

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Elaprase 2 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 6 mg of idursulfase. Each ml contains 2 mg of idursulfase*.

Excipient with known effect

Each vial contains 0.482 mmol of sodium.

For the full list of excipients, see section 6.1.

* idursulfase is produced by recombinant DNA technology in a continuous human cell line.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

A clear to slightly opalescent, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Elaprase is indicated for the long-term treatment of patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II).

Heterozygous females were not studied in the clinical trials.

4.2 Posology and method of administration

This treatment should be supervised by a physician or other healthcare professional experienced in the management of patients with MPS II disease or other inherited metabolic disorders.

Posology

Elaprase is administered at a dose of 0.5 mg/kg body weight every week by intravenous infusion over a 3 hour period, which may be gradually reduced to 1 hour if no infusion-associated reactions are observed (see section 4.4).

For instructions for use, see section 6.6.

Infusion at home may be considered for patients who have received several months of treatment in the clinic and who are tolerating their infusions well. Home infusions should be performed under the surveillance of a physician or other healthcare professional.

Special populations

Elderly patients

There is no clinical experience in patients over 65 years of age.

Patients with renal or hepatic impairment

There is no clinical experience in patients with renal or hepatic insufficiency. (see section 5.2).

Paediatric population

The dose for children and adolescents is the same as for adults, 0.5 mg/kg body weight weekly.

Method of administration

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

4.3 Contraindications

Severe or life-threatening hypersensitivity to the active substance or to any of the excipients listed in section 6.1 if hypersensitivity is not controllable.

4.4 Special warnings and precautions for use

Infusion-related reactions

Patients treated with idursulfase may develop infusion-related reactions (see section 4.8). During clinical trials, the most common infusion-related reactions included cutaneous reactions (rash, pruritus, urticaria), pyrexia, headache, hypertension, and flushing. Infusion-related reactions were treated or ameliorated by slowing the infusion rate, interrupting the infusion, or by administration of medicinal products, such as antihistamines, antipyretics, low-dose corticosteroids (prednisone and methylprednisolone), or beta-agonist nebulisation. No patient discontinued treatment due to an infusion reaction during clinical studies.

Special care should be taken when administering an infusion in patients with severe underlying airway disease. These patients should be closely monitored and infused in an appropriate clinical setting. Caution must be exercised in the management and treatment of such patients by limitation or careful monitoring of antihistamine and other sedative medicinal product use. Institution of positive-airway pressure may be necessary in some cases.

Delaying the infusion in patients who present with an acute febrile respiratory illness should be considered. Patients using supplemental oxygen should have this treatment readily available during infusion in the event of an infusion-related reaction.

Anaphylactoid/anaphylactic reactions

Anaphylactoid/anaphylactic reactions, which have the potential to be life threatening, have been observed in some patients treated with idursulfase up to several years after initiating treatment. Late emergent symptoms and signs of anaphylactoid/anaphylactic reactions have been observed as long as 24 hours after an initial reaction. If an anaphylactoid/anaphylactic reaction occurs the infusion should be immediately suspended and appropriate treatment and observation initiated. The current medical standards for emergency treatment are to be observed. Patients experiencing severe or refractory anaphylactoid/anaphylactic reactions may require prolonged clinical monitoring. Patients who have experienced anaphylactoid/anaphylactic reactions should be treated with caution when re-administering idursulfase, appropriately trained personnel and equipment for emergency resuscitation (including epinephrine) should be available during infusions. Severe or potentially life-threatening hypersensitivity is a contraindication to rechallenge, if hypersensitivity is not controllable (see section 4.3).

Patients with the complete deletion/large rearrangement genotype

Paediatric patients with the complete deletion/large rearrangement genotype have a high probability of developing antibodies, including neutralizing antibodies, in response to exposure to idursulfase. Patients with this genotype have a higher probability of developing infusion-related adverse events and tend to show a muted response as assessed by decrease in urinary output of glycosaminoglycans, liver size and spleen volume compared to patients with the missense genotype. Management of patients must be decided on an individual basis (see section 4.8).

Sodium

This medicinal product contains 0.482 mmol sodium (or 11.1 mg) per vial. This is equivalent to 0.6% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Traceability

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

4.5 Interaction with other medicinal products and other forms of interaction

No formal medicinal product interaction studies have been conducted with idursulfase.

Based on its metabolism in cellular lysosomes, idursulfase would not be a candidate for cytochrome P450 mediated interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data or limited amount of data from the use of idursulfase in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of idursulfase during pregnancy.

Breast-feeding

It is not known whether idursulfase is excreted in human breast milk. Available data in animals have shown excretion of idursulfase in milk (see section 5.3). A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from idursulfase therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

No effects on male fertility were seen in reproductive studies in male rats.

4.7 Effects on ability to drive and use machines

Idursulfase has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions that were reported for the 32 patients treated with 0.5 mg/kg idursulfase weekly in the TKT024 phase II/III 52-week placebo-controlled study were almost all mild to moderate in severity. The most common were infusion-related reactions, 202 of which were reported in 22 out of 32 patients following administration of a total of 1580 infusions. In the placebo treatment group 128 infusion-related reactions were reported in 21 out of 32 patients following administration of a total of 1612 infusions. Since more than one infusion-related reaction may have occurred during any single infusion, the above numbers are likely to overestimate the true incidence of infusion reactions. Related reactions in the placebo group were similar in nature and severity to those in the treated group. The most common of these infusion-related reactions included cutaneous reactions (rash, pruritus, urticaria, and erythema), pyrexia, flushing, wheezing, dyspnoea, headache, vomiting, abdominal pain, nausea, and chest pain. The frequency of infusion-related reactions decreased over time with continued treatment.

Tabulated list of adverse reactions

Adverse reactions are listed in table 1 with information presented by system organ class and frequency. Frequency is given as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$) or uncommon ($\geq 1/1,000$ to $< 1/100$). The occurrence of an adverse reaction in a single patient is defined as common

in view of the number of patients treated. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Adverse reactions only reported during the post marketing period are also included in the table with a frequency “not known” (cannot be estimated from the available data).

Table 1: Adverse reactions from clinical trials and post-marketing experience in patients treated with Elaprase.

| System organ class | Adverse reaction (preferred term) | | | |
|--|---|---|------------|--|
| | Very common | Common | Uncommon | Not known |
| Immune system disorders | | | | |
| | | | | Anaphylactoid/ anaphylactic reaction |
| Nervous system disorders | | | | |
| | Headache | Dizziness, tremor | | |
| Cardiac disorders | | | | |
| | | Cyanosis, arrhythmia, tachycardia | | |
| Vascular disorders | | | | |
| | Flushing | Hypertension, Hypotension | | |
| Respiratory, thoracic and mediastinal disorders | | | | |
| | Wheezing, dyspnoea | Hypoxia, bronchospasm, cough | Tachypnoea | |
| Gastrointestinal disorders | | | | |
| | Abdominal pain, nausea, diarrhoea, vomiting | Swollen tongue, dyspepsia | | |
| Skin and subcutaneous tissue disorders | | | | |
| | Urticaria, rash, pruritus, erythema | | | |
| Musculoskeletal and connective disorders | | | | |
| | | Arthralgia | | |
| General disorders and administration site conditions | | | | |
| | Pyrexia, chest pain | Infusion-site swelling, face oedema, oedema peripheral | | |
| Injury, poisoning and procedural complications | | | | |
| | Infusion-related reaction | | | |

Description of selected adverse reactions

Across clinical studies, serious adverse reactions were reported in a total of 5 patients who received 0.5 mg/kg weekly or every other week. Four patients experienced a hypoxic episode during one or several infusions, which necessitated oxygen therapy in 3 patients with severe underlying obstructive airway disease (2 with a pre-existing tracheostomy). The most severe episode occurred in a patient with a febrile respiratory illness and was associated with hypoxia during the infusion, resulting in a short seizure. In the fourth patient, who had less severe underlying disease, spontaneous resolution occurred shortly after the infusion was interrupted. These events did not recur with subsequent infusions using a slower infusion rate and administration of pre-infusion medicinal products, usually low-dose steroids, antihistamine, and beta-agonist nebulisation. The fifth patient, who had pre-existing

cardiopathy, was diagnosed with ventricular premature complexes and pulmonary embolism during the study.

There have been post-marketing reports of anaphylactoid/anaphylactic reactions (see section 4.4).

Patients with complete deletion/large rearrangement genotype have a higher probability of developing infusion related adverse events (see section 4.4).

Immunogenicity

Across 4 clinical studies (TKT008, TKT018, TKT024 and TKT024EXT), 53/107 patients (50%) developed anti-idursulfase IgG antibodies at some point. The overall neutralizing antibody rate was 26/107 patients (24%).

In the post-hoc immunogenicity analysis of data from TKT024/024EXT studies, 51% (32/63) patients treated with 0.5mg/kg weekly idursulfase had at least 1 blood sample that tested positive for anti-idursulfase antibodies, and 37 % (23/63) tested positive for antibodies on at least 3 consecutive study visits. Twenty-one percent (13/63) tested positive for neutralizing antibodies at least once and 13 % (8/63) tested positive for neutralizing antibodies on at least 3 consecutive study visits.

Clinical study HGT-ELA-038 evaluated immunogenicity in children 16 months to 7.5 years of age. During the 53-week study, 67.9% (19 of 28) of patients had at least one blood sample that tested positive for anti-idursulfase antibodies, and 57.1% (16 of 28) tested positive for antibodies on at least three consecutive study visits. Fifty-four percent of patients tested positive for neutralizing antibodies at least once and half of the patients tested positive for neutralizing antibodies on at least three consecutive study visits.

All patients with the complete deletion/large rearrangement genotype developed antibodies, and the majority of them (7/8) also tested positive for neutralizing antibodies on at least 3 consecutive occasions. All patients with the frameshift/splice site mutation genotype developed antibodies and 4/6 also tested positive for neutralizing antibodies on at least 3 consecutive study visits. Antibody-negative patients were found exclusively in the missense mutation genotype group (see sections 4.4 and 5.1).

Paediatric population

Adverse reactions reported in the paediatric population were, in general, similar to those reported in adults.

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

There is limited information regarding overdose with Elaprase. Evidence suggests that some patients may experience an anaphylactoid reaction due to overdose (see sections 4.3 and 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products – enzymes, ATC code: A16AB09.

Mechanism of action

Hunter syndrome is an X-linked disease caused by insufficient levels of the lysosomal enzyme iduronate-2-sulfatase. Iduronate-2-sulfatase functions to catabolize the glycosaminoglycans (GAG)

dermatan sulfate and heparan sulfate by cleavage of oligosaccharide-linked sulfate moieties. Due to the missing or defective iduronate-2-sulfatase enzyme in patients with Hunter syndrome, glycosaminoglycans progressively accumulate in the cells, leading to cellular engorgement, organomegaly, tissue destruction, and organ system dysfunction.

Idursulfase is a purified form of the lysosomal enzyme iduronate-2-sulfatase, produced in a human cell line providing a human glycosylation profile, which is analogous to the naturally occurring enzyme. Idursulfase is secreted as a 525 amino acid glycoprotein and contains 8 N-linked glycosylation sites that are occupied by complex, hybrid, and high-mannose type oligosaccharide chains. Idursulfase has a molecular weight of approximately 76 kD.

Treatment of Hunter syndrome patients with intravenous idursulfase provides exogenous enzyme for uptake into cellular lysosomes. Mannose-6-phosphate (M6P) residues on the oligosaccharide chains allow specific binding of the enzyme to the M6P receptors on the cell surface, leading to cellular internalization of the enzyme, targeting to intracellular lysosomes and subsequent catabolism of accumulated GAG.

Clinical efficacy and safety

The safety and efficacy of Elaprase has been shown in three clinical studies: two randomised, placebo-controlled clinical studies (TKT008 and TKT024) in adults and children above the age of 5 years and one open-label, safety study (HGT-ELA-038) in children between the age of 16 months and 7.5 years.

A total of 108 male Hunter syndrome patients with a broad spectrum of symptoms were enrolled in the two randomized, placebo-controlled clinical studies, 106 continued treatment in two open-label, extension studies.

Study TKT024

In a 52-week, randomized, double-blind, placebo-controlled clinical study, 96 patients between the ages of 5 and 31 years received Elaprase 0.5 mg/kg every week (n=32) or 0.5 mg/kg every other week (n=32), or placebo (n=32). The study included patients with a documented deficiency in iduronate-2-sulfatase enzyme activity, a percent predicted FVC <80%, and a broad spectrum of disease severity.

The primary efficacy endpoint was a two-component composite score based on the sum of the ranks of the change from baseline to the end of the study in the distance walked during six minutes (6-minute walk test or 6MWT) as a measure of endurance, and % predicted forced vital capacity (FVC) as a measure of pulmonary function. This endpoint differed significantly from placebo for patients treated weekly (p=0.0049).

Additional clinical benefit analyses were performed on individual components of the primary endpoint composite score, absolute changes in FVC, changes in urine GAG levels, liver and spleen volumes, measurement of forced expiratory volume in 1 second (FEV₁), and changes in left ventricular mass (LVM). The results are presented in Table 2.

Table 2. Results from pivotal clinical study at 0.5 mg/kg per week (Study TKT024).

| Endpoint | 52 weeks of treatment 0.5 mg/kg weekly | | | |
|---------------------------------|---|-------------|---|---------------------------------------|
| | Marginally weighted (OM) mean (SE) | | Mean treatment difference compared with placebo (SE) | P-value (compared with placebo) |
| | Idursulfase | Placebo | | |
| Composite (6MWT and %FVC) | 74.5 (4.5) | 55.5 (4.5) | 19.0 (6.5) | 0.0049 |
| 6MWT (m) | 43.3 (9.6) | 8.2 (9.6) | 35.1 (13.7) | 0.0131 |
| % Predicted FVC | 4.2 (1.6) | -0.04 (1.6) | 4.3 (2.3) | 0.0650 |

| | | | | |
|---|---------------|--------------|---------------|---------|
| FVC absolute volume (L) | 0.23 (0.04) | 0.05 (0.04) | 0.19 (0.06) | 0.0011 |
| Urine GAG levels (μg GAG/mg creatinine) | -223.3 (20.7) | 52.23 (20.7) | -275.5 (30.1) | <0.0001 |
| % Change in liver volume | -25.7 (1.5) | -0.5 (1.6) | -25.2 (2.2) | <0.0001 |
| % Change in spleen volume | -25.5 (3.3) | 7.7 (3.4) | -33.2 (4.8) | <0.0001 |

A total of 11 of 31 (36%) patients in the weekly treatment group versus 5 of 31 (16%) patients in the placebo group had an increase in FEV₁ of at least 0.2 l at or before the end of the study, indicating a dose-related improvement in airway obstruction. The patients in the weekly treatment group experienced a clinically significant 15% mean improvement in FEV₁ at the end of the study.

Urine GAG levels were normalized below the upper limit of normal (defined as 126.6 μg GAG/mg creatinine) in 50% of the patients receiving weekly treatment.

Of the 25 patients with abnormally large livers at baseline in the weekly treatment group, 80% (20 patients) had reductions in liver volume to within the normal range by the end of the study.

Of the 9 patients in the weekly treatment group with abnormally large spleens at baseline, 3 had spleen volumes that normalized by the end of the study.

Approximately half of the patients in the weekly treatment group (15 of 32; 47%) had left ventricular hypertrophy at baseline, defined as LVM index >103 g/m². Of these 6 (40%) had normalised LVM by the end of the study.

All patients received weekly idursulfase up to 3.2 years in an extension to this study (TKT024EXT).

Among patients who were originally randomised to weekly idursulfase in TKT024, mean maximum improvement in distance walked during six minutes occurred at Month 20 and mean percent predicted FVC peaked at Month 16.

Among all patients, statistically significant mean increases from treatment baseline (TKT024 baseline for TKT024 idursulfase patients and Week 53 baseline for TKT024 placebo patients) were seen in the distance walked 6MWT at the majority of time points tested, with significant mean and percent increases ranging from 13.7m to 41.5m (maximum at Month 20) and from 6.4% to 13.3% (maximum at Month 24) respectively. At most time points tested, patients who were from the original TKT024 weekly treatment group improved their walking distance to a greater extent than patients in the other 2 treatment groups.

Among all patients, mean % predicted FVC was significantly increased at Month 16, although by Month 36, it was similar to the baseline. Patients with the most severe pulmonary impairment at baseline (as measured by % predicted FVC) tended to show the least improvement.

Statistically significant increases from treatment baseline in absolute FVC volume were seen at most visits for all treatment groups combined and for each of the prior TKT024 treatment groups. Mean changes from 0.07 l to 0.31 l and percent ranged from 6.3% to 25.5% (maximum at Month 30). The mean and percent changes from treatment baseline were greatest in the group of patients from the TKT024 study who had received the weekly dosing, across all time points.

At their final visit 21/31 patients in the TKT024 Weekly group, 24/32 in the TKT024 EOW group and 18/31 patients in the TKT024 placebo group had final normalised urine GAG levels that were below the upper limit of normal. Changes in urinary GAG levels were the earliest signs of clinical improvement with idursulfase treatment and the greatest decreases in urinary GAG were seen within the first 4 months of treatment in all treatment groups; changes from Month 4 to 36 were small. The

higher the urinary GAG levels at baseline, the greater the magnitude of decreases in urinary GAG with idursulfase treatment.

The decreases in liver and spleen volumes observed at the end of study TKT024 (week 53) were maintained during the extension study (TKT024EXT) in all patients regardless of the prior treatment they had been assigned. Liver volume normalised by Month 24 for 73% (52 out of 71) of patients with hepatomegaly at baseline. In addition, mean liver volume decreased to a near maximum extent by Month 8 in all patients previously treated, with a slight increase observed at Month 36. The decreases in mean liver volume were seen regardless of age, disease severity, IgG antibody status or neutralising antibody status. Spleen volume normalised by Months 12 and 24 for 9.7% of patients in the TKT024 Weekly group with splenomegaly.

Mean cardiac LVMI remained stable over 36 months of idursulfase treatment within each TKT024 treatment group.

In a post-hoc analysis of immunogenicity in studies TKT024 and TKT024EXT (see section 4.8), patients were shown to have either the mis-sense mutation or the frameshift / nonsense mutation. After 105 weeks of exposure to idursulfase, neither antibody status nor genotype affected reductions in liver and spleen size or distance walked in the 6-minute walk test or forced vital capacity measurements. Patients who tested antibody-positive displayed less reduction in urinary output of glycosaminoglycans than antibody-negative patients. The longer-term effects of antibody development on clinical outcomes have not been established.

Study HGT-ELA-038

This was an open-label, multicenter, single-arm study of idursulfase infusions in male Hunter syndrome patients between the age of 16 months and 7.5 years.

Idursulfase treatment resulted in up to 60% reduction in urine output of glycosaminoglycans and in reductions of liver and spleen size: results were comparable to those found in study TKT024. Reductions were evident by week 18 and were maintained to week 53. Patients who developed a high titre of antibodies displayed less response to idursulfase as assessed by urine output of glycosaminoglycans and by liver and spleen size.

Analyses of genotypes of patients in study HGT-ELA-038

Patients were classified into the following groups: missense (13), complete deletion/large rearrangement (8), and frameshift/ splice site mutations (5). One patient was unclassified / unclassifiable.

The complete deletion/ large rearrangement genotype was most commonly associated with development of high titre of antibodies and neutralising antibodies to idursulfase and was most likely to display a muted response to the medicinal product. It was not possible, however, to accurately predict individual clinical outcome based on antibody response or genotype.

No clinical data exist demonstrating a benefit on the neurological manifestations of the disorder.

This medicinal product has been authorised under “exceptional circumstances”.

This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product.

The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Idursulfase is taken up by selective receptor-mediated mechanisms involving binding to mannose 6-phosphate receptors. Upon internalization by cells, it is localized within cellular lysosomes, thereby limiting distribution of the protein. Degradation of idursulfase is achieved by generally well

understood protein hydrolysis mechanisms to produce small peptides and amino acids, consequently renal and liver function impairment is not expected to affect the pharmacokinetics of idursulfase. Pharmacokinetic parameters measured during the first infusion at week 1 of studies TKT024 (0.5 mg/kg weekly arm) and HGT-ELA-038 are displayed in table 3 and table 4 below as a function of age and body weight, respectively.

Table 3. Pharmacokinetic parameters at week 1 as a function of age in Studies TKT024 and HGT-ELA-038

| | Study | | | |
|--|----------------------|-------------------|-------------------|---------------|
| | HGT-ELA-038 | TKT024 | | |
| Age (years) | 1.4 to 7.5 (n=27) | 5 to 11 (n=11) | 12 to 18 (n=8) | > 18 (n=9) |
| C _{max} (µg/mL) Mean ± SD | 1.3 ± 0.8 | 1.6 ± 0.7 | 1.4 ± 0.3 | 1.9 ± 0.5 |
| AUC _{0-∞} (min*µg/mL) Mean ± SD | 224.3 ± 76.9 | 238 ± 103.7 | 196 ± 40.5 | 262 ± 74.5 |
| CL (mL/min/kg) Mean ± SD | 2.4 ± 0.7 | 2.7 ± 1.3 | 2.8 ± 0.7 | 2.2 ± 0.7 |
| V _{ss} (mL/kg) Mean ± SD | 394 ± 423 | 217 ± 109 | 184 ± 38 | 169 ± 32 |

Patients in the TKT024 and HGT-ELA-038 studies were also stratified across five weight categories; as shown in the following table:

Table 4. Pharmacokinetic parameters at week 1 as a function of body weight in studies TKT024 and HGT-ELA-038

| Weight (kg) | <20 (n=17) | ≥ 20 and < 30 (n=18) | ≥ 30 and < 40 (n=9) | ≥ 40 and < 50 (n=5) | ≥ 50 (n=6) |
|---------------------------------------|---------------|-------------------------|------------------------|------------------------|---------------|
| C _{max} (µg/mL) Mean ± SD | 1.2 ± 0.3 | 1.5 ± 1.0 | 1.7 ± 0.4 | 1.7 ± 0.7 | 1.7 ± 0.7 |
| AUC _{0-∞} (min*µg/mL) | 206.2 ± 33.9 | 234.3 ± 103.0 | 231.1 ± 681.0 | 260.2 ± 113.8 | 251.3 ± 86.2 |
| CL (mL/min/kg) Mean ± SD | 2.5 ± 0.5 | 2.6 ± 1.1 | 2.4 ± 0.6 | 2.4 ± 1.0 | 2.4 ± 1.1 |
| V _{ss} (mL/kg) | 321 ± 105 | 397 ± 528 | 171 ± 52 | 160 ± 59 | 181 ± 34 |

A higher volume of distribution at steady state (V_{ss}) was observed in the lowest weight groups.

Overall, there was no apparent trend in either systemic exposure or clearance rate of idursulfase with respect to either age or body weight.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, repeated dose toxicity, toxicity to reproduction and development and to male fertility.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/ foetal development, parturition or postnatal development.

Animal studies have shown excretion of idursulfase in breast milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 20
Sodium chloride
Dibasic sodium phosphate heptahydrate
Monobasic sodium phosphate monohydrate
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years.
Chemical and physical in-use stability has been demonstrated for 8 hours at 25°C.

After dilution

From a microbiological safety point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2 to 8°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

5 ml vial (type I glass) with a stopper (fluoro-resin coated butyl rubber), one piece seal and blue flip-off cap. Each vial contains 3 ml of concentrate for solution for infusion.

Pack sizes of 1, 4 and 10 vials. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Each vial of Elaprase is intended for single use only and contains 6 mg of idursulfase in 3 ml of solution. Elaprase is for intravenous infusion and must be diluted in sodium chloride 9 mg/ml (0.9%) solution for infusion prior to use. It is recommended to deliver the total volume of infusion using a 0.2 µm in line filter. Elaprase should not be infused with other medicinal products in the infusion tubing.

- The number of vials to be diluted should be determined based on the individual patient's weight and the recommended dose of 0.5 mg/kg.
- The solution in the vials should not be used if it is discoloured or if particulate matter is present. The solution should not be shaken.
- The calculated volume of Elaprase should be withdrawn from the appropriate number of vials.
- The total volume required of Elaprase should be diluted in 100 ml of 9 mg/ml (0.9%) sodium chloride solution for infusion. Care must be taken to ensure the sterility of the prepared solutions since Elaprase does not contain any preservative or bacteriostatic agent; aseptic technique must be observed. Once diluted, the solution should be mixed gently, but not shaken.

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

7. MARKETING AUTHORISATION HOLDER

Takeda Pharmaceuticals International AG Ireland Branch
Block 2 Miesian Plaza
50-58 Baggot Street Lower
Dublin 2
D02 HW68
Ireland
medinfoEMEA@takeda.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/365/001-003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08 January 2007

Date of latest renewal: 09 September 2016

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**
- E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES**

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

Name and address of the manufacturer of the biological active substance

Shire (TK3)
205 Alewife Brook Parkway
Cambridge, MA 02138
USA

Shire
300 Shire Way
Lexington MA 02421
USA

Name and address of the manufacturer responsible for batch release

Takeda Pharmaceuticals International AG Ireland Branch
Block 2 Miesian Plaza
50-58 Baggot Street Lower
Dublin 2
D02 HW68
Ireland

Shire Pharmaceuticals Ireland Limited
Block 2 & 3 Miesian Plaza
50 – 58 Baggot Street Lower
Dublin 2
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, 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

- **Risk management plan (RMP)**

The marketing authorization holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

| Description | Due date |
|---|---------------------|
| Specific Obligation 1 – Hunter Outcome Survey (HOS): available data and updates will be provided within Annual Reassessments. | 31 March every year |
| Specific Obligation 5 – To evaluate the following long term clinical endpoints primarily through the HOS. These data will be re-evaluated annually and outcomes reported and discussed within the Annual Reassessments. <ul style="list-style-type: none"> - Assessment of long term pulmonary morbidity (e.g., incidence of infections, pulmonary function status) and mortality - Assessment of long term cardiovascular morbidity (e.g., incidence of events, and echocardiography data, where available) and mortality - Assessment of long term urinary GAG excretion patterns - Assessment of long term antibody levels, isotype and correlation to other therapeutic parameters | 31 March every year |

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Elaprase 2 mg/ml concentrate for solution for infusion
idursulfase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 6 mg of idursulfase. Each ml contains 2 mg of idursulfase

3. LIST OF EXCIPIENTS

Polysorbate 20
Sodium chloride
Dibasic sodium phosphate heptahydrate
Monobasic sodium phosphate monohydrate
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
3 ml
4 x 3 ml
10 x 3 ml

6 mg/3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Read the package leaflet before use
Intravenous use

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

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharmaceuticals International AG Ireland Branch
Block 2 Miesian Plaza
50-58 Baggot Street Lower
Dublin 2
D02 HW68
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/365/001
EU/1/06/365/002
EU/1/06/365/003

13. BATCH NUMBER

Lot

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

Elaprase 2 mg/ml sterile concentrate
idursulfase
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6 mg/3 ml

6. OTHER

Store in a refrigerator
Do not freeze

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Elaprase 2 mg/ml concentrate for solution for infusion idursulfase

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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, pharmacist or nurse.
- 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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Elaprase is and what it is used for
2. What you need to know before you use Elaprase
3. How to use Elaprase
4. Possible side effects
5. How to store Elaprase
6. Contents of the pack and other information

1. What Elaprase is and what it is used for

Elaprase is used as enzyme replacement therapy to treat children and adults with Hunter syndrome (Mucopolysaccharidosis II) when the level of the enzyme iduronate-2-sulfatase in the body is lower than normal, helping improve the symptoms of the disease. If you suffer from Hunter syndrome, a carbohydrate called glycosaminoglycan which is normally broken down by your body, is not broken down and slowly accumulates in various organs in your body. This causes cells to function abnormally, thereby causing problems for various organs in your body which can lead to tissue destruction and organ malfunction and failure. Typical organs where glycosaminoglycan accumulates are spleen, liver, lungs, heart, and connective tissue. In some patients glycosaminoglycan accumulates also in the brain. Elaprase contains an active substance called idursulfase which works by acting as a replacement for the enzyme that is at a low level, thereby breaking down this carbohydrate in affected cells.

Enzyme replacement therapy is usually administered as a long-term treatment.

2. What you need to know before you use Elaprase

Do not use Elaprase

If you have experienced severe or potentially life-threatening allergic-type reactions to idursulfase or any of the other ingredients of this medicine (listed in section 6) and these cannot be controlled with appropriate medical treatment.

Warnings and precautions

Talk to your doctor or nurse before using this medicine.

If you are treated with Elaprase you may experience side effects during or following an infusion (see section 4 Possible side effects). The most common symptoms are itching, rash, hives, fever, headache, increased blood pressure, and flushing (redness). Most of the time you can still be given this medicine even if these symptoms occur. If you experience an allergic side effect following administration of this medicine, you should contact your doctor immediately. You may be given additional medicines such as antihistamines and corticosteroids to treat or help prevent allergic-type reactions.

If severe allergic reactions occur, your doctor will stop the infusion immediately, and start giving you suitable treatment. You may need to stay in hospital.

The nature of your genotype (a genetic make up of all active genes in human cells, which determines one's specific, individual characteristics) may influence your therapeutic response to this medicine, as well as your risk of developing antibodies and infusion-related side effects. In individual cases, so-called 'neutralising antibodies' may develop, which may diminish activity of Elaprase and your response to treatment. The longer term effects of antibody development on response to treatment have not been established. Please consult your doctor for additional information.

Keeping a record

In order to improve the traceability of biological medicinal products, the name and batch number of the administered product should be clearly recorded by your healthcare professional. Speak with your healthcare professional if you are not sure.

Other medicines and Elaprase

There is no known interaction of this medicine with other medicines.

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding

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 taking this medicine.

Driving and using machines

This medicine has no or negligible influence on the ability to drive and use machines.

Elaprase contains sodium

This medicine contains 11.1 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 0.6% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Elaprase

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

This medicine will be given to you under the supervision of a doctor or nurse who is knowledgeable in the treatment of Hunter syndrome or other inherited metabolic disorders.

The recommended dose is an infusion of 0.5 mg (half a milligram) for every kg you weigh

Elaprase has to be diluted in sodium chloride 9 mg/ml (0.9%) solution for infusion before use. After dilution this medicine is given through a vein (drip feed). The infusion will normally last for 1 to 3 hours and will be given every week.

Use in children and adolescents

The recommended dosage in children and adolescents is the same as in adults.

If you use more Elaprase than you should

Consult your doctor if you have an overdose of this medication.

If you forget to use Elaprase

If you have missed an Elaprase infusion, please contact your doctor.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

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

Most side effects are mild to moderate and associated with the infusion, however some side effects may be serious. Over time the number of these infusion-associated reactions decreases.

If you have problems breathing, with or without bluish skin, tell your doctor straight away and seek immediate medical assistance.

Very common side effects (may affect more than 1 in 10 people) are:

- Headache
- Flushing (redness)
- Shortness of breath, wheezing
- Abdominal pain, nausea, vomiting, frequent and/or loose stools
- Chest pain
- Hives, rash, itching, redness of the skin
- Fever
- Infusion-related reaction (see section entitled “Warnings and precautions”)

Common side effects (may affect up to 1 in 10 people) are:

- Dizziness, tremor
- Rapid heartbeat, irregular heartbeat, bluish skin
- Increased blood pressure, decreased blood pressure
- Difficulty breathing, cough, low oxygen levels in your blood
- Swollen tongue, indigestion
- Pain in the joints
- Infusion-site swelling, swelling of the extremities, facial swelling

Uncommon side effects (may affect up to 1 in 100 people) are:

- Quickened breathing

Side effects for which frequency is not known (cannot be estimated from available data) are:

- Serious allergic reactions

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. 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 Elaprase

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

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C)

Do not freeze

Do not use this medicine if you notice that there is discolouration or presence of foreign particles.

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 Elaprase contains

The active substance is idursulfase, which is a form of the human enzyme iduronate-2-sulfatase. Idursulfase is produced in a human cell line by genetic engineering technology (it involves the introduction of genetic information into human cells in the lab, which will then produce the desired product).

Each vial of Elaprase contains 6 mg of idursulfase. Each ml contains 2 mg of idursulfase.

The other ingredients are Polysorbate 20, sodium chloride, dibasic sodium phosphate, heptahydrate, monobasic sodium phosphate, monohydrate and water for injections.

What Elaprase looks like and contents of the pack

This medicine is a concentrate for solution for infusion. It is supplied in a glass vial as a clear to slightly opalescent, colourless solution.

Each vial contains 3 ml of concentrate for solution for infusion.

Elaprase is supplied in pack sizes of 1, 4 and 10 vials per carton. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

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This leaflet was last revised in .

This medicine has been authorised under “exceptional circumstances”. This means that because of the rarity of this disease it has been impossible to get complete information on this medicine.

The European Medicines Agency will review any new information on the medicine every year and this leaflet will be updated as necessary.

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.

The following information is intended for healthcare professionals only:

Instructions for use, handling and disposal

1. Calculate the total dose to be administered and number of Elaprase vials needed.
2. Dilute the total volume of Elaprase concentrate for solution for infusion required in 100 ml of sodium chloride 9 mg/ml (0.9%) solution for infusion . It is recommended to deliver the total volume of the infusion using a 0.2 µm in line filter. Care must be taken to ensure the sterility of the prepared solutions since Elaprase does not contain any preservative or bacteriostatic agent; aseptic technique must be observed. Once diluted, the solution should be mixed gently, but not shaken.
3. The solution should be inspected visually for particulate matter and discolouration prior to administration. Do not shake.
4. It is recommended that administration is started as soon as possible. The chemical and physical stability of the diluted solution has been demonstrated for 8 hours at 25°C.
5. Do not infuse Elaprase concomitantly in the same intravenous line with other medicinal products.
6. For single use only. Any unused product or waste material should be disposed of in accordance with local requirements.