Professional Information for ELAPRASE®

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ELAPRASE® 6 mg/3 mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of 3 mL contains 6 mg of idursulfase.

Each mL contains 2 mg of idursulfase.

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

Sugar free.

Excipients with known effect:

Each vial contains 0,482 mmol of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

A clear to slightly opalescent, colourless solution that may have fine particulate matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ELAPRASE is indicated for patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II).

4.2 Posology and method of administration

ELAPRASE treatment should be supervised by a medical practitioner or other health care professional experienced in the management of patients with Hunter syndrome (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 preparation and administration instructions see section 6.6.

Infusion of ELAPRASE at home may be considered for patients who are tolerating their infusions well. Home infusions should be performed under the surveillance of a doctor or other health care professional.

Special populations:

Patients with renal or hepatic impairment

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

Elderly patients

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

Paediatric patients

The dose for children and adolescents is 0,5 mg/kg body weight weekly.

The safety and efficacy of ELAPRASE has not been established in paediatric patients less than 16 months of age.

Method of administration:

For preparation and administration instructions before use, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

4.4 Special warnings and precautions for use

RISK OF HYPERSENSITIVITY REACTIONS

Anaphylactoid/anaphylactic reactions, which have the potential to be life threatening, have been observed in some patients treated with ELAPRASE. Patients with compromised respiratory function or acute respiratory disease may be at risk of serious exacerbation of their respiratory dysfunction due to infusion related reactions. These patients require additional monitoring. Late-emergent anaphylactoid/anaphylactic reactions have been observed after ELAPRASE administration. Patients who have experienced severe and refractory anaphylactoid/anaphylactic reactions may require prolonged observation times. Due to the potential for severe infusion reactions appropriate medical support measures should be readily available when ELAPRASE is administered.

Patients treated with ELAPRASE 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 medicines, such as antihistamines, antipyretics, low-dose corticosteroids (prednisone or 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.

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

Patients who develop IgM or IgG antibodies are at a higher risk of infusion reactions and other adverse reactions, however, IgE antibodies have not been observed.
Paediatric patients with the complete deletion/large rearrangement genotype have a high probability of developing antibodies, including neutralising antibodies, in response to exposure to ELAPRASE. 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.

Anaphylactoid/anaphylactic reactions, which have the potential to be life threatening, have been observed in some patients treated with ELAPRASE 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 of ELAPRASE should be suspended immediately and appropriate treatment and observation should be 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 ELAPRASE. Appropriately trained personnel and equipment for emergency resuscitation (including epinephrine (adrenaline)) should be available during infusions. Severe or potentially life-threatening hypersensitivity is a contraindication to rechallenge.

Sodium

ELAPRASE 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.

4.5 Interaction with other medicines and other forms of interaction

No formal interaction studies have been conducted with ELAPRASE.

Based on its metabolism in cellular lysosomes, idursulfase would not be affected by cytochrome P450 mediated interactions.

4.6 Fertility, pregnancy and lactation

Safety during pregnancy and lactation has not been established.

Pregnancy

There are no or limited data available from the use of ELAPRASE in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). ELAPRASE is not recommended for use during pregnancy.

Breastfeeding

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

ELAPRASE may influence the patient's ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions that were reported for the 32 patients treated with 0,5 mg/kg ELAPRASE weekly in the Phase II/III 53-week placebo-controlled study, are listed in the table below with information presented by system organ class and frequency.

Frequency is given as very common (≥ 1/10, ≥ 10 %), common (≥ 1/100, < 1/10, between 1 % and 10 %) or uncommon (≥ 1/1 000, < 1/100, between 0,1 % and 1 %). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse reactions were defined as treatment-emergent events with suspected causality and excluded non-serious events that were reported only once in a single patient. Treatment emergent events with an excess incidence of at least 9 % compared with placebo were also considered as adverse reactions.

The most common reactions are infusion-related reactions including cutaneous reactions (rash, pruritus, urticaria and erythema), pyrexia, flushing, wheezing, dyspnoea, headache, vomiting, abdominal pain, nausea and chest pain.

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

System organ class	**Adverse reaction (preferred term)**
Immune system disorders Frequency not known:	anaphylactoid reaction/anaphylactic reaction*
Nervous system disorders Very common: Common:	headache dizziness, tremor
Cardiac disorders Common:	cyanosis, dysrhythmia, tachycardia

System organ class	Adverse reaction (preferred term)
Vascular disorders	
Very common:	flushing
Common:	hypertension, hypotension
Respiratory, thoracic and mediastinal disorders	
Very common:	wheezing, dyspnoea
Common:	hypoxia, bronchospasm, cough
Uncommon:	tachypnoea
Gastrointestinal disorders	
Very common:	vomiting, abdominal pain, nausea, diarrhoea
Common:	swollen tongue, dyspepsia
Skin and subcutaneous tissue disorders	
Very common:	urticaria, rash, pruritus, erythema
Musculoskeletal and connective tissue disorders	
Common:	arthralgia
General disorders and administration site conditions	
Very common:	pyrexia, chest pain
Common:	infusion site swelling, facial oedema, peripheral oedema
Injury, poisoning and procedural complications	
Very common:	infusion related reaction

* Side effects reported post-marketing.

Across studies, serious adverse reactions were reported in a total of 5 patients out of 64 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 resulting in a 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 corticosteroids, antihistamines, and beta-agonist nebulisation. The fifth patient, who had pre-existing cardiomyopathy, was diagnosed with ventricular premature complexes and pulmonary embolism during the study.

Post-marketing

There have been post-marketing reports of anaphylactoid/anaphylactic reactions.

Patients with complete deletion/large rearrangement genotype have a higher probability of developing infusion related adverse events.

Please see section 4.4 for further information.

Immunogenicity

Across 4 clinical studies (TKT008, TKT018, TKT024 and TKT024EXT), 53/107 patients (50 %) developed anti-idursulfase IgG antibodies at some point. The overall neutralising 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 0,5 mg/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 neutralising antibodies at least once and 13 % (8/63) tested positive for neutralising 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 neutralising antibodies at least once and half of the patients tested positive for neutralising 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 neutralising 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 neutralising 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 paediatric population were, in general, similar to those reported in adults.

Reporting of suspected adverse reactions

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

- The Pharmacovigilance Unit at Sanofi: za.drugsafety@sanofi.com (email) or

011 256 3700 (tel), or

- SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

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 section 4.3, 4.4 and 4.8. Treatment should be symptomatic and supportive if needed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 31 Enzymatic preparations.

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 ELAPRASE 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 internalisation of the enzyme, targeting to intracellular lysosomes and subsequent catabolism of accumulated glycosaminoglycans (GAG).

5.2 Pharmacokinetic properties

Idursulfase is taken up by selective receptor-mediated mechanisms involving binding to mannose 6-phosphate receptors. Upon internalisation by cells, it is localised 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.

Pharmacokinetics were evaluated in 10 patients at Week 1 and Week 27 following administration of 0,5 mg/kg weekly as a 3-hour infusion. There were no differences in pharmacokinetic parameters following 27 weeks of treatment.

Table 2: Mean pharmacokinetic parameters in study TKT024 (n=10)

Parameter	**Week 1 (SD)**	**Week 27 (SD)**
C_{max} (µg/mL)	1,5 (0,6)	1,1 (0,3)
AUC (min*µg/mL)	206 (87)	169 (55)
$T_{½}$ (min)	44 (19)	48 (21)
Cl (mL/min/kg)	3,0 (1,2)	3,40 (1,0)

V_{ss} (% BW)	21 (8)	25 (9)

Pharmacokinetics were also evaluated in study HGT-ELA-038 in patients aged 16 months to 7,5 years who received 0,5 mg/kg idursulfase as a 3-hour infusion.

Table 3: Mean pharmacokinetic parameters in Study HGT-ELA-038 (n=27)

Parameters	**Week 1 Mean (SD) n=27**	**Week 27 Mean (SD)** n=11**	**Week 27 Mean (SD)*** n=8**
C_{max} (µg/mL)	1,3 (0,8)	1,4 (0,4)	0,6 (0,5)
$AUC_{0-\infty}$ (min*µg/mL)	224,3 (76,9)	269,9 (78,3)	93,1 (81,8)
$T_{½}$ (min)*	160 (69)	138 (24)	64 (19)
Cl (mL/min/kg)	2,4 (0,7)	2,0 (1,0)	8,9 (6,1)
V_{ss} (mL/kg)	394 (423)	280 (102)	977 (653)

*$T_{½}$ values estimated in the terminal phase from 240 minutes to the last measureable data point

**Patients at week 27 who tested negative for anti-idursulfase IgG antibodies

*** Patients at week 27 who tested positive for anti-idursulfase IgG antibodies

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 4 and table 5 below as a function of age and body weight, respectively.

Table 4: Pharmacokinetic parameters at week 1 as 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
$AUC_{0-\infty}$ (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	168 ± 32

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

Table 5: 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
$AUC_{0-\infty}$ (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.

Summary of clinical studies

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 two randomised, placebo-controlled clinical studies, 106 continued treatment in two open-label, extension studies.

Study TKT024

In a 53-week, randomised, 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 (FEV_1), and changes in left ventricular mass (LVM).

Table 6: Results from pivotal clinical study at 0,5 mg/kg per week (Study TKT024).

Endpoint	**53 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)**
	ELAPRASE	**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 FEV_1 of at least 200 mL 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 FEV_1 at the end of the study.

Urine GAG levels were normalised 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 normalised 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/m^2. 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 13,7 m to 41,5 m (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.

5.3 Preclinical safety data

Nonclincial 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 idursalfase in breast milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 20;

sodium chloride;

sodium phosphate dibasic heptahydrate;

sodium phosphate monobasic monohydrate;

water for injection.

6.2 Incompatibilities

ELAPRASE must not be mixed with any other medicines, 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 – 8 °C.

6.4 Special precautions for storage

Store in a refrigerator (2 – 8 °C).

Do not freeze.

For single use only. Discard any unused portion.

For storage conditions after dilution, see section 6.3.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Clear, colourless, type 1 glass 5 mL vial with a fluoro-resin coated butyl rubber stopper, one piece aluminium seal and blue flip-off cap.

6.6 Special precautions for disposal and other handling

Instructions for dilution, 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.

Determine the number of vials to be diluted based on the individual patient's weight and the recommended dose of 0,5 mg/kg.

Do not use if the solution in the vial is discoloured.

Do not shake.

Withdraw the calculated volume of ELAPRASE from the appropriate number of vials.

Dilute the total volume required of ELAPRASE 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 appropriately.

7. HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

2 Bond Street

Midrand 1685

South Africa

8. REGISTRATION NUMBER

45/31/0333

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 29 September 2017

10. DATE OF REVISION OF THE TEXT

Date of revision: 09 November 2021.