

PRODUCT MONOGRAPH

^{Pr} **ELAPRASE™**

idursulfase

2 mg/mL concentrate for solution for infusion

Enzyme Replacement Therapy

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Date of Approval:
27 May 2008

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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:

- enzyme replacement therapy in patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II). ELAPRASE has been shown to improve walking capacity in these patients.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

RISK OF HYPERSENSITIVITY REACTIONS.

Anaphylactoid reactions, which have the potential to be life threatening, have been observed in some patients treated with ELAPRASE.

Patients with compromised respiratory function or acute respiratory disease may be at risk of serious exacerbation of their respiratory dysfunction due to infusion related reactions. These patients require additional monitoring. Late-emergent anaphylactoid reactions have been observed after ELAPRASE administration. Patients who have experienced 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.

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 1-888-550-6060.

Carcinogenesis and Mutagenesis

See Part II: Scientific Information, Toxicology, for animal data.

Hepatic

No studies have been performed in patients with hepatic impairment.

Immune

In clinical trials with ELAPRASE, 11 of 108 patients (10%) experienced anaphylactoid reactions during 19 of 8274 infusions (0.2%). 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.

The most common infusion-related reactions included cutaneous reactions (rash, pruritus, and urticaria), pyrexia, headache, hypertension, and flushing. Infusion-related reactions were treated or ameliorated by slowing the infusion rate, interrupting the infusion, or by administration of medicines, such as antihistamines, antipyretics, low-dose corticosteroids (prednisone 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.

Special care should be taken when administering an infusion in patients with severe underlying airway disease. These patients should be closely monitored and infused with ELAPRASE 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 medication use.

Consider delaying ELAPRASE infusion in patients who present with an acute febrile respiratory illness.

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

Across clinical studies, 53/106 patients (50%) developed anti-idursulfase IgG antibodies at some point. Six (6) of the IgG positive patients also tested positive for IgM antibodies, and 2 patients tested positive for IgA antibodies. No patient developed IgE antibodies during any study. Fourteen (14) of the IgG positive patients had antibodies that demonstrated neutralizing activity in an in vitro assay. In the 53-week placebo-controlled study, rates of seropositivity peaked by Weeks 18 to 27 and steadily declined thereafter for the remainder of the study.

In general, patients who tested positive for IgG antibodies were more likely to have infusion-related adverse events than those who did not test positive. However, overall rates of infusion-related adverse events declined over time, regardless of antibody status.

Renal

No studies have been conducted in patients with renal impairment.

Special Populations

Pregnant Women: There is no experience with ELAPRASE treatment in pregnant women. Reproduction studies in pregnant female animals have not been conducted with ELAPRASE. It is not known whether idursulfase crosses the placenta.

Nursing Women: It is not known whether ELAPRASE is excreted in human milk.

Pediatrics and Geriatrics:

Children, adolescents, and adults responded similarly to treatment with ELAPRASE. Studies in patients under the age of 5 and over the age of 65 have not been performed.

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 headache, fever, cutaneous reactions (rash, pruritus, erythema, and urticaria), and hypertension. 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 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 (n(%))

System Organ Class	Adverse Drug Reaction (Preferred Term)	ELAPRASE 0.5 mg/kg Weekly (n=32)	Placebo (n=32)
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
Eye disorders			
Common:	Lacrimation increased	2 (6.3)	0
Cardiac disorders			
Common:	Arrhythmia*	1 (3.1)	0
	Cyanosis	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)
Respiratory, thoracic and mediastinal disorders			
Common:	Cough	3 (9.4)	1 (3.1)
	Wheezing	2 (6.3)	0
	Tachypnoea	2 (6.3)	1 (3.1)
	Dyspnoea	1 (3.1)	1 (3.1)
	Bronchospasm	1 (3.1)	0
	Pulmonary embolism*	1 (3.1)	0
Gastrointestinal disorders			
Very common:	Dyspepsia	4 (12.5)	0
Common:	Nausea	3 (9.4)	3 (9.4)
	Abdominal pain	2 (6.3)	2 (6.3)
	Diarrhoea	2 (6.3)	1 (3.1)
	Swollen tongue	2 (6.3)	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 oedema	1 (3.1)	0
Musculoskeletal and connective tissue disorders			
Very Common:	Chest pain	7 (21.9)	0
Common:	Arthralgia	1 (3.1)	1 (3.1)

System Organ Class	Adverse Drug Reaction (Preferred Term)	ELAPRASE 0.5 mg/kg Weekly (n=32)	Placebo (n=32)
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: Oedema peripheral	2 (6.3)	0

* 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 less than those included in Table 1 (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, rhinorrhoea; 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, haemoglobin decreased, heart rate decreased, heart rate increased.

Table 2 enumerates treatment emergent adverse events (regardless of investigator causality assessment) that occurred in the 53-week placebo-controlled clinical trial 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 (n(%))

System Organ Class	Adverse Event (Preferred Term)	ELAPRASE 0.5 mg/kg Weekly (n=32)	Placebo (n=32)
Infections and infestations	Hordeolum	0	3 (9.4)
Psychiatric disorders	Depression	3 (9.4)	0
Nervous system disorders	Headache	19 (59.4)	14 (43.8)
	Dizziness	4 (12.5)	8 (25.0)
Ear and labyrinth disorders	Ear disorder	3 (9.4)	0
	Hypoacusis	1 (3.1)	4 (12.5)
Respiratory, thoracic, and mediastinal disorders	Cough	16 (50.0)	19 (59.4)
	Pharyngitis	13 (40.6)	10 (31.3)
	Dyspnoea	4 (12.5)	9 (28.1)
	Epistaxis	2 (6.3)	5 (15.6)
Gastrointestinal disorders	Diarrhoea	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
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
Musculoskeletal and connective tissue disorders	Chest pain	7 (21.9)	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)
Investigations	Alanine aminotransferase increased	0	4 (12.5)
	Aspartate aminotransferase increased	0	3 (9.4)
Injury, poisoning, and procedural complications	Arthropod bite	3 (9.4)	0
	Abrasion	0	3 (9.4)

Across studies, 53/106 patients (50%) developed anti-idursulfase IgG antibodies at some point. Six (6) of the IgG positive patients also tested positive for IgM antibodies, and 2 patients tested positive for IgA antibodies. No patient developed IgE antibodies during any study. Fourteen (14) of the IgG positive patients had antibodies that demonstrated neutralizing activity in an in vitro assay. In the 53-week study, rates of seropositivity peaked by Weeks 18 to 27 and steadily declined thereafter for the remainder of this study.

Patients who tested positive for IgG antibodies at any time during the clinical trials had an increased incidence rate of infusion-related reactions, including hypersensitivity reactions. However, overall rates of infusion-related adverse events declined over time, regardless of antibody status. The reduction of urinary GAG excretion was somewhat less in patients for whom circulating anti-idursulfase antibodies were detected.

Post-market Adverse Drug Reactions

In post-marketing experience, 2 patients 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, epinephrine, anti-histamines, corticosteroids and hospitalization in 1 patient, and with corticosteroids in the second patient. With appropriate pre-treatment and monitoring, both 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.

DRUG INTERACTIONS

No serious drug interactions have been reported.

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 (idursulfase) 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 judgment, when infusion-related reactions occur (see the Administration section of the product monograph).

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 1 to 3 hours. 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

There is no experience with overdosage of ELAPRASE in humans. Single intravenous doses of idursulfase up to 20 mg/kg were not lethal in male rats or cynomolgus monkeys (approximately 40 times the recommended human dose based on body weight) and there were no signs of toxicity.

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 cleaves the terminal 2-*O*-sulfate moieties from the glycosaminoglycans (GAG) dermatan sulfate and heparan sulfate. 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 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. Idursulfase is an enzyme that hydrolyzes the 2-sulfate esters of terminal iduronate sulfate residues from the glycosaminoglycans dermatan sulfate and heparan sulfate in the lysosomes of various cell types.

Pharmacodynamics

Idursulfase is a 525-amino acid glycoprotein with a molecular weight of approximately 76 kilodaltons. The enzyme contains eight asparagine-linked glycosylation sites occupied by complex oligosaccharide structures. 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. Idursulfase is an enzyme that hydrolyzes the 2-sulfate esters of terminal iduronate sulfate residues from the glycosaminoglycans dermatan sulfate and heparan sulfate in the lysosomes of various cell types.

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 internalization of the enzyme, targeting to intracellular lysosomes and subsequent catabolism of accumulated GAG.

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 characteristics of idursulfase were evaluated in several studies in patients with Hunter syndrome (see Table 3). 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 3 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%)

STORAGE AND STABILITY

Store at 2°C to 8°C (in a refrigerator).

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.

$$\text{Patient's weight (kg)} \times 0.5 \text{ mg per kg of ELAPRASE} \div 2 \text{ mg per mL} = \text{Total \# mL of ELAPRASE}$$

$$\text{Total \# mL of ELAPRASE} \div 3 \text{ mL per vial} = \text{Total \# of vials}$$

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:

Sodium chloride;
Sodium phosphate monobasic, monohydrate;
Sodium phosphate dibasic, heptahydrate;
Polysorbate 20;
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 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 4 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

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.

Study results

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 5), and on FVC absolute volume, urine GAG levels, liver and spleen volumes (see Table 6), and measurement of forced expiratory volume in 1 second (FEV_1), and left ventricular mass (LVM).

The analyses of the components of the composite score demonstrated that, for the 6MWT, 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 5 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 6 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 $>103 \text{ g/m}^2$. Of these, 6 patients (40%) had normalized LVM by the end of the study.

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 studies of safety pharmacology, single dose toxicity, repeated dose toxicity, and male fertility. Genotoxic and

carcinogenic potential are not expected. No reproductive toxicity studies in female animals have been performed. It is not known whether idursulfase crosses the placenta.

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. No reproductive toxicity studies in female animals have been performed. It is not known whether idursulfase crosses the placenta.

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 an enzyme replacement therapy for patients with Hunter syndrome and has been shown to improve walking capacity in these patients. 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.

When it should not be used:

Do not use ELAPRASE if you are allergic (hypersensitive) to idursulfase or any of the other nonmedicinal ingredients.

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 important nonmedicinal ingredients are:

The other ingredients are sodium chloride, sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, polysorbate 20, 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

Allergic reactions, which have the potential to be life threatening, have been observed in some patients treated with ELAPRASE.

Patients with compromised respiratory function or acute respiratory disease may be at risk of serious exacerbation of their respiratory dysfunction due to infusion related reactions. These patients require additional monitoring. Late-emergent allergic reactions have been observed after ELAPRASE administration. Patients who have experienced severe and refractory allergic reactions may require prolonged observation times.

Due to the potential for severe infusion reactions appropriate medical support measure 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 itching, rash, hives, fever, headache, increased blood pressure, and flushing (redness). 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.

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 1 to 3 hours and will be given every week.

Overdose:

There is no experience of overdose with ELAPRASE.

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 1-888-550-6060.

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

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
- 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, diarrhoea, swollen tongue
- Facial swelling, skin lesions (redness, eczema)
- Pain in the joints
- Swelling of the extremities

HOW TO STORE IT

Store at 2°C to 8°C (in a refrigerator).

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

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

Symptom/Effect		Talk with your doctor or pharmacist
Common (occurring in ≥ 5% of patients)	Drop in blood oxygen level from difficulty in breathing	Yes
Uncommon (occurring in < 5% of patients)	Seizure, blood clot in the lungs, missed or extra heartbeats	Yes

In clinical trials with ELAPRASE, 11 of 108 patients (10%) experienced allergic reactions during 19 of 8274 infusions (0.2%). 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

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting Paladin Labs Inc., at: 1-888-550-6060.

This leaflet was prepared by Shire Human Genetic Therapies, Inc.

Last revised: 28 January 2008.