PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

ALDURAZYME®, 500 U/5 mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient is laronidase. Each vial of 5 mL contains 500 U (2,9 mg) of laronidase.

1 mL contains 100 U (0,58 mg) of laronidase.

The activity unit (U) is defined as the hydrolysis of one micromole of substrate (4-MUI) per minute.

Laronidase is a recombinant form of human α-L-iduronidase and is produced by recombinant DNA technology using mammalian Chinese hamster ovary (CHO) cell culture.

Excipient with known effect:

Each vial of 5 mL contains 1,29 mmol sodium.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

A clear to slightly opalescent, and colourless to pale yellow liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ALDURAZYME is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of mucopolysaccharidosis I (MPS I; α-L-iduronidase deficiency) to treat the non-neurological manifestations of the disease (see section 5.1).

4.2 Posology and method of administration

ALDURAZYME treatment should be supervised by a medical practitioner experienced in the management of patients with MPS I or other inherited metabolic diseases.

Administration of ALDURAZYME should be carried out in an appropriate clinical setting where resuscitation equipment to manage medical emergencies would be readily available.

Posology

The recommended dosage regimen of ALDURAZYME is 100 U/kg body weight administered once every week as an intravenous infusion.

Special populations

Elderly patients

The safety and efficacy of ALDURAZYME in patients older than 65 years have not been established and no dosage regimen can be recommended in these patients.

Renal and hepatic insufficiency

The safety and efficacy of ALDURAZYME in patients with renal or hepatic insufficiency have not been evaluated and no dosage regimen can be recommended in these patients.

Paediatric population

The safety and effectiveness of ALDURAZYME have been established in patients 5 years of age and younger.

No dose adjustment is necessary for the paediatric population.

Overall, the safety and efficacy of ALDURAZYME treatment administered at 0,58 mg/kg (100 U/kg) every week in paediatric patients are consistent with that seen in adults.

Method of administration

ALDURAZYME is to be administered as an intravenous infusion.

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.

For information on pre-treatment, see section 4.4.

For instructions on dilution of ALDURAZYME before administration, see section 6.6.

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 medical practitioner.

Home infusion infrastructure, resources and procedures, including training, must be established and available to the health care professional. Home infusion should be supervised by a health care 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 medical practitioner and/or nurse 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 health care professional.

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.

4.3 Contraindications

Severe hypersensitivity (e.g. anaphylactic reaction) to the active ingredient or to any of the excipients listed in section 6.1 that also has occurred upon re-exposure (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicines, the name and the batch number of the administered product should be clearly recorded.

Infusion-associated reactions

Patients treated with ALDURAZYME may develop infusion-associated reactions (IARs) (including anaphylaxis), defined as any related adverse event occurring during the infusion or until the end of the infusion day (see section 4.8). Some of these IARs may be life-threatening (see below) and included respiratory failure, respiratory distress, stridor, tachypnoea, bronchospasm, obstructive airways disorder, hypoxia, hypotension, bradycardia and urticaria.

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.

Severe infusion-associated reactions have been reported in patients with pre-existent severe underlying upper airway involvement and therefore specifically these patients should continue to be closely monitored and only be infused with ALDURAZYME in an appropriate clinical setting where resuscitation equipment to manage medical emergencies would be readily available.

The risks and benefits of re-administering ALDURAZYME following a severe hypersensitivity or anaphylactic reaction should be considered. Extreme care should be exercised, with appropriate resuscitation measures available, if the decision is made to re-administer ALDURAZYME.

Caution should be exercised if epinephrine (adrenaline) is being considered for use in patients with MPS I due to the increased prevalence of coronary artery disease in these patients.

Patients with an acute underlying illness at the time of ALDURAZYME infusion appear to be at greater risk for IARs. Careful consideration should be given to the patient's clinical status prior to administration of ALDURAZYME.

Immunogenicity

Almost all patients are expected to develop IgG antibodies to laronidase, mostly within 3 months of initiation of treatment. Patients who have developed antibodies or symptoms of IARs should be treated with caution when administering ALDURAZYME (see sections 4.3 and 4.8).

In clinical studies IARs were usually manageable by slowing the rate of infusion and by (pre-) treating the patient with antihistamines and/or antipyretics (paracetamol or ibuprofen), thus enabling the patient to continue treatment.

As there is little experience on resumption of treatment following prolonged interruption, use caution due to the increased risk of hypersensitivity reaction after treatment interruption.

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 minimise the potential occurrence of IARs. If clinically indicated, administration of pre-treatment medicines with subsequent infusions of ALDURAZYME should be considered.

In case of a mild or moderate IAR, treatment with antihistamines and paracetamol or ibuprofen should be considered and/or a reduction in the infusion rate to half the infusion rate at which the

reaction occurred.

In case of a single severe IAR, the infusion should be stopped until the symptoms are resolved and treatment with antihistamines and paracetamol or ibuprofen should be considered. The infusion can be restarted with a reduction of the infusion rate to ½ – ¼ the rate of the infusion at which the reaction occurred.

In case of a recurrent moderate IAR or re-challenge after a single severe IAR, pre-treatment should be considered (antihistamines and paracetamol/ibuprofen and/or corticosteroids) and a reduction of the infusion rate to ½ – ¼ the rate of the infusion at which the previous reaction occurred.

Severe allergic-type hypersensitivity reactions are possible. If these reactions occur, immediate discontinuation of ALDURAZYME is recommended and appropriate medical treatment should be initiated. The current medical standards for emergency treatment are to be observed.

Laboratory tests for monitoring patients

Evaluation of bioactivity during the clinical studies included changes in urinary glycosaminoglycan (GAG) levels, which were shown to decrease in patients treated with ALDURAZYME compared to those treated with placebo.

As seen in the clinical studies, it is expected that patients will develop antibodies to ALDURAZYME. It is strongly recommended that patients be monitored periodically for IgG antibody formation.

Excipients

ALDURAZYME contains 30 mg sodium per vial, equivalent to 1,5 % of the WHO recommended maximum daily intake of 2 g sodium for an adult and 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

No interaction studies have been performed. Based on its metabolism, laronidase is an unlikely candidate for cytochrome P450-mediated interactions.

ALDURAZYME should not be administered simultaneously with chloroquine or procaine due to a potential risk of interference with the intracellular uptake of laronidase.

4.6 Fertility, pregnancy and lactation

Safe use during pregnancy and lactation has not been established.

Pregnancy

There are inadequate data on the use of ALDURAZYME in pregnant women. Animal studies do not indicate direct or indirect harmful effects on pregnancy, embryonal/fetal development, parturition and postnatal development (see section 5.3). The potential risk for humans is unknown. Therefore, ALDURAZYME should not be used during pregnancy.

Breastfeeding

Laronidase may be excreted in milk. Because there are no data available in neonates exposed to laronidase via breast milk, it is recommended to stop breastfeeding during ALDURAZYME treatment.

Fertility

There are no clinical data on the effects of laronidase on fertility. Preclinical data did not reveal any significant adverse finding.

4.7 Effects on ability to drive and use machines

No studies on the effects on ability to drive a vehicle or operate machinery have been performed.

4.8 Undesirable effects

Adverse drug 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 frequency not known (cannot be estimated from the available data).

System organ class	**Preferred term**	**Frequency**
Immune system disorders	anaphylactic reaction	common
Psychiatric disorders	restlessness	common
Nervous system disorders	headache	very common
	paraesthesia, dizziness	common
Cardiac disorders	tachycardia	common
Vascular disorders	flushing	very common
	hypotension, pallor, peripheral coldness	common
Respiratory, thoracic and mediastinal disorders	respiratory distress, dyspnoea, cough	common
	cyanosis, hypoxia, tachypnoea, bronchospasm, respiratory arrest	frequency not known
Gastrointestinal disorders	nausea, abdominal pain	very common
	vomiting, diarrhoea	common
Skin and subcutaneous tissue disorders	rash	very common
	angioneurotic oedema,	common

	swelling of face, urticaria, pruritus, cold sweat, alopecia, hyperhidrosis	
	erythema, facial oedema, laryngeal oedema, peripheral oedema	frequency not known
Musculoskeletal and connective tissue disorders	arthropathy, arthralgia, back pain, pain in extremity	very common
	musculoskeletal pain	common
General disorders and administration site conditions	pyrexia, infusion site reaction	very common
	chills, feeling hot, feeling cold, fatigue, influenza-like illness	common
	extravasation	frequency not known
Investigations	increased body temperature, decreased oxygen saturation	common

In a Phase 2 open-label study of 20 patients 5 years of age and younger treated for up to 52 weeks, the most common reported ADRs (> 1 patient/5 %) were: pyrexia (35 %), chills (20 %), and tachycardia, increased blood pressure, and decreased oxygen saturation (10 % each). Also, frequently reported ADRs from a Phase 1/2 open-label study of 10 patients treated for up to 3 years included angioedema, which occurred in 3 out of 10 patients.

The majority of the related adverse events in the clinical trials were infusion-associated reactions (IARs) that were mild to moderate in severity. IARs were reported in 24 of 45 (53 %) patients 6 years of age and older during ALDURAZYME treatment and 7 of 20 (35 %) patients 5 years of age and younger in the Phase 3 studies, and 7 of 20 patients (35 %) in the Phase 2 study. Over time the frequency of IARs decreased. Most IARs that required intervention were managed by

decreasing the infusion rate, temporarily stopping the infusion, and/or administering antipyretics and/or antihistamines.

The most frequently reported IARs in the Phase 3 studies were rash, flushing, headache, pyrexia, abdominal pain, diarrhoea, nausea, vomiting, and in patients 5 years of age and younger in the Phase 2 study were pyrexia, chills, increased blood pressure, decreased oxygen saturation, and tachycardia. In general, IARs from post-marketing reporting were similar in nature to those seen in clinical trials.

Overall infusion site reactions with ALDURAZYME administration are very common. During clinical trials and post-marketing experience, infusion/injection site reactions included: extravasation, swelling, pain, erythema, oedema, discomfort, urticaria, pallor, macule and warmth.

Serious adverse reactions

In the Phase 3 open-label extension study, a single patient with pre-existing airway obstruction experienced a severe anaphylactic reaction approximately 3 hours after the initiation of the infusion (at week 62 of treatment) which consisted of urticaria and airway obstruction. Resuscitation required emergency tracheostomy. This patient tested IgE-positive. In addition, a 3-year-old severely affected patient experienced an anaphylactic reaction and respiratory arrest. Both patients discontinued ALDURAZYME treatment.

Post-marketing adverse reactions

In addition to the infusion reactions reported in clinical trials, the following infusion reactions have been reported in patients during post-marketing use of ALDURAZYME: cough, dyspnoea, decreased oxygen saturation/hypoxia, tachypnoea, cyanosis, respiratory failure, medicine specific antibody, neutralising antibodies, hypersensitivity, bradycardia and manifestations of angioedema, such as facial oedema and laryngeal oedema, pharyngeal swelling, lip swelling, swollen tongue and hypertension. Additional significant ADRs have included serious reports of infusion-associated

bronchospasm that required treatment with epinephrine (adrenaline), corticosteroids and/or oxygen therapy. Some patients were successfully re-challenged.

Other infusion reactions reported in patients during post-marketing use include pallor, fatigue, erythema, peripheral oedema, paraesthesia, feeling hot and feeling cold.

There have been reports of extravasation in patients treated with ALDURAZYME. There have been no reports of tissue necrosis associated with extravasation.

Immunogenicity

During the clinical studies, almost all patients treated with ALDURAZYME developed IgG antibodies to ALDURAZYME, which tended to decrease over time. The presence of high IgG levels has been associated with variable urinary GAG reduction.

In addition, higher ADA (anti-drug antibodies) titres were also observed in MPS I Registry patients with severe disease. Patients with persistently high ADA titres tended to have less reduction in urinary GAG.

In the Phase 2 and 3 studies, 60 patients were tested for *in vitro* neutralising effects. Four patients (three in the Phase 3 study and one in the Phase 2 study) showed marginal to low level *in vitro* inhibition of laronidase enzymatic activity, which did not appear to impact clinical efficacy and/or urinary GAG reduction.

In patients with clinical decline, assessing urinary GAGs, ADA and neutralising antibodies should be considered.

The presence of antibodies was not consistently related to the incidence of IARs, although the onset of IARs typically coincided with the formation of IgG antibodies. Clinical trials and observational studies show only a small number of patients have tested positive for IgE antibodies.

The development of IgE antibodies may be associated with hypersensitivity or anaphylactic reactions.

Reporting of suspected adverse reactions

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

- The Pharmacovigilance Unit at Sanofi: za.drugsafety@sanofi.com (email), https://ae.reporting.sanofi/ (web portal) or +27 11 256 3700 (tel), or
- SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Treatment is symptomatic and supportive.

Inappropriate administration of ALDURAZYME (overdose and/or infusion rate higher than recommended) may be associated with adverse drug reactions. An excessively fast administration of ALDURAZYME may result in nausea, abdominal pain, headache, dizziness and dyspnoea.

If signs or symptoms occur associated with overdose or an infusion rate higher than recommended, the infusion must be stopped immediately. If medically appropriate, further intervention may be indicated.

5. PHARMACOLOGICAL PROPERTIES

Category and class: A.31 Enzymatic Preparations

Pharmacotherapeutic group: Enzymes.

ATC code: A16AB05

5.1 Pharmacodynamic properties

Mucopolysaccharide storage (MPS) disorders are caused by the deficiency of specific lysosomal enzymes required for the catabolism of glycosaminoglycans (GAGs). MPS I is a heterogeneous and multisystemic disorder characterised by the deficiency of α-L-iduronidase, a lysosomal hydrolase which catalyses the hydrolysis of terminal α-L-iduronic residues of dermatan sulphate and heparan sulphate. Reduced or absent α-L-iduronidase activity results in the accumulation of the GAGs, dermatan sulphate and heparan sulphate, in many cell types and tissues.

The rationale for enzyme replacement therapy is to restore a level of enzymatic activity sufficient to hydrolyse the accumulated substrate and to prevent further accumulation.
After intravenous infusion, laronidase is rapidly removed from the circulation and taken up by cells into lysosomes, most likely via mannose 6-phosphate receptors.

Purified laronidase is a glycoprotein with a molecular weight of approximately 83 kDa. Laronidase is comprised of 628 amino acids after cleavage of the N-terminus. The molecule contains 6 *N*-linked oligosaccharide modifications sites.

5.2 Pharmacokinetic properties

Absorption

After intravenous infusion, laronidase is taken up by cells into lysosomes, most likely via mannose 6-phosphate receptors.
The pharmacokinetics of laronidase were evaluated in 12 patients with MPS I who received 0,58 mg/kg (100 U/kg) of ALDURAZYME as a 4 hour infusion. After the 1st, 12th and 26th weekly infusions, the mean maximum plasma concentrations (C_{max}) ranged from 1,2 to 1,7 µg/mL for the 3 timepoints. The mean area under the plasma concentration-time curve (AUC∞) ranged from 4,5 to 6,9 µg•h/mL. The mean volume of distribution (Vz) ranged from 0,24 to 0,6 L/kg. Mean plasma clearance (CL) ranged from 1,7 to 2,7 mL/min/kg, and the mean elimination half-life (t½) ranged from 1,5 to 3,6 hours.

The pharmacokinetic profile in an open-label study of 20 patients aged 5 years or younger was similar to that of older patients.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, repeated dose toxicity and toxicity to reproduction. Genotoxic and carcinogenic potential are not expected.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 80

Sodium chloride

Sodium phosphate dibasic heptahydrate

Sodium phosphate monobasic monohydrate

Water for injection.

6.2 Incompatibilities

In the absence of compatibility studies, ALDURAZYME must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Concentrate (unopened vial): 36 months.

Diluted solution: From a microbiological safety point of view, ALDURAZYME 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.

6.4 Special precautions for storage

Concentrate (unopened vial): Store in a refrigerator at 2 °C – 8 °C.

Do not freeze.

DO NOT USE ALDURAZYME after the expiration date on the vial label.

Diluted solution: The diluted preparation contains no preservatives.

This may be used in very young children. Use immediately.

For storage conditions after dilution of ALDURAZYME, see section 6.3.

6.5 Nature and contents of container

5 mL concentrate for solution in a clear, transparent type I glass vial with a grey, siliconised, butyl rubber stopper and an aluminium seal with an orange polypropylene flip-off cap.

Pack size: 1 vial.

6.6 Special precautions for disposal and other handling

Preparation with 0,9 % sodium chloride:

Each vial of ALDURAZYME is intended for single use only.

The concentrate for solution for infusion has to be diluted with sodium chloride 9 mg/mL (0,9 %) solution for infusion using aseptic technique. It is recommended that the diluted ALDURAZYME solution be administered to patients using an infusion set equipped with a 0,2 µm in-line filter.

Preparation of the ALDURAZYME infusion (use aseptic technique):

- Determine the number of vials to be diluted based on the individual patient's weight. Remove the required vials from the refrigerator approximately 20 minutes in advance in order to allow them to reach room temperature.
- Before dilution, visually inspect each vial for particulate matter and discolouration. The clear to slightly opalescent and colourless to pale yellow solution should be free of visible particles. Do not use vials exhibiting particles or discolouration.
- Determine the total volume of infusion based on the individual patient's weight – either 100 mL (if body weight is less than or equal to 20 kg) or 250 mL (if body weight is more than 20 kg) of

sodium chloride 9 mg/mL (0,9 %) solution for infusion.

- Withdraw and discard a volume of the 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.
- 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.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

44/31/0500

9. DATE OF FIRST AUTHORISATION

06 August 2015

10. DATE OF REVISION OF THE TEXT

12 June 2025