Ireland

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Agalsidase beta
home infusion therapy:

A guide for healthcare professionals treating patients with Fabry disease

VERSION NO. 4.0

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

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via contacting HPRA Pharmacovigilance, website: www.hpra.ie. Side effects should also be reported to Sanofi: Tel: 01 403 5600 e-mail: IEPharmacovigilance@sanofi.com

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1. OBJECTIVES AND GOALS

The objective of the Healthcare Professional Home Infusion Guide is **to minimise the risks of hypersensitivity reactions and medication errors in the home infusion setting.** It contains relevant information for prescribing and administering agalsidase beta and training of the patient or caregiver for home infusion.

Enzyme replacement therapy is available for some of the lysosomal storage disorders and, to improve convenience and quality of life, **the intravenous treatment can be transferred to the patient's home if specific requirements can be fulfilled [1-3].** Agalsidase beta infusion therapy is available for treatment of patients with Fabry disease and is generally well tolerated [4-6].

If the requirements can be fulfilled, **the patient can receive treatment within the living environment which increases comfort and flexibility of infusion timing.** Moreover, it reduces the constraints of hospital resources [1].

The decision to transfer agalsidase beta treatment to the patient's home setting is made by the treating physician and should take into account patient preferences and medical status.

The home infusion will take place under the responsibility of the treating physician. Distribution of the educational material should only be executed if the treating physician decides that the patient is eligible for home infusion treatment. **It is the responsibility of the treating physician to ensure a safe administration trying to avoid risks of medication errors and hypersensitivity reactions.** This should be checked and documented by the treating physician.

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2. INFORMATION FOR HCPS PRESCRIBING AGALSIDASE BETA

- The prescribing HCP is **responsible for the initiation of all necessary administrative actions** which will allow the other parties involved (patient and/or caregiver(s), administering HCP, pharmacy) to proceed.
- The prescribing HCP is **responsible for ensuring that a rapid and reliable line of communication is available** for the other parties.
- The prescribing HCP is **responsible for selection of the infusion rate and dose**. The infusion rate of agalsidase beta that was tolerated by the patient in a more controlled setting (e.g., in the hospital or other medical setting) must not be changed in the home setting, unless necessary due to safety considerations. **Any changes in agalsidase beta administration must be clearly documented in the Logbook.**
- If a patient experiences an adverse event during home infusion, they will 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.

2.1 Information on the risk of medication errors

Medication errors may potentially be more likely to occur in the home setting because of insufficient understanding of the instructions for use of the product. The most frequently reported medication error events post-treatment are: 'product dose omission', 'inappropriate schedule of product administration', 'product use issue' and 'incorrect dose administered'. The majority of medication error events pertained to dose or deviation from the standard schedule.

In cases of medication error associated with an adverse event(s), the concomitant adverse events most frequently reported were those events commonly seen with infusion-associated reactions or due to underlying Fabry disease, such as malaise, pain, pain in extremity, pyrexia or fatigue.

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2.2 Assessing eligibility for home infusion

Before making any arrangements, the physician overseeing the patient's clinical care must determine if the patient fulfils the following primary criteria for transfer of hospital-based infusion therapy to the patient's home setting:

- **The patient is considered medically stable and has been tolerating their infusions well.** A comprehensive evaluation must be completed before deciding on transfer of therapy.
- **The patient must have received agalsidase beta infusions in a controlled setting for several months.**
- **The patient must have a history of adherence to the prescribed infusion schedule.**

2.3 Information on the Logbook for HCPs prescribing agalsidase beta

The Logbook serves **as a means of communication** for all involved in administering agalsidase beta in the home-setting and **must be provided to each patient upon initiation of treatment with agalsidase beta**.

The Logbook will allow the prescribing HCP to document the requirements for home infusion.

In the Logbook, **the prescribing HCP** should include:

- Date of the first infusion at home.
- Administration details of dose, frequency, rate of infusion, the required reconstituted volume and total volume in infusion bag.
- What pre-medications are required, if any.
- Reason for home infusion.
- Findings and actions from the initial interview.
- Details of the support to be provided by the administering HCP.
- What action to take, including which emergency medications to administer in the event of a hypersensitivity reaction in line with current medical standards for emergency treatment.
- The contact details of the prescribing HCP and the country-specific national emergency number.

The Logbook should be updated with any subsequent changes to the prescription.

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2.4 Patient materials

- It is important that all patients receiving home infusion are provided with the "Manual for patients with Fabry disease who receive home infusion", the Logbook and the package leaflet (the package leaflet is available on the medicines.ie website: www.medicines.ie).

3. INFORMATION FOR HCPS ADMINISTERING THE INFUSION

3.1 Information on the risk of medication errors

Medication errors may potentially be more likely to occur in the home setting because of insufficient understanding of the instructions for use of the product. The most frequently reported medication error events post-treatment are: 'product dose omission', 'inappropriate schedule of product administration', 'product use issue' and 'incorrect dose administered'. The majority of medication error events pertained to dose or deviation from the standard schedule.

To minimise the risk of medication errors associated with home infusion, the administering HCP:

- Should strictly follow the prescribed method of preparation and administration of agalsidase beta as stated in this manual.
- Should strictly follow the administration requirements of agalsidase beta detailed by the prescribing HCP in the Logbook.
- Should ensure that the patient and/or caregiver is properly trained on how to administer/self-administer agalsidase beta.

In cases of medication error associated with an adverse event(s), the concomitant adverse events most frequently reported were those events commonly seen with infusion-associated reactions or due to underlying Fabry disease, such as malaise, pain, pain in extremity, pyrexia or fatigue.

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3.2 Information on the risk of hypersensitivity reactions

A small number of patients have experienced reactions suggestive of immediate (Type I) hypersensitivity.

In the event of a severe allergic or anaphylactic-type reaction, the following actions should be taken:

- The infusion should be immediately discontinued.
- The prescribing HCP should be contacted and/or the country-specific national emergency number described in the Logbook.
- Emergency treatment should be initiated as per the instructions provided by the prescribing HCP in the Logbook.
- Any hypersensitivity reaction, and action taken, should be recorded in the Logbook.

Signs and symptoms of hypersensitivity reactions include localised swelling of the face, mouth and throat, bronchoconstriction, hypotension, urticaria, dysphagia, rash, dyspnoea, flushing, chest discomfort, pruritus and nasal congestion.

The administering HCP should ensure the patient and/or caregiver is properly trained on how to recognise hypersensitivity reactions and what actions to take if self-administering.

3.3 Information on the Logbook for HCPs administering the infusion

The Logbook serves as a **means of communication** for all involved in administering agalsidase beta in the home-setting and **must be updated each time the patient is administered treatment with agalsidase beta.**

The administering HCP should update the Logbook with details of every infusion session.

This includes:

- The required reconstitution volume.
- The number of vials used.
- The duration of the administration.
- The rate of administration.
- Details of any problems related to the infusion.

The administering HCP should train the patient/caregiver on how to complete the Logbook in the event of self-administration.

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The patient should be advised to **take the Logbook along to the hospital at each appointment** and bring it home afterwards.

4. ADMINISTRATION OF AGALSIDASE BETA

Instructions for use relating to the reconstitution, dilution and administration can be found in the Summary of Product Characteristics (SmPC). The SmPC is available on the medicines.ie website: www.medicines.ie

4.1 Prescription

The agalsidase beta dose, required reconstituted volume, infusion rate, premedication, emergency medication, as well as any changes will be determined by the treating physician. The prescription must be written in the Logbook. Any changes of this prescription (dose or infusion rate) must again be reported in the Logbook.

4.2 Supplies

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

- Vials of agalsidase beta (5 mg or 35 mg per vial); must be stored in a clean refrigerator at a temperature of between +2°C and +8°C.
- Sterile water for injection to reconstitute agalsidase beta.
- NaCl 0.9% solution, 2 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 2 ml, 10 ml and 50 ml syringes depending on dose of agalsidase beta.

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- 3 x sterile hypodermic needles (1.1 x 40 mm).
- 1 x infusion needle.
- In-line low protein-binding 0.2 micron filter.
- Infusion-administration set (infusion line).
- Tape.
- Sterile skin cleansing swabs.
- Sharps bin.
- Hand wash.
- Tourniquet.
- Additional requisites if using a venous access device: heparin, NaCl 0.9% solution, needles, syringes, dressing pack, sterile gloves, Gripper needle.
- Pre-infusion treatment medication (if applicable; as described in the Logbook).
- Emergency medication (as described in Logbook).

4.3 STEP 1: Preparation of the materials

4.3 Preparations

NOTE: The instructions for use (reconstitution, dilution and administration) can be found in the SmPC. A detailed description is provided in this section.

1. Prepare a clean work area and lay out the requisites.
2. The vials with agalsidase beta must 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 agalsidase beta after the labelled expiry date).
4. Verify if the number of vials received is correct.
5. Prepare only the number of vials required for one infusion.

Note: The storage instructions as described in the instructions for use in the SmPC must be followed.

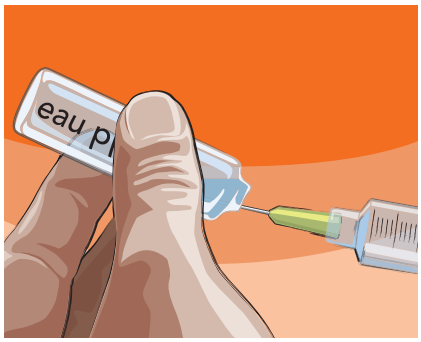
The SmPC is available on the medicines.ie website: www.medicines.ie

4.4 STEP 2: Disinfect the vial

4.4 Reconstituting agalsidase beta

1. Remove the flip-off cap from the agalsidase beta vial.
2. Disinfect the rubber stopper of the agalsidase beta vial with chlorhexidine and allow to air dry.
3. Open the sterile water for injections.
4. Draw the required amount (ml) of sterile water into the syringe.

   For 35 mg vials, reconstitute each vial with 7.2 ml water for injection.
   For 5 mg vials, reconstitute each vial with 1.1 ml water for injection.



4.4 STEP 4: Draw the required amount of sterile water into the syringe

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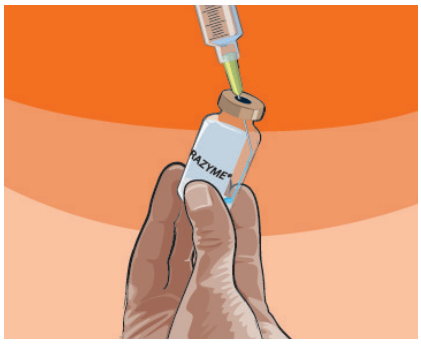
5. Avoid forcefully ejecting the water for injections from the syringe onto the powder, to minimise foaming. This should be done by slow drop-wise addition of the water for injection down the inside of the vial. Roll and tilt each vial gently. Do not invert, swirl or shake the vial.
6. Repeat the process for more agalsidase beta vials, if required.
7. Small bubbles may appear after the mixing.
8. Let the solution settle for a few minutes to allow any bubbles present to disappear and to ensure that the powder is properly reconstituted.
9. After reconstitution, agalsidase beta must be inspected visually before use. The reconstituted solution must be a clear, colourless liquid and free from foreign matter. Because this is a protein solution, slight flocculation/ cloudiness (described as thin translucent fibres) may occur occasionally after dilution.
10. If foreign matter or discolouration of the liquid is noticed, the product must not be used and the HCP and/or treating physician must be informed.
11. It is recommended that the vials be diluted promptly after reconstitution to minimise protein particle formation over time.
12. Any unused product or waste material must be disposed of in accordance with local requirements.



4.4 STEP 5: Avoid forcefully ejecting the water for injections from the syringe

4.5 Dilution

1. Disinfect the cap/opening of 1 or 2 bags of NaCl 0.9% solution using chlorhexidine and allow to air dry.
2. The volume of reconstituted agalsidase beta solution must be the same as the prescribed volume in the Logbook.
3. Insert the needle in the cap of the infusion bag and slowly withdraw a volume of NaCl 0.9% solution, equivalent to the volume of the reconstituted agalsidase beta solution to be added.

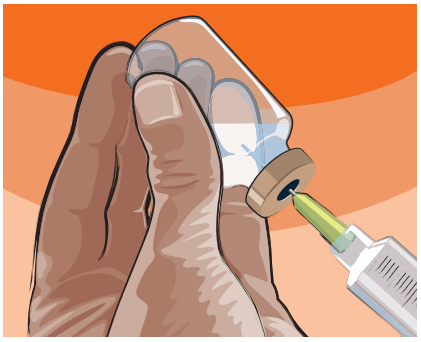
   For instance, if the prescribed reconstituted volume is 14 ml, remove 14 ml (2 x 7 ml) from the bag of NaCl solution. Never remove more than half the content of the bag of NaCl solution to ensure that at least half the diluted solution consists of NaCl solution.

4. Remove the airspace within the infusion bag by withdrawing the air into a 50 ml syringe.
5. Slowly withdraw the reconstituted solution from each vial up to the total volume required.

   At the point when these quantities have been drawn, the reconstituted product should not contain any foam.

6. Gently inject the total volume of the reconstituted agalsidase beta solution into the bag of NaCl 0.9% solution.
7. Carefully mix this agalsidase beta solution by gently inverting or lightly massaging the infusion bag. Do not shake or excessively agitate the infusion bag.

4.5 STEP 3: Slowly withdraw the required volume of NaCl 0.9% solution, equivalent to the volume of the reconstituted agalsidase beta



4.5 STEP 5: Slowly withdraw the reconstituted solution from each vial up to the total volume required

4.5 STEP 5: The reconstituted product should not contain any foam

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8. The diluted solution should be filtered through an in-line low protein-binding 0.2 micron filter during administration.

4.6 Filling the infusion line

1. Remove the infusion system from the package and close it using the roller clamp. Connect the in-line filter to the infusion line.
2. Connect the spike in the NaCl 0.9% solution bag that does not contain agalsidase beta 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 agalsidase beta to the y-system. Keep the clamp closed.

4.7 Inserting the needle in the vein

In case of self-infusion, the adult person present during the infusion session should have been adequately trained (by the HCP, treating physician, or his/her medical designate) on the technique of needle insertion.

1. Ensure that some strips of tape 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 infusion 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. Use tape to keep the needle in place. Connect the system with filter to the needle.
7. Remove the tourniquet; 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 using a new needle. Open the clamp for NaCl 0.9% solution.
8. Adjust the infusion rate according to the prescription (Logbook) and open the valve. Sit down and relax while the infusion takes place.

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4.8 Administration

- From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage and conditions are the responsibility of the user. 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 and away from light.
- The agalsidase beta dose, infusion rate, as well as any changes, will be determined by the treating physician. The treatment must not be altered in the home setting, unless medically warranted at the discretion of the treating physician.
- After the agalsidase beta infusion has been completed, the system is flushed with NaCl 0.9% solution at the same rate and the needle removed.

4.9 Preparation of the agalsidase beta infusion in case of venous access device

When the patient has a venous access device for the delivery of agalsidase beta, the patient and/or caregiver(s) will be shown how to care for the device by the HCP, if this has not already been demonstrated during hospital-based infusions.

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(s) will be informed of the following necessary steps:

- When in use, cover site with transparent occlusive dressing. No dressing is required when not in use.
- Flush with 5 ml NaCl 0.9% solution before and after each use.
- Flush with 5 ml heparin (100 U/ml) after each use.

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5. TRAINING ON PREPARATION AND ADMINISTERING AGALSIDASE BETA

(for patients who are going to self-administer the product)

In principle, the initial instructions will be given in the hospital and the level of support required from the administrating HCP in the home setting will be discussed and agreed by the prescribing HCP and the patient and/or caregiver(s).

The administrating HCP will carry out the entire procedure for at least the first infusion at the patient's home. Subsequently, should the patient then prefer to carry out the procedure him/herself, or with the assistance of a caregiver, the following conditions must be followed:

- **The patient and/or caregiver(s) will receive adequate training from the administrating HCP on how the infusion is being prepared and administered.**
  The administrating HCP will explain and demonstrate the complete infusion procedure to the patient and/or caregiver(s), including training in hand hygiene, proper disinfection and aseptic handling when preparing the infusion.
- At subsequent visits, **the administrating HCP will be present to assist, if required, until the patient and/or caregiver(s) feels confident with the entire infusion procedure.**
- While reconstituting and administering agalsidase beta, **the procedures described** in the Fabrazyme Summary of Product Characteristics and in **section 4 "Administration of agalsidase beta" of this document must be adhered to,** and each administration of agalsidase beta should be recorded in the Logbook.
- In case of any problems with the reconstitution and administration of agalsidase beta, the patient or caregiver(s) should discontinue reconstitution or administration and contact the administering or prescribing HCP to determine appropriate action (contact details in Logbook).

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- **If self-infusion skills have been acquired, the infusion should always be administered in the presence of an adult** knowledgeable about the infusion procedures and adequately trained on how to handle a hypersensitivity reaction or medication error, as assessed by the treating physician or administering HCP.
- **The patient and/or caregiver must be informed about the associated risks of home infusion and what actions to take in the event of a hypersensitivity reaction or medication error.**
- **If the patient feels the treatment is not efficacious, he/she should consult the treating physician.**

5.1 Patient materials

The administering HCP should ensure that all patients receiving home infusion are provided with the "Manual for patients with Fabry disease who receive home infusion", the Logbook and the package leaflet (the package leaflet is available on the medicines.ie website: www.medicines.ie).

6. AGALSIDASE BETA SAFETY INFORMATION

Please refer to the current SmPC for complete information on the safety of agalsidase beta. (The SmPC is available on the medicines.ie website: www.medicines.ie).

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7. SAFETY REPORTING

Healthcare professionals are asked to report any suspected adverse reactions via contacting HPRA Pharmacovigilance, website: www.hpra.ie.

Side effects should also be reported to Sanofi Pharmacovigilance: Tel: 01 403 5600 e-mail: IEPharmacovigilance@sanofi.com

If the patient becomes aware that a mistake was made in the preparation and/or administration of the drug, the patient or HCP should inform the treating physician to determine appropriate action. Any medication errors should be reported as a spontaneous report to Sanofi's Pharmacovigilance Department by the treating physician.

8. FURTHER INFORMATION

Please refer to the Summary of Product Characteristics for complete indication statements and further information about the approved use of agalsidase beta. The SmPC is available on the medicines.ie website; www.medicines.ie

Other detailed information on agalsidase beta is available at the following website: HPRA (see www.hpra.ie) or via Sanofi medical information Tel: 014035600.

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9. REFERENCES

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