**ANNEX I**

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Aldurazyme 100 U/ml 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 (see section 5.1).

### 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

Severe 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

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

Hypersensitivity reactions (including anaphylaxis)
Hypersensitivity reactions, including anaphylaxis have been reported in patients treated with Aldurazyme (see section 4.8). Some of these reactions were life threatening and included respiratory failure/distress, stridor, obstructive airways disorder, hypoxia, hypotension, bradycardia, and urticaria.

Appropriate medical support measures, including cardiopulmonary resuscitation equipment should be readily available when Aldurazyme is administered.
If anaphylaxis or other severe hypersensitivity reactions occur, the infusion of Aldurazyme should be discontinued immediately Caution should be exercised if epinephrine is being considered for use in patients with MPS I due to the increased prevalence of coronary artery disease in these patients. In patients with severe hypersensitivity, desensitization procedure to Aldurazyme may be considered. If the decision is made to re-administer the product, extreme care should be exercised, with appropriate resuscitation measures available.

If mild or moderate hypersensitivity reactions occur, the infusion rate may be slowed or temporarily stopped.

Once a patient tolerates the infusion, the dose may be increased to reach the approved dose.

Infusion-associated reactions (IARs)
IARs, defined as any related adverse event occurring during the infusion or until the end of the infusion day were reported in patients treated with Aldurazyme (see section 4.8).

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.

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. 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.

Severe IARs 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.

In case of a single severe IAR, the infusion should be stopped until the symptoms are resolved and symptomatic treatment (e.g. with antihistamines and antipyretics/ anti-inflammatories) should be considered. The benefits and risk of re-administering Aldurazyme following severe IARs 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 antipyretics/anti-inflammatories 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.
In case of a mild or moderate IAR, symptomatic treatment (e.g. with antihistamines and antipyretics/anti-inflammatories) should be considered and/or a reduction in the infusion rate to half the infusion rate at which the reaction occurred.

Once a patient tolerates the infusion, the dose may be increased to reach the approved dose.

Immunogenicity
Based on the randomized, double-blind, placebo-controlled Phase 3 clinical trial, almost all patients are expected to develop IgG antibodies to laronidase, mostly within 3 months of initiation of treatment.

As with any intravenous protein medicinal product, severe allergic-type hypersensitivity reactions are possible.
IARs and hypersensitivity reactions may occur independently of the development of anti-drug antibodies (ADAs).
Patients who have developed antibodies or symptoms of IARs should be treated with caution when administering Aldurazyme (see sections 4.3 and 4.8).

Patients treated with Aldurazyme should be closely monitored and all cases of infusion-associated reactions, delayed reactions and possible immunological reactions reported. Antibody status, including IgG, IgE, neutralizing antibodies for enzyme activity or enzyme reuptake, should be regularly monitored and reported.

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.

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).

## 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 | Hypersensitivity |
| Psychiatric disorders | | Restlessness | |
| Nervous system disorders | Headache | Paraesthesia, dizziness | |
| Cardiac disorders | | Tachycardia | Bradycardia |
| Vascular disorders | Flushing | Hypotension, pallor, peripheral coldness | Hypertension |
| Respiratory, thoracic and mediastinal disorders | | Respiratory distress, dyspnoea, cough | Cyanosis, hypoxia, tachypnoea, bronchospasm, respiratory arrest, laryngeal oedema, respiratory failure, pharyngeal swelling, stridor, obstructive airways disorder |
| Gastrointestinal disorders | Nausea, abdominal pain | Vomiting, diarrhoea | Lip swelling, swollen tongue |
| Skin and subcutaneous tissue disorders | Rash | Angioedema, swelling face, urticaria, pruritus, cold sweat, alopecia, hyperhidrosis | Erythema, facial edema, |
| 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, injection site pain | Extravasation, oedema peripheral |
| Investigations | | Body temperature increased, oxygen saturation decreased | Drug specific antibody, neutralizing antibodies, blood pressure increased |

* During clinical trials and post-marketing experience, infusion/injection site reactions notably included: swelling, erythema, oedema, discomfort, urticaria, pallor, macule, and warmth.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

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

In such situations and according to the patient's clinical status, the infusion should be stopped or the infusion rate slowed down immediately. If medically appropriate, further intervention may be indicated.

## 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 chloride
Sodium phosphate monobasic, monohydrate
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:
3 years

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 sizes: 1, 10 and 25 vials.
Not all pack sizes may be marketed.

## 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.

Aldurazyme 100 U/ml concentrate for solution for infusion reconstituted in 0.9% sodium chloride has an osmolality of 415 – 505 mOsm/kg and a pH of 5.2 – 5.9.

**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

Sanofi B.V., Paasheuvelweg 25, 1105 BP Amsterdam, The Netherlands.

# 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/253/001-003

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 June 2003
Date of latest renewal: 10 June 2008

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

# ANNEX II

**A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

BioMarin Pharmaceutical Inc, Galli Drive Facility, 46 Galli Drive, Novato, CA 94949, USA

Name and address of the manufacturer responsible for batch release

Genzyme Ireland Ltd, IDA Industrial Park, Old Kilmeaden Road, Waterford, Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2)

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON (1 VIAL, 10 VIALS, 25 VIALS)**

## 1. NAME OF THE MEDICINAL PRODUCT

Aldurazyme 100 U/ml concentrate for solution for infusion
laronidase

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 U of laronidase.
Each vial of 5 ml contains 500 U of laronidase.

## 3. LIST OF EXCIPIENTS

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

## 4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of concentrate for solution for infusion.
10 vials of concentrate for solution for infusion.
25 vials of concentrate for solution for infusion.

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

For single use only.

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution should be discarded.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:
Sanofi B.V.
Paasheuvelweg 25
1105 BP Amsterdam
The Netherlands

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/253/001 1 Vial
EU/1/03/253/002 10 Vials
EU/1/03/253/003 25 Vials

## 13. BATCH NUMBER

Batch

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Aldurazyme 100 U/ml concentrate for solution for infusion
laronidase
Intravenous use

## 2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Batch

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

## 6. OTHER

Store at 2°C – 8°C.

Sanofi B.V. - NL

# B. PACKAGE LEAFLET

**Package leaflet: Information for the user**

**Aldurazyme 100 U/ml concentrate for solution for infusion**
Laronidase

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**:


## 1. What Aldurazyme is and what it is 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.

## 2. What you need to know before you are given Aldurazyme

**You should not be given Aldurazyme**
If you are allergic (hypersensitive) to laronidase or any of the other ingredients of this medicine (listed in section 6).

**Warnings and precautions**
Talk to your doctor before using Aldurazyme.
Contact your doctor immediately if treatment with Aldurazyme causes:
- Allergic reactions, including anaphylaxis (a severe allergy reaction) – see under section 4 "Possible side effects". Some of these reactions may be life-threatening. Symptoms may include respiratory failure/distress (inability of lungs to work properly), stridor (high-pitched breathing sound) and other disorders due to obstruction of airways, rapid breathing, excessive contraction of the airway muscles causing breathing difficulty (bronchospasm), lack of oxygen in body tissues (hypoxia), low blood pressure, slow heart rate, or itchy rash (urticaria).

- Infusion-associated reactions, i.e. any side effect occurring during the infusion or until the end of the infusion day- see under section 4 "Possible Side Effects" below for symptoms.

If these reactions occur, the Aldurazyme infusion should be stopped immediately and appropriate treatment will be started by your doctor.
These reactions may be particularly severe if you have a pre-existing MPS I-related upper airway obstruction.
You may be given additional medications to help prevent allergic-type reactions, such as antihistamines, medicine to reduce fever (e.g. paracetamol) and/or corticosteroids.
Your doctor will also decide if you can continue receiving Aldurazyme.

**Other medicines and Aldurazyme**
Inform your doctor if you are using medicines containing chloroquine or procaine, due to a possible risk of decreasing the action of Aldurazyme.

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

**Pregnancy, breast-feeding and fertility**
There is not enough experience of the use of Aldurazyme in pregnant women. You should not be given Aldurazyme during pregnancy unless clearly necessary.
It is not known whether Aldurazyme appears in breast milk. It is recommended to stop breast-feeding during treatment with Aldurazyme.
No information is available on the effects of Aldurazyme on fertility.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

**Driving and using machines**
The effects on the ability to drive and to use machines have not been studied.

**Aldurazyme contains sodium**
This medicine contains 30 mg sodium (main component of cooking/table salt) per vial. This is equivalent to 1.5% of the recommended maximum daily dietary intake of sodium for an adult.

## 3. How Aldurazyme is given

Instruction for use - dilution and administration
The concentrate for solution for infusion has to be diluted before administration and is for intravenous use (see information for health care professionals).
Administration of Aldurazyme should be carried out in an appropriate clinical setting where resuscitation equipment to manage medical emergencies would be readily available.

Dosage
The recommended dosage regimen of Aldurazyme is 100 U/kg body weight given once every week as an intravenous infusion. The initial infusion rate of 2 U/kg/h may be gradually 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.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

**If you miss an infusion of Aldurazyme**
If you have missed an Aldurazyme infusion, please contact your doctor.

**If you are given more Aldurazyme than needed**
If the dose of Aldurazyme given is too high or the infusion is too fast, adverse drug reactions may occur. Receiving an excessively fast infusion of Aldurazyme may cause nausea, abdominal pain, headache, dizziness and difficulty breathing (dyspnoea). In such situations, the infusion should be

stopped or the infusion rate slowed down immediately. Your doctor will decide if further intervention is required.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects were mainly seen while patients were being given the medicine or shortly after (infusion-associated reactions). If you experience any reaction like this, you should **contact your doctor immediately.** The number of these reactions decreased the longer that patients were on Aldurazyme. The majority of these reactions were mild or moderate in intensity. However, severe systemic allergic reaction (anaphylactic reaction) has been observed in patients during or up to 3 hours after Aldurazyme infusions. Some of the symptoms of such a severe allergic reaction were life-threatening and included extreme difficulty breathing, swelling of the throat, low blood pressure, and low oxygen level in the body. A few patients who had a prior history of severe MPS I related upper airway and pulmonary involvement, experienced severe reactions including bronchospasm (airway constriction), respiratory arrest, and swelling of the face. The frequency of bronchospasm and respiratory arrest is unknown. The frequency of severe allergic reaction (anaphylactic reaction) and swelling of the face is considered common and may affect up to 1 in 10 people.

Very common symptoms (may affect more than 1 in 10 people) which were not serious include
- headache,
- nausea,
- abdominal pain,
- rash,
- joint disease,
- joint pain,
- back pain,
- pain in arms or legs,
- flushing,
- fever, chills,
- increased heart rate,
- increased blood pressure,
- reaction at the infusion site such as swelling, redness, build-up of fluid, discomfort, itchy rash, pale colour of the skin, discoloured skin, or sensation of being warm.

<u>Other side effects include the following:</u>

**Common (may affect up to 1 in 10 people)**
- increased body temperature
- tingling
- dizziness
- cough
- difficulty in breathing
- vomiting
- diarrhoea
- rapid swelling under the skin in areas such as the face, throat, arms and legs which can be life-threatening if throat swelling blocks the airway
- hives
- itching
- hair loss
- cold sweat, heavy sweating
- muscle pain

- paleness
- cold hands or feet
- feeling hot, feeling cold
- fatigue
- influenza like illness
- pain at injection site
- restlessness

**Not known (frequency cannot be estimated from the available data)**
- allergic reactions (hypersensitivity)
- abnormally slower heart rate
- increased or abnormally high blood pressure
- voice box swelling
- bluish color of the skin (due to lower levels of oxygen in the blood)
- fast breathing
- redness of the skin
- leakage of the medicine into the surrounding tissue at the site of injection, where it can cause damage
- inability of the lungs to work properly (respiratory failure)
- throat swelling
- high-pitched breathing sound
- obstruction of airways causing difficulty in breathing
- lip swelling
- tongue swelling
- swelling especially of the ankles and feet due to fluid retention
- drug specific antibody, a blood protein produced in response to medicine
- antibody that neutralizes the effect of medicine

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Aldurazyme

Keep this medicine out of the sight and reach of children.

You should not be given this medicine after the expiry date which is stated on the label after the letters EXP. The expiry date refers to the last day of that month.

Unopened vials:
Store in a refrigerator (2°C – 8°C).

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Aldurazyme contains**
- The active substance is laronidase. One ml of the solution in the vial contains 100 U of laronidase. Each vial of 5 ml contains 500 U of laronidase.
- The other ingredients are sodium chloride, sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, polysorbate 80, water for injections.

**What Aldurazyme looks like and contents of the pack**
Aldurazyme is supplied as a concentrate for solution for infusion. It is a solution that is clear to slightly opalescent, and colourless to pale yellow.

Pack size: 1, 10 and 25 vials per carton. Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

Marketing Authorisation Holder
Sanofi B.V., Paasheuvelweg 25, 1105 BP Amsterdam, The Netherlands.

Manufacturer

Genzyme Ireland Ltd., IDA Industrial Park, Old Kilmeaden Road, Waterford, Ireland

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**This leaflet was last revised in**

**Other sources of information**
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

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The following information is intended for healthcare professionals only:

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 an 0.2 μm in-line filter.

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.

Aldurazyme should not be mixed with other medicinal products in the same infusion.

**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 bodyweight is less or equal than 20 kg) or 250 ml (if bodyweight is more than 20 kg) of 0.9% sodium chloride intravenous solution.
- 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.
- 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.