Important Safety Information
HCP Guide - Home Infusion for Nexviazyme (Avalglucosidase alfa) (aRMM)

This manual is not intended to suggest or recommend home infusion therapy for any patient. The decision to use home infusion therapy is made by the treating physician, who knows the patient's current clinical status and previous infusion history, in consultation with the patient. This manual is solely to share information that might be helpful to healthcare professionals and their patients when treated via home infusion therapy.

This document has been reviewed and approved by the Saudi Food and Drug Authority (SFDA)

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HCP Guide - Home Infusion for (avalglucosidase alfa)

1. Objectives and goals

- The main objective of this document is to **provide guidance to healthcare professionals for the management of patients receiving Avaglucosidase alfa at home** to mitigate the important risks "medication errors in home infusion setting" and "infusion associated reactions including hypersensitivity and anaphylactic reactions with or without development of IgG and IgE antibodies."

- Enzyme replacement therapy (ERT) is available for some of the lysosomal storage disorders. Avaglucosidase alfa infusion therapy is available for treatment of patients with Pompe disease and is generally well tolerated [1]. To improve patient's convenience and quality of life, **ERT can be transferred to the patient's home if specific requirements can be fulfilled [2-3].**

- If the requirements can be fulfilled, **the patient can receive treatment within the living environment which increases comfort and flexibility of infusion schedule.** It avoids spending time travelling to and from the hospital, and patients will be able to follow a normal schooling program and organize social and professional activities more easily. Moreover, it reduces the constraints of hospital resources.

- **The decision to transfer Avaglucosidase alfa infusion to the patient's home setting is made by the treating physician** and should consider 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 reduce and mitigate the risk of IARs, in particular hypersensitivity reactions.** This should be checked and documented by the treating physician.

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

2. Requirements and organization of home infusion

- The treating physician is responsible for the organization of the home infusion and needs to agree upon the home infusion procedure. The infusion nurse will carry out the entire procedure for the infusions at the patient's home.

- Once the patient has been considered eligible for home infusion based on the primary criteria, a set of requirements must be considered to ensure that Avaglucosidase alfa infusions can be safely, efficiently, and reliably delivered at the patient's home.

- In principle, the initial instructions and training of the infusion nurse will be given in the hospital and the level of support required from the infusion nurse in the home setting will be discussed and agreed by the treating physician and the patient and/or caregiver(s).

a. Patient

General

• The patient and/or caregiver(s) **have been informed by the treating physician about the treatment to be provided at home, the associated risks, and the provision of medical assistance at home,** like hypersensitivity reactions and medication errors' and must agree to the treatment at home.

• The patient and/or caregiver(s) **understand the illness and can recognize adverse events like hypersensitivity reactions and medication errors** and understand the procedure to be followed should these occur.

• **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 Avaglucosidase alfa and other infusion supplies.

• The patient has been **informed that the infusion should always be administered in the presence of an adult,** i.e. the infusion nurse adequately trained on how to handle in case of an infusion associated reaction (IAR) and medication errors and/or a caregiver.

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 Avaglucosidase alfa infusions at home.

The patient **has venous access or a central venous access device** that allows adequate infusion.

b. Treating Physician

The treating physician **is responsible for the initiation of all necessary administrative actions** which will allow the other parties involved (patient and/or caregiver(s), infusion nurse, pharmacy) to proceed.

• **The treating physician is responsible for selection of the infusion rate and dose.** The infusion rate of Avaglucosidase alfa that was tolerated by the patient in a more controlled setting (e.g., in the hospital or in another appropriate setting of outpatient care) must not be changed in the home setting, unless necessary due to safety considerations.

• **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 to the patient in order to avoid risks of medication errors and reduce and mitigate the risk of IARs, in particular hypersensitivity reactions**. This should be checked and documented by the treating physician.

• **Pre-infusion treatment,** if administered in the hospital or another appropriate setting of outpatient care (e.g. antihistamines, paracetamol, ibuprofen, corticosteroids), **must be provided based on the patient-specific prescription.** This treatment must not be altered in the home setting, unless medically warranted at the discretion of the treating physician.

• **Emergency treatment must be available and provided** based on the patient-specific prescription.

• The treating physician **must ensure that a rapid and reliable line of communication is available** to expedite an emergency response in case immediate medical attention is required.

• **Patients experiencing adverse reactions (ADRs) need to contact the treating physician or his/her medical designate immediately.** Subsequent infusions may need to occur in a hospital or in another appropriate setting of outpatient care until no such adverse reaction is present at the discretion of the treating physician or his/her medical designate.

• **Regular disease monitoring of the home-infused patient** is the responsibility of the treating physician.

• **Appropriate scheduling and monitoring of the infusions** is the responsibility of the treating physician and infusion nurse.

c. Pharmacy and Infusion Equipment

Treatment and all necessary equipment will be provided according to local arrangements and regulations.

d. Infusion Nurse

The infusion nurse will have a **coordinating role** vis-à-vis the treating physician and the patient and/or caregiver(s) in organizing the treatment at home, and will establish with the treating physician, patient and/or caregiver(s) the level of support necessary in the home.

• The infusion nurse is **qualified to give IV infusions,** has been appropriately trained on the administration of Avaglucosidase alfa , and is trained on the possible adverse events (including serious adverse events such as anaphylactoid reactions) and the actions to be taken should they occur.

• The infusion nurse **will strictly follow the prescribed method of preparation and administration** of Avaglucosidase alfa as stated in this Guide

• The infusion nurse will strictly follow the prescribed dose and infusion rate of Avaglucosidase alfa as stated by the treating physician.

• The infusion nurse **records each administration of Avaglucosidase alfa**

• **Appropriate scheduling and monitoring of the infusions** is the responsibility of the treating physician and infusion nurse.

• **Medications must be available to respond to an emergency situation,** if necessary. **In the event of IAR, the infusion nurse must discontinue the infusion and phone the treating physician . The treating physician and/or the country-specific national emergency number must also be phoned if an IAR occurs shortly after completion of the infusion. Any IAR must be recorded in a Logbook or equivalent for subsequent reporting to the MAH by the infusion nurse or the treating physician (see Section 6)**

3. Administration

• Instructions for use relating to the reconstitution, dilution and administration can be found in the Summary of Product Characteristics (SPC) of Avaglucosidase alfa [1]. A detailed description is provided in this section.

a. Prescription

• Avaglucosidase alfa 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 a Logbook or equivalent. Any changes of this prescription (dose or infusion rate) must again be reported in a Logbook Or equivalent.

b. Supplies

• Supplies are generally provided by the hospital/pharmacy to the patient or to a third party with the appropriate prescription:

• Vials of Avaglucosidase alfa, powder for concentrate for solution for infusion (100 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 Avaglucosidase alfa (10 ml per vial).

• 5% glucose in water for IV administration. See table 1 for needed volume based on prescribed dose.

• 5% glucose in water to flush infusion line post-infusion.
• Chlorhexidine 0.5% in alcohol 70% (antiseptic solution).
• Appropriate number of 10 mL, 20 mL and 50 mL syringes depending on dose of Avaglucosidase alfa.
• Sterile hypodermic needles (caliber Gauge 20G or 21G). Plan 2 needles per 4 vials.
• In-line low protein-binding 0.2 µm filter.
• Supply for the installation of a peripheral venous path or central venous path according to local guidelines.
• Supply needed for IV infusion according to local guidelines and material required to comply with hygienic and aseptic conditions as well as waste disposal rules according to local guidelines
• Pretreatment medication (if applicable)
• Emergency medication

c. Preparation

NOTE: The instructions for use (reconstitution, dilution and administration) can be found in the Avaglucosidase alfa SPC [1]. A detailed description is provided in this section.

Patients with an acute underlying illness at the time of Avaglucosidase alfa infusion appear to be at greater risk for IARs. Thus, the infusion nurse must check the patient medical status before starting the preparation of Avaglucosidase alfa .

Before reconstitution, it is also recommended to install the venous pathway (peripheral venous catheter), or to connect the patient's central venous pathway, according to local protocols, to ensure Avaglucosidase alfa can be administered immediately after its reconstitution.

- Check the number of vials is appropriate.
- Remove the vials from the refrigerator and set aside for approximately 30 minutes to allow them to reach room temperature.
- Check the expiry date printed on the bottom of the vial pack (do not use Avaglucosidase alfa after the labelled expiry date).

d. Reconstitution

Aseptic technique should be used during reconstitution.

- Remove the flip-off cap from the Avaglucosidase alfa vial.
- Disinfect the rubber stopper of the Avaglucosidase alfa vial with chlorhexidine and allow to air dry.
- Open the sterile water for injections.
- Draw the required amount (ml) of sterile water into the syringe.
    - Each vial should be reconstituted by slowly injecting 10.0 ml of water for injections (WFI) to each vial. Each vial will yield 100 mg/10 ml (10 mg/ml).
- Avoid forceful impact of the WFI on the powder and foaming. This is performed by slow drop-wise addition of the WFI down the inside of the vial and not directly onto the lyophilized powder.
- Each vial should be tilted and rolled gently to dissolve the lyophilized powder. It should not be inverted, swirled, or shaken.
- Small bubbles may appear after the mixing. Let the solution settle for a few minutes to allow any bubbles present to disappear and to ensure that the powder is properly reconstituted.
- Repeat the process for all Avaglucosidase alfa vials. To limit the risk of coring the cap, needles may be changed every 4 vials.

- Immediate visual inspection should be performed on the reconstituted vials for particulate matter and discoloration. If upon immediate inspection particles are observed or if the solution is discolored, the reconstituted medicinal product should not be used. The solution should be allowed to become dissolved.
- It is recommended that the vials be diluted promptly after reconstitution to minimize protein particle formation over time.

From a microbiological point of view, the reconstituted product should be used immediately. If not used for dilution immediately, in-use storage times and conditions prior to dilution are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C.

e. Dilution

The reconstituted solution should be diluted in 5% glucose in water to a final concentration of 0.5 mg/ml to 4 mg/ml. See Table 1 for the recommended total infusion volume based on the patient weight.

- Disinfect the cap/opening of 1 bag of 5% glucose solution using chlorhexidine and allow to air dry.
- Insert the needle in the cap of the infusion bag and withdraw a volume of 5% glucose solution, equivalent to the volume of the reconstituted Avaglucosidase alfa solution to be added. This corresponds to 1 mL for 10mg of prescribed Avaglucosidase alfa .
    - For example, if the prescribed dose is 1200 mg, the volume of Avaglucosidase alfa to be diluted is 1200mg x 10mg/mL = 120 mL. Therefore, 120 mL should be removed from the 5% bag of glucose solution.
- The reconstituted solution should be added slowly and directly into the 5% glucose solution. Foaming or agitation of the infusion bag should be avoided. Air introduction into the infusion bag should be avoided.
- Mix the infusion bag solution by gently invert or massage the infusion bag. It should not be shaken.

Table 1. Projected intravenous infusion volumes for Nexviazyme administration by patient weight at 20 and 40 mg/kg Dose

Patient Weight Range (kg)	Total infusion volume for 20 mg/kg (ml)	Total infusion volume for 40 mg/kg (ml)
1.25 to 5	50	50
5.1 to 10	50	100
10.1 to 20	100	200
20.1 to 30	150	300
30.1 to 35	200	400
35.1 to 50	250	500
50.1 to 60	300	600
60.1 to 100	500	1000
100.1 to 120	600	1200
120.1 to 140	700	1400
140.1 to 160	800	1600
160.1 to 180	900	1800
180.1 to 200	1000	2000

From a microbiological point of view, the medicinal product should be used immediately after dilution. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, followed by 9 hours at room temperature (up to 25°C) to allow for infusion.

f. Administration

- Once Avaglucosidase alfa has been diluted, attach the tubing to the infusion bag.
- Connect a low protein binding, 0.2 µm in line filter to the infusion bag
    - *This step avoids administration of inadvertently introduced particles during dose IV preparation.*
- Prime the infusion line with the diluted Avaglucosidase alfa via gravity and connect the infusion line to the patient vein path.
- **Before starting the infusion, check the patient's pulse, blood pressure, respiratory rate and temperature.**
- After the infusion is complete, the intravenous line should be flushed with glucose 5% in water at the same rate and the needle removed.
- Nexviazyme should not be infused in the same intravenous line with other medicinal products.

Avaglucosidase alfa 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.

4. Safety information

a. Recognition of adverse drug reactions (ADRs)

• The most frequently reported adverse drug reactions (ADRs) are infusion associated reactions (IAR) whether administered at hospital or in another appropriate setting of outpatient care.

• An infusion associated reaction (IAR) is defined as any adverse event (AE) occurring during the infusion or during the hours following infusion and assessed as potentially causally related to the administration of the product (Avaglucosidase alfa) Related events occurring after the post-infusion period may be considered IARs at the discretion of the reporter.

• In clinical studies with Avaglucosidase alfa, IARs were reported to occur at any time during and/or within a few hours after the infusion of Avaglucosidase alfa and were more likely with higher infusion rates.

• Hypersensitivity reactions, including anaphylaxis, have also been reported in Nexviazyme-treated patients.

• Table 2 illustrates the observed signs and symptoms of IAR/hypersensitivity/anaphylactic reactions. Please refer to section 4 of the current Summary of Product Characteristics (SPC) for complete information on the safety of Avaglucosidase alfa [1].

Table 2. Observed signs and symptoms of IARs/hypersensitivity/anaphylactic reactions

Respiratory	Respiratory distress Cough Breath sounds abnormal

	Oxygen saturation decreased
Cardiovascular	Tachycardia Flushing Hypertension
Gastrointestinal	Nausea Diarrhea Vomiting Lip swelling Swollen tongue
Cutaneous	Erythema Pruritus Rash Urticaria Hyperhidrosis
Nervous system	Dizziness Headache Tremor
General disorders and administration site conditions	Chest discomfort Chills Fatigue Influenza like illness Pain
Eye	Ocular hyperemia
Musculoskeletal	Pain in extremity

- Patients with an acute underlying illness at the time of Nexviazyme infusion appear to be at greater risk for IARs.
- Patients with advanced Pompe disease may have compromised cardiac and respiratory function, which may predispose them to a higher risk of severe complications from IARs.
- Antihistamines, antipyretics, and/or corticosteroids can be given to prevent or reduce IARs. However, IARs may still occur in patients after receiving pre-treatment.

b. Clinical management of ADRs

The majority of IARs and hypersensitivity reactions were mild or moderate and were managed with standard clinical practices (see section 4.4 and 4.8 of Avaglucosidase alfa SPC for further details) [1].

If the patient experiences IAR including hypersensitivity and anaphylactic reactions during the home infusion, the infusion process should be stopped immediately but not removed, and appropriate medical treatment should be initiated if needed. Please see figures 1 and 2 as examples. **Subsequent infusions may need to occur in a hospital or in an appropriate setting of outpatient care until no such adverse reaction is present**. Dose and infusion rate must not be changed without consulting the responsible physician.

Figure 1. Clinical management of mild to moderate reactions

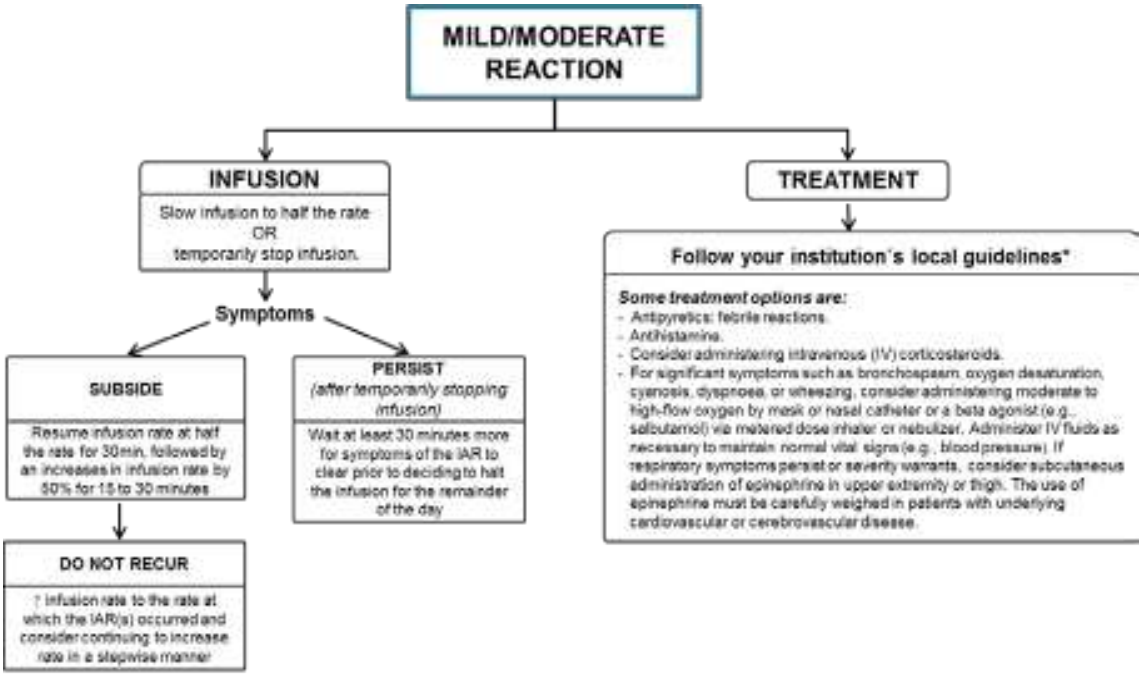

Figure 2. Clinical management of severe reactions

5. Safety reporting

• An adverse event (AE) is defined as any untoward physical, psychological, or behavioral 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 in-patient hospitalization or prolongation of an existing hospitalization.
- 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 jeopardize 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)

Call Center: 19999

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

Website: https://ade.sfda.gov.sa/

And SANOFI Pharmacovigilance:

Phone: +966-544-284-797

E-mail: Ksa_pharmacovigilance@sanofi.com

If the patient becomes aware that a mistake was made in the preparation and/or administration of the drug, the patient or infusion nurse 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.

6. Further information

Please refer to the SPC for complete indication statements and further information about the approved use of Avaglucosidase alfa

7. References

[1] Avaglucosidase alfa SPC

[2] Hughes DA, Milligan A, Mehta A (2007). Home therapy for lysosomal storage disorders. Br J Nurs 16:1384, 6-9

[3] Parini R, Pozzi K, Di Mauro S, et al (2010). Intravenous enzyme replacement therapy: hospital vs home. Br J Nurs 19:892-4, 6-8