## 1. NAME OF THE MEDICINAL PRODUCT

Aldurazyme
concentrate for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 100 U (approximately 0.58 mg) of laronidase.
Each vial of 5 ml contains 500 U 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(s) with known effect:

Each vial of 5 ml contains 1.29 mmol sodium.
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 solution.

## 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.

### 4.2 Posology and method of administration

Aldurazyme treatment should be supervised by a physician 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.

*Paediatric population*
No dose adjustment is necessary for the paediatric population.

*Elderly*
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 impairment*
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.

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 instruction on dilution of the medicinal product before administration, see section 6.6.

## 4.3 Contraindications

Hypersensitivity (e.g. anaphylactic reaction) to the active substance or to any of the excipients listed in section 6.1 (see sections 4.4 and 4.8).

## 4.4 Special warnings and precautions for use

Infusion-associated reactions
Patients treated with Aldurazyme may develop infusion-associated reactions (IARs), 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 severe (see below).

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 IAR 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.

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.

Based on the Phase 3 clinical trial, 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 theoretical 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 medications with subsequent infusions of Aldurazyme should be considered.

In case of a mild or moderate IAR, treatment with antihistamines and paracetamol/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/ibuprofen should be considered. The infusion can be restarted with a reduction of the infusion rate to 1/2 – 1/4 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 1/2 – 1/4 the rate of the infusion at which the previous reaction occurred.

As with any intravenous protein product, 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.

Excipients
This medicinal product 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).

Traceability
In order to improve the traceability of biological medicinal products, the name of the administered product should be clearly recorded. It is recommended to record the batch number as well.

## 4.5 Interaction with other medicinal products 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

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/foetal development, parturition and postnatal development (see section 5.3). The potential risk for humans is unknown. Therefore Aldurazyme should not be used during pregnancy unless clearly necessary.

Breast-feeding
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 breast-feeding 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 (see section 5.3).

## 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

## 4.8 Undesirable effects

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.

| **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 | |

A single patient with pre-existing airway compromise developed a severe reaction three hours from the start of the infusion (at week 62 of treatment) consisting of urticaria and airway obstruction, requiring tracheostomy. This patient tested positive for IgE.

Additionally, a few patients who had a prior history of severe MPS I- related upper airway and pulmonary involvement, experienced severe reactions including bronchospasm, respiratory arrest, and facial oedema (see section 4.4).

Paediatric population
ADRs to Aldurazyme reported during a Phase 2 study in a total of 20 patients, under 5 years of age and mainly of the severe phenotype, treated up to 12 months are listed below. ADRs were all mild to moderate in severity.

| **MedDRA System Organ Class** | **MedDRA Preferred term** | **Frequency** |
|---|---|---|
| Cardiac disorders | tachycardia | Very common |
| General disorders and administration site conditions | pyrexia | Very common |
| | chills | Very common |
| Investigations | blood pressure increased | Very common |
| | oxygen saturation decreased | Very common |

In a phase 4 study 33 MPS I patients received 1 of 4 dose regimens: 100 U/kg IV every week (recommended dose), 200 U/kg IV every week, 200 U/kg IV every 2 weeks or 300 U/kg IV every 2 weeks. The recommended dose group had the fewest number of patients who experienced ADRs and IARs. The type of IARs was similar to those seen in other clinical studies.

Description of selected adverse reactions

*Immunogenicity*
Almost all patients developed IgG antibodies to laronidase. Most patients seroconverted within 3 months of initiation of treatment; although seroconversion in patients under 5 years old with a more severe phenotype occurred mostly within 1 month (mean 26 days versus 45 days in patients 5 years and older). By the end of the Phase 3 study (or at time of early study withdrawal), 13/45 patients had no detectable antibodies by radioimmunoprecipitation (RIP) assay, including 3 patients that had never seroconverted. Patients with absent to low antibody levels showed a robust reduction in urinary GAG level, whereas patients with high antibody titers showed variable reduction in urinary GAG. The clinical significance of this finding is unknown since there were no consistent relationships between IgG antibody level and clinical efficacy endpoints.

In addition 60 patients in the Phase 2 and 3 studies 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.

The presence of antibodies did not appear to be related to the incidence of IARs, although the onset of IARs typically coincided with the formation of IgG antibodies. The occurrence of IgE antibodies was not fully explored.

Reporting of suspected adverse reactions
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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il/

## 4.9 Overdose

No case of overdose has been reported.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Enzymes.
ATC code: A16AB05.

MPS I disease

Mucopolysaccharide storage 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 sulfate and heparan sulfate. Reduced or absent α-L-iduronidase activity results in the accumulation of the GAGs, dermatan sulfate and heparan sulfate in many cell types and tissues.

Mechanism of action

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.

Clinical efficacy and safety
Three clinical trials were performed with Aldurazyme to assess its efficacy and safety. One clinical study focussed mainly on assessing the effect of Aldurazyme on the systemic manifestations of MPS I such as poor endurance, restrictive lung disease, upper airway obstruction, reduced joint range of motion, hepatomegaly and visual impairment. One study mainly assessed the safety and pharmacokinetics of Aldurazyme in patients less than 5 years old, but some efficacy measurements were included as well. The third study was conducted to evaluate the pharmacodynamics and safety of different dose regimens of Aldurazyme.
To date there are no clinical data that demonstrate any benefit on the neurological manifestations of the disorder.

The safety and efficacy of Aldurazyme was assessed in a randomised, double-blind, placebo controlled, Phase 3 Study of 45 patients, ranging in age from 6 to 43 years. Although patients representing the full range of the disease spectrum were enrolled, the majority of the patients were of the intermediate phenotype, with only one patient exhibiting the severe phenotype. Patients were enrolled with a Forced Vital Capacity (FVC) less than 80% of the predicted value and had to be able to stand for 6 minutes and to walk 5 meters. Patients received either 100 U/kg of Aldurazyme or placebo every week for a total of 26 weeks. The primary efficacy endpoints were changes in percent of predicted normal FVC and absolute distance travelled in the six-minute walk test (6MWT). All patients subsequently enrolled in an open label extension study where they all received 100 U/kg of Aldurazyme every week for an additional 3.5 years (182 weeks).

Following 26 weeks of therapy, Aldurazyme-treated patients showed improved respiratory function and walking ability as compared to placebo as indicated below.

| | **Phase 3, 26 weeks of treatment compared to placebo** | | | |
|---|---|---|---|---|
| | | | p value | Confidence interval (95%) |

| | | | | |
|---|---|---|---|---|
| **Percent Predicted FVC (percentage point)** | mean | 5.6 | - | |
| | median | 3.0 | 0.009 | 0.9 - 8.6 |
| **6MWT (meters)** | mean | 38.1 | - | |
| | median | 38.5 | 0.066 | -2.0 - 79.0 |

The open label extension study showed improvement and/or maintenance of these effects up to 208 weeks in the Aldurazyme/Aldurazyme group and 182 weeks in the Placebo/Aldurazyme group as indicated in the table below.

| | **Aldurazyme/Aldurazyme** | **Placebo/Aldurazyme** |
|---|---|---|
| | At 208 weeks | At 182 weeks |
| **Mean change from pre-treatment baseline** | | |
| Percent predicted FVC (%)[1] | - 1.2 | - 3.3 |
| 6MWT (meters) | + 39.2 | + 19.4 |
| Apnea/Hypopnea Index (AHI) | - 4.0 | - 4.8 |
| Shoulder flexion Range Of Motion (degrees) | + 13.1 | + 18.3 |
| CHAQ/HAQ Disability Index [2] | - 0.43 | - 0.26 |

[1] The decrease in percent predicted FVC is not clinically significant over this timeframe, and absolute lung volumes continued to increase commensurate with changes in height in growing paediatric patients.
[2] Both groups exceeded the minimal clinically important difference (-0.24)

Of the 26 patients with abnormal liver volumes at pre-treatment baseline, 22 (85%) achieved a normal liver size by the end of the study. There was a rapid reduction in the excretion of urinary GAG (µg/mg creatinine) within the first 4 weeks, which was maintained through the remainder of the study. Urinary GAG levels decreased by 77% and 66% in the Placebo/Aldurazyme and Aldurazyme/Aldurazyme groups, respectively; at the end of the study one-third of the patients (15 of 45) had reached normal urinary GAG levels.

To address the heterogeneity in disease manifestation across patients, using a composite endpoint that summed up clinically significant changes across five efficacy variables (percent predicted normal FVC, 6MWT distance, shoulder flexion range of motion, AHI, and visual acuity) the global response was an improvement in 26 patients (58%), no change in 10 patients (22%), and a deterioration in 9 patients (20%).

A Phase 2 open-label, 1-year study was conducted that mainly assessed the safety and pharmacokinetics of Aldurazyme in 20 patients less than 5 years of age at the time of enrolment (16 patients with the severe phenotype and 4 with the intermediate phenotype). The patients were scheduled to receive Aldurazyme 100 U/kg weekly infusions for a total duration of 52 weeks. Four patients underwent dosage increases to 200 U/kg for the last 26 weeks because of elevated urinary GAG levels at Week 22.
Eighteen patients completed the study. Aldurazyme was well tolerated at both dosages. The mean urinary GAG level declined by 50% at Week 13 and was reduced by 61% at the end of the study. Upon study completion, all patients showed reductions in liver size and 50% (9/18) had normal liver size. The proportion of patients with mild left ventricular hypertrophy decreased from 53% (10/19) to 17% (3/18), and mean left ventricular mass normalized for body surface area decreased by 0.9 Z-Score (n=17). Several patients showed an increase in height (n=7) and weight (n=3) for age Z-score. The younger patients with the severe phenotype (< 2.5 years) and all 4 patients with the intermediate phenotype exhibited a normal rate of mental development, whereas the older patients with a severe phenotype made limited or no gains in cognition.

A phase 4 study was conducted to evaluate the pharmacodynamic effects on urinary GAGs, liver volume, and 6MWT, of different Aldurazyme dose regimens. In this 26-week open label study, 33 MPS I patients received 1 of 4 dose regimens of Aldurazyme: 100 U/kg IV every week (recommended dose), 200 U/kg IV every week, 200 U/kg IV every 2 weeks; or 300 U/kg IV every 2 weeks. No definite benefit was shown with the higher doses over the recommended dose. The

200 U/kg IV every 2 weeks regimen may be an acceptable alternative for patients with difficulty receiving weekly infusions; however, there is no evidence that the long term clinical efficacy of these two dose regimens is equivalent.

### 5.2 Pharmacokinetic properties

After intravenous administration of laronidase with an infusion time of 240 minutes and at a dose of 100 U/kg body weight pharmacokinetic properties were measured at Weeks 1, 12 and 26.

| **Parameter** | **Infusion 1**<br><br>Mean ± SD | **Infusion 12**<br><br>Mean ± SD | **Infusion 26**<br><br>Mean± SD |
|---|---|---|---|
| **Cmax (U/ml)** | 0.197 ± 0.052 | 0.210 ± 0.079 | 0.302 ± 0.089 |
| **$AUC_{\infty}$ (h•U/ml)** | 0.930 ± 0.214 | 0.913 ± 0.445 | 1.191 ± 0.451 |
| **CL (ml/min/kg)** | 1.96 ± 0.495 | 2.31 ± 1.13 | 1.68 ± 0.763 |
| **Vz (l/kg)** | 0.604 ± 0.172 | 0.307 ± 0.143 | 0.239 ± 0.128 |
| **Vss (l/kg)** | 0.440 ± 0.125 | 0.252 ± 0.079 | 0.217 ± 0.081 |
| **$t_{1/2}$ (h)** | 3.61 ± 0.894 | 2.02 ± 1.26 | 1.94 ± 1.09 |

$C_{max}$ showed an increase over time. The volume of distribution decreased with continued treatment, possibly related to antibody formation and/or decreased liver volume.
The pharmacokinetic profile in patients less than 5 years old was similar to that of older and less severely affected patients.

Laronidase is a protein and is expected to be metabolically degraded through peptide hydrolysis. Consequently, impaired liver function is not expected to affect the pharmacokinetics of laronidase in a clinically significant way. Renal elimination of laronidase is considered to be a minor pathway for clearance (see section 4.2).

### 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

Sodium phosphate monobasic, monohydrate
Sodium chloride
Sodium phosphate dibasic, heptahydrate
Polysorbate 80
Water for injections

### 6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### 6.3 Shelf life

Unopened vials:
The expiry date of the product is indicated on the packaging materials.

Diluted solutions:
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.

### 6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

For storage conditions after dilution of the medicinal product, see section 6.3.

### 6.5 Nature and contents of container

5 ml concentrate for solution in a vial (type I glass) with a stopper (siliconised chlorobutyl rubber) and a seal (aluminium) with a flip-off cap (polypropylene).

Pack size: 1 vial.

### 6.6 Special precautions for disposal and other handling

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 (below 30˚C).
- Before dilution, visually inspect each vial for particulate matter and discoloration. The clear to slightly opalescent and colourless to pale yellow solution should be free of visible particles. Do not use vials exhibiting particles or discoloration.
- Determine the total volume of infusion based on the individual patient's weight, either 100 ml (if body weight is less or equal than 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 medicinal product or waste material should be disposed of in accordance with local requirements.

## 7 MARKETING AUTHORISATION HOLDER AND IMPORTER AND ITS ADDRESS

Sanofi-aventis Israel Ltd
10 Beni Gaon, P.O.B 8090, Netanya 4250499

## 8. MARKETING AUTHORISATION NUMBER

130-42-30779

Revised in January 2023 according to MoH guidelines.