PRODUCT MONOGRAPH

Pr ELAPRASE®*

idursulfase

2 mg/mL concentrate for solution for infusion

Enzyme Replacement Therapy

Shire Human Genetic Therapies, Inc.
300 Shire Way
Lexington, MA 02421
www.shire.com

Importer/Distributor:
Shire Pharma Canada ULC
22 Adelaide Street West,
Suite 3800
Toronto Ontario M5H 4E3

Date of Initial Approval:
June 13, 2007

Date of Revision:
September 3, 2019

Control # 193666

*ELAPRASE is a registered trade-mark used under licence from Shire Human Genetic Therapies, Inc.

TABLE OF CONTENTS

Pr ELAPRASE®

idursulfase

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous (IV)	2 mg/mL concentrate for solution for infusion	None

INDICATIONS AND CLINICAL USE

ELAPRASE (idursulfase) is indicated for:

- long-term enzyme replacement therapy in patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II).

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For complete listing, see the **Dosage Forms, Composition and Packaging** section of the product monograph.

- Any ELAPRASE re-treatment of patients who developed hypersensitivity reactions is at the discretion of the healthcare provider upon successful management of the symptoms.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Risk of hypersensitivity reactions: 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.**

- **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 symptoms and signs of anaphylactoid/anaphylactic reactions have been observed after ELAPRASE administration as long as 24 hours after an initial reaction. If an anaphylactoid/anaphylactic reaction occurs, the infusion of ELAPRASE should be immediately suspended and appropriate treatment and observation initiated. The current medical standards for emergency treatment are to be followed. Patients experiencing severe or 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.**

General

ELAPRASE is not expected to affect the ability to drive or use machines.

A registry for patients with Hunter syndrome (the Hunter Outcome Survey) has been established in order to better understand the variability and progression of the disease and monitoring and evaluation of treatments. Patients should be encouraged to participate in the process and advised that their participation may involve a long-term follow-up. Information on the registry program may be obtained by calling 1-800-268-2772.

Carcinogenesis and Mutagenesis

See **Part II: Scientific Information, Toxicology**, **Mutagenicity and Carcinogenicity Studies**, for animal data.

Cardiovascular

Caution should be exercised when administering ELAPRASE to patients susceptible to fluid overload, or patients with underlying respiratory illness or compromised cardiac and/or respiratory function for whom fluid restriction is indicated. These patients may be at risk of serious exacerbations of their cardiac or respiratory status during infusion.

Hepatic

No studies have been performed in patients with hepatic impairment.

Immune

Hypersensitivity

Allergic reactions have included respiratory distress, hypoxia, decreased blood pressure, angioedema, or seizure. If severe allergic or anaphylactoid reactions occur, it is recommended that the administration of ELAPRASE be discontinued immediately and appropriate treatment initiated. The current medical standards for emergency treatment are to be observed.

In clinical trials with ELAPRASE, 16 of 108 (15%) patients experienced hypersensitivity reactions during 26 of 8,274 infusions (0.3%) that involved adverse events in at least two of the following three body systems: cutaneous, respiratory, or cardiovascular. Of these 16 patients, 11 experienced anaphylactic reaction during 19 of 8,274 infusions (0.2%) with symptoms of bronchospasm, cyanosis, dyspnea, erythema, edema (facial and peripheral), flushing, rash, respiratory distress, urticarial, vomiting, and wheezing.

Infusion Reactions

In clinical trials with ELAPRASE, the most common infusion-related reactions included cutaneous reactions (rash, pruritus, and urticaria), flushing, hypertension, pyrexia, wheezing, hypoxia, dyspnea, headache, abdominal pain, nausea, dyspepsia, chest pain, and infusion site swelling. 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 and methylprednisolone), or beta-agonist nebulization. Reactions were more severe in patients with compromised respiratory function or respiratory illnesses. No patient discontinued treatment with ELAPRASE due to an infusion reaction during clinical studies.

Patients using supplemental oxygen should have this treatment readily available during infusion in the event of an infusion-related reaction.

Renal

No studies have been conducted in patients with renal impairment.

Respiratory

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.

Special Populations

Pregnant Women

There are no data from studies in pregnant women. Results in animals show that idursulfase is present in the fetal circulation in utero (see **Toxicology, Reproduction and Teratology**). 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. Caution should be used when giving ELAPRASE to pregnant women after consideration of risks and benefits.

Nursing Women

Because of results in animals that show that idursulfase is excreted in the breast milk (see **Toxicology, Reproduction and Teratology**), caution should be used when giving ELAPRASE to nursing women after consideration of risks and benefits.

Pediatrics

Patients in the clinical studies were age 16 months and older. Children, adolescents, and adults responded similarly to treatment with ELAPRASE.

Geriatrics

Studies in patients over the age of 65 have not been performed.

Patients with the Complete Deletion, Large Rearrangement Genotype

Pediatric patients with complete deletion, large gene rearrangement genotype have a high probability of developing antibodies, including neutralizing antibodies in response to exposure to ELAPRASE. Patients with this genotype have a higher probability of developing infusion-related events and tend to show a muted response as assessed by decrease in urine 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.

Monitoring and Laboratory Tests

No special laboratory tests are required for patients receiving ELAPRASE, other than the usual tests that are required for monitoring patients with Hunter syndrome.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse reactions were commonly reported in association with infusions. The most common infusion-related reactions were cutaneous reactions (rash, pruritus, and urticaria), flushing, hypertension, pyrexia, wheezing, dyspnea, headache, abdominal pain, nausea, dyspepsia, chest pain, and infusion site swelling. The frequency of infusion-related reactions decreased over time with continued ELAPRASE treatment. Adverse drug reactions (ADRs) that were reported during the 53-week placebo-controlled study were almost all mild to moderate in severity.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

Table 1 lists those adverse drug reactions observed during the 53-week placebo-controlled study in the patients 5 years and older treated with 0.5 mg/kg weekly ELAPRASE compared to patients receiving placebo. Information is presented by system organ class and frequency. Frequency is given as very common (>1/10) or common (>1/100, <1/10). The occurrence of an event in a single patient is defined as common in view of the small number of patients treated in the trial.

Adverse drug reactions were defined in Table 1 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 drug reactions. Adverse reactions occurring only in placebo-treated patients are excluded. Note: All types of rash and all types of urticaria have been combined.

Table 1: Adverse Drug Reactions in the 53-week Placebo-controlled Clinical Trial (5 Years and Older) (n(%))

System Organ Class	Adverse Drug Reaction (Preferred Term)	ELAPRASE 0.5 mg/kg Weekly (n=32)	Placebo (n=32)
Cardiac disorders			
Common:	Arrhythmia*	1 (3.1)	0
	Cyanosis	1 (3.1)	0
Eye disorders			
Common:	Lacrimation increased	2 (6.3)	0
Gastrointestinal disorders			
Very common:	Dyspepsia	4 (12.5)	0
Common:	Nausea	3 (9.4)	3 (9.4)

Table 1: Adverse Drug Reactions in the 53-week Placebo-controlled Clinical Trial (5 Years and Older) (n(%))			
System Organ Class	**Adverse Drug Reaction (Preferred Term)**	**ELAPRASE 0.5 mg/kg Weekly (n=32)**	**Placebo (n=32)**
	Abdominal pain	2 (6.3)	2 (6.3)
	Diarrhea	2 (6.3)	1 (3.1)
	Swollen tongue	2 (6.3)	0
General disorders and administration site conditions			
Very Common:	Pyrexia	7 (21.9)	8 (25.0)
	Infusion site swelling	4 (12.5)	1 (3.1)
Common:	Edema peripheral	2 (6.3)	0
Musculoskeletal and connective tissue disorders			
Very Common:	Chest pain	7 (21.9)	0
Common:	Arthralgia	1 (3.1)	1 (3.1)
Nervous system disorders			
Very Common:	Headache	9 (28.1)	8 (25.0)
Common:	Dizziness	2 (6.3)	2 (6.3)
	Tremor	2 (6.3)	0
Respiratory, thoracic and mediastinal disorders			
Common:	Cough	3 (9.4)	1 (3.1)
	Tachypnoea	2 (6.3)	1 (3.1)
	Wheezing	2 (6.3)	0
	Bronchospasm	1 (3.1)	0
	Dyspnoea	1 (3.1)	1 (3.1)
	Pulmonary embolism*	1 (3.1)	0
Skin and subcutaneous tissue disorders			
Very Common:	Rash	8 (25.0)	6 (18.8)
	Pruritus	7 (21.9)	3 (9.4)
	Urticaria	5 (15.6)	0
Common:	Erythema	2 (6.3)	0
	Eczema	1 (3.1)	0
	Face edema	1 (3.1)	0
Vascular disorders			
Very Common:	Hypertension	6 (18.8)	6 (18.8)
Common:	Flushing	3 (9.4)	3 (9.4)
	Hypotension	2 (6.3)	3 (9.4)

* see serious adverse reactions below

In clinical studies, serious adverse reactions were reported in a total of 5 patients who received 0.5 mg/kg of ELAPRASE 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 tracheostomy). 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 this 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 steroids, antihistamine, and beta-agonist nebulization. The fifth patient, who had pre-existing cardiopathy, was diagnosed with ventricular premature complexes and pulmonary embolism during the study.

Adverse drug reactions that occurred in the 0.5 mg/kg weekly ELAPRASE group with a frequency of a single event reported are listed here by MedDRA System Organ Class and preferred term:

Blood and Lymphatic System Disorders: Anemia, lymphadenitis, thrombocytopenia

Psychiatric Disorders: Anxiety

Nervous System Disorders: Depressed level of consciousness, hyperaesthesia

Eye Disorders: Conjunctivitis allergic, vision blurred

Ear and Labyrinth Disorders: Vertigo

Cardiac Disorders: Palpitations

Respiratory, Thoracic and Mediastinal Disorders: Nasal congestion, pharyngitis, rhinorrhea

Gastrointestinal Disorders: Abdominal pain upper, gastroenteritis, loose stools

Musculoskeletal and Connective Tissue Disorders: Back pain, bone pain, muscle cramp, myalgia, neck pain

Renal and Urinary Disorders: Enuresis, nocturia

General Disorders and Administration Site Conditions: Feeling cold, inflammation localized, injection site joint swelling, malaise, pain, rigors, sensation of foreign body

Investigations: Blood alkaline phosphatase increased, blood bilirubin increased, blood lactate dehydrogenase increased, blood uric acid increased, hemoglobin decreased, heart rate decreased, heart rate increased

Table 2 enumerates treatment emergent adverse events (TEAEs) (regardless of investigator causality assessment) that occurred in the 53-week placebo-controlled clinical trial in patients 5 years and older, with a difference of more than 2 patients between the 0.5 mg/kg weekly ELAPRASE and placebo treatment groups. Reported frequencies of adverse events have been classified by MedDRA terms.

Table 2: Treatment Emergent Adverse Events with a Difference of More Than 2 Patients Between 0.5 mg/kg Elaprase Weekly and Placebo Treatment Groups (5 years and older) (n(%))

System Organ Class	Adverse Event (Preferred Term)	ELAPRASE 0.5 mg/kg Weekly (n=32)	Placebo (n=32)
Ear and labyrinth disorders	Ear disorder	3 (9.4)	0
	Hypoacusis	1 (3.1)	4 (12.5)
Gastrointestinal disorders	Diarrhea	11 (34.4)	15 (46.9)
	Vomiting	8 (25.0)	16 (50.0)
	Abdominal pain upper	5 (15.6)	2 (6.3)
	Dyspepsia	4 (12.5)	0
General disorders and administration site conditions	Infusion site swelling	4 (12.5)	1 (3.1)
	Asthenia	3 (9.4)	0
	Fall	0	4 (12.5)
	Catheter site pain	0	3 (9.4)
Infections and infestations	Hordeolum	0	3 (9.4)
Injury, poisoning, and procedural complications	Arthropod bite	3 (9.4)	0
	Abrasion	0	3 (9.4)
Investigations	Alanine aminotransferase increased	0	4 (12.5)
	Aspartate aminotransferase increased	0	3 (9.4)
Musculoskeletal and connective tissue disorders	Chest pain	7 (21.9)	0
Nervous system disorders	Headache	19 (59.4)	14 (43.8)
	Dizziness	4 (12.5)	8 (25.0)
Psychiatric disorders	Depression	3 (9.4)	0
Respiratory, thoracic, and mediastinal disorders	Cough	16 (50.0)	19 (59.4)
	Pharyngitis	13 (40.6)	10 (31.3)
	Dyspnea	4 (12.5)	9 (28.1)
	Epistaxis	2 (6.3)	5 (15.6)
Skin and subcutaneous tissue disorders	Rash	14 (43.8)	11 (34.4)
	Pruritus	10 (31.3)	5 (15.6)
	Urticaria	5 (15.6)	0
	Acne	3 (9.4)	0

Table 3 enumerates TEAEs (regardless of investigator causality assessment) that occurred in an open-label trial (patients aged 7 years and younger, administered ELAPRASE 0.5 mg/kg weekly) in more than 2 patients. Reported frequencies of adverse events have been classified by MedDRA terms.

Table 3 Treatment Emergent Adverse Events Occurring in More Than 2 Patients by System Organ Class and Preferred Term (7 years and younger) (Safety Population, N=28)

System Organ Class	Adverse Events (Preferred Term)	Patients n (%)
Cardiac disorders	Left ventricular hypertrophy	4 (14.3)
Ear and labyrinth disorders	Deafness	4 (14.3)
Gastrointestinal disorders	Vomiting	10 (35.7)
	Diarrhea	7 (25.0)
General disorders and administration site conditions	Pyrexia	25 (89.3)
Infections and infestations	Upper respiratory tract infection	18 (64.3)
	Respiratory tract infection	12 (42.9)
	Rhinitis	11 (39.3)
	Viral upper respiratory tract infection	9 (32.1)
	Otitis media acute	7 (25.0)
	Pharyngitis	7 (25.0)
	Gastroenteritis	6 (21.4)
	Upper respiratory tract infection bacterial	6 (21.4)
	Pneumonia	5 (17.9)
	Sinusitis	5 (17.9)
	Bronchitis	4 (14.3)
	Bronchopneumonia	4 (14.3)
	Otitis media	4 (14.3)
	Gastrointestinal infection	3 (10.7)
	Otitis externa	3 (10.7)
	Viral infection	3 (10.7)
	Viral pharyngitis	3 (10.7)
Psychiatric disorders	Agitation	4 (14.3)
	Sleep disorder	3 (10.7)
Respiratory, thoracic and mediastinal disorders	Cough	16 (57.1)
	Nasal congestion	6 (21.4)
	Allergic cough	3 (10.7)
	Asthma	3 (10.7)
	Rhinorrhea	3 (10.7)
	Sleep apnea syndrome	3 (10.7)
Skin and subcutaneous tissue disorders	Rash	7 (25.0)
	Urticaria	4 (14.3)

Immunogenicity
Across 4 clinical studies (TKT008, 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 neutralizing 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 neutralizing response defined as 3 consecutive samples positive for 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, urine GAG (glycosaminoglycans) levels decreased in all antibody status groups, but there was a mild to moderate decrease in the magnitude of the ELAPRASE-induced urine GAG response in patients with antibodies, NAb 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.

Another 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% (16 of 28) tested positive for antibodies on at least three consecutive study visits. Fifty-four percent of these patients tested positive for NAb at least once and half of the patients tested positive for NAb 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 NAb on at least 3 consecutive occasions. All patients with the frameshift/splice site mutation genotype developed antibodies and 4/6 also tested positive for NAb on at least 3 consecutive study visits. Antibody negative patients were found exclusively in the missense mutation genotype group.

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post-approval use of ELAPRASE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In post-marketing experience, late-emergent symptoms and signs of anaphylactoid/anaphylactic reactions have occurred up to 24 hours after treatment and recovery from an initial reaction. In addition, some patients experienced repeated anaphylaxis over a two- to four-month period, up to several years after initiating ELAPRASE treatment (see **Warnings and Precautions**).

A seven year-old male patient with Hunter syndrome, who received ELAPRASE at twice the recommended dosage (1 mg/kg weekly) for 1.5 years, experienced two anaphylactic events after 4.5 years of treatment. Treatment was withdrawn.

Serious adverse reactions that resulted in death included cardiac failure, cardiorespiratory arrest, pneumonia, respiratory distress, and respiratory failure.

DRUG INTERACTIONS

Overview

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

Drug-Drug Interactions

No formal drug interaction studies have been conducted with ELAPRASE.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- ELAPRASE is intended for use under the supervision of a physician or other experienced health care provider.

- The infusion rate may be slowed and/or temporarily stopped, based on clinical judgement, when infusion-related reactions occur (see **Administration**)

Recommended Dose and Dosage Adjustment

ELAPRASE is administered at a dose of 0.5 mg/kg body weight every week by intravenous infusion.

Administration

The total volume of infusion may be administered over a period of 3 hours, 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 minute 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, based on clinical judgment, when infusion-related reactions occur.

See **Special Handling Instructions** for method of dilution.

OVERDOSAGE

One patient with Hunter syndrome, who received ELAPRASE at twice the recommended dosage for one and a half years, experienced two anaphylactic reactions over a 3-month period 4.5 years after initiating ELAPRASE treatment.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL 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. This enzyme hydrolyzes the 2-sulfate esters of terminal iduronate sufate residues from the glycosaminoglycans (GAG) dermatan sulfate and heparan sulfate in the lysosomes of various cell types. Due to the missing or defective iduronate-2-sulfatase 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 progressive organ system dysfunction.

ELAPRASE is a formulation of idursulfase, a purified form of human iduronate-2-sulfatase, a lysosomal enzyme. Idursulfase is produced by recombinant DNA technology in a human cell line.

Pharmacodynamics

In the pivotal TKT024 study, urine GAG levels decreased in patients treated with ELAPRASE weekly compared to placebo patients ($p<0.0001$). Among all 32 weekly ELAPRASE treated patients, 16 (50%) had normalized urine GAG levels below the upper limit of normal (defined as 126.6 µg GAG/mg creatinine) at Week 53. None of the placebo patients had normalized urine GAG levels that fell below the upper limit of normal by Week 53.

Treatment of Hunter syndrome patients with ELAPRASE provides exogenous enzyme for uptake into cellular lysosomes. Mannose-6-phosphate (M6P) residues on the external oligosaccharide chains of the ELAPRASE molecule 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. The pharmacodynamic effect of ELAPRASE treatment as measured by urine GAG, was less pronounced in subjects who developed an immune response to ELAPRASE.

In the extension Study (TKT024EXT) in which all patients received weekly idursulfase, reductions in mean urine GAG levels were maintained in the TKT024 Weekly group, and the TKT024EOW (every other week) dose group experienced further mean reductions in urine GAG levels following transition to the weekly dose. At the completion of TKT024EXT, mean urine 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.

Pharmacodynamic effects of ELAPRASE treatment were assessed in children ≤5 years old in Study HGT-ELA-038. In this study the age range of enrolled patients at baseline was 16 months to 7.5 years and they were analyzed in three age groups (one year old, two to four year old and five year old or more). In Study HGT-ELA-038 ELAPRASE treatment resulted in a mean decrease from baseline of approximately 40 to 60% in urine GAG levels at Week 53 depending on the age group. The magnitude of decreases was comparable to the previous registration Study TKT024, which reported an approximately 60% decrease for the same weekly ELAPRASE dose at Week 53. Decreases in urine GAG levels were evident in all age groups and appeared as early as the Week 18 time point and continued through Week 53. The pharmacodynamic effect of ELAPRASE treatment as measured by urine GAG, was less pronounced in subjects who developed an immune response to ELAPRASE.

Pharmacokinetics

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. Since metabolic degradation of this product is expected to occur in cells via normal proteolytic mechanisms, no metabolism studies were conducted in humans.

The pharmacokinetic (PK) characteristics of idursulfase were evaluated in several studies in patients with Hunter syndrome (see Table 4). 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.

Table 4: Comparison of Initial and Repeat-Dose PK Parameters for All Evaluable Patient Samples – Based on Idursulfase Concentration Data (Mean (SD))

Week	PK Parameter				
	C_{max} (µg/mL)	AUC (min* µg/mL)	$T_{1/2}$ (min)	Cl (mL/min/kg)	V_{ss} (% BW)
TKT024 Week 1 (n=28)	1.64 (0.55)	234 (82)	50 (36)	2.55 (0.97)	19.2% (7.5%)
TKT024 Week 27 (n=30)	1.17 (0.41)	165 (48)	39 (17)	3.45 (1.03)	23.3% (10.8%)
TKT024EXT Week 1 (n= 44)	1.20 (0.65)	192 (70)	60 (16)	2.95 (0.93)	24.3% (12.3%)

In Study TKT024EXT, in which patients received idursulfase 0.5 mg/kg weekly as a 3-hour infusion, there were no changes in pharmacokinetic parameters with repeat dosing (Week 18, n=68) and pharmacokinetic 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=19). 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.

Key PK 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.

STORAGE AND STABILITY

Store at 2°C to 8°C (in a refrigerator), and protect from light.

Do not freeze or shake.

Do not use ELAPRASE after the expiration date on the vial.

This product contains no preservatives. The product should be diluted in an infusion bag using strict aseptic technique. The diluted solution should be used immediately. If immediate use is not possible, the diluted solution can be stored refrigerated at 2°C to 8°C for up to 24 hours, or must be administered within 8 hours if held at room temperature.

SPECIAL HANDLING INSTRUCTIONS

ELAPRASE should be prepared and administered by a healthcare professional.

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 per kg of ELAPRASE ÷ 2 mg per mL =
   Total # mL of ELAPRASE

   Total # mL of ELAPRASE ÷ 3 mL per vial = Total # of vials

   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, colorless solution. Do not use if the solution in the vials is discolored or particulate matter is present. ELAPRASE should not be shaken.

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

4. Using strict aseptic technique, dilute the total calculated volume of ELAPRASE in 100 mL of 0.9% Sodium Chloride Injection, USP. Once diluted into normal saline, the solution in the infusion bag should be mixed gently, but not shaken. Diluted solution stored at room temperature should be discarded if not administered within 8 hours of preparation. Diluted solution may be stored refrigerated for up to 24 hours.

5. Use of an infusion set equipped with a 0.2 micrometer (μm) filter is recommended. ELAPRASE should not be infused with other products in the infusion tubing.

6. 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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ELAPRASE is a sterile, aqueous, clear to slightly opalescent, colorless solution supplied in a 5 mL Type I glass vial. The vials are closed with a butyl rubber stopper with fluororesin coating and an aluminum overseal with a blue flip-off plastic cap. Each vial of ELAPRASE contains a 2.0 mg/mL solution of idursulfase protein (6.0 mg) in an extractable volume of 3.0 mL, and is for single use only.

The concentrate must be further diluted; see **Special Handling Instructions**.

ELAPRASE is available in a pack size of 1 vial per carton.

The following is a list of excipients used in the ELAPRASE formulation:

Polysorbate 20;
Sodium chloride;
Sodium phosphate dibasic, heptahydrate;
Sodium phosphate monobasic, monohydrate;
Water for Injection.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: idursulfase

Chemical name: iduronate-2-sulfatase

Molecular formula and molecular mass:

Idursulfase is a glycoprotein with a molecular weight of approximately 76 kilodaltons, consisting of 525 amino acids.

Structural formula:

This molecule consists of 525 amino acids. Idursulfase is human iduronate-2-sulfatase manufactured by recombinant DNA technology in a continuous human cell line. The amino acid sequence of idursulfase, determined by sequencing of cDNA in the Master Cell Bank and Working Cell Bank and confirmed by peptide mass mapping and N-terminal sequencing, is illustrated below. The 8 sites of N-linked glycosylation are noted.

Amino Acid Sequence of Idursulfase

1 Ser Glu Thr Gln Ala Asn Ser Thr Thr Asp Ala Leu Asn Val Leu Leu Ile Ile Val Asp

21 Asp Leu Arg Pro Ser Leu Gly Cys Tyr Gly Asp Lys Leu Val Arg Ser Pro Asn Ile Asp

41 Gln Leu Ala Ser His Ser Leu Leu Phe Gln Asn Ala Phe Ala Gln Gln Ala Val Cys Ala

61 Pro Ser Arg Val Ser Phe Leu Thr Gly Arg Arg Pro Asp Thr Thr Arg Leu Tyr Asp Phe

81 Asn Ser Tyr Trp Arg Val His Ala Gly Asn Phe Ser Thr Ile Pro Gln Tyr Phe Lys Glu

101 Asn Gly Tyr Val Thr Met Ser Val Gly Lys Val Phe His Pro Gly Ile Ser Ser Asn His

121 Thr Asp Asp Ser Pro Tyr Ser Trp Ser Phe Pro Pro Tyr His Pro Ser Ser Glu Lys Tyr

141 Glu Asn Thr Lys Thr Cys Arg Gly Pro Asp Gly Glu Leu His Ala Asn Leu Leu Cys Pro

161 Val Asp Val Leu Asp Val Pro Glu Gly Thr Leu Pro Asp Lys Gln Ser Thr Glu Gln Ala

181 Ile Gln Leu Leu Glu Lys Met Lys Thr Ser Ala Ser Pro Phe Phe Leu Ala Val Gly Tyr

201 His Lys Pro His Ile Pro Phe Arg Tyr Pro Lys Glu Phe Gln Lys Leu Tyr Pro Leu Glu

221 Asn Ile Thr Leu Ala Pro Asp Pro Glu Val Pro Asp Gly Leu Pro Pro Val Ala Tyr Asn

241 Pro Trp Met Asp Ile Arg Gln Arg Glu Asp Val Gln Ala Leu Asn Ile Ser Val Pro Tyr

261 Gly Pro Ile Pro Val Asp Phe Gln Arg Lys Ile Arg Gln Ser Tyr Phe Ala Ser Val Ser

281 Tyr Leu Asp Thr Gln Val Gly Arg Leu Leu Ser Ala Leu Asp Asp Leu Gln Leu Ala Asn

301 Ser Thr Ile Ile Ala Phe Thr Ser Asp His Gly Trp Ala Leu Gly Glu His Gly Glu Trp

321 Ala Lys Tyr Ser Asn Phe Asp Val Ala Thr His Val Pro Leu Ile Phe Tyr Val Pro Gly

341 Arg Thr Ala Ser Leu Pro Glu Ala Gly Glu Lys Leu Phe Pro Tyr Leu Asp Pro Phe Asp

361 Ser Ala Ser Gln Leu Met Glu Pro Gly Arg Gln Ser Met Asp Leu Val Glu Leu Val Ser

381 Leu Phe Pro Thr Leu Ala Gly Leu Ala Gly Leu Gln Val Pro Pro Arg Cys Pro Val Pro

401 Ser Phe His Val Glu Leu Cys Arg Glu Gly Lys Asn Leu Leu Lys His Phe Arg Phe Arg

421 Asp Leu Glu Glu Asp Pro Tyr Leu Pro Gly Asn Pro Arg Glu Leu Ile Ala Tyr Ser Gln

441 Tyr Pro Arg Pro Ser Asp Ile Pro Gln Trp Asn Ser Asp Lys Pro Ser Leu Lys Asp Ile

461 Lys Ile Met Gly Tyr Ser Ile Arg Thr Ile Asp Tyr Arg Tyr Thr Val Trp Val Gly Phe

481 Asn Pro Asp Glu Phe Leu Ala Asn Phe Ser Asp Ile His Ala Gly Glu Leu Tyr Phe Val

501 Asp Ser Asp Pro Leu Gln Asp His Asn Met Tyr Asn Asp Ser Gln Gly Gly Asp Leu Phe

521 Gln Leu Leu Met Pro

Asn - marks sites of N-linked glycosylation

Physicochemical properties:

ELAPRASE (idursulfase) is a clear to slightly opalescent, colorless solution. As supplied, ELAPRASE has a pH of approximately 6.

CLINICAL TRIALS

Study Demographics and Trial Design

Table 5: Summary of Patient Demographics for Clinical Trials in Specific Indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
TKT024	Pivotal, Phase II/III, randomized, double-blind, placebo-controlled	0.5 mg/kg idursulfase weekly or every other week or placebo, intravenous infusion, 52 weeks of infusions	n=96	14 years (5 – 31 years)	Male
TKT024EXT	Phase II/III multi-center, single-arm, open-label extension study of TKT024	0.5 mg/kg idursulfase weekly, intravenous infusion, 156 weeks of infusion	n=94	15 years* (6-30 years)	Male
HGT-ELA-038	Open-label, multicenter, single-arm study	0.5 mg/kg idursulfase weekly, intravenous infusion, 52 weeks of infusion	n=28	4 years (1.4-7.5 years)	Male

*Age at first infusion of 0.5 mg/kg weekly idursulfase

TKT024 Study

The safety and efficacy of ELAPRASE were evaluated in a randomized, double-blind, placebo controlled clinical study of 96 patients with Hunter syndrome. The study included patients with a documented deficiency in iduronate-2-sulfatase enzyme activity who had a percent predicted forced vital capacity (%-predicted FVC) less than 80%. Patients who were unable to perform the appropriate pulmonary function testing or those who could not follow protocol instructions were excluded from the study. Patients received ELAPRASE 0.5 mg/kg every week (n=32), ELAPRASE 0.5 mg/kg every other week (n=32), or placebo (n=32). The study duration was 53 weeks.

The primary efficacy outcome assessment in the 53-week placebo-controlled study was a two-component composite score based on the sum of the ranks of the change from baseline to Week 53 in distance walked during a six-minute walk test (6-MWT) and the ranks of the change in %-predicted FVC. This two-component composite primary endpoint differed statistically significantly between the three groups, and the difference was greatest between the placebo group and the weekly treatment group (weekly ELAPRASE vs. placebo, p=0.0049).

Additional clinical benefit analyses were performed on individual components of the primary endpoint composite score (6-MWT and %-predicted FVC, see Table 6), and on FVC absolute

volume, urine GAG levels, liver and spleen volumes (see Table 7), and measurement of forced expiratory volume in 1 second (FEV1), and left ventricular mass (LVM).

The analyses of the components of the composite score demonstrated that, for the 6-MWT, the weekly ELAPRASE group mean adjusted difference in meters walk from baseline to Week 53 was 35 meters compared to placebo (p=0.0131).

The change in %-predicted FVC in the weekly group was 4.3% greater compared to placebo, however this was not statistically significant.

Table 6: Primary Treatment Comparisons: ANCOVA Analysis of Change from Baseline to Week 53 in Distance Walked in 6-Minute Walk Test and in Percent Predicted Forced Vital Capacity (Mean (SE))

Treatment Comparison	n	Baseline	Week 53 Change		Adjusted 95% CI	p-value
			Observed	Adjusted[a]		
Total Distance Walked in 6MWT (m)						
ELAPRASE Weekly	32	391.63 (19.10)	44.28 (12.31)	36.95 (10.89)		
Placebo	32	392.47 (18.72)	7.28 (9.46)	1.86 (11.84)		
Difference				35.09 (13.69)	7.66, 62.52	0.0131
Forced Vital Capacity (% of Predicted)						
ELAPRASE Weekly	32	55.30 (2.80)	3.45 (1.77)	1.29 (1.73)		
Placebo	32	55.57 (2.18)	0.75 (1.70)	-2.99 (1.85)		
Difference				4.28 (2.27)	-0.27, 8.83	0.0650

Table 7: Secondary Treatment Comparisons: ANCOVA Analysis of Change from Baseline to Week 53 in Forced Vital Capacity Absolute Volume, Normalized Urine GAG, and Liver and Spleen Volumes (Mean (SE))

Treatment Comparison	n	Baseline	Week 53 Change		Adjusted 95% CI[a]	p-value
			Observed	Adjusted		
Forced Vital Capacity Absolute Volume (L)						
ELAPRASE Weekly	32	1.19 (0.10)	0.22 (0.05)	0.18 (0.04)		
Placebo	32	1.09 (0.09)	0.06 (0.03)	-0.01 (0.04)		
Difference				0.19 (0.06)	0.08, 0.30	0.0011
Normalized Urine GAG (µg/mg creatinine)						
ELAPRASE Weekly	32	325.59 (25.79)	-189.23 (25.76)	-224.90 (22.10)		
Placebo	32	419.40 (34.37)	18.16 (29.94)	50.63 (21.29)		
Difference				-275.54 (30.10)	-335.82, -215.25	<0.0001
Liver Volume (cc)[a]						
ELAPRASE Weekly	31	1262.30 (49.83)	-25.34% (1.57)	-25.61% (1.66)		
Placebo	30	1197.78 (47.81)	-0.85% (1.60)	-0.44 % (1.62)		
Difference				25.16% (2.19)	-29.56%, -20.77%	<0.0001
Spleen Volume (cc) [a]						
ELAPRASE Weekly	31	316.18 (39.46)	-25.05% (2.36)	-25.12% (3.48)		
Placebo	30	287.49 (29.96)	7.21% (4.15)	8.10% (3.62)		
Difference				-33.22% (4.79)	-42.82%, -23.61%	<0.0001

[a] ANCOVA analysis was based upon percentage change from baseline

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 ELAPRASE weekly.

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.

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

A total of 11 of 31 (36%) patients in the ELAPRASE weekly group versus 5 of 31 (16%) patients in the placebo group had an increase in FEV1 of at least 200 cc at or before the end of the study, indicating an improvement in airway obstruction. The patients in the weekly

ELAPRASE treated group experienced a clinically significant 15% mean improvement in FEV1 at the end of the study.

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

TKT024 Extension Study
Patients who participated in the controlled study were eligible to continue treatment in an open label extension study. 94 patients enrolled and received ELAPRASE 0.5 mg/kg weekly.

Statistically significant improvements from baseline in mean and percent increases in distance walked in the 6-MWT ranged from 13.7 (SE 4.76) to 41.5 (SE 9.55) meters and from 6.4% (SE 2.71) to 11.7% (SE 2.96), respectively (maximum at Month 20). Patients who were treated with weekly ELAPRASE in the controlled study generally improved their walking distance to a greater extent than patients in the other treatment groups.

Statistically significant increases from baseline in absolute FVC volume ranged from 0.07 L (SE 0.018) to 0.31 L (SE 0.059) and percent changes ranged from 6.32% (SE 1.317) to 25.47% (SE 4.129) (maximum at Month 30). The mean and percent changes from treatment baseline were greatest in patients who initiated therapy with weekly ELAPRASE. Percentage predicted FVC remained stable in all Hunter syndrome patients treated for 2 to 3 years with idursulfase 0.5 mg/kg weekly.

Reductions in mean urine GAG levels were maintained in patients initially treated with weekly ELAPRASE, and those initially treated every other week experienced further mean reductions. At the completion of the extension study, mean urine GAG levels fell below the upper limit of normal in patients who initiated treatment with ELAPRASE and were near normal in those who were initially in the placebo group and later switched to enzyme therapy. Change in the urine GAG levels was the earliest sign of clinical improvement with ELAPRASE treatment and the greatest decreases in urine GAG were seen in the first 4 months of treatment. 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 iduronate-2-sulfatase activity category. The higher the urine GAG levels at baseline, the greater the magnitude of decreases in urine GAG with treatment.

The decrease in liver and spleen volumes at Week 53 was maintained during the extension study in all patients regardless of prior TKT024 treatment assignment. Seventy one out of 94 patients had hepatomegaly at baseline. Liver volume normalized 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.

HGT-ELA-038 Study
An open-label, multicenter, single-arm study was conducted to assess the safety of ELAPRASE infusions for male patients with Hunter syndrome who were 1.4 to 7.5 years-old. In addition, the study evaluated efficacy, clinical outcomes, and ELAPRASE pharmacokinetics in this patient population.

All patient groups experienced a decrease in urine uGAG 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 neutralizing 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.

Comparative Bioavailability Studies
No comparative bioavailability studies have been performed with ELAPRASE.

DETAILED PHARMACOLOGY

An animal model of Hunter syndrome, the iduronate-2-sulfatase knockout (IKO) mouse, exhibits many of the physical characteristics of Hunter syndrome seen in humans, including coarse features, skeletal defects (including thickened digits), hepatomegaly, and a reduced lifespan. Elevated glycosaminoglycan (GAG) levels are observed in urine and tissues throughout the body and widespread cellular vacuolization is observed histopathologically. The IKO model was used to evaluate the dose levels and dose regimen of idursulfase required to degrade stored GAG in this animal model.

A series of pharmacodynamic studies was conducted in which idursulfase was administered IV at weekly intervals to IKO mice. The doses of idursulfase ranged from 0.1 to 5.0 mg/kg. These studies established that idursulfase caused a reduction in urinary and tissue (liver, spleen, kidney and heart) GAG, indicating that idursulfase was active, reached target organs and was likely taken up into the lysosomes where catabolism of excess GAG occurs. From these studies it was determined that doses as low as 0.1 mg/kg resulted in a measurable pharmacodynamic effect.

Another set of pharmacodynamic studies was performed to establish dose frequency. IKO mice were administered weekly, every other week, or monthly IV injections of idursulfase. Clear reductions in urinary and tissue GAG were observed after dosing regimens ranging from 8 weeks

to approximately 6 months. Long-term administration (12 and 24 weeks) of 1 mg/kg idursulfase administered weekly and every other week were both effective in reducing tissue GAG concentrations in various tissues, and were more effective than monthly dosing.

Idursulfase was detected in all organs and tissues examined in a ^{125}I-radiolabeled rat biodistribution study. Tissue half-lives were similar for the major organs and were approximately 1 to 2 days for liver, kidney, heart, spleen, and bone (including marrow). The accumulation and retention of idursulfase in these organs and tissues is consistent with the distribution of M6P receptors in tissues and organs in mammals.

TOXICOLOGY

Nonclinical data reveal no special hazard for humans based on conventional animal studies of safety pharmacology, single dose toxicity, repeated dose toxicity, male fertility and female reproduction. Genotoxic and carcinogenic potential are not expected.

Acute Toxicity Studies

The acute toxicity of idursulfase was evaluated in rats and cynomolgus monkeys. Doses of up to 20 mg/kg body weight for both species, representing 40 times the recommended dose in humans, have been tested without any adverse toxicity.

Repeat-dose Toxicity Studies

A 6-month, repeat-dose toxicity study was conducted in cynomolgus monkeys at doses up to 0.5, 2.5, and 12.5 mg/kg body weight/week. A no adverse effect level of at least 12.5 mg/kg body weight idursulfase was established since there were no adverse, treatment-related findings observed at any dose level tested (a dose of 25 times the recommended dose in humans).

Reproduction and Teratology

A male fertility study was performed in rats at doses up to 5 mg/kg body weight, twice weekly or 10 times the human dose. There was no evidence of impaired male fertility at any dose level tested. Hence, the NOAEL was determined to be at least 5 mg/kg body weight/dose.

Results from a single-dose distribution study in female rats showed that idursulfase is excreted in breast milk and is present in the fetal circulation in utero.

Results in animals do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development at doses up to 12.5 mg/kg.

Mutagenicity and Carcinogenicity Studies

No animal studies have been conducted to assess the mutagenic, genotoxic, and carcinogenic potential for idursulfase. This is consistent with the ICH guideline S1A, "Guidelines on the Need for Carcinogenicity Studies of Pharmaceuticals." As a purified form of the naturally occurring enzyme iduronate-2-sulfatase, such potential is not expected for idursulfase.

PART III: CONSUMER INFORMATION

PrELAPRASE®*
idursulfase

This leaflet is part III of a three-part "Product Monograph" published when ELAPRASE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ELAPRASE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
ELAPRASE is a long-term enzyme replacement therapy in patients with Hunter syndrome. Treatment with ELAPRASE should be supervised by a physician or other experienced health care provider.

What it does:
Patients with Hunter syndrome do not produce enough of their own enzyme, iduronate-2-sulfatase. The reduced iduronate-2-sulfatase levels in patients result in the accumulation of substances called glycosaminoglycans (GAG) in a number of cell types and tissues. ELAPRASE is an enzyme replacement therapy that is intended to restore sufficient levels of enzyme to assist in the removal of these accumulated substances and to reduce further accumulation.

What the medicinal ingredient is:
The active substance in ELAPRASE is idursulfase (2 mg/mL). Idursulfase is a form of the human enzyme iduronate-2-sulfatase. It is produced by recombinant DNA technology.

What the nonmedicinal ingredients are:
polysorbate 20, sodium chloride, sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate and water for injection.

What dosage forms it comes in:
2 mg/mL concentrate for solution for infusion in a clear, glass vial (bottle).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Risk of hypersensitivity reactions: 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.**
- **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 signs and symptoms of anaphylactoid/anaphylactic reactions have been observed after ELAPRASE administration as long as 24 hours after an initial reaction. If an anaphylactoid/anaphylactic reaction occurs, the infusion of ELAPRASE should be immediately suspended and appropriate treatment and observation initiated. The current medical standards for emergency treatment are to be followed. Patients experiencing severe and refractory anaphylactoid 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.**

If you are treated with ELAPRASE you may experience reactions during or following an infusion. Most infusion reactions are mild or moderate but some may be serious. The most common symptoms are rash, itching, flushing, hypertension, wheezing, cough, headache, abdominal pain, nausea, chest pain, and swelling. Most of the time, you can still be given ELAPRASE even if these symptoms occur. If you experience an allergic side effect following administration of ELAPRASE, 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-type (hypersensitivity) reactions occur, your doctor may consider stopping the infusion immediately, and should start giving you suitable treatment.

If you have a fever and an acute illness affecting your lungs, your doctor may delay your infusion.

The nature of your genetic mutation may influence your therapeutic response to ELAPRASE, as well as your risk of developing antibodies and infusion-related adverse events; please consult your doctor.

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.

INTERACTIONS WITH THIS MEDICATION

There is no known interaction of ELAPRASE with other medicines.

PROPER USE OF THIS MEDICATION

Usual dose:
ELAPRASE has to be diluted in 9 mg/mL (0.9%) sodium chloride solution before use. The usual dose is an infusion of 0.5 mg (half a milligram) for every kg you weigh. This would be about 18 mg or 3 vials (bottles) of ELAPRASE for a 36 kg individual.

After dilution ELAPRASE is given through a vein (drip feed).

The infusion will normally last for 3 hours, which may be gradually reduced to 1 hour if no infusion-related reactions are observed and will be given every week.

Overdose:
One patient with Hunter syndrome, who received ELAPRASE at twice the recommended dosage for one and a half years, experienced two anaphylactic reactions over a 3-month period 4.5 years after initiating ELAPRASE treatment.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, ELAPRASE can cause side effects, although not everybody gets them. Most side effects are mild to moderate and generally are associated with the infusion; however some side effects may be serious and may need treatment. Over time the number of these infusion-associated reactions generally decreases.

Very common side effects (more than 1 per 10) are:
- Headache
- Increased blood pressure
- Heartburn
- Chest pain
- Hives, rash, itching
- Fever, and infusion site swelling

Common side effects (more than 1 per 100) are:
- Dizziness, tremor
- Teary eyes
- Changes in the way your heart beats, bluish skin
- Decreased blood pressure, flushing (redness)
- Difficulty breathing, wheezing, blood clot in the lung artery, cough, quickened breathing
- Abdominal pain, nausea, diarrhea, swollen tongue
- Facial swelling, skin lesions (redness, eczema)
- Pain in the joints
- Swelling of the extremities

Allergic reactions have included temporary breathing difficulty, decreased blood pressure, or swelling. In a more severe reaction, in a single patient, a seizure occurred because of a drop in blood oxygen level from difficulty in breathing. Inform your doctor immediately if you have any of these side effects. Patients with compromised respiratory function or acute respiratory disease are at greater risk for infusion-related reactions.

If you notice any side effects not mentioned in this leaflet, please inform your doctor.

A registry (the Hunter Outcome Survey) has been established in order to better understand the variability and progression of the disease and monitoring and evaluation of treatments. All patients are encouraged to participate and advised that their participation may involve long-term follow-up. Information on this registry program is available by calling 1-800-268-2772.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common/ Very common (occurring in ≥5% in controlled clinical studies)	Fever	√		
	Difficulty breathing		√	
	Bluish skin discoloration		√	
	Rash or Hives	√		
Uncommon (occurring in <5% in controlled clinical studies)	Seizure, blood clot in the lungs		√	
	Missed or extra heartbeats	√		

This is not a complete list of side effects. For any unexpected effects while taking ELAPRASE, contact your doctor or pharmacist.

HOW TO STORE IT

Store at 2°C to 8°C (in a refrigerator), and protect from light.

Do not freeze or shake.

Reporting Side effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:
- Online at www.healthcanada.gc.ca/medeffect
- By calling 1-866-234-2345 (toll-free);
- By completing a Patient Side Effect Reporting Form and sending it by :
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to : Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

Postage paid labels and the Patient Side Effects Reporting Form are available at www.healthcanada.gc.ca/medeffect

Note : Contact your health professional if you need information about how to manage your side effects The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about ELAPRASE:
- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website http://hc-sc.gc.ca/index-eng.php, the manufacturer's website www.shirecanada.com, or by calling 1-800-268-2772.

This leaflet was prepared by Shire Human Genetic Therapies, Inc.
300 Shire Way
Lexington, MA 02421

Last revised: 03 September 2019

* ELAPRASE is a registered trade-mark used under licence from Shire Human Genetic Therapies, Inc.