ELAPRASE ™ (idursulfase)

Solution for intravenous infusion

WARNING

Risk of anaphylaxis.

Life-threatening anaphylactic reactions have been observed in some patients during ELAPRASE infusions. Therefore, appropriate medical support should be readily available when ELAPRASE is administered. Biphasic anaphylactic reactions have also been observed after ELAPRASE administration and patients who have experienced anaphylactic reactions may require prolonged observation. 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.

DESCRIPTION

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.

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. The enzyme activity of idursulfase is dependent on the post-translational modification of a specific cysteine to formylglycine. Idursulfase has a specific activity ranging from 41 to 77 U/mg of protein (one unit is defined as the amount of enzyme required to hydrolyze 1 µmole of heparin disaccharide substrate per hour under the specified assay conditions).

ELAPRASE is intended for intravenous infusion and is supplied as a sterile, nonpyrogenic clear to slightly opalescent, colorless solution that must be diluted prior to administration in 0.9% Sodium Chloride Injection, USP. Each vial contains an extractable volume of 3.0 mL with an idursulfase concentration of 2.0 mg/mL at a pH of approximately 6, providing 6.0 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.

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.

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

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 PK parameter values between Week 1 and Week 27.

Table 1 Pharmacokinetic Parameters (Mean, Standard Deviation)

Pharmacokinetic Parameter	Week 1	Week 27
C_{max} (μg/mL)	1.5 (0.6)	1.1 (0.3)
AUC (min*μg/mL)	206 (87)	169 (55)
$t_{1/2}$ (min)	44 (19)	48 (21)
Cl (mL/min/kg)	3.0 (1.2)	3.4 (1.0)
V_{ss} (% BW)	21 (8)	25 (9)

CLINICAL STUDIES

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%. The patients' ages ranged from 5 to 31 years. 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 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).

Examination of the individual components of the composite score showed that, in the adjusted analysis, the weekly ELAPRASE-treated group experienced a 35 meter greater mean increase in the distance walked in six minutes compared to placebo. The changes in %-predicted FVC were not statistically significant (Table 2).

Table 2 Clinical Study Results

	ELAPRASE Weekly n=32[a]			Placebo n=32[a]			ELAPRASE Weekly – Placebo
	Baseline	**Week 53**	**Change[b]**	**Baseline**	**Week 53**	**Change[b]**	**Difference in Change**
Results from the 6-Minute Walk Test (Meters)							
Mean ± SD	392 ± 108	436 ± 138	44 ± 70	393 ± 106	400 ± 106	7 ± 54	37 ± 16[c] 35 ± 14[d] (p=0.01)
Median	397	429	31	403	412	-4	
Percentiles (25^{th}, 75^{th})	316, 488	365, 536	0, 94	341, 469	361, 460	-30, 31	
Results from the Forced Vital Capacity Test (% of Predicted)							
Mean ± SD	55.3 ± 15.9	58.7 ± 19.3	3.4 ± 10.0	55.6 ± 12.3	56.3 ± 15.7	0.8 ± 9.6	2.7 ± 2.5[c] 4.3 ± 2.3[d] (p=0.07)
Median	54.9	59.2	2.1	57.4	54.6	-2.5	
Percentiles (25^{th}, 75^{th})	43.6, 69.3	44.4, 70.7	-0.8, 9.5	46.9, 64.4	43.8, 67.5	-5.4, 5.0	

[a] One patient in the placebo group and one patient in the ELAPRASE group died before Week 53; imputation was by last observation carried forward in the intent-to-treat analysis

[b] Change, calculated as Week 53 minus Baseline

[c] Observed mean ± SE

[d] ANCOVA model based mean ± SE, adjusted for baseline disease severity, region, and age.

Measures of bioactivity were urinary GAG levels and changes in liver and spleen size. Urinary GAG levels were elevated in all patients at baseline. Following 53 weeks of treatment, mean urinary GAG levels were markedly reduced in the ELAPRASE weekly group, although GAG levels still remained above the upper limit of normal in half of the ELAPRASE-treated patients. Urinary GAG levels remained elevated and essentially unchanged in the placebo group. Sustained reductions in both liver and spleen volumes were observed in the ELAPRASE weekly group through Week 53 compared to placebo. There were essentially no changes in liver and spleen volumes in the placebo group.

INDICATIONS AND USAGE

ELAPRASE is indicated for patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II). ELAPRASE has been shown to improve walking capacity in these patients.

CONTRAINDICATIONS

None.

WARNINGS

Anaphylaxis and Allergic Reactions (see BOXED WARNING)

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. 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. Interventions for biphasic reactions have included hospitalization, and treatment with epinephrine, inhaled beta-adrenergic agonists, and corticosteroids.

In clinical trials with ELAPRASE, 16/108 patients (15%) experienced infusion 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 significant allergic reactions during 19 of 8,274 infusions (0.2%). One of these episodes occurred in a patient with a tracheostomy and severe airway disease, who received an ELAPRASE infusion while he had a pre-existing febrile illness, and then experienced respiratory distress, hypoxia, cyanosis, and seizure with loss of consciousness.

Because of the potential for severe infusion reactions, appropriate medical support should be readily available when ELAPRASE is administered. Because of the potential for biphasic anaphylactic reactions after ELAPRASE administration, patients who experience initial severe or refractory reactions may require prolonged observation.

When severe infusion reactions occurred during clinical studies, subsequent infusions were managed by use of antihistamines and/or corticosteroids prior to or during infusions, a slower rate of ELAPRASE administration, and/or early discontinuation of the ELAPRASE infusion if serious symptoms developed. With these measures, no patient discontinued treatment permanently due to an allergic reaction.

Patients with compromised respiratory function or acute respiratory disease may be at higher risk of life-threatening complications from infusion reactions. Consider delaying the ELAPRASE infusion in patients with concomitant acute respiratory and/or febrile illness.

If a severe reaction occurs, immediately suspend the infusion of ELAPRASE and initiate appropriate treatment, depending on the severity of the symptoms. Consider resuming the infusion at a slower rate, or, if the reaction is serious enough to warrant it, discontinue the ELAPRASE infusion for that visit.

PRECAUTIONS

Information for Patients

A Hunter Outcome Survey has been established in order to understand better the variability and progression of Hunter syndrome (MPS II) in the population as a whole, and to monitor and evaluate long-term treatment effects of ELAPRASE. Patients and their physicians are encouraged to participate in this program. For more information, visit www.elaprase.com or call OnePath^{SM} at 1-866-888-0660.

Drug Interactions

No formal drug interaction studies have been conducted with ELAPRASE.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential or studies to evaluate mutagenic potential have not been performed with ELAPRASE.

ELAPRASE at intravenous doses up to 5 mg/kg, administered twice weekly (about 1.6 times the

recommended human weekly dose based on body surface area) had no effect on fertility and reproductive performance in male rats.

Pregnancy: Teratogenic Effects: Category C

Reproduction studies in pregnant female animals have not been conducted with ELAPRASE. It is also not known whether ELAPRASE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ELAPRASE should be given to pregnant women only if clearly needed.

Nursing Mothers

It is not known whether this product is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ELAPRASE is administered to a nursing woman.

Pediatric Use

Patients in the clinical studies were age five and older (see CLINICAL STUDIES). Children, adolescents, and adults responded similarly to treatment with ELAPRASE. Safety and efficacy have not been established in pediatric patients less than five years of age.

Geriatric Use

Clinical studies of ELAPRASE did not include patients aged 65 or over. It is not known whether geriatric patients respond differently from younger patients.

ADVERSE REACTIONS

The most serious infusion-related adverse reactions reported with ELAPRASE were anaphylactic and allergic reactions (see **BOXED WARNING** and **WARNINGS**).

In clinical studies, the most frequent serious adverse events related to the use of ELAPRASE were hypoxic episodes. Other notable serious adverse reactions that occurred in the ELAPRASE treated patients but not in the placebo patients included one case each of: cardiac arrhythmia, pulmonary embolism, cyanosis, respiratory failure, infection, and arthralgia.

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.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a product cannot be directly compared to rates in the clinical trials of another product and may not reflect the rates observed in practice.

Table 3 enumerates those adverse reactions that were reported during the 53-week, placebo-controlled study that occurred in at least 10% of patients treated with ELAPRASE weekly administration, and that occurred more frequently than in the placebo patients. The most common (>30%) adverse reactions were pyrexia, headache, and arthralgia.

Table 3 Summary of Adverse Reactions Occurring in at Least 10% of Patients Treated with ELAPRASE Weekly in the 53-week Controlled Trial and Occurring More Frequently than in the Placebo Group

Adverse Event	ELAPRASE 0.5 mg/kg Weekly (n=32)		Placebo (n=32)	
Pyrexia	20	(63%)	19	(59%)
Headache	19	(59%)	14	(44%)
Arthralgia	10	(31%)	9	(28%)
Limb pain	9	(28%)	8	(25%)
Pruritus	9	(28%)	5	(16%)
Hypertension	8	(25%)	7	(22%)
Malaise	7	(22%)	6	(19%)
Visual disturbance	7	(22%)	2	(6%)
Wheezing	6	(19%)	5	(16%)
Abscess	5	(16%)	0	(0%)
Musculoskeletal dysfunction NOS	5	(16%)	3	(9%)
Chest wall musculoskeletal pain	5	(16%)	0	(0%)
Urticaria	5	(16%)	0	(0%)
Superficial injury	4	(13%)	3	(9%)
Anxiety, irritability	4	(13%)	1	(3%)
Atrial abnormality	4	(13%)	3	(9%)
Adverse events resulting from injury	4	(13%)	2	(6%)
Dyspepsia	4	(13%)	0	(0%)
Infusion site edema	4	(13%)	3	(9%)
Skin disorder NOS	4	(13%)	1	(3%)
Pruritic rash	4	(13%)	0	(0%)

Immunogenicity

Fifty-one percent (32 of 63) of patients in the weekly ELAPRASE treatment arm in the clinical study (53-week placebo-controlled study with an open-label extension) 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 neutralize idursulfase activity in vitro. The incidence of antibodies that inhibit cellular uptake of idursulfase into cells is currently unknown, and the incidence of IgE antibodies to idursulfase is not known. Patients who developed IgG antibodies at any time had an increased incidence of infusion reactions, including allergic reactions. The reduction of urinary GAG excretion was less in patients in whom circulating anti-idursulfase antibodies were detected. The relationship between the presence of anti-idursulfase antibodies and clinical efficacy outcomes is unknown.

The data reflect the percentage of patients whose test results were positive for antibodies to idursulfase in specific assays, and are highly dependent on the sensitivity and specificity of these assays. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence

of antibodies to idursulfase with the incidence of antibodies to other products may be misleading.

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 and cynomolgus monkeys (approximately 6.5 and 13 times, respectively, of the recommended human dose based on body surface area) and there were no clinical signs of toxicity.

DOSAGE AND ADMINISTRATION

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 Injection, USP. 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. Use of an infusion set equipped with a 0.2 micrometer (µm) filter is recommended.

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 (see STORAGE). 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, or discontinued for that visit, based on clinical judgment, if infusion reactions were to occur (see WARNINGS). ELAPRASE should not be infused with other products in the infusion tubing.

Preparation and Administration Instructions: Use Aseptic Techniques

ELAPRASE should be prepared and administered by a health care 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. 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 should be discarded if not administered or refrigerated within 8 hours of preparation. Diluted solution may be stored refrigerated for up to 48 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.

STORAGE

Store ELAPRASE vials under refrigeration at 2°C to 8°C (36°F to 46°F), 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 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 (36°F to 46°F) for up to 48 hours, or must be administered within 8 hours if held at room temperature.

HOW SUPPLIED

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.

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Rx Only

ELAPRASE is manufactured for:

Shire Human Genetic Therapies, Inc.
700 Main Street
Cambridge, MA 02139
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OnePath[SM] phone # 1-866-888-0660

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