding interactions with other medication are not available.

4.6. Fertility, pregnancy and lactation
Pregnancy
Safety in pregnancy has not been established.

Limited data are available suggesting that the use of CEREZYME is beneficial to control the underlying Gaucher disease in pregnancy. This data indicate no malformative toxicity for the fetus by CEREZYME, although the statistical evidence is low. Fetal demise has been reported rarely, although it is not clear whether this is 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/fetal development, parturition and postnatal development. It is not known whether CEREZYME passes via the placenta to the developing fetus.

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 individualisation of the dose, according to the needs of the patient and therapeutic response.

Caution should be exercised when prescribing to pregnant women.

Lactation:
It is not known whether imiglucerase is excreted in human breast milk, however, the enzyme is likely to be digested in the child's gastrointestinal tract. Many substances are excreted in human milk, therefore caution should be exercised when CEREZYME is administered to a nursing woman.

4.7. Effects on ability to drive and use machines
CEREZYME has no or negligible influence on the ability to drive a vehicle and use machines.

4.8. Undesirable effects
Since the approval of CEREZYME in May 1994, a worldwide post-marketing database of spontaneously-reported adverse events and adverse events discussed in the medical literature has been maintained. The percentage of events for each reported adverse reaction term has been calculated, using the number of patients from these sources as the denominator for total patient exposure to CEREZYME since 1994. Actual patient exposure is difficult to obtain due to the voluntary nature of the data-base and continuous accrual and loss of patients over that span of time. The actual number of patients exposed to CEREZYME since 1994 is likely to be greater than estimated from these voluntary sources and, therefore, the percentage calculated for the frequencies of adverse reactions are most likely greater than the actual incidences. Experience in patients treated with CEREZYME has revealed that approximately 13,8 % of patients experienced adverse events, which were judged to be related to CEREZYME administration and which occurred with an increase in frequency.

Tabulated list of adverse reactions:
Adverse reactions are listed by system organ class and frequency: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000), not known (cannot be estimated from the available data).

System organ class	Common	Uncommon	Not Known
Immune system disorders	Hypersensitivity[1] Anaphylactoid reactions[2]		
Nervous system disorders	Fatigue[4] Dizziness[4] Headache[4]		
Cardiac disorders	Cyanosis* Tachycardia[4]		
Vascular disorders	Hypotension* Flushing*		
Respiratory, thoracic and mediastinal disorders	Chest discomfort* Dyspnoea* Coughing*		
Gastrointestinal disorders	Nausea[4] Vomiting[4] Abdominal pain[4] Diarrhoea[4]		
Skin and subcutaneous tissue disorders	Angioedema* Urticaria* Pruritus* Rash[4]		Transient peripheral oedema
General disorders and administration site conditions	Backache[4] Fever[4] Chills[4]	Infusion site discomfort, pruritus, burning, swelling or sterile abscess at the site of venipuncture[3]	

1. Symptoms suggestive of hypersensitivity (* marked in the table above) have been noted in approximately 6,6 % of patients. Onset of such symptoms has occurred during or shortly after infusions.
2. Each of these events was found to occur in < 1,5 % of the total patient population. Pretreatment with antihistamines and/or corticosteroids and reduced rate of infusion has allowed continued use of CEREZYME in most patients. Also see section 4.4.
3. Some of the adverse events were related to the route of administration. Each of these events was found to occur in < 1 % of the total patient population.
4. Additional adverse reactions have been reported in approximately 6,5 % of patients treated with CEREZYME. Each of these events was found to occur in < 1,5 % of the total patient population therefore the frequency for all is "common".

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of CEREZYME is important. It allows continued monitoring of the benefit/risk balance of CEREZYME. Health care providers are asked to report any suspected adverse reactions to:

- The Pharmacovigilance Unit at Sanofi: za.drugsafety@sanofi.com (email) or 011 256 3700 (tel), or
- SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9. Overdose
Experience with doses up to 240 U/kg every 2 weeks have been reported. At that dose there have been no reports of obvious toxicity.

5. PHARMACOLOGICAL PROPERTIES
5.1. Pharmacodynamic properties
Category and class: A 31. Enzymatic preparation.
Pharmacotherapeutic group: Enzymes – Imiglucerase (recombinant macrophage targeted ß-glucocerebrosidase).
ATC code: A16AB02.

CEREZYME is an analogue of the human enzyme ß-glucocerebrosidase produced by recombinant DNA technology. ß-Glucocerebrosidase (D-glucosyl-N-acylsphingosine glucohydrolase, E.C. 3.2.1.45) is a lysosomal glycoprotein enzyme, which catalyses the hydrolysis of the glycolipid glucocerebroside to glucose and ceramide. Gaucher disease is a rare recessively inherited metabolic disorder that results from a deficiency of the lysosomal enzyme acid ß-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 hyperimmunoglobulinaemia, 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.

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.
It is reported that enzyme replacement therapy has stabilised and/or slowed the progression of neurological involvement in some patients with chronic neuronopathic disease. However, no controlled clinical studies have been conducted.

5.2. Pharmacokinetic properties
During one hour intravenous infusions of four doses (7,5, 15, 30, 60 U/kg) of CEREZYME, 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 ± SD: 14,5 ± 4,0 mL/min/kg). The volume of distribution corrected for weight ranged from 0,09 to 0,15 L/kg (0,12 ± 0,02 L/kg). These variables do not appear to be influenced by dose or duration of infusion. However, only one or two patients were studied at each dose level and infusion rate. The pharmacokinetics of CEREZYME do not appear to be different from placenta-derived glucocerebrosidase.
In patients who develop IgG antibodies to CEREZYME, an apparent effect on serum enzyme levels resulted in diminished volume of distribution and clearance and increased elimination half-life compared to patients without antibodies (see section 4.4).

6. PHARMACEUTICAL PARTICULARS
6.1. List of excipients
Trisodium citrate (for pH adjustment)
Disodium hydrogen citrate (for pH adjustment)
Mannitol
Polysorbate 80.

6.2. Incompatibilities
In the absence of compatibility studies CEREZYME should not be mixed with other medicines.

6.3. Shelf life
Unopened vials:
36 months

Reconstituted solution:
Since CEREZYME does not contain any preservatives, vials should be promptly diluted after reconstitution and not be stored for subsequent use. CEREZYME after reconstitution, has been shown to be stable for up to 12 hours when stored at room temperature (25 °C) and at 2 – 8 °C.

Diluted solution:
From a microbiological safety point of view, the diluted solution 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 – 8 °C, protected from light.

6.4. Special precautions for storage
Store at 2 – 8 °C.
Discard any unused portion of the solution.
Do not use CEREZYME after the expiration date on the vial.

6.5. Nature and contents of container
The sterile lyophilised powder is packed into 20 mL clear glass vials, each packed into a unit carton.
Pack size: 1 vial.

6.6. Special precautions for disposal and other handling
Each vial of CEREZYME is for single use only.

CEREZYME powder for concentrate for solution for infusion has to be reconstituted with sterile water for injection, 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 dosage regimen and remove the vials from the refrigerator.

Relatively low toxicity, combined with the extended time course of response, allows small dosage adjustments to 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 techniques:

Reconstitution:
Reconstitute each vial with 10,2 mL sterile water for injection. 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.
The final concentration and administration volume are provided in the following table:

	400 unit vial
Sterile water for reconstitution	10,2 mL
Final volume of reconstituted product	10,6 mL
Concentration after reconstitution	40 U/mL
Withdrawal volume	10,0 mL
Units of enzyme within final volume	400 units

After reconstitution, the solution is a clear, colourless liquid, free from foreign matter. The reconstituted solution should be further diluted. Before further dilution, visually inspect the reconstituted solution in each vial for foreign particles and discolouration. Do not use vials exhibiting foreign particles or discolouration. Since CEREZYME does not contain any preservatives, vials should be promptly diluted after reconstitution and not be stored for subsequent use.

For in-use storage time after reconstitution, see section 6.3.

Dilution:
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. The appropriate amount of CEREZYME for each patient is diluted with 0,9 % sodium chloride injection, to a final volume of 100 – 200 mL.

Administration:
Because CEREZYME is a protein solution, slight flocculation (described as thin translucent fibres) occurs occasionally after dilution. The diluted solution may be filtered through an in-line low protein-binding 0,2 µm filter during administration in order 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 to 8 °C under protection from light; but microbiological safety will depend on the reconstitution and dilution having been performed aseptically.

For in-use storage time after dilution, refer to section 6.3.

7. HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd,
Hertford Office Park, Building I, 5th Floor
90 Bekker Road, Vorna Valley
Midrand 2196
South Africa

8. REGISTRATION NUMBER

36/31/0179

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

7 March 2003

10. DATE OF REVISION OF THE TEXT

15 August 2022

Namibia
Scheduling status: NS2
Registration No.: 14/31/0064

Cerezyme®
imiglucerase