PRODUCT INFORMATION

ELAPRASE®
(idursulfase)

NAME OF THE MEDICINE

ELAPRASE (idursulfase) 6 mg/3 mL concentrate for intravenous solution for infusion.

DESCRIPTION

ELAPRASE (idursulfase) is a purified form of the lysosomal enzyme, iduronate-2-sulfatase. Idursulfase is produced by recombinant DNA technology in a human cell line providing a human glycosylation profile. Idursulfase is a 525 amino acid glycoprotein with 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.

ELAPRASE, for intravenous infusion, is supplied as a sterile, aqueous, clear to slightly opalescent colourless solution that must be diluted prior to administration in 0.9% Sodium Chloride for Injection.

The solution in each vial contains an idursulfase concentration of 2 mg/mL at a pH of approximately 6. The extractable volume of 3 mL from each vial provides 6 mg idursulfase, 24.0 mg sodium chloride, 6.75 mg sodium phosphate monobasic monohydrate, 2.97 mg sodium phosphate dibasic heptahydrate and 0.66 mg polysorbate 20. ELAPRASE does not contain preservatives; vials are for single use only.

Pharmacology

Mechanism of Action

Hunter syndrome (Mucopolysaccharidosis II, MPS II) is an X-linked recessive disease caused by insufficient levels of the lysosomal enzyme iduronate-2-sulfatase (I2S). I2S functions to catabolise the glycosaminoglycans (GAG) dermatan sulphate and heparan sulphate by cleavage of oligosaccharide-linked sulphate moieties. Due to the missing or defective I2S enzyme in patients with Hunter syndrome, GAG progressively accumulate in the lysosomes of a variety of cells, leading to cellular engorgement, organomegaly, tissue destruction and organ system dysfunction.

Treatment of Hunter syndrome patients with 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 GAG.

Pharmacokinetics

The pharmacokinetic characteristics of idursulfase were evaluated in several studies in patients with Hunter syndrome. The serum concentration of idursulfase was quantified using an antigen-specific ELISA assay. The area under the concentration-time curve (AUC) increased in a greater than dose proportional manner as the dose increased from 0.15 mg/kg to 1.5 mg/kg following a single 1-hour infusion of ELAPRASE. The pharmacokinetic parameters at the recommended dose regimen (0.5 mg/kg ELAPRASE administered weekly as a 3 hour infusion) were determined at Week 1 and Week 27 in 10 patients ages 7.7 to 27 years (Table 1). There were no apparent differences in Pharmacokinetic parameter values between Week 1 and Week 27.

Table 1: Mean Pharmacokinetic Parameters in Study TKT024 (n=10)

Pharmacokinetic 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)
$t_{1/2}$ (min)	44 (19)	48 (21)
Cl (mL/min/kg)	3.0 (1.2)	3.4 (1.0)
V_{ss} (% BW)	21 (8)	25 (9)

In study TKT024EXT, in which patients received idursulfase 0.5 mg/kg weekly as a 3-hour infusion, there were no changes in PK parameters with repeat dosing (week 18, n=68) and PK parameters were similar to those in study TKT024. There was no effect of anti-idursulfase IgG antibodies on the PK of idursulfase.

PK was also evaluated in study HGT-ELA-038 in patients aged 16 months to 7.5 years who received 0.5 mg/kg ELAPRASE as a 3-hour infusion. PK was evaluated at Week 1 (n=27) and Week 27 (n=11) (see Table 2). Serum concentrations were less than the lower limit of quantification (LLOQ) at all time points in 8 of 27 subjects (30%) at week 27 and measurable only at some sampling times in the remaining 19 subjects (70%). The PK profiles of all 11 antibody-negative subjects at Week 27 were similar to those at Week 1. The 8 antibody-positive subjects with measurable serum concentration levels exhibited significantly higher clearance rates at Week 27 compared to Week 1.

Table 2: Mean Pharmacokinetic Parameters in Study HGT-ELA-038 (n=27)

Parameter	Week 1 Mean (SD) N=27	Week 27 Mean (SD)** N=11
C_{max} (µg/mL)	1.3 (0.8)	1.4 (0.4)
$AUC_{0-\infty}$ (min*µg/mL)	224.3 (76.9)	269.9 (78.3)
$t_{1/2}$ (min) *	160 (69)	138 (24)
Cl (mL/min/kg)	2.4 (0.7)	2.0 (1.0)
V_{ss} (mL/kg)	394 (423)	280 (102)

* $t_{1/2}$ values estimated in the terminal phase from 240 min to the last measurable data point

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

Source: Module5.3.3.2 HGT-ELA-038 Research and Development Report # 725-1i0-11-1676 Amendment A Clinical Pharmacology and Pharmacokinetics, Table 7, page 43.

The systemic exposure (C_{max} and $AUC_{0-\infty}$) and clearance (Cl and V_{ss}) of ELAPRASE observed at Week 1 in studies TKT024 and HGT-ELA-038 are summarised in Table 1 and Table 2. In the analysis, the patients in TKT024 and HGT-ELA-038 were segmented by age into paediatric (5 to 11 years; n=11), adolescent (12 to 18 years; n=8) and adult populations (>18 years; n=9) (see Table 3).

Table 3: Pharmacokinetic Parameters 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
$AUC_{0-\infty}$ (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	169 ± 32

At Week 1, ELAPRASE demonstrated comparable systemic exposure (i.e. C_{max} and AUC) and clearance rates (i.e. Cl) behaviours across the different age groups.

The systemic exposure (C_{max} and $AUC_{0-\infty}$) and clearance (CL and V_{ss}) of ELAPRASE observed at Week 1 for the TKT024 and HGT-ELA-038 studies are summarised in Table 4. In the analysis, patients in the TKT024 and HGT-ELA-038 studies were stratified across five weight categories; < 20 kg, ≥ 20 and < 30 kg, ≥ 30 and < 40 kg, ≥ 40 and < 50 kg and ≥ 50 kg.

Source: Module5.3.3.2 HGT-ELA-038 Research and Development Report # 725-1i0-11-1676 Amendment A Clinical Pharmacology and Pharmacokinetics, Table 9, page 14.

Table 4: Pharmacokinetic Parameters 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) Mean ±SD	206.2 ± 33.9	234.3 ± 103.0	231.1 ± 68.1	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) Mean ±SD	321 ± 105	397 ± 528	171 ± 52	160 ± 59	181 ± 34

Key pharmacokinetic parameters for ELAPRASE were comparable across the different weight groups. These results indicate that the total systemic exposure and clearance rate of ELAPRASE are not affected by body weight. However, 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 ELAPRASE with respect to either age or body weight.

CLINICAL TRIALS

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.

Safety of ELAPRASE infusions has been assessed in children less than 7.5 years of age in an open-label, multicentre, single-arm study of 28 male patients.

TKT024

In a 53-week, randomised, double-blind, placebo-controlled clinical study (TKT024), 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 Forced Vital Capacity (FVC) <80% and a broad spectrum of disease severity (see Table 5).

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 FVC as a measure of pulmonary function. This endpoint differed significantly from placebo for patients treated with ELAPRASE weekly (p=0.0049(see Table 5).

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).

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 ELAPRASE weekly. None of the placebo patients had normalised urine GAG levels that fell to below the upper limit of normal by week 53.

Of the 25 patients with abnormally large livers at baseline in the ELAPRASE weekly group, 80% (20 patients) had reductions in liver volume to within the normal range by the end of the study. 4.3% of the patients in the placebo group who had hepatomegaly at baseline improved to normal by Week 53.

Of the 9 patients in the ELAPRASE weekly group with abnormally large spleens at baseline, 3 had spleen volumes that normalised by the end of the study. Among the patients with enlarged spleens at baseline, 18.18% of the placebo patients normalised by Week 53.

Approximately half of the patients in the ELAPRASE weekly group (15 of 32; 47%) had left ventricular hypertrophy (LVH) at baseline, defined as LVM index >103 g/m^2. Of these, 6 (40%) had normalised LVM by the end of the study. 22.22% of the placebo patients with LVH at baseline had normal LVM by Week 53.

Table 5: Clinical Study Results

Endpoint	53 Weeks of Treatment		
	0.5 mg/kg Weekly		
	Mean (SE) Adjusted Change from Baseline	Mean (SE) Difference Compared to Placebo	p-value (Compared to Placebo)
Composite (6MWT & % Predicted FVC)	N/A[a]	19.0 (6.5)	0.0049
6MWT (m)	37.0 (10.9)	35.1 (13.7)	0.0131
% Predicted FVC	1.3 (1.7)	4.3 (2.3)	0.0650
FVC Absolute Volume (mL)	180 (40)	190 (60)	0.0011
Urine GAG Levels (µg GAG/mg creatinine)	-224.9 (22.1)	-275.5 (30.1)	< 0.0001
% Change in Liver Volume	-25.6 (1.7)	-25.2 (2.2)	< 0.0001
% Change in Spleen Volume	-25.1 (3.5)	-33.2 (4.8)	< 0.0001

[a] the analysis of the composite endpoint encompasses the sum of the ranks of change from baseline

TKT024EXT

In the extension study (TKT024EXT) in which all patients received weekly idursulfase, statistically significant mean increases from treatment baseline were seen in the distance walked in the 6MWT at the majority of time points tested, with significant mean and percent increases ranging from 13.7 m to 41.5 m and from 6.4% to 11.7%, respectively, (maximum at Month 20). At most time points tested, patients in the original TKT024 Weekly group improved their walking distance to a greater extent than patients in the other 2 treatment groups.

Percentage predicted FVC remained stable in all Hunter syndrome patients treated for 2 to 3 years with idursulfase 0.5 mg/kg weekly.

At the completion of TKT024EXT, mean urinary GAG levels fell below the upper limit of normal in the TKT024 Weekly and EOW dose groups and were near normal in the TKT024 placebo group. Changes in the urine GAG levels were the earliest signs of clinical improvement with idursulfase treatment and the greatest decreases in urine GAG were seen in the first 4 months of treatment in all treatment groups. In those patients whose urine GAG levels fell to within the normal range, this fall was regardless of patient age, disease severity at baseline, and residual IS activity category. The higher the urine GAG levels at baseline the greater the magnitude of decreases in urine GAG with idursulfase treatment.

The decrease in liver and spleen volumes at week 53 were maintained during the extension study (TKT024EXT) in all patients regardless of prior TKT024 treatment assignment. Seventy one out of 94 patients had hepatomegaly at baseline. Liver volume normalised by Month 24 for 73% (52 out of 71) of these patients. In addition, mean liver volume decreased to a near maximum extent by Month 8 in all TKT024 treatment groups, increasing slightly from this nadir at Month 36. Decreases in mean

liver volume were seen regardless of age, disease severity, antibody status, or neutralizing antibody status. For the study population as a whole, mean spleen volume also decreased rapidly after the initiation of idursulfase and remained well below mean baseline volume for the duration of the extension study.

In the extension study (TKT024EXT) the mean left ventricular mass index returned to baseline.

HGT-ELA-038

In an open-label, multicentre, single-arm study HGT-ELA-038, 28 male patients between the ages of 16 months and 7.5 years received ELAPRASE 0.5 mg/kg every week.

The study was designed to assess the safety of ELAPRASE infusions for male patients with Hunter syndrome who are ≤ 5 years old. In addition, this study was to evaluate efficacy, clinical outcomes and ELAPRASE pharmacokinetics in this patient population.

The primary pharmacodynamic endpoint of this study was measurement of urinary GAG clearance. Exploratory efficacy endpoints included mean change in liver size and spleen volume as measured by ultrasound.

All patient groups experienced a decrease in urinary GAG levels, liver size and spleen volume after initiation of ELAPRASE treatment. Patients with the complete deletion/large rearrangement genotype had a less pronounced decrease in uGAG levels than patients with the missense mutation genotype. In the patients with the complete deletion/large rearrangement genotype the initial response was followed by an increase in the liver size to approximately baseline values at 53 weeks and spleen volume also increased but remained below baseline values at 53 weeks. Patients with frameshift/splice genotype had the least pronounced response to ELAPRASE. These genotype-based results are consistent with the antibody-based analysis, which showed that patients with antibodies and neutralising antibodies had a slightly less pronounced decrease in uGAG, liver size and spleen volume. However, individual patients with a complete deletion/large rearrangement genotype and high titer antibodies experienced a therapeutic response similar or better than some patients with a missense mutation genotype and no antibody response.

No data are available on the effect of Elaprase on the neurological or skeletal manifestations of Hunter Syndrome.

INDICATIONS

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

CONTRAINDICATIONS

Hypersensitivity (anaphylactic reaction) to the active substance or to any of the excipients.

PRECAUTIONS

Serious hypersensitivity reactions including life threatening anaphylactoid reactions have been observed in some patients during ELAPRASE infusions. Reactions have included respiratory

distress, hypoxia, hypotension, seizure, loss of consciousness, urticaria and/or angioedema of the throat or tongue.

Late emergent or biphasic anaphylactoid reactions have also been reported to occur after administration of ELAPRASE approximately 24 hours after treatment and recovery from an initial anaphylactoid reaction that occurred during ELAPRASE infusion. Patients who have experienced initial anaphylactoid reactions may require prolonged observation.
Interventions for biphasic reactions have included hospitalisation, and treatment with adrenaline, inhaled beta-adrenergic agonists, and corticosteroids.

Patients with compromised respiratory function or acute respiratory disease may be at risk of serious acute exacerbation of their respiratory compromise due to infusion reactions, and require additional monitoring.

Infusion/Hypersensitivity reactions

Patients treated with ELAPRASE may develop infusion-related reactions (see ADVERSE EFFECTS). 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 medications, such as antihistamines, antipyretics, low-dose corticosteroids (prednisone and methylprednisolone) or beta-agonist nebulisation.

No patient discontinued treatment with ELAPRASE due to an infusion reaction during clinical studies.

Severe infusion-related reactions were reported occasionally in patients with severe underlying obstructive airway disease. These patients should therefore be closely monitored and infused with ELAPRASE in an appropriate clinical setting. Delaying ELAPRASE infusion should be considered 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.
The most serious infusion-related reactions include anaphylactoid reactions. Biphasic anaphylactoid reactions have also been reported with Elaprase. The most common infusion-related reactions include cutaneous reactions (rash, pruritis, urticaria), flushing, hypertension, pyrexia, wheezing, hypoxia, dyspnoea, headache, abdominal pain, nausea, dyspepsia, chest pain, and infusion site swelling. If severe allergic or anaphylactoid-type reactions occur, it is recommended that the administration of ELAPRASE be discontinued immediately and appropriate medical treatment and observation initiated. The current medical standards for emergency treatment are to be observed. Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available when ELAPRASE is administered because of the potential for severe infusion reactions.

Late-emergent anaphylactoid reactions have been observed after ELAPRASE administration. (See ADVERSE EFFECTS, Post-Marketing Surveillance). With appropriate pre-treatment and monitoring, patients continued weekly ELAPRASE treatments. Because of the potential for late-emergent anaphylactoid reactions, patients who experience initial severe or refractory reactions may require prolonged observation dependant on the clinical needs.

Effect on Fertility
A fertility study was performed in male rats at intravenous doses up to 5 mg/kg, administered twice weekly, and has not revealed evidence of impaired male fertility due to ELAPRASE.

Use in Pregnancy: Category B2
There are no adequate and well-controlled studies in pregnant women, and no relevant reproductive toxicity studies have been conducted with idursulfase in animals. Therefore ELAPRASE should be given to a pregnant woman only if clearly needed and after a careful risk/benefit analysis has been conducted for both the mother and foetus.

Use in Lactation
It is not known whether ELAPRASE is excreted in human milk. Therefore, it recommended that the patient should not breast-feed whilst treated with ELAPRASE.

Animal studies show that ELAPRASE is excreted in breast milk and is present in the foetal circulation in utero. Caution should be used when giving ELAPRASE to pregnant or lactating women after consideration of risks and benefits. It is not known whether ELAPRASE can cause foetal harm when administered to a pregnant woman or can affect reproductive capacity. ELAPRASE should not be administered during pregnancy except when the indication and need are clear and the potential benefit is judged by the physician to substantially justify the risk.

Paediatric Use
Patients in the clinical studies were aged 16 months to 18 years of age. Children, adolescents and adults responded similarly to treatment with ELAPRASE.

Use in the Elderly
Clinical studies of ELAPRASE did not include patients aged 65 and over therefore it has not been determined whether they would respond differently from younger patients.

Genotoxicity
Studies with idursulfase have not been performed to evaluate genotoxic potential.

Carcinogenicity
Studies with idursulfase have not been performed to evaluate carcinogenic potential.

Effects on Laboratory tests
Across studies there were no clinical meaningful changes in clinical laboratory parameters.

Patients with the complete deletion/large rearrangement genotype
Patients with complete deletions are more likely to manifest a severe form of MPS II disease compared to other known genotypes. 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 assessed by decrease in uGAG levels, liver size and spleen volume compared to the patients with the missense genotype. In general, patients with the frameshift/splice site mutation genotype develop antibody responses between those seen in patients with complete deletion/large rearrangement or missense genotypes. However, individual patients with a complete deletion genotype or high titre antibodies experienced a therapeutic response similar to, or better than some patients with a missense mutation genotype and no antibody response.

Use in Renal/Hepatic Impaired Patients

Because ELAPRASE is not cleared through renal or hepatic mechanisms, it is believed that patients with renal or hepatic insufficiency would not respond differently to treatment with ELAPRASE and therefore would not require a dose adjustment.

INTERACTIONS WITH OTHER MEDICINES

No formal drug interaction studies have been conducted with ELAPRASE. As ELAPRASE is an enzyme, it would be an unlikely candidate for cytochrome P450 mediated drug-drug interactions.

ADVERSE EFFECTS

TKT024

The most common adverse reactions observed in the 53-week, placebo-controlled study were infusion-related reactions. In the weekly ELAPRASE treatment group 202 infusion-related reactions were reported in 22 of 32 patients following administration of 1580 weekly infusions.

In the every other week ELAPRASE treatment group 145 infusion-related reactions were reported in 22 of 32 patients following administration of 1629 bi-weekly infusions. In the placebo treatment group 128 infusion-related reactions were reported in 21 of 32 patients. Infusion-related reactions reported in the placebo group were similar in nature and severity to those in the ELAPRASE-treated groups.

Table 6 presents adverse drug reactions for ELAPRASE in a placebo-controlled clinical trial and represents a subset of the data presented in Table 7.

Table 6: Adverse drug reactions for ELAPRASE compared with controls in 53-week Placebo-controlled Clinical Trial, TKT024, (0.5 mg/kg ELAPRASE Weekly or Every other Week)

System Organ Class Adverse Drug Reaction (Preferred term)	ELAPRASE (0.5mg/kg weekly) N=32	ELAPRASE (0.5mg/kg biweekly) N=32	PLACEBO N=32
Nervous system disorders **Headache**	19 (59.4 %)	21 (65.6%)	14 (43.8%)
Cardiac Disorders **Cyanosis** **Arrthythmia** **Tachycardia**	 1 (3.1 %) 1 (3.1 %) 1 (3.1 %)	 1 (3.1 %) 1 (3.1 %) 3 (9.4%)	 0 (0%) 0 (0%) 2 (6.3%)
Vascular Disorders **Hypertension** **Flushing** **Hypotension**	 8 (25%) 5 (15.6%) 3 (9.4%)	 5 (15.6%) 5 (15.6%) 2 (6.3%)	 7 (21.9%) 6 (18.8%) 4 (12.5%)
Respiratory Thoracic and Mediastinal Disorders **Wheezing** **Dyspnoea** **Bronchospasm**	 5 (15.6%) 4 (12.5%) 3 (9.4%)	 5 (15.6%) 3 (9.4%) 2 (6.3%)	 5 (15.6%) 9 (28.1%) 5 (15.6%)

System Organ Class Adverse Drug Reaction (Preferred term)	ELAPRASE (0.5mg/kg weekly) N=32	ELAPRASE (0.5mg/kg biweekly) N=32	PLACEBO N=32
Tachypnoea	2 (6.3%)	0 (0%)	2 (6.3%)
Hypoxia	1 (3.1%)	3 (9.4%)	1 (3.1 %)
Gastrointestinal Disorders			
Abdominal pain	11 (34.4%)	17 (53.1%)	11 (34.4%)
Nausea	7 (21.9%)	9 (28.1 %)	9 (28.1%)
Dyspepsia	4 (12.5%)	4 (12.5%)	0 (0%)
Swollen tongue	2 (6.3%)	0 (0%)	0 (0%)
Skin and Subcutaneous Tissue Disorders			
Pruritis	10 (31.3%)	6 (18.8%)	5 (15.6%)
Rash	8 (25%)	11 (34.4%)	11 (34.4%)
Urticaria	5 (15.6%)	4 (12.5%)	0 (0%)
Erythema	2 (6.3%)	1 (3.1%)	1 (3.1 %)
Musculoskeletal and Connective Tissue Disorders			
Chest Pain	5 (15.6%)	3 (9.4%)	0(0%)
General Disorders and Administration Site Conditions			
Infusion-related reaction	22 (68.8%)	22 (68.8%)	21 (65.6%)
Pyrexia	20 (62.5%)	18 (56.3%)	19 (59.4%)
Infusion site swelling	4 (12.5%)	4 (12.5%)	1 (3.1 %)
Face oedema	1 (3.1 %)	0(0%)	0 (0%)
Oedema peripheral	2 (6.3%)	0(0%)	1 (3.1 %)

In clinical studies, the most frequent serious adverse events related to the use of ELAPRASE were hypoxic episodes, which necessitated oxygen therapy in three patients with severe underlying obstructive airway disease. The most severe episode, which was associated with a short seizure, occurred in a patient who received his infusion while he had a febrile respiratory exacerbation. In one 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 medication, usually with low-dose corticosteroids, antihistamine and beta-agonist nebulisation.

The most common adverse drug reactions are listed in Table 7. Information is presented by system organ class and frequency (very common > 1/10; common > 1/100, <1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The most serious infusion-related reactions include anaphylactoid reactions. Biphasic anaphylactoid reactions have also been reported with Elaprase. The most common infusion-related reactions include cutaneous reactions (rash, pruritis, urticaria), flushing, hypertension, pyrexia, wheezing, hypoxia, dyspnoea, headache, abdominal pain, nausea, dyspepsia, chest pain, and infusion site swelling. An infusion-related reaction was defined as an AE that occurred on the day of the infusion (i.e. within 24 hours after receiving an infusion), began either during or after the infusion, was judged as possibly or probably related to study drug, and was not associated with protocol-defined testing or assessments. Infusion-related reactions were treated or ameliorated by slowing the infusion rate, interrupting the

infusion or by administration of medications such as antihistamines, antipyretics, low dose corticosteroids (prednisone and methylprednisolone) or beta-agonist nebulisation. The frequency of infusion-related reactions decreased over time with continued ELAPRASE treatment.

The most common adverse reactions requiring intervention were infusion-related reactions, as described above (see ADVERSE EFFECTS, Post-Marketing Surveillance).

Table 7: Adverse Drug Reactions Reported with ELAPRASE

System Organ Class	Adverse Drug Reaction (Preferred Term)
Immune system disorders Frequency not known:	Anaphylactoid reaction
Nervous system disorders Very Common:	Headache
Cardiac disorders Common:	Cyanosis Arrhythmia Tachycardia
Vascular disorders Very Common:	Hypertension Flushing
Common:	Hypotension
Respiratory, thoracic and mediastinal disorders Very common:	Wheezing Dyspnoea
Common:	Hypoxia Tachypnoea Bronchospasm
Gastrointestinal disorders Very common:	Vomiting Abdominal pain Nausea Dyspepsia
Common:	Swollen tongue
Skin and subcutaneous tissue disorders Very Common:	Urticaria Rash Pruritus
Common:	Erythema
General disorders and administration site conditions Very Common:	Pyrexia Chest pain Infusion site swelling
Common:	Face oedema Oedema peripheral
Injury, poisoning and procedural complications Very common:	Infusion-related reaction

Note that clinical trials are conducted under widely varying conditions therefore the observed

adverse reaction rates may not predict the rates observed in patients in clinical practice.

Safety in young children

In a 53-week open-label safety study (HGT-ELA-038) including 20 children aged 16 months to 4 years and 8 children aged 5 to 7 years at study entry, the safety profile of weekly ELAPRASE 0.5 mg/kg doses was similar to that observed in previous clinical studies with almost all adverse reactions being infusion-related reactions.

Immunogenicity

Across 4 clinical studies (TKT08, TKT018, TKT024, TKT024EXT) assessing immunogenicity, 53/107 (50%) patients exposed to ELAPRASE developed anti - idursulfase IgG antibodies. All IgG-positive serum samples were tested for neutralising antibodies (NAb) activity. A maximum of 26 of 107 patients (24.3%) tested positive for any NAb at some time during treatment with idursulfase.

In a post-hoc analysis of immunogenicity in TKT024/024EXT, approximately half (51%) of the patients exposed to weekly ELAPRASE 0.5 mg/kg for 2 years developed an antibody response and 13% developed a persistent neutralising response defined as 3 consecutive samples positive NAb. There was no statistically significant association between antibody status and the effect of ELAPRASE on the clinical endpoints (6MWT or %FVC). All antibody status groups showed improvement on ELAPRASE, although the magnitude of the effect was less pronounced in antibody-positive patients. Similarly, uGAG levels decreased in all antibody status groups, but there was a mild to moderate decrease in the magnitude of the ELAPRASE-induced uGAG response in patients with antibodies, neutralising antibodies and those who tested positive for antibodies on at least three consecutive visits. Thus, regardless of antibody status, ELAPRASE treatment resulted in pharmacodynamic and clinical effects.

A fifth 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-ELAPRASE antibodies, and 57.1% (15 of 28) tested positive for antibodies on at least three consecutive study visits. Fifty-four percent of these 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.

There was a clear link between genotype and immunogenicity. 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.

Post-Marketing Surveillance

Rare cases have been reported of patients who have had symptoms and signs suggestive of late-emergent anaphylactoid reactions approximately 24 hours after treatment and recovery from an initial anaphylactoid reaction. These symptoms required treatment with inhaled beta-adrenergic agonists, adrenaline, anti-histamines, corticosteroids and hospitalisation. With appropriate pre-treatment and monitoring, patients continued weekly ELAPRASE treatments. Because of the potential for late-emergent anaphylactoid reactions, patients who experience initial severe or refractory reactions may require prolonged observation dependant on the clinical needs.

DOSAGE AND ADMINISTRATION

The recommended dosage regimen of ELAPRASE is 0.5 mg/kg of body weight administered every week as an intravenous infusion.

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

ELAPRASE is a concentrated solution for intravenous infusion and must be diluted in 100 mL of 0.9% Sodium Chloride for Injection. Each vial of ELAPRASE contains 3 mL (6 mg) of idursulfase. Vials are for single use only. Use of an infusion set equipped with a 0.2 micron (μm) filter is recommended.

The total volume of infusion should be delivered over a 3 hour period, which may be gradually reduced to 1 hour if no infusion-related reactions are observed. Patients may require longer infusion times due to infusion reactions; however, infusion times should not exceed 8 hours. The initial infusion rate should be 8 mL/hr for the first 15 minutes. If the infusion is well tolerated, the rate may be increased by 8 mL/hr increments at 15 minutes intervals in order to administer the full volume within the desired period of time. However, at no time should the infusion rate exceed 100 mL/hr. The infusion rate may be slowed and/or temporarily stopped, or discontinued for that visit, based on clinical judgement, if infusion reactions were to occur (see PRECAUTIONS). ELAPRASE should not be infused with other products in the infusion tubing.

Preparation and Administration Instructions: Use Aseptic Techniques

1. Determine the total volume of ELAPRASE to be administered and the number of vials needed based on the patient's weight and the recommended dose of 0.5 mg/kg.

   Patient's weight (kg) × 0.5 mg/kg of ELAPRASE ÷ 2 mg/mL/vial = Total # mL of ELAPRASE
   Total # mL of ELAPRASE ÷ 3 mL/vial = Total # of vials

   If the number of vials calculated indicates that a partial vial is required, round up to determine the number of whole vials needed from which to withdraw the calculated volume of ELAPRASE to be administered.

2. Perform a visual inspection of each vial. ELAPRASE is a clear to slightly opalescent, colourless solution. Do not use if the solution in the vials is discoloured or particulate matter is present. ELAPRASE should not be shaken.

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

4. Dilute the total calculated volume of ELAPRASE in 100 mL of 0.9% Sodium Chloride for Injection. Once diluted into normal saline, the solution in the infusion bag should be mixed gently, but not shaken. To reduce microbial hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2°- 8°C for no more than 24 hours.

5. ELAPRASE is supplied in single-use vials. Remaining ELAPRASE left in a vial after withdrawing the patient's calculated dose should be disposed of in accordance with local requirements.

OVERDOSAGE

There is no experience with overdose of ELAPRASE in humans. Single-dose studies of idursulfase have been performed in male rats and cynomolgus monkeys at doses up to 40 times the human dose with no signs of toxicity.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia) or the New Zealand National Poisons Information Centre (telephone 0800 POISON or 0800 764 766) for advice on management.

PRESENTATION AND STORAGE CONDITIONS

ELAPRASE is a sterile, aqueous, clear to slightly opalescent colourless solution supplied in a 5 mL Type I glass vial. The vials are closed with a butyl rubber stopper with fluororesin coating and an aluminium overseal with a blue flip-off plastic cap.

Store ELAPRASE under refrigeration at 2°C-8°C. Do not freeze or shake. Protect from light. Do not use ELAPRASE after the expiration date on the vial.

ELAPRASE is for single use in one patient only. This product contains no preservatives. To reduce microbial hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2°- 8°C for no more than 24 hours.

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POISON SCHEDULE OF THE MEDICINE

S4, Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

21 February 2008

DATE OF MOST RECENT AMENDMENT

9 December 2015

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