

# New Zealand Data Sheet

## ELAPRASE<sup>®</sup>

(idursulfase concentrate for intravenous solution for infusion)

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### NAME OF THE MEDICINE

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

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### DESCRIPTION

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ELAPRASE (idursulfase) is a purified form of the lysosomal enzyme, iduronate-2-sulfatase. Idursulfase is produced by recombinant DNA technology in a human cell line providing a human glycosylation profile. Idursulfase is a 525 amino acid glycoprotein with 8 *N*-linked glycosylation sites that are occupied by complex, hybrid and high-mannose type oligosaccharide chains. Idursulfase has a molecular weight of approximately 76 kD.

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

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

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### PHARMACOLOGY

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#### Mechanism of Action

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

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

### Pharmacokinetics

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

**Table 1: Pharmacokinetic Parameters (Mean, Standard Deviation)**

Pharmacokinetic Parameter	Week 1	Week 27
C <sub>max</sub> (□g/mL)	1.5 (0.6)	1.1 (0.3)
AUC (min*□g/mL)	206 (87)	169 (55)
t <sub>1/2</sub> (min)	44 (19)	48 (21)
Cl (mL/min/kg)	3.0 (1.2)	3.4 (1.0)
V <sub>ss</sub> (% BW)	21 (8)	25 (9)

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## CLINICAL TRIALS

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

In a 53-week, randomised, double-blind, placebo-controlled clinical study, 96 patients between the ages of 5 and 31 years received ELAPRASE 0.5 mg/kg every week (n=32) or 0.5 mg/kg every other week (n=32) or placebo (n=32). The study included patients with a documented deficiency in iduronate-2-sulfatase enzyme activity, a percent predicted Forced Vital Capacity (FVC) <80% and a broad spectrum of disease severity.

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

Additional clinical benefit analyses were performed on individual components of the primary endpoint composite score, absolute changes in FVC, changes in urine GAG levels, liver and spleen volumes, measurement of forced expiratory volume in 1 second (FEV<sub>1</sub>) and changes in left ventricular mass (LVM).

**Table 2: Clinical Study Results**

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

<sup>a</sup> the analysis of the composite endpoint encompasses the sum of the ranks of change from baseline

Urine GAG levels were normalised below the upper limit of normal (defined as 126.6 µg GAG/mg creatinine) in 50% of the patients receiving ELAPRASE weekly. None of the placebo patients had normalised urine GAG levels that fell to below the upper limit of normal by week 53.

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

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

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

(40%) had normalised LVM by the end of the study. 22.22% of the placebo patients with LVH at baseline had normal LVM by Week 53.

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

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## INDICATIONS

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

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## CONTRAINDICATIONS

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There are no known contraindications to the use of ELAPRASE. Hypersensitivity (anaphylactic reaction) to the active substance or to any of the excipients.

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## PRECAUTIONS

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Serious hypersensitivity reactions including life threatening anaphylactic reactions have been observed in some patients during ELAPRASE infusions. Reactions have included respiratory distress, hypoxia, hypotension, seizure, loss of consciousness, urticaria and/or angioedema of the throat or tongue.

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

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

### **Infusion/Hypersensitivity reactions**

Patients treated with ELAPRASE may develop infusion-related reactions (see ADVERSE EFFECTS). The most common infusion-related reactions included cutaneous reactions (rash, pruritus, urticaria), pyrexia, headache, hypertension and flushing. Infusion-related reactions were treated or ameliorated by slowing the infusion rate, interrupting the infusion or by administration of medications, such as antihistamines, antipyretics, low-dose

corticosteroids (prednisone and methylprednisolone) or beta-agonist nebulisation. No patient discontinued treatment with ELAPRASE due to an infusion reaction during clinical studies.

Severe infusion-related reactions were reported occasionally in patients with severe underlying obstructive airway disease. These patients should therefore be closely monitored and infused with ELAPRASE in an appropriate clinical setting. Delaying ELAPRASE infusion should be considered in patients who present with an acute febrile respiratory illness. Patients using supplemental oxygen should have this treatment readily available during infusion in the event of an infusion-related reaction.

Allergic-type hypersensitivity reactions are possible as with any intravenous protein product. If severe allergic or anaphylactic-type reactions occur, it is recommended that the administration of ELAPRASE be discontinued immediately and appropriate medical treatment and observation initiated. The current medical standards for emergency treatment are to be observed. Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available when ELAPRASE is administered because of the potential for severe infusion reactions.

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

### **Interactions with Other Medicines**

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

### **Carcinogenesis**

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

### **Genotoxicity**

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

### **Effect on Fertility**

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

### **Use in Pregnancy: Category B2**

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

### **Use in Lactation**

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

### **Paediatric Use**

Patients in the clinical studies were age 5 and older. Children, adolescents and adults responded similarly to treatment with ELAPRASE.

### **Use in the Elderly**

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

### **Effects on Laboratory tests**

Across studies there were no clinically meaningful changes in clinical laboratory parameters.

### **Use in Renal/Hepatic Impaired Patients**

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

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## **ADVERSE EFFECTS**

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In clinical studies, the most frequent serious adverse events related to the use of ELAPRASE were hypoxic episodes, which necessitated oxygen therapy in 3 patients with severe underlying obstructive airway disease. The most severe episode, which was associated with a short seizure, occurred in a patient who received his infusion while he had a febrile respiratory exacerbation. In one patient who had less severe underlying disease, spontaneous resolution occurred shortly after the infusion was interrupted. These events did not recur with subsequent infusions using a slower infusion rate and administration of pre-infusion medication, usually with low-dose corticosteroids, antihistamine and beta-agonist nebulisation.

The most common adverse reactions observed in the 53-week, placebo-controlled study were infusion-related reactions. In the weekly ELAPRASE treatment group 202 infusion-related reactions were reported in 22 of 32 patients. In the every other week ELAPRASE treatment group 145 infusion-related reactions were reported in 22 of 32 patients. In the placebo treatment group 128 infusion-related reactions were reported in 21 of 32 patients. Infusion-related reactions reported in the placebo group were similar in nature and severity to those in the ELAPRASE-treated groups.

All infusion-related reactions were reported as mild to moderate in severity except for one case of arrhythmia and pulmonary embolism which was reported as severe. The most common infusion-related reactions included cutaneous reactions (rash, pruritus, urticaria), pyrexia, headache, hypertension and flushing. Infusion-related reactions were treated or

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

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

Clinical trials are conducted under widely varying conditions therefore the observed adverse reaction rates may not predict the rates observed in patients in clinical practice.

**Table 3** lists those treatment-emergent adverse events that were reported during the 53-week placebo-controlled study with an excess incidence compared with placebo of at least 9% (ie, 3 of 32 patients) in either of the ELAPRASE-treated groups.

**Table 3: Number and Percentage of Patients with Selected Adverse Events in the 53-week Placebo-controlled Study**

Adverse Event	Placebo (n=32) No. (%)	0.5 mg/kg ELAPRASE (n=32 per group)	
		Every Other Week No. (%)	Weekly No. (%)
Headache	14 (44)	21 (66)	19 (59)
Nasopharyngitis	15 (47)	19 (59)	17 (53)
Abdominal Pain	13 (41)	19 (59)	16 (50)
Arthralgia	9 (28)	14 (44)	10 (31)
Pruritus	5 (16)	6 (19)	10 (31)
Rash Pruritic	0	5 (16)	5 (16)
Infusion Site Swelling	1 (3)	4 (13)	4 (13)
Urticaria	0	4 (13)	5 (16)
Dyspepsia	0	4 (13)	4 (13)
Anxiety	0	4 (13)	2 (6)
Chest Wall Pain	0	0	4 (13)

Twelve patients participated in the 24-week, placebo-controlled study and subsequently received treatment in an open-label extension study with ELAPRASE for up to an additional 36 months. Observed adverse events were not different in nature or severity compared to the 53-week study.

### **Immunogenicity**

Fifty-one percent (32 of 63) of patients treated only with weekly ELAPRASE in clinical studies (53-week, placebo-controlled study and an open label, extension study) developed anti-idursulfase IgG antibodies as assessed by ELISA or conformation specific antibody assay and confirmed by radioimmunoprecipitation assay (RIP). Sera from 4 out of 32 RIP confirmed anti-idursulfase antibody positive patients were found to neutralise idursulfase

activity *in vitro*. No patients tested positive for IgE antibodies to idursulfase as assessed by ELISA.

Patients who developed IgG antibodies at any time had an increased incidence of infusion reactions. The reduction of urinary GAG excretion was somewhat less in patients for whom circulating anti-idursulfase antibodies were detected. The relationship between anti-idursulfase antibodies and clinical efficacy outcomes is unclear.

### **Post-Marketing Surveillance**

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

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## **DOSAGE AND ADMINISTRATION**

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

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

The total volume of infusion should be delivered 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 minutes intervals in order to administer the full volume within the desired period of time. However, at no time should the infusion rate exceed 100 mL/hr. The infusion rate may be slowed and/or temporarily stopped, or discontinued for that visit, based on clinical judgement, if infusion reactions were to occur (see PRECAUTIONS). ELAPRASE should not be infused with other products in the infusion tubing.

### **Preparation and Administration Instructions: Use Aseptic Techniques**

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

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

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

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

2. Perform a visual inspection of each vial. ELAPRASE is a clear to slightly opalescent, colourless solution. Do not use if the solution in the vials is discoloured or particulate matter is present. ELAPRASE should not be shaken.
3. Withdraw the calculated volume of ELAPRASE from the appropriate number of vials.
4. Dilute the total calculated volume of ELAPRASE in 100 mL of 0.9% Sodium Chloride for Injection. Once diluted into normal saline, the solution in the infusion bag should be mixed gently, but not shaken. To reduce microbial hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2°-8°C for no more than 24 hours.
5. ELAPRASE is supplied in single-use vials. Remaining ELAPRASE left in a vial after withdrawing the patient's calculated dose should be disposed of in accordance with local requirements.

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## OVERDOSAGE

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

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## PRESENTATION AND Storage CONDITIONS

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

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

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

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## MEDICINE CLASSIFICATION

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Prescription medicine

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## NAME AND ADDRESS OF THE SPONSOR

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### AUSTRALIA

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### **ELAPRASE is manufactured by:**

Shire Human Genetic Therapies, Inc. USA

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## DATE OF APPROVAL

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August 2004

ELAPRASE<sup>®</sup> is a registered trademark of Shire Human Genetic Therapies, Inc.  
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