EU-RISK MANAGEMENT PLAN FOR ALDURAZYME® (LARONIDASE)

Data Lock Point (DLP)	30-APR-2022
RMP Version number	Version 1.3
Date of final sign-off	06-NOV-2023

[redacted]

Table 1 - RMP version to be assessed as part of this application

Rationale for submitting an updated RMP	Risk management plan updated to address the [redacted] comments received on RMP v1.2[redacted]
Summary of significant changes in this RMP	**RMP Part II Module SVII:** Updated the risk table for risk "Medication errors in home infusion settings". **RMP Part V:** Updated the details of home infusion guide for patient/care giver including an infusion diary. **RMP Part VI**: Updated to align with relevant RMP sections. **Annex 6:** Updated key elements of home infusion guide for HCP and home infusion guide for patient/caregiver including an infusion diary [redacted] **Annex 8**: Updated to reflect the current changes in the RMP.

HCP: Healthcare Professional; [redacted] RMP: Risk Management Plan.

Table 2 - Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within
Not applicable	-	-

RMP: Risk Management Plan.

Table 3 - Details of the currently approved RMP

Version number	Not applicable (first submission)
Approved with procedure	Not applicable (first submission)
Date of approval (opinion date)	Not applicable (first submission)

RMP: Risk Management Plan.

Table 4 - QPPV name and signature

QPPV name	[redacted][a], [redacted]
QPPV signature	Electronic signature on file

a Deputy QPPV by delegation from Heike Schoepper, QPPV for Sanofi.

QPPV: Qualified Person Responsible for Pharmacovigilance.

[redacted]

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ABBREVIATIONS

ADR:	Adverse Drug Reaction
AE:	Adverse Event
AEGIS:	Adverse Experience Gathering Information System
ATC:	Anatomical Therapeutic Chemical
BLA:	Biologic License Application
CI:	Confidence Interval
COVID-19:	Coronavirus Disease 2019
DLP:	Data Lock Point
DNA:	Deoxyribonucleic Acid
e-CTD:	Electronic Common Technical Document
EEA:	European Economic Area
EMA:	European Medicines Agency
EPAR:	European Public Assessment Report
ERT:	Enzyme Replacement Therapy
EU:	European Union
FDA:	Food and Drug Administration
GAG:	Glycosaminoglycan
HCP:	Healthcare Professional
HI:	Home Infusion
HSCT:	Hematopoietic Stem Cell Transplantation
IAR:	Infusion-Associated Reaction
IBD:	International Birth Date
ICAP:	International Charitable Access Program
IgE:	Immunoglobulin E
IgG:	Immunoglobulin G
IgM:	Immunoglobulin M
INN:	International Nonproprietary Name
IV:	Intravenous
JPAC:	Australia, Japan, New Zealand and South Korea
MAH:	Marketing Authorization Holder
MPS I:	Mucopolysaccharidosis Type I
n:	Number of Patients
N:	Total Number of Patients
PBRER:	Periodic Benefit-Risk Evaluation Report
PL:	Package Leaflet
PRAC:	Pharmacovigilance Risk Assessment Committee
PSUR:	Periodic Safety Update Report
PT:	Preferred Term
PTC:	Product Technical Complaint
Q:	Quarter

[redacted]

QoL:	Quality of Life
QPPV:	Qualified Person Responsible for Pharmacovigilance
RMP:	Risk Management Plan
SAR:	Serious Adverse Reaction
SD:	Standard Deviation
SmPC:	Summary of Product Characteristics
US:	United States

[redacted]

RISK MANAGEMENT PLAN - PART I: PRODUCT (S) OVERVIEW

Table 5 - Product Overview

Active substance(s) (INN or common name)	Laronidase
Pharmacotherapeutic group(s) (ATC Code)	Enzymes (A16AB05)
Marketing Authorization Holder	Sanofi B.V.
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	ALDURAZYME
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical class: Laronidase is a recombinant form of human α-L-iduronidase. Purified laronidase is a glycoprotein with a molecular weight of approximately 83 kD and 628 amino acids after cleavage of the N-terminus. The molecule contains 6 N-linked oligosaccharide modifications sites.
	Summary of mode action: The rationale for enzyme replacement therapy (ERT) is to restore a level of enzymatic activity sufficient to hydrolyse the accumulated substrate and to prevent further accumulation. After IV infusion, laronidase is rapidly removed from the circulation and taken up by cells into lysosomes, most likely via mannose-6-phosphate receptors.
	Important information about its composition: • Sodium chloride • Sodium phosphate monobasic, monohydrate • Sodium phosphate dibasic, heptahydrate • Polysorbate 80 • Water for injection Laronidase is produced by recombinant DNA technology using mammalian Chinese Hamster Ovary cell culture.
Hyperlink to the product information	Refer to e-CTD sequence 0090, Module 1.3.1 English proposed Product Information.
Indication(s) in the EEA	Current: Laronidase 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.
	Proposed: Not applicable

Dosage in the EEA	Current: Laronidase treatment should be supervised by a physician experienced in the management of patients with MPS I or other inherited metabolic diseases. Administration of laronidase infusions should be carried out in an appropriate clinical setting where resuscitation equipment to manage medical emergencies is readily available. Posology The recommended dosage regimen of laronidase is 100 U/kg body weight administered once every week. Method of administration Laronidase is to be administered as an IV 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 to 4 hours.
	Proposed: Not applicable
Pharmaceutical form(s) and strength(s)	Current: Concentrate for solution for infusion. A clear to slightly opalescent, and colorless to pale yellow solution.
	Proposed: Not applicable
Will the product be subject to additional monitoring in the EU?	No

ATC: Anatomical Therapeutic Chemical; DNA: Deoxyribonucleic Acid; e-CTD: Electronic Common Technical Document; EEA: European Economic Area; ERT: Enzyme Replacement Therapy; EU: European Union; INN: International Nonproprietary Name; IV: Intravenous; MPS I: Mucopolysaccharidosis Type I; RMP: Risk Management Plan.

RISK MANAGEMENT PLAN - PART II MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Laronidase is indicated for long-term ERT in patients with a confirmed diagnosis of MPS I to treat the non-neurological manifestations of the disease.

Mucopolysaccharidosis Type I is a panethnic, chronic and progressive, autosomal recessive lysosomal storage disease affecting both sexes. Precise figures for MPS I incidence are lacking, but estimated incidence is approximately one case per 100 000 births: in England and Wales from 1981-2003, global incidence was 1.07 cases per 100 000 births. (1) An Australian study estimates that MPS I incidence is 0.9 cases per 100 000 births. (2)

Mucopolysaccharidosis Type I has been broadly categorized into Scheie syndrome, Hurler-Scheie syndrome and Hurler syndrome, representing clinical phenotypes ranging from least severe to most severe. The prevalence of the sub-syndromes of MPS I were Hurler syndrome: 0.76/100 000, Hurler-Scheie syndrome 0.24/100 000 and Scheie syndrome 0.07/100 000. (3) ALDURAZYME (laronidase) is indicated for patients with Hurler and Hurler-Scheie forms of MPS I and for patients with the Scheie form who have moderate to severe symptoms.

The epidemiology of the disease is summarized in the following table:

Table 6 - Epidemiology of the Mucopolysaccharidosis Type I (MPS I)

<table>
<tr><th>Indication</th><th>Mucopolysaccharidosis Type I (MPS I)</th></tr>
<tr><td>Birth incidence and population prevalence</td><td>In the US, the incidence was found to be 0.98 per 100 000 live births, and prevalence was found to be 2.67 per 1 million.
Global incidence of MPS I is approximately 1 case per 100 000 births, with Hurler syndrome accounting for about 57% of the cases, Hurler-Scheie for about 23% of the cases, and Scheie syndrome for about 20% of the cases. (1)(2)(3)
In Europe, birth prevalence data for MPS I are available in several countries, with reported birth prevalence per 100 000 being as follows: Switzerland 0.19, Czech Republic 0.72, Denmark 0.54, Norway 1.85, Sweden 0.67, Germany 0.69, the Netherlands 1.19, Northern Ireland 1.66, United Kingdom 1.07, Poland 0.22 and Portugal 1.33. (4)</td></tr>
<tr><td>Demographics of the population in the authorized indication(s)</td><td><u>Demographics of the target population</u>
Demographics of MPS I patients can be derived from the worldwide MPS I Registry. (5) A total of 1069 patients enrolled in the MPS I Registry as of 06-Mar-2014, were described in the 2014 Global Annual Regulatory report. A summary of patient clinical phenotype, as well as current, geographic region, age of symptom onset, age of diagnosis, and age of first treatment, are presented below.
Table 6a
<table><tr><th>Baseline characteristics</th><th>Hurler</th><th>Hurler-Scheie</th><th>Scheie</th><th>Undetermined</th></tr><tr><td>Number of patients (%)</td><td>639 (59.8)</td><td>233 (21.8)</td><td>127 (11.9)</td><td>70 (6.5)</td></tr><tr><td>Asia Pacific n (%)</td><td>7 (1.1)</td><td>5 (2.1)</td><td>12 (9.4)</td><td>2 (2.9)</td></tr></table></td></tr>
</table>

Indication	Mucopolysaccharidosis Type I (MPS I)

Europe n (%)	287 (44.9)	101 (43.3)	63 (49.6)	27 (38.6)
Latin America n (%)	84 (13.1)	57 (24.5)	22 (17.3)	23 (32.9)
Middle East n (%)	0	2 (0.9)	0	0
North America n (%)	261 (40.8)	68 (29.2)	30 (23.6)	18 (25.7)
Mean age of symptom onset (years) (SD)	0.8 (1.0)	2.6 (3.2)	6.1 (5.8)	1.0 (1.4)
Mean age of diagnosis (years) (SD)	1.4 (1.9)	5.1 (5.9)	12.5 (10.9)	4.1 (7.0)
Mean age of first treatment (years) (SD)	2.5 (3.0)	10.6 (9.2)	20.8 (13.2)	8.8 (10.2)

n: Number of Patients; SD: Standard Deviation.

Additionally, the following current data (as of 05-Aug-2022) is available for patients in the MPS I Registry study.

Table 6b: Enrollment and Characteristics of Patients in the MPS I Registry

	Statistic	All Patients
Total patients enrolled, Oct-2003 to Aug-2022	N	1342
Time from diagnosis to most recent follow-up, years[a]	N	1315
	Mean (SD)	10.5 (8.71)
	Median (25^{th}, 75^{th})	8.8 (3.5, 15.5)
	Min, Max	0.0, 44.1
Age at most recent follow-up, years[b]	N	1341
	Mean (SD)	14.2 (11.42)
	Median (25^{th}, 75^{th})	11.4 (5.8, 18.6)
	Min, Max	0.1, 65.4

a Patients missing date of diagnosis will not have time from diagnosis to most recent follow-up calculated.

b Patients missing date of birth will not have age at most recent follow-up.

MPS I: Mucopolysaccharidosis Type I; N: Total Number of Patients; SD: Standard Deviation.

Risk factors for the disease

Mucopolysaccharidosis Type I disease is referred to as an autosomal recessive disorder. A person is born with the disease by inheriting two faulty MPS I genes, one from each parent. There is no known environmental risk factor.

Main existing treatment options	Among the available approaches to treat MPS I, HSCT is typically recommended for patients with Hurler syndrome under 2 years of age with normal cognition (developmental quotient >70), as it can prolong survival, preserve neurocognition, and ameliorate some somatic features. (6) However, due to its significant morbidity and mortality, HSCT is

Indication	Mucopolysaccharidosis Type I (MPS I)
	reserved for the most severe form of MPS I. (6)(7)(8) The allogenic stem cell infusion is given following conditioning with chemotherapeutic agents used to suppress the immune response; when successful, the transplant is a one-time procedure, though graft failure may necessitate subsequent transplants. Enzyme replacement therapy with laronidase is the primary treatment option for patients with Hurler-Scheie and Scheie syndromes. Laronidase is also used to treat Hurler patients who are not candidates for HSCT because of age, health status, access to transplant, or parental choice. Laronidase must be given as a weekly peripheral or central IV infusion and is a lifelong therapy. (3)
Natural history of the indicated condition in the untreated population including mortality and morbidity	Hurler syndrome describes patients with the most severe form of MPS I, with signs and symptoms typically appearing in infancy and a median age of death of 6.8 years when untreated. (1) Patients with Scheie syndrome present later in childhood and demonstrate slower symptom progression with preservation of cognition and survival into adulthood. (9) Hurler-Scheie describes an intermediate form with no or mild cognitive impairment and death usually occurring in adolescence or early adulthood when untreated.
Important co-morbidities	Clinical manifestations of MPS I show a chronic multisystemic and progressive course which differs across clinical phenotypes. (10) The disease is highly heterogeneous, spanning a spectrum of severity. Symptoms across the types include facial dysmorphism, ophthalmologic manifestations, visceral involvement, skeletal involvement, cardiopulmonary manifestations, and neurological impairment. Children with Hurler syndrome appear normal at birth and develop the characteristic appearance over the first years of life. (11) Concomitant medications often used in this target population are those prescribed to treat comorbidities.

HSCT: Hematopoietic Stem Cell Transplantation; IV: Intravenous; MPS I: Mucopolysaccharidosis Type I; SD: Standard Deviation; US: United States.

RISK MANAGEMENT PLAN - PART II MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Several non-clinical safety studies were conducted to evaluate the toxicology profile of laronidase for use as an ERT in patients with MPS I disease. The toxicology program conducted with laronidase includes single-dose studies in rats and dogs, repeat-dose studies in dogs (8 weeks) and cynomolgus monkeys (26 weeks), fertility and reproductive toxicity study in rats and developmental toxicity study in rats. Non-clinical evaluation with in vivo models of MPS I disease has shown laronidase is able to reverse biochemical and histopathological manifestations of the disease. Toxicological evaluation in rats, dogs, and monkeys suggest an acceptable safety profile for human use.

The key non-clinical safety findings are presented in the following table.

Table 7 - Key safety findings from non-clinical studies and relevance to human usage

Key Safety Findings	Relevance to human usage
Toxicity • Single-dose toxicity studies Acute IV toxicity studies in the rat at doses of 0.29 mg/kg, 0.58 mg/kg and 5.8 mg/kg and in the dog at doses of 0.116, 1.16 mg/kg and 11.6 mg/kg demonstrated that laronidase did not produce toxicity at the highest doses tested in each species. The maximum doses tested in rats and dogs are equivalent to approximately 1.0 and 6.4 mg/kg, respectively, in humans, based upon equivalent body surface area.	
Repeat-dose toxicity studies When administered to beagle dogs via 4 hour IV infusion at 1.66 mg/kg once weekly for 8 weeks, laronidase induced responses that included facial edema, emesis, mucoid stools and/or excessive salivation; the effects were transient and resolved by the end of infusion in most cases. The status of the cardiovascular system during these events was found to be within normal limits. All dogs developed IgG antibodies in this study and fixed complement during the infusions where IARs occurred.	Hypersensitivity reactions similar to those observed in cynomolgous monkeys and dogs have been documented in human clinical trials (Study ALID 006-01). These reactions have been added to the important identified risk of "Infusion-associated reactions including hypersensitivity and anaphylaxis" (see [Part II module SVII]) and are included in the product label. They are also monitored by routine pharmacovigilance assessments.
In a 26 week IV toxicity study of laronidase in cynomolgus monkeys at doses of 0.166 mg/kg, 1.66 mg/kg, and 16.6 mg/kg, given as an 8 hour infusion weekly, there were no treatment-related mortalities, differences in body weight, or differences in food consumption. The sole abnormal clinical sign was edema, which was observed in one monkey in the 16.6 mg/kg dose treatment group and was judged to hypersensitivity response to a recombinant human protein. There were no observations noted with subsequent dosing. By week 13, all treated monkeys developed antibodies with levels ranging from 61 to 8844 A_{450} U/μL. Antibody	

Key Safety Findings	Relevance to human usage
response was dependent on dose of laronidase; there was no difference in antibody levels between the sexes. Antibody levels decreased in approximately half of the monkeys between weeks 13 and 26 and increased in the remaining animals; these changes were not dose-dependent. Treatment with laronidase at 16.6 mg/kg increased total leukocyte, lymphocyte, eosinophil, and/or monocyte counts at 1 or more time intervals. The changes were small in magnitude, their underlying cause was not clear from the other data evaluated and they are not considered to be biologically significant. There was no evidence of laronidase accumulation in the liver, which is the organ found to have the highest laronidase levels in biodistribution studies. • Reproductive toxicity studies In a study of fertility and reproduction toxicity in male and female rats (Study IDU-PC-013), laronidase was administered daily by IV route at doses of 0.036 mg/kg, 0.36 mg/kg, and 3.6 mg/kg. There were no mortalities. No effects on mating and fertility parameters were observed and there were no treatment-related effects on sperm parameters or findings on gross necropsy. There was no effect on litter parameters or treatment-related fetal effects. There was no reproductive toxicity seen at doses up to 3.6 mg/kg (equivalent to 0.58 mg/kg, in humans, based upon equivalent body surface area). In a study of developmental toxicity in rats, laronidase was administered daily by IV route at doses of 0.036 mg/kg, 0.36 mg/kg, and 3.6 mg/kg. No mortality or other treatment-related clinical signs were observed, and there were no laronidase-related effects on litter parameters.	Development of IgG antibodies against laronidase has been observed in most patients receiving laronidase during 2 pivotal trials and during the postmarketing phase. Immunoglobulin E antibody formation has also been observed. As observed in cynomolgous monkeys, small changes in total leukocyte, lymphocyte, eosinophil and monocyte counts were observed in MPS I patients during the pivotal clinical trials of Laronidase (ALID 003-99 and ALID 006-01). The n with hematology values that shifted from normal to abnormal were very small and not considered clinically relevant in either treatment group. No reproductive toxicity and no developmental toxicity were reported in animals. No issues have been observed in postmarketing experience (see [Part II module SVII]).
Other toxicity-related information or data • Safety pharmacology Cardiovascular and respiratory parameters were examined in dogs with no results reported that indicated any potential safety pharmacological effects.	Not applicable

IAR: Infusion-Associated Reaction; IgE: Immunoglobulin E; IgG: Immunoglobulin G; IV: Intravenous; MPS I: Mucopolysaccharidosis Type I; n: Number of Patients.

Animal models studied in the non-clinical setting provided sufficient information to estimate the occurrence of certain safety risks. However, based on limitations of the animal models, a complete prediction of the risks in the clinical setting is not always possible.

RISK MANAGEMENT PLAN - PART II MODULE SIII: CLINICAL TRIAL EXPOSURE

Laronidase is a recombinant α-L-iduronidase, a lysosomal hydrolase that catalyzes hydrolysis of terminal α-L-iduronic acid residues of dermatan sulphate and heparan sulphate. Mucopolysaccharidosis Type I disease is characterized by the deficiency of α-L-iduronidase. Reduced or absent α-L-iduronidase activity results in the accumulation of the glycosaminoglycan (GAG) substrates, dermatan sulphate and heparan sulphate, throughout the body and leads to widespread cellular, tissue, and organ dysfunction. The rationale of laronidase therapy in MPS I disease is to provide exogenous enzyme for uptake into lysosomes and increase the catabolism of GAG. Laronidase uptake by cells into lysosomes is most likely mediated by the mannose-6-phosphate-terminated oligosaccharide chains of laronidase binding to specific mannose-6-phosphate receptors. Exposure of human subjects to laronidase in the clinical trial setting was limited given the orphan indication, a brief overview is provided in and Table 8.

Laronidase is indicated for long-term ERT in patients with MPS I to treat the non-neurological manifestations of the disease.

Laronidase was shown to improve pulmonary function and walking ability. As laronidase does not cross the blood-brain barrier, it has not been evaluated for efficacy in the central nervous system manifestations of the disorder.

Laronidase is marketed as ALDURAZYME, a concentrated solution for IV infusion; 1 mL contains approximately 0.58 mg (100 U) of laronidase. Each 5 mL vial contains approximately 2.9 mg (500 units) in an extractable volume of 5.0 mL.

Laronidase was first registered in the US; the Biologic License Application (BLA 125058) for laronidase 5 mL/vial (2.9 mg/vial) received Food and Drug Administration (FDA) approval on 30 April 2003 for the treatment of patients with Hurler and Hurler-Scheie forms of MPS I and for patients with the Scheie form who have moderate to severe symptoms. The risks and benefits of treating mildly affected patients with the Scheie form have not been established. In the EU, the 500 U/5 mL vial presentation received marketing authorization approval from the European Commission (centralized procedure) on 10 June 2003 (EU/1/03/253/001-003) for long-term ERT in patients with a confirmed diagnosis of MPS I to treat the non-neurological manifestations of the disease.

Total exposure in 8 completed and 1 open label/ongoing laronidase studies is 126 patients as shown in Table 8. Duration of exposure to laronidase in the clinical studies ranged from 26 weeks to 6 years at doses varying from 0.58 mg/kg every week to 1.8 mg/kg every 2 weeks. The ages of treated patients in the clinical trials ranged from 0.5 to 43 years.

There is one local clinical trial with recent active enrollment, with 2 patients treated as of DLP. Moreover, as laronidase is a mature product, a summary based on duration of exposure would be of limited relevance compared to the postmarketing experience accumulated since international birth date (IBD) of 30 April 2003. The exposure by age/gender is shown for the completed and

open-label/ongoing (ALID01803) studies in Table 8 while the exposure by race is shown in Table 9.

Table 8 - Exposure by age/gender

Age (yr)	Male	Female	Total
<18	57	48	105
18 to 65	8	13	21
66 to 75	0	0	0
>75	0	0	0
Total	65	61	126

Table 9 - Exposure by racial origin

Racial group	Number of subjects
Caucasian	98
Black	2
Asian	7
Other	12
Unknown	7
Total	126

RISK MANAGEMENT PLAN - PART II MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Table 10 - Important exclusion criteria in pivotal studies in the development programme

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Pregnancy/lactation	Pregnant and lactating patients were not involved in the clinical development of product as they are not the intended target population at this time. This absence of clinical data is reflected in the claimed precautions for use in pregnant or lactating patients. Therefore, the use of product in pregnant or lactating females is considered as missing information.	Yes	Not applicable
Patients under 5 years old	Patients younger than 5 years old were not included in the pivotal study as they would have been unable to perform tests for primary end points assessment.	No	Data available from clinical trial ALID-014-02

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

As a consequence of the rarity of MPS I disease, the n populations treated in the pre-authorization phase has been limited. Therefore, limitations of adverse drug reactions (ADRs) detection, especially the uncommon and rare ones, might have been initially related to the size of the studied population. Laronidase has been now in clinical use since 1997 and data from postmarketing exposure compensated for limitations in the clinical trial development program in detecting ADRs in the exposed population.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table 11 - Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant or breast-feeding women	• The safety and efficacy of laronidase in pregnant or lactating women has not been established in the pre-authorization phase. To date, the safety and efficacy of laronidase in pregnant or lactating women has not been established. • It is not known whether the active form of laronidase is excreted in human milk.

Type of special population	Exposure
Patients with relevant comorbidities • Patients with hepatic impairment • Patients with renal impairment	• The safety and efficacy of laronidase in patients with hepatic insufficiency have not been evaluated and no dosage regimen can be recommended in these patients. • The safety and efficacy of laronidase in patients with renal insufficiency have not been evaluated and no dosage regimen can be recommended in these patients.
Patients of different racial and/or ethnic origins	The studies were conducted globally. No ethnic groups were excluded from the studies; A Japanese specific study was conducted (ALID02205) and the conclusion for Japanese patients was similar to what was observed in Western countries.
Subpopulations carrying known and relevant genetic polymorphisms	There have been no investigations of subpopulations with genetic polymorphisms.
Other • Geriatric use	The safety and efficacy of laronidase in elderly has not been established and no dosage regimen can be recommended in these patients.

Pregnant or breast-feeding women

Very limited data are available concerning the use of laronidase in pregnant or breast-feeding women. However, pregnant and breast-feeding women are part of the target population. Animal studies do not indicate direct or indirect harmful effects on pregnancy, embryonal/fetal development, parturition and post-natal development. The potential risk for humans is unknown. Therefore, laronidase should not be used during pregnancy unless clearly necessary. Laronidase may be excreted in milk. Because there are very limited data available in neonates exposed to laronidase via breast milk, it is recommended to stop breast-feeding during laronidase treatment. Due to limited information, the use of laronidase in pregnant or breast-feeding women is considered as missing information. In order to collect additional information, an ongoing monitoring through a MPS I pregnancy sub-registry study (ALID04911) and a lactation study (ALID01803) have been set up.

Patients of different racial and/or ethnic origins

To date, there is no evidence of differences in the safety profile of laronidase in patients of different racial or ethnic origins.

Subpopulations carrying known and relevant genetic polymorphisms

To date, there is no information suggesting the existence of polymorphism relevant to the efficacy or safety of laronidase in the current indication.

Patients with renal or hepatic impairment

The safety and efficacy of laronidase in patients with renal or hepatic insufficiency have not been evaluated.

Geriatric use

The safety and efficacy of laronidase in patients older than 65 years have not been established.

[redacted]

RISK MANAGEMENT PLAN - PART II MODULE SV: POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

The majority of laronidase use is within the approved indication of patients with MPS I. In the EU, laronidase is indicated for long-term ERT in patients with a confirmed diagnosis of MPS I to treat the non-neurological manifestations of the disease while in the US laronidase is indicated for patients with Hurler and Hurler-Scheie forms of MPS I and for patients with the Scheie form who have moderate to severe symptoms. The risks and benefits of treating mildly affected patients with the Scheie form have not been established. No significant safety findings on misuse have been identified. Laronidase is indicated for and used in pediatric populations, there is no specific safety concern related to its use in this patient population.

SV.1.1 Method used to calculate exposure

The method of estimation of patients treated with commercial laronidase by the marketing authorization holder (MAH) is based on direct interactions of MAH with regional offices at country level. Because laronidase is dosed in milligrams per kilogram and administered to a patient population with varying weights, the calculated number of vials distributed is not useful from a dose calculation perspective. Therefore, the estimated n treated with commercial laronidase is calculated from sales figures received from the MAH's regional offices, on the basis of direct interaction with prescribing physicians. Prescribers are queried as to how many patients are treated or how many prescriptions for laronidase are written, depending on individual country regulations. This information is then checked by MAH by analyzing the order patterns. Patients who received laronidase treatment via clinical trials or the International Charitable Access Program (ICAP) may have transferred to commercial product upon reimbursement. Patients are only counted in one category with the intent to avoid overlap between the ICAP, clinical trial and commercial exposure data.

SV.1.2 Exposure

Table 12 - Worldwide Estimated Patient Exposure to Laronidase (30 April 2022)

Country or Territory Area	Number of patients treated		
	Commercial	Charitable	Total
Africa	335	7	342
Asia	44	24	68
[redacted]	[redacted]	[redacted]	[redacted]
Eurasia and Middle East	362	1	363
Europe	407	1	408
JPAC	61	2	63
Latin America	314	13	327
North America	216	0	216

JPAC: Australia, Japan, New Zealand and South Korea.

[redacted]

RISK MANAGEMENT PLAN - PART II MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 Potential for misuse for illegal purposes

Laronidase has no known pharmacological addictive effect that could lead to misuse for illegal purposes and is not listed among drugs with addictive potential by the European Monitoring Centre for Drugs and Drug Addiction. Thus, this concern is not applicable to laronidase.

[redacted]

RISK MANAGEMENT PLAN - PART II MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

The following safety topics will be discussed in this section and will be presented in Section SVII.1.1 (if the risks are not considered important for inclusion in the list of safety concerns in the RMP) or in Section SVII.1.2 (if the risks are considered important for inclusion in the list of safety concerns in the RMP):

- Infusion site reactions (Section SVII.1.1)
- Infusion-associated reactions including hypersensitivity and anaphylaxis (Section SVII.1.2)
- Medication errors in home infusion (HI) setting (Section SVII.1.2)
- Use of laronidase in pregnant and lactating women (Section SVII.1.2)

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason(s) for not including an identified or potential risk in the list of safety concerns in the RMP

Infusion site reactions is an identified risk, not considered important. Infusion site reactions are frequently reported with laronidase, the events are associated with local injury/inflammation at the injection/infusion site. The reactions are mostly mild and of short duration.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Table 13 - Important identified risk considered for inclusion in the list of safety concerns: Infusion-associated reactions including hypersensitivity and anaphylaxis

Infusion-associated reactions including hypersensitivity and anaphylaxis	
Scientific evidence that has led to the inclusion	Data from clinical trials, postmarketing surveillance data. As with any IV protein product, allergic-type hypersensitivity reactions are possible. Infusion-associated reactions constitute most of the related AEs in the clinical trials. Infusion-associated reactions were 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 age group of study (up to one year of treatment). In clinical trials most patients developed IgG antibodies. Testing for IgE antibodies was rarely indicated during the clinical studies. In the postmarketing experience, approximately 1% of patients experienced severe or serious infusion allergic reactions and were tested positive for IgE. The most SARs reported with laronidase treatment during clinical trials were anaphylactic and allergic reactions. A patient with pre-existing airway compromise developed a severe reaction 3 hours from the start of the infusion (at week 62 of treatment) consisting of urticaria and airway obstruction, requiring tracheostomy. During the postmarketing experience, most of AEs associated with laronidase infusions were mild to moderate in severity. The onset of hypersensitivity related symptoms

[redacted]

Infusion-associated reactions including hypersensitivity and anaphylaxis	
	generally occurred during or shortly after infusions. Life-threatening anaphylaxis, including anaphylactic reactions and anaphylactic shock have been reported. Severe IARs have been reported in patients with pre-existent severe underlying upper airway involvement. Patients with an acute underlying illness at the time of laronidase infusion appear to be at greater risk for IARs.
Risk-benefit impact	Infusion associated reactions are a known risk with enzyme replacement therapies. This risk is managed routinely by the prescribing physicians that are experienced in the risk and management of IARs. The impact of IARs on the benefit-risk balance is considered manageable based on the anticipated experience of this specialized HCP community.

AE: Adverse Event; HCP: Healthcare Professional; IAR: Infusion-Associated Reactions; IgG: Immunoglobulin G; IgE: Immunoglobulin E; IV: Intravenous; SAR: Serious Adverse Reaction.

Table 14 - Important potential risks considered for inclusion in the list of safety concerns: Medication errors in home infusion (HI) setting

Medication errors in home infusion (HI) setting	
Scientific evidence that has led to the inclusion	Medication errors have been reported with laronidase involving product dose omission issue, inappropriate schedule of product administration and other indicative events. Access to HI should minimize the patients issue of missing doses. However, there are potential issues regarding medication errors in HI setting, as follows: • dosage may vary as patient's weight may change over time. • recommended rate of infusion administration (slow infusion, on average 3 hours) and necessary changes to rate. • healthcare professional experience in performing venipunctures, administering infusions, handling IARs.
Risk-benefit impact	The review of available information has not shown any difference between the settings at home and in the clinic. Enzyme replacement therapy with laronidase provides clinical benefit to patients. The expected benefits (if recommendations for laronidase infusion are followed) are increased access to properly administered weekly infusions (with use of recommended doses) and potential increase in QoL. The benefit-risk balance remains positive. There is no deleterious impact on the benefit-risk balance anticipated for this product.

HI: Home Infusion; IAR: Infusion-Associated Reaction; QoL: Quality of Life.

Table 15 - Missing information considered for inclusion in the list of safety concerns: Use of laronidase in pregnant and lactating women

Use of laronidase in pregnant and lactating women	
Scientific rationale for anticipating a different safety profile in the particular subpopulation/use that has led to the inclusion	• Infants are at risk of toxicity from drugs used by adults; toxicity may occur prenatally when they are exposed via placental transfer or postnatally when exposed through breast milk. • The first trimester of pregnancy involves major development/embryofetal organogenesis; it is a critical period for drug toxicity via transplacental exposure. • No risk has been identified from pre-clinical data.
Risk-benefit impact	Two Phase IV studies are on-going to assess exposure during pregnancy and lactation. To date no risk has been identified. (12) However, data is limited.

[redacted]

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Not applicable since first RMP.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

The following risks have been identified for laronidase:

- Important identified risk:
  - Infusion-associated reactions including hypersensitivity and anaphylaxis
- Important potential risk:
  - Medication errors in home infusion setting
- Missing information:
  - Use of laronidase in pregnant and lactating women

SVII.3.1 Presentation of important identified risks and important potential risks

Table 16 - Identified risk: Infusion-associated reactions including hypersensitivity and anaphylaxis

Identified Risk	**Infusion-associated reactions including hypersensitivity and anaphylaxis**
Potential mechanism	Potential mechanisms for infusion associated reactions including hypersensitivity and anaphylaxis include: • Immunoglobulin E mediated. • Immunoglobulin G mediated with complement activation. • Cytokine release but the mechanism is unclear. • Nonspecific immunogenic mechanism not understood to date. • Direct stimulation of mast cells by drug with release of histamine. • Related to higher infusion rate, ie, protein load. Possible factors associated with the induction of IgG antibodies to laronidase: • Foreignness of laronidase (recognized as a non-self-protein which is impacted by genotype), chemical complexity, route, frequency, rate of infusion, and dose of administration. Induction of the antibody response involves the following steps: • Immune recognition-antigen associated with major histocompatibility complex molecule is recognized as non-self by the immunocompetent cells. • Stimulation of B-lymphocyte response by complex interactions between T, B and accessory cells. • Continuing proliferation and differentiation of B-cells into plasma cells by several cytokines. In theory, the binding of IgG to laronidase may potentially affect its pharmacokinetics, its tissue and cell distribution (enzyme redirected to Fc receptors-expressing cells such as white blood cells) and/or its cellular uptake (inhibition of cellular uptake mediated by mannose-6-phosphate, mannose and asialoglycoprotein receptors).

[redacted]

Identified Risk	Infusion-associated reactions including hypersensitivity and anaphylaxis
Evidence source(s) and strength of evidence	Data from clinical trials, postmarketing data, literature.
Characterization of the risk	Frequency with 95% CI: All IARs are considered related and constitute the majority of the related AEs in the clinical trials. Infusion-associated reactions were 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). The most frequent ADRs were: headache, nausea, abdominal pain, rash, arthralgia, back pain, pain at extremity, flushing, pyrexia, infusion site reactions, blood pressure increased, oxygen saturation decreased, tachycardia and chills. Postmarketing experience of IARs revealed reporting of cyanosis, hypoxia, tachypnoea, pyrexia, vomiting, chills and erythema, in which some of these reactions were severe. Severity and nature of risk: Infusion-associated reactions including hypersensitivity and anaphylaxis are defined as any related AE occurring during the infusion or until the end of the infusion day (or up to 24 hours). As with any IV protein product, allergic-type hypersensitivity reactions are possible. The majority of AEs associated with laronidase infusions were mild to moderate in severity. The onset of hypersensitivity related symptoms generally occurred during or shortly after infusions. The majority of the related AEs in the clinical trials were classified as 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 SARs reported with laronidase treatment during clinical trials were anaphylactic and allergic reactions. The frequency of infusion reactions decreased over time with continued use of laronidase. Severe IARs have been reported in patients with pre-existent severe underlying upper airway involvement. Patients with an acute underlying illness at the time of laronidase infusion appear to be at greater risk for IARs. A single patient with pre-existing airway compromise developed a severe reaction 3 hours from the start of the infusion (at week 62 of treatment) consisting of urticaria and airway obstruction, requiring tracheostomy. Postmarketing experience has shown a similar pattern of AEs and according to this the risk-benefit profile of laronidase has not changed since product approval in 2003. Seriousness/outcomes: The majority of AEs associated with laronidase infusions reported in patients were non-serious. In most cases involving serious hypersensitivity reactions, the patients recovered, and there were no sequelae. Background incidence/prevalence: Infusion-associated reaction including hypersensitivity are specific to the biologic product and do not occur in untreated patients with MPS I disease. Impact on individual patient: Treatment interruption or possible discontinuation.
Risk factors and risk groups	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. Severe infusion associated reactions have been reported in patients with pre-existent

Identified Risk	Infusion-associated reactions including hypersensitivity and anaphylaxis
	severe underlying upper airway involvement. Patients with an acute underlying illness at the time of laronidase infusion appear to be at greater risk for IARs.
Preventability	• Avoid use in patients with an acute underlying illness. • Infuse laronidase only in appropriate clinical setting (with available resuscitation equipment) for patients with pre-existent severe underlying upper airway involvement. • Discontinue the infusion immediately if severe allergic-type hypersensitivity occurs. • Avoid using epinephrin (for a severe hypersensitivity reaction) in MPS I patients (as these patients may have underlying coronary artery disease). • Minimize the potential occurrence of IARs with initial administration of ALDURAZYME or upon re-administration following interruption of treatment by using pre-treatment medicines (antihistamines and/or antipyretics) approximately 60 minutes prior to the start of the infusion. • Manage IARs (mild to moderate) by slowing the rate of infusion and by (pre-) treating the patient with antihistamines and/or antipyretics. • Reduce the infusion rate to 1/2 - 1/4 the rate of the infusion at which the reaction occurred. • Consider desensitization procedure to ALDURAZYME in patients with severe hypersensitivity.
Impact on the benefit-risk balance of the product	Increased morbidity in case of severe hypersensitivity/ anaphylaxis. Additionally, severe hypersensitivity or anaphylactic reactions may lead to treatment interruption or possible discontinuation. If laronidase must be discontinued, there will be a major impact on QoL due to lack of therapeutic benefit (for the non-neurological manifestations of MPS I) as no other medicine is currently approved to treat MPS I.
Public health impact	Unlikely due to rarity of the disease.

ADR: Adverse Drug Reaction; AE: Adverse Event; CI: Confidence Interval; IAR: Infusion-Associated Reaction; IgG: Immunoglobulin G; IV: Intravenous; MPS I: Mucopolysaccharidosis Type I; QoL: Quality of Life; SAR: Serious Adverse Reaction.

Table 17 - Potential risk: Medication errors in home infusion settings

Potential Risk	Medication errors in home infusion settings
Potential mechanism	There is potential for human/HCP error in the HI setting when administering the product (inappropriate dosage - underdosage or overdosage, inappropriate product reconstitution, inappropriate rate of infusion).
Evidence source(s) and strength of evidence	Real-world data from 2 medical and pharmacy insurance claims databases were retrospectively analyzed to assess the safety of laronidase infusions administered in a hospital or outpatient clinic and in patients' homes. These data were used to compare rates of AEs and IARs in hospital/clinic and in home settings in patients receiving laronidase infusions from 01-Jan-2007 to 30-Sep-2018. Thirteen of 30 (43%) patients in the [redacted] database A and 14 of 87 (56%) in the [redacted] database B with a diagnosis code for MPS I and treatment claims for laronidase received infusions at home. Adverse events were identified from diagnosis codes in claims for up to 30 days after HIs ([redacted] n = 24; 9141 person-days of exposure, [redacted] n = 55; 19 295 person-days of exposure). (13) According to analysis of this Real-world data review, the nature and incidence of AEs and IARs were similar for hospital/clinic and HIs and were consistent with the known documented safety profile of laronidase. In addition, a thorough postmarketing review of the Global safety database (for a period of 5 years +, which included follow-up cases for reports received during the 5-year period) was performed and reported medication error data were characterized

[redacted]

Potential Risk	Medication errors in home infusion settings
	in section below. There are limitations to this review like incomplete reporting through the voluntary, spontaneous nature of the AE reports in the postmarketing experience. Also, consistent tracking of information on administration settings has only been established recently. The HI data field was implemented on 01-Oct-2019; further, on 24-Nov-2022 changes were implemented in the AEGIS user manual for better capturing information of laronidase administration in the home setting.
Characterization of the risk	A comparative pharmacovigilance analysis of all reported AEs and recorded administration settings was performed, which included comparison between the settings: hospital (HI data field = No) versus HI (HI data field = Yes) versus unknown and missing setting (HI data field = unknown plus HI data field = blank), for events reported during period from 01-Jan-2018 through 31-Dec-2022. This review involved limited data as retrieval and categorization of cases was based on the HI database field, which was created on 01-Oct-2019. Eight thousand nine hundred and seventy eight events (2566 cases) were received during the review period of 01-Jan-2018 to 31-Dec-2022. Infusion in a home setting was recorded in 565 events (160 cases). Of the retrievable cases (based on the HI database field), medication errors were reported at a similar frequency in the HI and the "no home infusion" groups (around 3% of the AEs) and less frequently than in the "unknown/missing" group (approximately 6%). The majority of the medication errors (for the 3 groups, including the unknown and missing category (HI status = unknown plus HI status = blank data field groups) were non-serious events. For the AEs reported during or after COVID-19 pandemic period, categorized as unknown and missing category, all the medication error events were non-serious. Regarding the HI group, only one serious medication error was reported, and the medication error event was not related to product laronidase ([redacted] patient was hospitalized for a central catheter change, PT: Device Malfunction). Most of the medication errors were related to Inappropriate schedule of product administration (patients receiving ALDURAZYME on alternate weeks or interval greater than a week) or Incorrect dose administered. There was a similar pattern between AEs reported in patients infused at home and patients not infused at home. The most frequent medication error type involved patients who were receiving laronidase on alternate weeks instead of weekly (recommended administration). Regarding potential higher dosage risk, a postmarketing case (of infusion related reactions) involving higher (than recommended) rate of infusion has been identified and it reported adverse reactions including nausea, abdominal pain, headache, dizziness and dyspnea. Further analysis was performed on case narratives of HI data field status = blank (N = 2146 cases, corresponding to 6933 AEs) to identify potential HI cases. A total of 66 cases corresponding to 233 events were retrieved. There were 8 medication errors reported in this subgroup, all were non-serious events. Overall, no new signals or safety concerns were identified from the initial review (Safety evaluation report laronidase and use in home setting) which was based on the HI status entered in the HI data field of AE global information system/pharmacovigilance database. And, similarly, no new signals or safety concerns were identified from an additional review of case-narratives for cases categorized as "HI status = blank" which showed terms indicating potential HI administration. However, given the nature and inherent limitations of postmarketing experience, as well as recent implementation of better

[redacted]

Potential Risk	Medication errors in home infusion settings
	tracking of HI setting in the cases, caution should be exercised when interpreting the data and more data will increase the robustness of the conclusions. Overall, based on 2 observational studies and the postmarketing data review, no new safety concerns were identified. The risk-benefit appears to be unaltered when laronidase is used in accordance with the recommendations for its use.
Risk factors and risk groups	The impact of a potential medication error is anticipated to be greater in the following patient groups: • Patients who did not tolerate well previous laronidase infusion. • Patients with pre-existent severe underlying upper airway involvement. • Patients with an acute underlying illness appear to be at greater risk for IARs and should not receive HI.
Preventability	Recommendations regarding HI administration are described in the SmPC sections 4.2 and 6.6 with detailed instruction on risk mitigation including eligibility of patients for HI, and on reconstitution, dose calculation, infusion preparation and administration. Measures to prevent anaphylactic reactions or shock in a home setting: • Home infusion should not be recommended for patients who have not tolerated prior infusions or developed severe hypersensitivity/IAR. • Utilize preventive measures recommended for product prior to infusions. The MAH plans to mitigate the occurrence of medication errors and prevent severe IARs by providing a home infusion guide to HCPs wherein recommendations on patients' eligibility for HI and proper conditions of HI (in terms of equipment, pretreatment, and emergency treatments) are emphasized. Furthermore, only qualified HCP should perform HI. Infusion-associated reactions could be prevented by using pre-medication and by following infusion rates recommended per product labeling. Appropriate medical support, including personnel trained in emergency measures, should be readily available on site when laronidase is administered.
Impact on the benefit-risk balance of the product	The benefit-risk impact should be weighed against the underlying risk/natural history of the conditions of the MPS I patients and the burden on the patient's life and health care systems. Only qualified HCPs should conduct HI. Patient's eligibility for HI and product usage recommendations should be strictly followed. Benefit-risk should not be altered if guidance is followed.
Public health impact	Not anticipated if HI is well managed (there should be fewer patient hospitalizations and less missed weekly laronidase administrations, more QoL for the patients).

AE: Adverse Event; AEGIS: Adverse Experience Gathering Information System; COVID-19: Coronavirus Disease 2019; HCP: Healthcare Professional; HI: Home Infusion; IAR: Infusion-Associated Reaction; IV: Intravenous; MAH: Marketing Authorization Holder; MPS I: Mucopolysaccharidosis Type I; n: Number of Patients; N: Total Number of Patients; PT: Preferred Term; QoL: Quality of Life, SmPC: Summary of Product Characteristics.

SVII.3.2 Presentation of the missing information

Table 18 - Missing information: Use of laronidase in pregnant and lactating women

Missing Information	Use of laronidase in pregnant and lactating women
Evidence source(s) and strength of evidence	Postmarketing experience, literature, (12)(14)(15)(16)(17) on-going sub-registry studies.

[redacted]

Missing Information	Use of laronidase in pregnant and lactating women
Population in need for further characterization	Infants may be at risk of toxicity from drugs used by adults; toxicity may occur prenatally when they are exposed via placental transfer or postnatally when exposed through breast milk. The first trimester of pregnancy involves major development/embryofetal organogenesis; it is a critical period for drug toxicity via transplacental exposure. Animal studies did not indicate direct or indirect harmful effects on pregnancy, embryonal/fetal development, parturition, and postnatal development. There has been no risk (related to exposure during pregnancy and/or breastfeeding) identified from a cumulative review of global safety data and literature. To date the pregnancy sub-registry (ALID04911) and lactation (ALID01803) studies have had very limited enrollment. Regarding study ALID01803, the article by Castorina et al described the first mother-infant pair to complete this on-going, prospective, open-label, Phase 4 trial. The mother [redacted] with attenuated MPS I (Scheie syndrome), received laronidase for three years and continued treatment throughout her second pregnancy and while lactating. A healthy 2.5 kg male was delivered by elective cesarean section at 37 weeks. He was breastfed for three months. No laronidase was detected in breast milk. The infant never developed anti-laronidase IgM antibodies, never had inhibitory antibody activity in a cellular uptake assay, and always had normal urinary GAG levels. No drug-related AEs were reported. [redacted] the boy is healthy with normal growth and development. In this first prospectively monitored mother-infant pair, laronidase during pregnancy and breastfeeding was uneventful. (12)

AE: Adverse Event; GAG: Glycosaminoglycan; IgM: Immunoglobulin M; MPS I: Mucopolysaccharidosis Type I.

[redacted]

RISK MANAGEMENT PLAN - PART II MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

Summary of the safety concerns	
Important identified risk	Infusion-associated reactions including hypersensitivity and anaphylaxis
Important potential risk	Medication errors in home infusion setting
Missing information	Use of laronidase in pregnant and lactating women

RISK MANAGEMENT PLAN - PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are deemed necessary to monitor the risks of laronidase.

The safety profile of laronidase will continue to be further characterized in real clinical conditions of use through postmarketing safety surveillance, encompassing analysis of spontaneous reporting of ADRs in periodic safety reports, product technical complaints (PTCs) relating to AEs, and signal detection.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

The MAH has set up a pregnancy sub registry (ALID04911) and lactation study (ALID01803) to optimize the collection of data on laronidase use during pregnancy and breast-feeding, and document cases appropriately.

Table 19 - Additional pharmacovigilance activities (category 1 to 3) summary

A Multicenter, Multinational, Open-Label Study of the Effects of Aldurazyme (laronidase) Treatment on Lactation in Women with MPS I and Their Breastfed Infants (Cat. 3)
Study short name and title Lactation study (ALID01803)
Rationale and study objectives The objective of this study is to determine whether laronidase affects lactation in women with MPS I disease by: • Determining whether laronidase activity is present in the breast milk of mothers with MPS I disease who are being treated with laronidase during lactation. • Determining whether laronidase affects the growth, development, and immunologic response of breastfed infants born to mothers with MPS I disease who are being treated with laronidase during lactation.
Study design Multicenter, multinational, open-label study of the effects of ALDURAZYME treatment on lactation in women with MPS I and their breastfed infants.
Study populations Mothers treated with ALDURAZYME who intend to breastfeed their infants while receiving ALDURAZYME will be eligible for enrollment into this study. Mothers being treated with ALDURAZYME infusion during lactation will have to provide signed written informed consent for themselves and their infants prior to any protocol-related procedures being performed. Consent for all infants enrolled in the study will be obtained from the infant's legally authorized guardian. If a mother is younger than 18 years of age, consent for mother and infant will be obtained from the legal guardian.
Milestones Final report: Q3 2024 Due to the rarity of the disease and the complexity of the study, only one patient was recruited and completed the study. The study will remain opened pending FDA assessment and agreement to close it.

[redacted]

A Sub-Registry to Observe the Effect of Aldurazyme Treatment on Pregnancy and Infant Growth in Women with MPS I Disease (Cat. 3)
Study short name and title
Pregnancy Sub registry (ALID04911)
Rationale and study objectives
The objectives of the data collection in the MPS I pregnancy sub-registry through spontaneous reporting is to evaluate pregnancy outcomes including complications.
Study design
Multi-center, international, longitudinal, observational program designed to track pregnancy outcomes for any pregnant woman enrolled in the MPS I Registry, regardless of whether she is receiving disease therapy (such as ERT with laronidase) and irrespective of the commercial product with which she may be treated.
Study populations
Pregnant women with a definite diagnosis of MPS I, enrolled in the MPS I Registry.
Milestones
The MPS-I Pregnancy Sub-Registry is a long-term observational program. There is currently no end date. Analysis is submitted within the PBRER/PSUR.

ERT: Enzyme Replacement Therapy; FDA: Food and Drug Administration; MPS I: Mucopolysaccharidosis Type I; PBRER: Periodic Benefit-Risk Evaluation Report; PSUR: Periodic Safety Update Report; Q: Quarter.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 20 - Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Lactation study (ALID01803) Ongoing	• Determining whether laronidase activity is present in the breast milk of mothers with MPS I disease who are being treated with laronidase during lactation. • Determining whether laronidase affects the growth, development, an immunologic response of breastfed infants born to mothers with MPS I disease	Use of laronidase in pregnant and lactating women.	Final report	Q3 2024

[redacted]

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	who are being treated with laronidase during lactation.			
Pregnancy Sub registry (ALID04911) Ongoing	The objectives of the data collection in the MPS I pregnancy sub-registry through spontaneous reporting is to evaluate pregnancy outcomes including complications.	Use of laronidase in pregnant and lactating women.	Analysis is submitted within PBRER/PSUR	Not applicable

MPS I: Mucopolysaccharidosis Type I; PBRER: Periodic Benefit-Risk Evaluation Report; PSUR: Periodic Safety Update Report; Q: Quarter.

RISK MANAGEMENT PLAN - PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

No imposed post-authorization efficacy studies as a condition of the marketing authorization or which are specific obligations in the context of conditional marketing authorization or marketing authorization under exceptional circumstances are planned or ongoing for laronidase.

RISK MANAGEMENT PLAN - PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1 ROUTINE RISK MINIMIZATION MEASURES

Table 21 - Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Infusion-associated reactions including hypersensitivity and anaphylaxis	**Routine risk communication:** • SmPC: Labeled in section 4.8 • PL: Labeled in section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • SmPC: Labeled in sections 4.3 and 4.4 • PL: Labeled in section 2 **Other routine risk minimization measures beyond the Product Information:** **Legal status:** Prescription only medicine.
Medication errors in home infusion setting	**Routine risk communication:** • SmPC: Labeled in sections 4.2 and 6.6 • PL: Labeled in sections 3 and 5 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Decision criteria to have a patient move to home are included in SmPC section 4.2, as well as the description of HI infrastructure, resources, and procedures. • The precautions for disposal, instructions for reconstitution and dilution as well as the description of infusion preparation and administration are included in SmPC section 6.6. **Other routine risk minimization measures beyond the Product Information:** **Legal status:** Prescription only medicine.
Use of laronidase in pregnant and lactating women	**Routine risk communication:** • SmPC: Labeled in section 4.6 • PL: Labeled in section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** **Legal status:** Prescription only medicine.

HI: Home infusion; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

V.2 ADDITIONAL RISK MINIMIZATION MEASURES

Table 22 - Additional risk minimization measures

Home infusion guide for HCP	
Objectives	This guide will serve as training document for all HCPs including treating physicians and HCP who will perform infusion at home to prevent the following safety concerns: • "Medication errors in the home infusion setting" and • "Infusion associated reactions including hypersensitivity and anaphylaxis".
Rationale for the additional risk minimization activity	This guide will provide clear guidance on preparation, reconstitution, and administration of the product at home, as well as recognition and management of the important identified risks "Infusion associated reactions". This guide will provide information on the medication errors and associated risks in the home setting and actions to prevent them.
Target audience and planned distribution path	Target Audience: All HCPs including treating physician and home care/infusion HCPs who will perform the infusion at home. Distribution path: This above-mentioned material will be adapted country by country and dispensation will depend on each local situation: face to face, website, mailing. Local adaptations through digital solutions are possible according to local requirements/national health system. Periodicity of distribution: One single distribution after release of the material, redistribution if updated version of the materials, and for new prescribers.
Plans to evaluate the effectiveness of the interventions and criteria for success	Routine effectiveness measurements via monitoring of the distribution.
Home infusion guide for patient/caregiver including an infusion diary	
Objectives	To mitigate the risk of "infusion associated reactions including hypersensitivity and anaphylaxis in HI setting".
Rationale for the additional risk minimization activity	This guide contains information on signs and symptoms related to IARs and recommended actions for the management of the ADRs when symptoms occur, as well as an infusion diary for the patient that can be used to record the infusions and document any product-related IARs, including allergic-type hypersensitivity reactions before, during or after the infusion.
Target audience and planned distribution path	Target audience: Patients and caregivers Distribution path: The patient guide will be distributed to the patients by their treating/prescribing physician who has received the material. Periodicity of distribution: One single distribution after release of the material and redistribution if there is any update in the materials and for new patients.

Home infusion guide for HCP	
Plans to evaluate the effectiveness of the interventions and criteria for success	Routine effectiveness measurements via monitoring of the distribution.

ADR: Adverse Drug Reaction; HCP: Healthcare Professional. HI: Home Infusion; IAR: Infusion-Associated Reaction.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 23 - Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Infusion-associated reactions including hypersensitivity and anaphylaxis	**Routine risk minimization measures:** • SmPC: Labeled in sections 4.3, 4.4 and 4.8 • PL: Labeled in sections 2 and 4 • Prescription only medicine **Additional risk minimization measures:** • Home infusion guide for HCP • Home infusion guide for patient/caregiver including an infusion diary	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities** None
Medication errors in home infusion setting	**Routine risk minimization measures:** • SmPC: Labeled in sections 4.2 and 6.6 • PL: Labeled in sections 3 and 5 • Prescription only medicine **Additional risk minimization measures:** Home infusion guide for HCP	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities** None
Use of laronidase in pregnant and lactating women	**Routine risk minimization measures:** • SmPC: Labeled in section 4.6 • PL: Labeled in section 2 • Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities** • Pregnancy sub registry (ALID04911) • Lactation study (ALID01803)

HCP: Healthcare Professional; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

RISK MANAGEMENT PLAN - PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for ALDURAZYME (Laronidase)

This is a summary of the risk management plan (RMP) for ALDURAZYME. The RMP details important risks of ALDURAZYME, how these risks can be minimized, and how more information will be obtained about ALDURAZYME's risks and uncertainties (missing information).

ALDURAZYME's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals (HCPs) and patients on how ALDURAZYME should be used.

This summary of the RMP for ALDURAZYME should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of ALDURAZYME's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

ALDURAZYME is authorized for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Mucopolysaccharidosis Type I (MPS I; α-L-iduronidase deficiency) to treat the non-neurological manifestations of the disease. It contains laronidase as the active substance and it is given by intravenous (IV) route.

Further information about the evaluation of ALDURAZYME's benefits can be found in ALDURAZYME's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/aldurazyme

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of ALDURAZYME, together with measures to minimize such risks and the proposed studies for learning more about ALDURAZYME's risks, are outlined in the next sections.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of ALDURAZYME, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, outlined in the next sections.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of ALDURAZYME is not yet available, it is listed under "missing information" outlined in the next section.

II.A List of important risks and missing information

Important risks of ALDURAZYME are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of ALDURAZYME. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 24 - List of important risks and missing information

Important identified risk	Infusion-associated reactions including hypersensitivity and anaphylaxis
Important potential risk	Medication errors in home infusion setting
Missing information	Use of laronidase in pregnant and lactating women

II.B Summary of important risks

Table 25 - Important identified risk with corresponding risk minimization activities: Infusion-associated reactions including hypersensitivity and anaphylaxis

Infusion-associated reactions including hypersensitivity and anaphylaxis	
Evidence for linking the risk to the medicine	Data from clinical trials, postmarketing data, literature.
Risk factors and risk groups	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. Severe infusion associated reactions have been reported in patients with pre-existent severe underlying upper airway involvement. Patients with an acute underlying illness at the time of laronidase infusion appear to be at greater risk for IARs.

Infusion-associated reactions including hypersensitivity and anaphylaxis	
Risk minimization measures	**Routine risk minimization measures:** • SmPC: Labeled in sections 4.3, 4.4 and 4.8 • PL: Labeled in sections 2 and 4 • Prescription only medicine **Additional risk minimization measures:** • Home infusion guide for HCP • Home infusion guide for patient/caregiver including an infusion diary

HCP: Healthcare Professional; IAR: Infusion-Associated Reactions; IgG: Immunoglobulin G; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 26 - Important potential risk with corresponding risk minimization activities: Medication errors in home infusion setting

Medication errors in home infusion setting	
Evidence for linking the risk to the medicine	Real-world data from 2 medical and pharmacy insurance claims databases were retrospectively analyzed to assess the safety of laronidase infusions administered in a hospital or outpatient clinic and in patients' homes. These data were used to compare rates of AEs and IARs in hospital/clinic and in home settings in patients receiving laronidase infusions from 01-Jan-2007 to 30-Sep-2018. Thirteen of 30 (43%) patients in the [redacted] database A and 14 of 87 (56%) in the [redacted] database B with a diagnosis code for MPS I and treatment claims for laronidase received infusions at home. Adverse events were identified from diagnosis codes in claims for up to 30 days after HIs ([redacted] n = 24; 9141 person-days of exposure, [redacted] n = 55; 19 295 person-days of exposure). (13) According to analysis of this Real-world data review, the nature and incidence of AEs and IARs were similar for hospital/clinic and HIs and were consistent with the known documented safety profile of laronidase. In addition, a thorough postmarketing review of the Global safety database (for a period of 5 years +, which included follow-up cases for reports received during the 5-year period) was performed and reported medication error data were characterized in section below. There are limitations to this review like incomplete reporting through the voluntary, spontaneous nature of the AE reports in the postmarketing experience, Also, consistent tracking of information on administration settings has only been established recently. The HI data field was implemented on 01-Oct-2019; further, on 24-Nov-2022 changes were implemented in the AEGIS user manual for better capturing information of laronidase administration in the home setting.
Risk factors and risk groups	The impact of a potential medication error is anticipated to be greater in the following patient groups: • Patients who did not tolerate well previous laronidase infusion. • Patients with pre-existent severe underlying upper airway involvement. • Patients with an acute underlying illness appear to be at greater risk for IARs and should not receive HI.
Risk minimization measures	**Routine risk minimization measures:** • SmPC: Labeled in sections 4.2 and 6.6 • PL: Labeled in sections 3 and 5

Medication errors in home infusion setting	
	• Prescription only medicine **Additional risk minimization measures:** Home infusion guide for HCP

AE: Adverse Event; AEGIS: Adverse Event Global Information System; HCP: Healthcare Professional; HI: Home Infusion; IAR: Infusion Associated Reaction; MPS 1: Mucopolysaccharidosis Type I; n: Number of Patients; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 27 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities: Use of laronidase in pregnant and lactating women

Use of laronidase in pregnant and lactating women	
Risk minimization measures	**Routine risk minimization measures:** • SmPC: Labeled in section 4.6 • PL: Labeled in section 2 • Prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	• Pregnancy sub registry (ALID04911) • Lactation study (ALID01803)

PL: Package Leaflet; SmPC: Summary of Product Characteristics.

II.C Post-authorization development plan

II.C.1 *Studies which are conditions of the marketing authorization*

There are no studies which are conditions of the marketing authorization or specific obligation of ALDURAZYME.

II.C.2 *Other studies in post-authorization development plan*

Table 28 - Other studies in post-authorization development plan

Lactation study (ALID01803)
Purpose of the study: The objective of this study is to determine whether laronidase affects lactation in women with MPS I disease by: • Determining whether laronidase activity is present in the breast milk of mothers with MPS I disease who are being treated with laronidase during lactation. • Determining whether laronidase affects the growth, development, and immunologic response of breastfed infants born to mothers with MPS I disease who are being treated with laronidase during lactation.
Pregnancy Sub registry (ALID04911)
Purpose of the study: The objectives of the data collection in the MPS I pregnancy sub-registry through spontaneous reporting is to evaluate pregnancy outcomes including complications.

MPS I: Mucopolysaccharidosis Type I.

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[redacted]

RISK MANAGEMENT PLAN - PART VII: ANNEXES

[redacted]

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

NOT APPLICABLE

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

[redacted]

Draft key messages of the additional risk minimization measures

The Marketing Authorization Holder (MAH) shall ensure that in each Member State where laronidase is marketed and/or home infusion is authorized, all Healthcare Professionals (HCPs) who are expected to prescribe, dispense, and administer laronidase have access to/are provided with the following educational guide to be disseminated as per local requirements/national health system:

- Home infusion guide for HCP

Additionally, following educational guide will be distributed to the patients/caregivers by their treating/prescribing physician who has received the material from the MAH:

- Home infusion guide for patient/caregiver including an infusion diary

Healthcare Professional educational materials: Home infusion guide for HCP

The HCP guide contains the following key safety information to support the HCPs in the management of patients receiving laronidase in the home setting.

Information for HCPs prescribing laronidase:

- Criteria to determine eligibility for home infusion
- Requirement and organization of the home infusion including equipment, pre-treatment and emergency treatments

Information for HCPs administering laronidase:

- Medical evaluation of the patient prior to administration of the infusion at home
- Requirements and organization of the home infusion including equipment, pre-treatment and emergency treatments
- Details on the preparation and administration of laronidase including all the steps of preparation, reconstitution, dilution and administration. Information on signs and symptoms related to infusion associated reactions and recommended actions for the management of the adverse drug reactions (ADRs) when symptoms occur

Patient educational material: Home infusion guide for patient/caregiver including an infusion diary

The patient/caregiver guide contains the following key safety information:

- Information on the risk of hypersensitivity reactions including the signs and symptoms of hypersensitivity and the recommended actions when symptoms occur
- An Infusion Diary that can be used to record the infusions and document any product-related Infusion-Associated Reactions (IARs), including allergic-type hypersensitivity reactions before, during or after the infusion.

[redacted]