Aldurazyme® (laronidase) Home Infusion Guide for Health Care Professionals

Version 1.0, 15 Feb 2024

This document is approved by The Executive Directorate of Pharmacovigilance, at SFDA.

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 prescribing Health Care Professional (HCP), who knows the patient's current clinical status and previous infusion history, in consultation with the patient and/or his/her caregiver. This manual is solely to share information that might be helpful to HCP and their patients/caregivers when treated via home infusion therapy.

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What Aldurazyme is and what is it used for?

Aldurazyme is used to treat patients with MPS I disease (Mucopolysaccharidosis I). It is given to treat the non-neurological manifestations of the disease.

People with MPS I disease have either a low level or no level of an enzyme called α-L-iduronidase, which breaks down specific substances (glycosaminoglycans) in the body. As a result, these substances do not get broken down and processed by the body as they should. They accumulate in many tissues in the body, which causes the symptoms of MPS I.

Aldurazyme is an artificial enzyme called laronidase. This can replace the natural enzyme which is lacking in MPS I disease.

02
OBJECTIVES AND GOALS

- The main objective of this document is to provide guidance to healthcare professionals for the management of patients receiving Aldurazyme 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."

- Aldurazyme infusion therapy is the only available approved therapy for the treatment of the non-neurological manifestations of individuals affected by Mucopolysaccharidosis type I (MPS I) disease and is generally well tolerated. To improve patient's convenience and quality of life, Enzyme replacement therapy (ERT) infusions can be transferred to the patient's home if specific requirements can be fulfilled. If the requirements can be fulfilled, the patient can receive treatment within the living environment which increases comfort and flexibility of infusion schedule.

- The decision to transfer Aldurazyme infusion to the patient's home setting is made by the prescribing HCP and should reflect patient and/or caregiver preferences and medical status.

- The home infusion will take place under the responsibility of the prescribing HCP. Distribution of the educational material should only be executed if the prescribing HCP decides that the patient is eligible for home infusion treatment.

- It is the responsibility of the prescribing HCP to ensure a safe administration trying to avoid risks of medication errors and reduce and mitigate the risk of infusion associated reactions (IARs), particularly hypersensitivity reactions.

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

03
INFORMATION FOR HCP PRESCRIBING ALDURAZYME

3.A) GENERAL REQUIREMENTS FOR HOME INFUSION

- Infusion of Aldurazyme at home may be considered for patients who are tolerating their infusions well and have no history of moderate or severe IARs for a few months. The decision to have a patient move to home infusion should be made after evaluation and upon recommendation by the treating HCP.

- Home infusion infrastructure, resources, and procedures, including training, must be established and available to the healthcare professional. Home infusion should be supervised by a healthcare professional who should be always available during the home infusion and for a specified time after infusion. Appropriate information should be given by the treating HCP and/or infusion HCP to the patient and/or caregiver prior to initiation of home infusion.

- Dose and infusion rate should remain constant while at home, and not be changed without supervision of a prescribing HCP.

- If the patient experiences adverse reactions during the home infusion, the infusion process should be stopped immediately, and appropriate medical treatment should be initiated (see section 4.4). Subsequent infusions may need to occur in a hospital or in an appropriate setting of outpatient care until no such adverse reaction is present.

- Before making any arrangements for setting up Aldurazyme® infusion at home, the prescribing HCP determines whether the patient meets the eligibility criteria below:

  - *After a complete medical assessment, the patients' condition is deemed stable to receive infusions at home.*
  - *The prescribing HCP is responsible for the recommendation to administer Aldurazyme infusions at home.*
  - *A patient's underlying co-morbidities and ability to adhere to the home infusion requirements need to be considered when evaluating the patient for eligibility to receive home infusion.*
  - *Patient must not be affected by an advanced disease state that puts him or her at higher risk of complications that require advanced medical resuscitation measures only available on a hospital setting.*

- *The patient has been tolerating the infusion well in a hospital or outpatient setting and has no history of moderate to severe IARs for a few months.*
- *The patient has reasonably uncomplicated venous access or may have a central venous access device placed that allows adequate infusion.*
- *The patient must be willing and able to comply with home infusion procedures, patients' home environment should be adequate to perform the home infusion procedure.*
- *Home infusion infrastructure, resources, and procedures, including training, must be established and available to the healthcare professional.*

- Dose and infusion rate should remain constant while at home, and not be changed without supervision of a prescribing HCP.

3.B) REQUIREMENTS AND ORGANIZATION OF HOME INFUSION

- The prescribing HCP is responsible for the organization of the home infusion and needs to recommend the home infusion procedure. The infusion health care professional (HCP) 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 Aldurazyme infusions can be safely, efficiently, and reliably delivered at the patient's home.

- In principle, the initial instructions and training of the infusion HCP will be provided according to local regulations, by the health institution (hospital) or the correspondent experienced HCP and the level of support required from the infusion HCP in the home setting will be discussed and agreed by the prescribing HCP and the patient and/or caregiver(s).

3.C) PATIENT READINESS

- The patient and/or caregiver(s) have been informed by the prescribing HCP 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 favorable to home infusion therapy including a clean environment with electricity, water, telephone access, refrigeration, and physical space to support storage of Aldurazyme and other infusion supplies.

- The patient/caregiver must be informed that the infusion should always be administered in the presence of an experienced HCP, i.e., the infusion HCP who must be adequately trained on how to act in case of an infusion associated reaction (IAR).

- The patient must be physically and mentally able to undergo the infusions at home.
- The prescribing HCP is responsible for the recommendation to receive Aldurazyme® infusions at home.
- The patient has venous access or a central venous access device that allows adequate infusion.
- The patient must adhere to regular disease monitoring as required by the prescribing HCP .
- The patient and/or the caregiver must receive the patient/caregiver guide which includes information about the signs and symptoms of IARs and the recommended actions for their management. In additionan Infusion Diary should be given to the patient/caregiver to record the infusion details and document any adverse events and IARs, including allergic-type hypersensitivity reactions before, during or after the infusion. In this guide some contact data must be filled in by the prescribing HCP. This guide should be completed by the patient/caregiver, kept by the patient at home and be shown to the treating HCP during regular follow-up visits.

3.D) HCPS PRESCRIBING ALDURAZYME

- 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), infusion HCP, pharmacy) to proceed with home infusion.
- The prescribing HCP has informed patient and/or caregiver(s) about the disease, treatment and home infusion procedure as listed in section 3. C PATIENT READINESS.
- The prescribing HCP is responsible for selection of the infusion rate and dose. The infusion rate of Aldurazyme that was previously tolerated by the patient in hospital or outpatient setting must not be changed in the home setting, unless necessary due to safety considerations.
- The home infusion will take place under the accountability of the prescribing HCP. Distribution of the educational material should only be executed if the prescribing HCP decides that the patient is eligible for home infusion treatment. It is the responsibility of the prescribing HCP to ensure a safe administration of therapy to the patient to avoid risks of medication errors and reduce and mitigate the risk of IARs, in particular hypersensitivity reactions. The infusion HCP should inform immediately the prescribing HCP if an IAR or hypersensitivity occurs.
- The prescribing HCP prescribes the medication including all necessary equipment for administration of Aldurazyme® at home.
- 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 prescribing HCP.

- Emergency treatment must be available and provided based on the patient-specific prescription in case of IARs. Instructions (e.g., in a logbook or equivalent) and a documented emergency plan must be given to the infusion HCP prior to setting up home infusion. In addition, cardiopulmonary resuscitation equipment should be readily available during the infusion at home.

- The prescribing HCP must make Sanofi aware about the occurrence of an event. It is recommended that the prescribing HCP records the sequence of the event/s and treatment/s implemented to resolve the event/s in the patient's medical chart to ensure adequate decision making for continuity of the home treatment.

- A report must be submitted to The National Pharmacovigilance Center (NPC) including the batch number of the administered product to improve traceability.

Call Center: 19999
E-mail: npc.drug@sfda.gov.sa
Website: https://ade.sfda.gov.sa/
As well as Sanofi Pharmacovigilance Department
Telephone: +966 54 4284 797, Fax: +966-11-205-7662
Email: Ksa_pharmacovigilance@sanofi.com

- The prescribing HCP must ensure that a rapid and reliable line of communication is available between him/her and the HCP performing the infusion at home, to expedite an emergency response in case immediate medical attention is required.

- Patients experiencing adverse reactions (ADRs) need to contact the prescribing HCP or his/her medical designate immediately. Events can occur during the infusion or up to several hours after the infusion has ended. 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 prescribing HCP or his/her medical designate.

- Regular disease monitoring of the home-infused patient is the responsibility of the prescribing HCP.

- Appropriate scheduling and monitoring of the infusions are the responsibility of the prescribing HCP and infusion HCP. In addition, the prescribing HCP establishes an infusion protocol to be documented by the infusion HCP (e.g., logbook or equivalent).

- The prescribing HCP must give the patient/caregiver guide to the patient/caregiver. This guide includes as, an annex, an infusion diary where patients may record the infusions and any side effects, during or after the infusion. Any adverse events (i.e., headache, etc.) experienced by the patient prior to the start of the infusion should also be recorded.

3.E) PRESCRIPTION

- The Aldurazyme dose, required volume, infusion rate, premedication, emergency medication, as well as any changes will be determined by the prescribing HCP. Any changes of the prescription (dose or infusion rate) must be documented. The prescription must be written in accordance to local regulations.

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INFORMATION REGARDING THE ADMINISTRATION OF ALDURAZYME®

Instructions for use relating to the dilution and administration can be found in the Summary of Product Characteristics (SmPC) of Aldurazyme. A detailed description is provided in this section.

- Pharmacy and Infusion Equipment Treatment and all necessary equipment will be provided according to local arrangements and regulations.

4.A) INFUSION HCP

- The infusion HCP will have a coordinating role with the prescribing HCP and the patient and/or caregiver(s) in organizing the treatment at home, and will establish with the prescribing HCP, patient and/or caregiver(s) the level of support necessary in the home.

- The infusion HCP is qualified to give IV infusions, has been appropriately trained on MPSI and the administration of Aldurazyme. In addition, he/she is trained in recognizing adverse events likely to occur (including serious adverse events such as anaphylactic reactions) and in the actions to be implemented to manage adverse events.

- Before the infusion, the infusion HCP will evaluate the patient to check the general condition of the patient to detect any condition that could interfere with the infusion. Any abnormalities should be noted on the infusion diary. If the patient has any acute illnesses the prescribing HCP should be consulted before proceeding with the infusion.

- The infusion HCP will strictly follow the prescribed method of preparation and administration of Aldurazyme and monitors the infusion, as prescribed by the prescribing HCP. The Infusion HCP verifies the presence of the prescribed premedication, emergency medication and equipment.

- The infusion HCP does not change the dose of Aldurazyme® and the infusion protocol (rate, duration, and steps of infusion) of Aldurazyme® prescribed by the prescribing HCP, unless necessary due to safety considerations.

- The infusion HCP documents each Aldurazyme® infusion in a logbook or equivalent and shares these with the prescribing HCP on regular basis as agreed with the prescribing HCP .

- Appropriate scheduling and monitoring of the infusions are the responsibility of the prescribing HCP and infusion HCP, in agreement with the patient or patient's caregiver.

- In case of occurrence of an adverse event, such as hypersensitivity reactions, medication errors in the home infusion setting, or IARs, during or after the infusion, the HCP must follow the patient-specific emergency measures provided by the prescribing HCP in an emergency plan. This can include lowering the infusion rate, stopping temporarily or discontinuing the infusion.

- In case of adverse events, the infusion HCP immediately contacts the prescribing HCP and/or calls the national emergency number. The infusion HCP documents the adverse event in a logbook or equivalent and reports adverse events, including medication errors in the home infusion setting, to ensure timely and accurate reporting to local health authorities and Sanofi according to local regulations.

4.B) REQUIRED SUPPLIES

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

- Vials of Aldurazyme, (500U per vial-5ml per vial, 100U/ml); must be stored in a clean refrigerator at a temperature of between +2°C and +8°C.

- Saline Solution 0.9% for IV administration. Bags of 100 ml for patients weighing 20 kg or less and bags of 250 ml for patient's weighing more than 20 Kg.

- Saline Solution 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 Aldurazyme.

- Sterile hypodermic needles. 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 management of 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 according to local Standard of care.

4.C) PREPARATION

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

Before starting the preparation of Aldurazyme, the infusion HCP must evaluate the patients' medical status including vital signs, and sign of fever or infection. Patients with an acute underlying illness, including a respiratory infection that may prompt respiratory distress, at the time of Aldurazyme® infusion appear to be at greater risk for IARs. In such cases, the infusion must not be performed, and treatment should be resumed when the patient has fully recovered, at the discretion of the prescribing HCP.

Before preparation of the infusion, 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 Aldurazyme infusion can be administered immediately after its preparation.

Infusion HCP should make sure the vials get to room temperature prior to preparing the solution for infusion, which can be done while placing the intravenous line. Vials should be removed from the refrigerator and set aside for approximately 20 minutes in advance in order to allow them to reach room temperature (below 30˚C)

- Check the number of vials is appropriate to the patient's weight,
- Consider that 1 vial contains 5ml of solution, and 1ml contains 100U, hence 1ml per kilo of the patient will be required for an appropriate dosing, since according to SmPC dose is 100U/Kg/week.
- Due to the frequent weight variation in this patient populations, it is highly recommended to have an updated weight measurement within the past 6 months, and within the 3 months in children younger than 6 years old.
- Check the expiry date printed on the bottom of the vial pack (do not use Aldurazyme after the labelled expiry date).
- Check that the solution contained in the vials is clear and without any residue. Solution should be transparent.
- Vials should not be shaken.

4.D) DILUTION

Aldurazyme solution should be diluted in 0.9% saline solution.

Once the number of vials to be required for the infusion has been determined and they have acquired room temperature, the preparation of the infusion solution should be immediately started.

Before dilution, each vial should be visually inspected for particulate matter and discoloration. The clear to slightly opalescent and colorless to pale yellow solution should be free of visible particles. Vials exhibiting particles or discoloration should not be used. Information for proceeding with this step can also be found in the SmPC for Aldurazyme.

- Disinfect the cap/opening of 1 bag of 0.9% saline solution using chlorhexidine and allow to air dry.
- Insert the needle in the cap of the infusion bag and withdraw a volume of 0.9% saline solution, equivalent to the volume of the Aldurazyme solution to be added.
- Withdraw and discard a volume of sodium chloride 9 mg/ml (0.9%) solution for infusion from the infusion bag equal to the total volume of Aldurazyme to be added.
- Withdraw the required volume from the Aldurazyme vials and combine the withdrawn volumes.
- Add the combined volumes of Aldurazyme to the sodium chloride 9 mg/ml (0.9%) solution for infusion.
- Aldurazyme solution should be added slowly and directly into the 0.9% saline solution. Foaming or agitation of the infusion bag should be avoided. Air introduction into the infusion bag should be avoided.
- Mix the solution for infusion gently.
- Prior to use visually inspect the solution for particulate matter. Only clear and colourless solutions without visible particles should be used.
- Adjustment to weight:

  If the patient's weight is less or equal to 20 kg, the total infusion volume should be 100ml of prepared infusion.

- Example: patient weight: 15 kg.

  - *Considering each ml of Aldurazyme contains 100U, and weekly dose for Aldurazyme is 100U/Kg/week, this equals 1ml/Kg/week. So, for this patient 15 ml of Aldurazyme will be needed. Each vial of Aldurazyme contains 5 ml. This patient will require 3 vials. The total volume of Aldurazyme is 15 ml. once determined, you should add the volume of Aldurazyme to complete the 100ml of infusion solution with 0.9% saline.*

  - *1ml Aldurazyme X patient weight (kg)/5, in this example 1X15/5=3 vials, and then: 100 ml -15ml of Aldurazyme= 85 ml of 0.9% saline solution to complete the 100 ml of total volume.*

- If the patient's weight is more than 20 kg, the total infusion volume should be 250 ml.

- Example: patient's weight: 35 kg.

  - *Considering each ml of Aldurazyme contains 100U, and weekly dose for Aldurazyme is 100U/Kg/week, this equals 1ml/Kg/week. So, for this patient 35 ml of Aldurazyme will be needed. Each vial of Aldurazyme contains 5 ml, so you will need 7 vials. You should add the volume of Aldurazyme to complete the 250ml of infusion solution with 0.9% saline.*

  - *1 ml Aldurazyme X patient weight (kg)/5, in this example 1X35/5=7 vials, and then: 250 ml -35ml of Aldurazyme= 215 ml of 0.9% saline solution to complete the 250 ml of total volume.*

- Mix the infusion bag solution by gently inverting or massaging the infusion bag. Do not shake the infusion bag because this abrupt movement can denaturalize (break) the enzyme, and it would lose effectiveness.

- The total volume of the infusion is determined by the patient's body weight and should be delivered over approximately 3 to 4 hours.

*From a microbiological safety point of view, the product should be used immediately. If not used immediately, in-use storage should not be longer than 24 hours at 2°C - 8°C provided that dilution has taken place under controlled and validated aseptic conditions.

4.E) ADMINISTRATION

- Once Aldurazyme 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 Aldurazyme via gravity and connect the infusion line to the patient's vein path.
- Before starting the infusion, check the patient's pulse, blood pressure, respiratory rate and body temperature.
- The initial infusion rate of 2 U/kg/h may be incrementally increased every fifteen minutes, if tolerated, to a maximum of 43 U/kg/h. The total volume of the administration should be delivered in approximately 3-4 hours.
  - *Table 1 shows the incremental Rates for 100 mL ALDURAZYME® Infusion (For use with Patients Weighing 20 kg or Less)*
  - *Table 2 shows the incremental Rates for 250 mL ALDURAZYME® Infusion (For use with Patients Weighing Greater than 20 kg)*

Table 1. Incremental Rates for 100 mL ALDURAZYME® Infusion (For use with Patients Weighing 20 kg or Less)

Infusion Rate	Criteria for infusion rate increase
2ml/h for 15 min	Obtain vital signs, if stable then increase the rate to...
4ml/h for 15 min	Obtain vital signs, if stable then increase the rate to...
8ml/h for 15 min	Obtain vital signs, if stable then increase the rate to...
16ml/h for 15 min	Obtain vital signs, if stable then increase the rate to...
32ml/h for approximately 3 hs	For the remainder of the infusion

Table 2. Incremental Rates for 250 mL ALDURAZYME® Infusion (For use with Patients Weighing Greater than 20 kg)

Infusion Rate	Criteria for infusion rate increase
5ml/h for 15 min	Obtain vital signs, if stable then increase the rate to...
10ml/h for 15 min	Obtain vital signs, if stable then increase the rate to...
20ml/h for 15 min	Obtain vital signs, if stable then increase the rate to...
40ml/h for 15 min	Obtain vital signs, if stable then increase the rate to...
80ml/h for approximately 3 hs	For the remainder of the infusion

- At the end of the infusion, flush the infusion line with 0.9% Sodium Chloride Injection, using the same infusion rate as the one used for the last part of the infusion.
- Aldurazyme should not be infused in the same intravenous line with other medicinal products.

The Aldurazyme dose, infusion rate, as well as any changes, will be determined by the prescribing HCP. The treatment must not be altered in the home setting, unless medically warranted at the discretion of the prescribing HCP. The infusion and any observations should be documented in a logbook or equivalent.

05

INFORMATION FOR HCPS PRESCRIBING ALDURAZYME® AND FOR THE HCP ADMINISTERING ALDURAZYME®

5.A) HCP PRESCRIBING ALDURAZYME

The prescribing HCP is responsible for initiating all the administrative procedures authorising the other stakeholders (patient and/or caregiver(s), infusion HCP, home healthcare provider, pharmacy, etc.) to act and discuss with the patient and/or caregiver the level of support to be provided in the home setting.

5.B) ALDURAZYME® SAFETY INFORMATION

Please refer to section 4 of the SmPC

i) 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 the infusion and assessed as potentially causally related to the administration of the product (Aldurazyme). Related events occurring after the post-infusion period may be considered IARs at the discretion of the reporter.
- IARs may occur at any time during and/or within a few hours after the infusion and are more likely with higher infusion rates.
- Hypersensitivity reactions, including anaphylaxis, have also been reported in Aldurazyme®-treated patients.

- Patients treated with Aldurazyme should be closely monitored and all cases of infusion-associated reactions, delayed reactions and possible immunological reactions reported. Antibody status should be regularly monitored and reported.

- With initial administration of Aldurazyme or upon re-administration following interruption of treatment, it is recommended that patients be administered pre-treatment medicines (antihistamines and/or antipyretics) approximately 60 minutes prior to the start of the infusion, to minimize the potential occurrence of IAR.

Summary of the safety profile

The majority of the related adverse events in the clinical trials were classified as infusion- associated reactions (IARs), experienced by 53% of the patients in the Phase 3 study (treated for up to 4 years) and 35% of the patients in the under 5 study (up to 1 year of treatment). Some of the IARs were severe. Over time the number of these reactions decreased. The most frequent adverse drug reactions (ADRs) were: headache, nausea, abdominal pain, rash, arthralgia, backpain, pain at extremity, flushing, pyrexia, infusion site reactions, blood pressure increased, oxygen saturation decreased, tachycardia and chills. Post-marketing experience of infusion- associated reactions revealed reporting of cyanosis, hypoxia, tachypnoea, pyrexia, vomiting, chills and erythema, in which some of these reactions were severe.

Tabulated list of adverse reactions:

ADRs to Aldurazyme reported during the Phase 3 study and its extension in a total of 45 patients age 5 years and older and treated up to 4 years are listed below using the following categories of

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) and not known (cannot be estimated from the available data). Due to the small patient population, an ADR reported in a single patient is classified as common.

Table 3. Observed signs and symptoms of IARs/hypersensitivity/anaphylactic reactions)

MedDRA System Organ Class	Very common	Common	Not known
Immune system disorders		Anaphylactic reaction	
Psychiatric disorders		Restlessness	
Nervous system disorders	Headache	Paraesthesia, dizziness	
Cardiac disorders		Tachycardia	
Vascular disorders	Flushing	Hypotension, pallor, peripheral coldness	
Respiratory, thoracic and mediastinal disorders		Respiratory distress, dyspnoea, cough	Cyanosis, hypoxia, tachypnoea, bronchospasm, respiratory arrest
Gastrointestinal disorders	Nausea, abdominal pain	Vomiting, diarrhoea	
Skin and subcutaneous tissue disorders	Rash	Angioneurotic edema, swelling face, urticaria, pruritus, cold sweat, alopecia, hyperhidrosis	Erythema, facial edema, laryngeal edema, edema peripheral
Musculoskeletal and connective tissue disorders	Arthropathy, arthralgia, back pain, pain in extremity	Musculoskeletal pain	
General disorders and administration site conditions	Pyrexia, infusion site reaction	Chills, feeling hot, feeling cold, fatigue, influenza like illness	Extravasation
Investigations		Body temperature increased, oxygen saturation decreased	

- Antihistamines, antipyretics, and/or corticosteroids and slowing the rate of infusion can prevent or reduce IARs. However, IARs may still occur in patients after receiving pre-treatment.
- Patients with an acute underlying illness at the time of Aldurazyme infusion appear to be at greater risk for IARs.
- Patients with advanced MPS I disease may have compromised cardiac and respiratory function, which may predispose them to a higher risk of severe complications from IARs.
- Appropriate measures for emergency support and monitoring as determined by the prescribing HCP should be in place according to the patients' individual emergency plan.
- Infusion rate may have to be decreased to address the worsening.
- Patients should also be monitored after infusion for a time span defined by the prescribing HCP.

ii) 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 Aldurazyme SmPC for further details).

Appropriate measures for emergency support and monitoring should be in place according to the patients' individual emergency plan, as determined by the prescribing HCP.

If the patient experiences IAR including hypersensitivity and anaphylactic reactions during the home infusion, the infusion process should be stopped immediately but the venous access should not be removed.

The measures indicated in the individual emergency plan should be followed based on the severity of the IAR, i.e., stopping temporarily or completely, and initiating appropriate medical treatment if needed. Please see Figure 1 and Figure 2 for exemplary clinical management in case of mild/moderate or severe adverse events.

Subsequent infusions may need to occur in a hospital or in an appropriate setting of outpatient care until no such adverse reaction occurs and the treating HCP determines that it is acceptable to return to home infusion.

Dose and infusion rate must not be changed for subsequent infusions without consulting the prescribing HCP.

Figure 1: Clinical management of mild to moderate reactions.

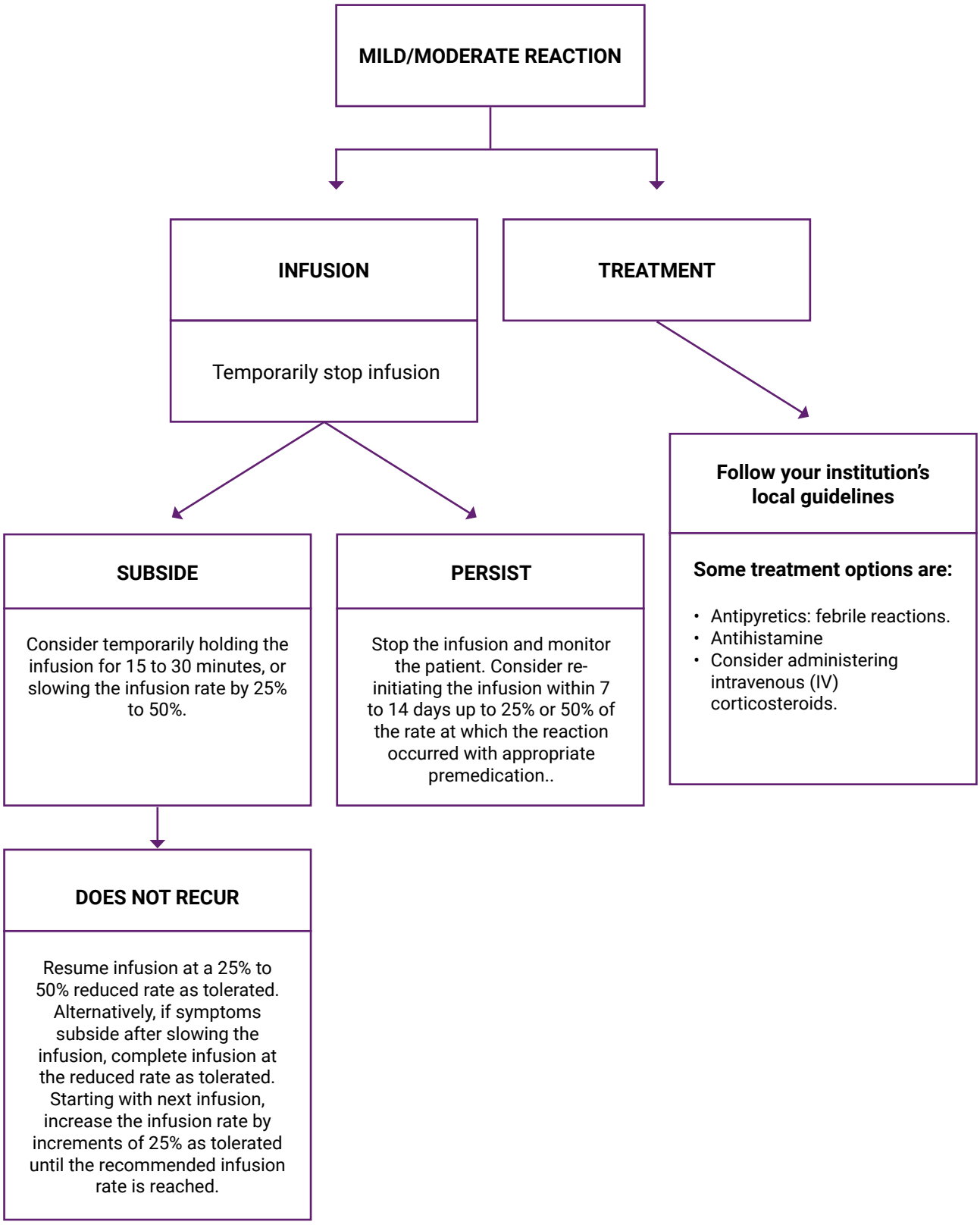
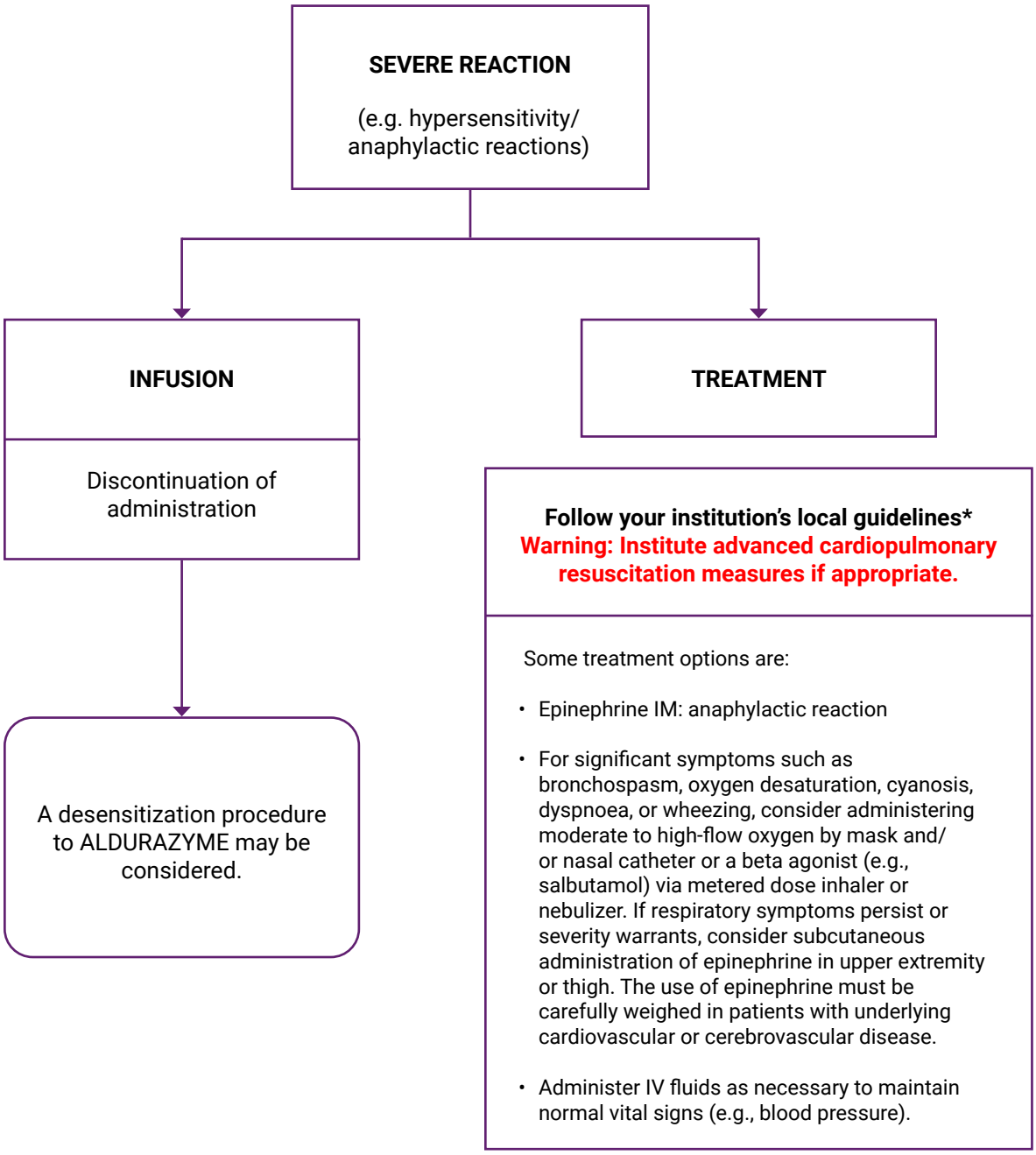


Figure 2: Clinical management of severe reactions.



*Contraindications should always be weighed against the benefit or need to use epinephrine as a life-saving measure in case of life-threatening anaphylactic reactions.

*Anaphylactic reactions symptoms such as respiratory failure, respiratory distress, stridor, tachypnea, bronchospasm, obstructive airway disorder, hypoxia, hypotension, bradycardia, and urticaria.

5.C) SAFETY REPORTING

An adverse event (AE) is defined as any physical, psychological, or behavioral symptom or sign in a patient receiving a medicinal product, caused or not caused by the ongoing treatment.

Events can be serious or non-serious, and the seriousness are assessed by the reporter or by the Pharmacovigilance officers.

A serious adverse event (SAE) is defined by 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).

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

5.D) ADDITIONAL INFORMATION

Please refer to the SmPC for complete indication statements and further information about the approved use of Aldurazyme.

A report must be submitted to The National Pharmacovigilance Center (NPC) including the batch number of the administered product to improve traceability.

The National Pharmacovigilance Centre (NPC- Saudi Food and Drug Authority (SFDA):
Call Center: 19999
E-mail: npc.drug@sfda.gov.sa
Website: https://ade.sfda.gov.sa/

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