elaprase® (idursulfase)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ELAPRASE safely and effectively. See full prescribing information for ELAPRASE.

ELAPRASE® (idursulfase) injection, for intravenous use
Initial U.S. Approval: 2006

WARNING: RISK OF ANAPHYLAXIS

See full prescribing information for complete boxed warning.

Life-threatening anaphylactic reactions, presenting as respiratory distress, hypoxia, hypotension, urticaria and/or angioedema of throat or tongue have occurred in some patients during and up to 24 hours after ELAPRASE infusions. Closely observe patients during and after ELAPRASE administration and be prepared to manage anaphylaxis. Inform patients of the signs and symptoms of anaphylaxis and have them seek immediate medical care should symptoms occur. Patients with compromised respiratory function or acute respiratory disease may be at risk of serious acute exacerbation of their respiratory compromise due to hypersensitivity reactions, and require additional monitoring. (5.1, 5.3, 6)

----------INDICATIONS AND USAGE----------

ELAPRASE is a hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme indicated for patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II). ELAPRASE has been shown to improve walking capacity in patients 5 years and older. In patients 16 months to 5 years of age, no data are available to demonstrate improvement in disease-related symptoms or long term clinical outcome; however, treatment with ELAPRASE has reduced spleen volume similarly to that of adults and children 5 years of age and older. The safety and efficacy of ELAPRASE have not been established in pediatric patients less than 16 months of age (1).

----------DOSAGE AND ADMINISTRATION----------

The recommended dosage is 0.5 mg per kg of body weight administered once every week as an intravenous infusion (2).

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 6 mg/3 mL (2 mg/mL) in single-use vial (3)

----------CONTRAINDICATIONS----------

- None (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity Reactions Including Anaphylaxis: Ensure that personnel administering product are adequately trained in cardio-pulmonary resuscitative measures, and have ready access to emergency medical services (EMS) (5.1).
- Risk of Hypersensitivity, Serious Adverse Reactions, and Antibody Development in Hunter Syndrome Patients with Severe Genetic Mutations: Hunter syndrome patients aged 7 years and younger with complete gene deletion, large gene rearrangement, nonsense, frameshift, or splice site mutations experienced a higher incidence of hypersensitivity reactions, serious adverse reactions, and anti-idursulfase antibody development (5.2).
- Risk of Acute Respiratory Complications: Patients with compromised respiratory function or acute febrile or respiratory illness may be at higher risk of life-threatening complications from hypersensitivity reactions. Careful consideration should be given to the patient's clinical status prior to administration of ELAPRASE and consider delaying the ELAPRASE infusion (5.3).

----------ADVERSE REACTIONS----------

The most common adverse reactions occurring in at least three patients (≥9%) aged five years and older were headache, pruritus, musculoskeletal pain, urticaria, diarrhea, and cough. The most common adverse reactions occurring in at least three patients (≥10%) aged seven years and younger were pyrexia, rash, vomiting, and urticaria. In all clinical trials, the most common adverse reactions requiring medical intervention were hypersensitivity reactions, and included rash, urticaria, pruritus, flushing, pyrexia, and headache (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Shire Medical Information at 1-866-888-0660 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF ANAPHYLAXIS

Life-threatening anaphylactic reactions have occurred in some patients during and up to 24 hours after ELAPRASE infusions. Anaphylaxis, presenting as respiratory distress, hypoxia, hypotension, urticaria and/or angioedema of throat or tongue have been reported to occur during and after ELAPRASE infusions, regardless of duration of the course of treatment. Closely observe patients during and after ELAPRASE administration and be prepared to manage anaphylaxis. Inform patients of the signs and symptoms of anaphylaxis and have them seek immediate medical care should symptoms occur. Patients with compromised respiratory function or acute respiratory disease may be at risk of serious acute exacerbation of their respiratory compromise due to hypersensitivity reactions, and require additional monitoring *[see Warnings and Precautions (5.1, 5.3) and Adverse Reactions (6)]*.

1 INDICATIONS AND USAGE

ELAPRASE is indicated for patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II). ELAPRASE has been shown to improve walking capacity in patients 5 years and older.

In patients 16 months to 5 years of age, no data are available to demonstrate improvement in disease-related symptoms or long term clinical outcome; however, treatment with ELAPRASE has reduced spleen volume similarly to that of adults and children 5 years of age and older.

The safety and efficacy of ELAPRASE have not been established in pediatric patients less than 16 months of age *[see Use in Specific Populations (8.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dosage regimen of ELAPRASE is 0.5 mg per kg of body weight administered once weekly as an intravenous infusion.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

2.2 Preparation Instructions

Prepare and use ELAPRASE according to the following steps using aseptic technique:

a. 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 number of vials

Round up to the next whole vial to determine the total number of vials needed. Remove the required number of vials from the refrigerator to allow them to reach room temperature.

b. Before withdrawing the ELAPRASE solution from the vial, visually inspect each vial for particulate matter and discoloration. The ELAPRASE solution should be clear to slightly opalescent and colorless. Do not use if the solution is discolored or if there is particulate matter in the solution. Do not shake the ELAPRASE solution.

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

d. Add the calculated volume of ELAPRASE solution to a 100 mL bag of 0.9% Sodium Chloride Injection, USP for intravenous infusion.

e. Mix gently. Do not shake the solution.

2.3 Administration Instructions

Administer the diluted ELAPRASE solution to patients using a low-protein-binding infusion set equipped with a low-protein-binding 0.2 micrometer (µm) in-line filter.

The total volume of infusion should be administered over a period of 3 hours, which may be gradually reduced to 1 hour if no hypersensitivity reactions are observed. Patients may require longer infusion times if hypersensitivity reactions occur; however, infusion times should not exceed 8 hours. The initial infusion rate should be 8 mL per hour for the first 15 minutes. If the infusion is well tolerated, the rate of infusion may be increased by 8 mL per hour increments every 15 minutes. The infusion rate should not exceed 100 mL per hour. The infusion rate may be slowed, temporarily stopped, or discontinued for that visit in the event of hypersensitivity reactions *[see Warnings and Precautions (5.1)]*. ELAPRASE should not be infused with other products in the infusion tubing.

2.4 Storage and Stability

ELAPRASE does not contain preservatives; therefore, after dilution with saline, the infusion bags should be used immediately. If immediate use is not possible, the diluted solution should be stored refrigerated at 2°C to 8°C (36°F to 46 °F) for up to 24 hours. Other than during infusion, do not store the diluted ELAPRASE solution at room temperature. Any unused product or waste material should be discarded and disposed of in accordance with local requirements.

3 DOSAGE FORMS AND STRENGTHS

Injection: 6 mg/3 mL (2 mg/mL) in single-use vials

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions Including Anaphylaxis

Serious hypersensitivity reactions, including anaphylaxis, have occurred during and up to 24 hours after infusion. Some of these reactions were life-threatening and included respiratory distress, hypoxia, hypotension, urticaria, and angioedema of the throat or tongue, regardless of duration of the course of treatment.

If anaphylactic or other acute reactions occur, immediately discontinue the infusion of ELAPRASE and initiate appropriate medical treatment. When severe reactions have occurred during clinical trials, subsequent infusions were managed with antihistamine and/or corticosteroids prior to or during infusions, a slower rate of ELAPRASE infusion, and/or early discontinuation of the ELAPRASE infusion *[see Adverse Reactions (6)]*.

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 reactions during 19 of 8,274 infusions (0.2%) with symptoms of bronchospasm, cyanosis, dyspnea, erythema, edema (facial and peripheral), flushing, rash, respiratory distress, urticaria, vomiting, and wheezing.

In postmarketing reports, patients receiving ELAPRASE experienced anaphylactic reactions up to several years after initiating treatment. Some patients were reported to have repeated anaphylactic events over a two- to four-month time period. Medical management included treatment with antihistamines, inhaled beta-adrenergic agonists, corticosteroids, oxygen, and vasopressors. Treatment was discontinued for some patients, while others continued treatment with premedication and a slower infusion rate.

Due to the potential for severe reactions, appropriate medical support should be readily available when ELAPRASE is administered. Observe patients closely for an appropriate period of time after administration of ELAPRASE, taking into account the time to onset of anaphylaxis seen in premarketing clinical trials and postmarketing reports. Inform patients of the signs and symptoms of anaphylaxis, and instruct them to seek immediate medical care should signs and symptoms occur.

5.2 Risk of Hypersensitivity, Serious Adverse Reactions, and Antibody Development in Hunter Syndrome Patients with Severe Genetic Mutations

In the clinical trial of Hunter syndrome patients aged 7 years and younger, patients with complete gene deletion, large gene rearrangement, nonsense, frameshift, or splice site mutations experienced a higher incidence of hypersensitivity reactions, serious adverse reactions, and anti-idursulfase antibody development than Hunter syndrome patients with missense mutations. Eleven of 15 (73%) patients with complete gene deletion, large gene rearrangement, nonsense, frameshift, or splice site mutations and five of 12 (42%) patients with missense mutations experienced hypersensitivity reactions. Nine of 15 (60%) patients with complete gene deletion, large gene rearrangement, nonsense, frameshift, or splice site mutations and two of 12 (17%) patients with missense mutations had serious adverse reactions. All 15 patients with complete gene deletion, large gene rearrangement, nonsense, frameshift, or splice site mutations developed anti-idursulfase (ELAPRASE) antibodies, compared to only 3 patients with missense mutations (Table 2). Thirteen patients with these mutations developed neutralizing antibodies, which interfere with ELAPRASE uptake into the cell or ELAPRASE enzyme activity, compared to only one patient with missense mutation *[see Warnings and Precautions (5.1), Adverse Reactions (6.1, 6.2), and Use in Specific Populations (8.4)]*.

5.3 Risk of Acute Respiratory Complications

Patients with compromised respiratory function or acute febrile or respiratory illness at the time of ELAPRASE infusion may be at higher risk of life-threatening complications from hypersensitivity reactions. Careful consideration should be given to the patient's clinical status prior to administration of ELAPRASE and consider delaying the ELAPRASE infusion. One patient with a tracheostomy, severe airway disease, and acute febrile illness experienced respiratory distress, hypoxia, cyanosis, and seizure with a loss of consciousness during ELAPRASE infusion.

5.4 Risk of Acute Cardiorespiratory Failure

Caution should be exercised when administering ELAPRASE to patients susceptible to fluid overload, or patients with acute underlying respiratory illness or compromised cardiac and/or respiratory function for whom fluid restriction is indicated. These patients may be at risk of serious exacerbation of their cardiac or respiratory status during infusions. Appropriate medical support and monitoring measures should be readily available during ELAPRASE infusion, and some patients may require prolonged observation times that should be based on the individual needs of the patient *[see Adverse Reactions (6.1, 6.3)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

The following serious adverse reactions are described below and elsewhere in the labeling:

- Hypersensitivity Reactions Including Anaphylaxis *[see Warnings and Precautions (5.1)]*

In clinical trials, the most common adverse reactions (>10%) following ELAPRASE treatment were hypersensitivity reactions, and included rash, urticaria, pruritus, flushing, pyrexia, and headache. Most hypersensitivity reactions requiring intervention were ameliorated with slowing of the infusion rate, temporarily stopping the infusion, with or without administering additional treatments including antihistamines, corticosteroids, or both prior to or during infusions.

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

Clinical Trials in Patients 5 Years and Older

A 53-week, double-blind, placebo-controlled clinical trial of ELAPRASE was conducted in 96 male patients with Hunter syndrome, ages 5-31 years old. Of the 96 patients, 83% were White, non-Hispanic. Patients were randomized to three treatment groups, each with 32 patients: ELAPRASE 0.5 mg/kg once weekly, ELAPRASE 0.5 mg/kg every other week, or placebo. Hypersensitivity reactions were reported in 69% (22 of 32) of patients who received once-weekly treatment of ELAPRASE.

Table 1 summarizes the adverse reactions that occurred in at least 9% of patients (≥3 patients) in the ELAPRASE 0.5 mg/kg once weekly group and with a higher incidence than in the placebo group.

Table 1. Adverse Reactions that Occurred in the Placebo-Controlled Trial in At Least 9% of Patients in the ELAPRASE 0.5 mg/kg Once Weekly Group and with a Higher Incidence than in the Placebo Group (5 Years and Older)

System Organ Class Adverse Reaction	ELAPRASE (0.5 mg/kg weekly) N=32 n (%)	Placebo N=32 n (%)
Gastrointestinal disorder		
Diarrhea	3 (9%)	1 (3%)
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal Pain	4 (13%)	1 (3%)
Nervous system disorders		
Headache	9 (28%)	8 (25%)
Respiratory, thoracic and mediastinal disorders		
Cough	3 (9%)	1 (3%)
Skin and subcutaneous tissue disorders		
Pruritus	8 (25%)	3 (9%)
Urticaria	5 (16%)	0 (0%)

Additional adverse reactions that occurred in at least 9% of patients (≥3 patients) in the ELAPRASE 0.5 mg/kg every other week group and with a higher incidence than in the placebo group included: rash (19%), flushing (16%), fatigue (13%), tachycardia (9%), and chills (9%).

Extension Trial

An open-label extension trial was conducted in patients who completed the placebo-controlled trial. Ninety-four of the 96 patients who were enrolled in the placebo-controlled trial consented to participate in the extension trial. All 94 patients received ELAPRASE 0.5 mg/kg once weekly for 24 months. No new serious adverse reactions were reported. Approximately half (53%) of patients experienced hypersensitivity reactions during the 24-month extension trial. In addition to the adverse reactions listed in Table 1, common hypersensitivity reactions occurring in at least 5% of patients (≥5 patients) in the extension trial included: rash (23%), pyrexia (9%), flushing (7%), erythema (7%), nausea (5%), dizziness (5%), vomiting (5%), and hypotension (5%).

Clinical Trial in Patients 7 Years and Younger

A 53-week, open-label, single-arm, safety trial of once weekly ELAPRASE 0.5 mg/kg treatment was conducted in patients with Hunter syndrome, ages 16 months to 4 years old (n=20) and ages 5 to 7.5 years old (n=8) at enrollment. Patients experienced similar adverse reactions as those observed in clinical trials in patients 5 years and older, with the most common adverse reactions following ELAPRASE treatment being hypersensitivity reactions (57%). A higher incidence of the following common hypersensitivity reactions were reported in this younger age group: pyrexia (36%), rash (32%), and vomiting (14%). The most common serious adverse reactions occurring in at least 10% of patients (≥3 patients) included: bronchopneumonia/pneumonia (18%), ear infection (11%), and pyrexia (11%).

Twenty-seven patients had results of genotype analysis: 15 patients had complete gene deletion, large gene rearrangement, nonsense, frameshift, or splice site mutations and 12 patients had missense mutations.

Safety results demonstrated that patients with complete gene deletion, large gene rearrangement, nonsense, frameshift, or splice site mutations are more likely to

experience hypersensitivity reactions and have serious adverse reactions following ELAPRASE administration, compared to patients with missense mutations. Table 2 summarizes these findings.

Table 2. Impact of Antibody Status and Genetic Mutations on Occurrence of Serious Adverse Reactions and Hypersensitivity in Patients 7 Years and Younger Treated with ELAPRASE

				Anti-idursulfase antibodies (Ab)		Anti-idursulfase neutralizing antibodies (Nab)	
			Total	Positive	Negative	Positive	Negative
Antibody Status Reported (patients)			28	19	9	15	13
Serious Adverse Reactions* (patients)			13	11	2	9	4
Hypersensitivity (patients)			16	12	4	10	6
Patients with genotype data			27				
MUTATIONS	Missense Mutation (n=12)	Antibody status	12	3	9	1	11
		Serious Adverse Reactions	2	0	2	0	2
		Hypersensitivity Reactions	5	1	4	0	5
	Complete Gene Deletion, Large Gene Rearrangement, Nonsense, Frameshift, Splice Site Mutations (n=15)	Antibody Status	15	15	0	13	2
		Serious Adverse Reactions	9	9	0	7	2
		Hypersensitivity Reactions	11	11	0	10	1

* Serious adverse reactions included: bronchopneumonia/pneumonia, ear infection, and pyrexia *[see Adverse Reactions (6.1)]*.

6.2 Immunogenicity

Clinical Trials in Patients 5 Years and Older

As with all therapeutic proteins, there is potential for immunogenicity. In clinical trials in patients 5 years and older, 63 of the 64 patients treated with ELAPRASE 0.5 mg/kg once weekly or placebo for 53 weeks, followed by ELAPRASE 0.5 mg/kg once weekly in the extension trial, had immunogenicity data available for analysis. Of the 63 patients, 32 (51%) patients tested positive for anti-idursulfase IgG antibodies (Ab) at least one time (Table 2). Of the 32 Ab-positive patients, 23 (72%) tested positive for Ab at three or more different time points (persistent Ab). The incidence of hypersensitivity reactions was higher in patients who tested positive for Ab than those who tested negative.

Thirteen of 32 (41%) Ab-positive patients also tested positive for antibodies that neutralize idursulfase uptake into cells (uptake neutralizing antibodies, uptake NAb) or enzymatic activity (activity NAb) at least one time, and 8 (25%) of Ab-positive patients had persistent NAb. There was no clear relationship between the presence of either Ab or NAb and therapeutic response.

Clinical Trial in Patients 7 Years and Younger

In the clinical trial in patients 7 years and younger, 19 of 28 (68%) patients treated with ELAPRASE 0.5 mg/kg once weekly tested Ab-positive. Of the 19 Ab-positive patients, 16 (84%) tested positive for Ab at three or more different time points (persistent Ab). In addition, 15 of 19 (79%) Ab-positive patients tested positive for NAb, with 14 of 15 (93%) NAb-positive patients having persistent NAb.

All 15 patients with complete gene deletion, large gene rearrangement, nonsense, frameshift, or splice site mutations tested positive for Ab (Table 2). Of these 15 patients, neutralizing antibodies were observed in 13 (87%) patients. The NAbs in these patients developed earlier (most reported to be positive at Week 9 rather than at Week 27, as reported in clinical trials in patients older than 5 years of age) and were associated with higher titers and greater *in vitro* neutralizing activity than in patients older than 5 years of age. The presence of Ab was associated with reduced systemic idursulfase exposure *[see Clinical Pharmacology (12.3)]*.

The immunogenicity 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. The observed incidence of positive antibody 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.

6.3 Postmarketing Experience

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 anaphylactic reactions have occurred up to 24 hours after initial treatment and recovery from an initial anaphylactic reaction. In addition, patients experienced repeated anaphylaxis over a two- to four-month period, up to several years after initiating ELAPRASE treatment *[see Warnings and Precautions (5.1)]*.

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 has been withdrawn *[see Overdosage (10)]*.

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies with ELAPRASE use in pregnant women. Available data from a small number of postmarketing cases with ELAPRASE use in pregnancy are insufficient to inform drug-associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes. In an animal reproduction study, no evidence of adverse effects on pre- and post-natal development was observed with twice weekly intravenous administration of idursulfase to pregnant rats from gestation day 6 through lactation day 19 at about 4 times the recommended human weekly dose of 0.5 mg/kg based on body surface area *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In a pre- and post-natal development study, idursulfase was administered to pregnant rats twice weekly, intravenously, from gestation day 6 through lactation day 19. No significant adverse effects on pre- and post-natal development of the offspring were observed at twice weekly intravenous doses up to 12.5 mg/kg (about 4 times the recommended human weekly dose of 0.5 mg/kg based on body surface area).

8.2 Lactation

Risk Summary

There are no data on the presence of idursulfase in human milk, the effects on the breastfed infant, or the effects on milk production. Idursulfase was excreted in breast milk of lactating rats *(see Data)*. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ELAPRASE and any potential adverse effects on the breastfed child from ELAPRASE or from the underlying maternal condition.

Data

Idursulfase was excreted in breast milk of lactating rats at a concentration higher (4- to 5-fold) than the maximum blood concentration, when administered as a single intravenous dose up to 2.5 mg/kg. The concentration of drug in animal milk does not necessarily predict the concentration of drug in human milk.

8.4 Pediatric Use

Clinical trials with ELAPRASE were conducted in 96 patients with Hunter syndrome, ages 5 to 31 years old, with the majority of the patients in the pediatric age group (median age 15 years old). In addition, an open-label, uncontrolled clinical trial was conducted in 28 patients with Hunter syndrome, ages 16 months to 7.5 years old. Patients 16 months to 5 years of age demonstrated reduction in spleen volume that was similar to that of adults and children 5 years and older. However, there are no data to support improvement in disease-related symptoms or long term clinical outcome in patients 16 months to 5 years of age *[see Clinical Studies (14)]*.

The safety and effectiveness of ELAPRASE have not been established in pediatric patients less than 16 months of age.

8.5 Geriatric Use

Clinical studies of ELAPRASE did not include patients older than 31 years of age. It is not known whether older patients respond differently from younger patients.

10 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.

11 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 46 to 74 units/mg of protein (one unit is defined as the amount of enzyme required to hydrolyze 1 micromole of heparin disaccharide substrate per hour under the specified assay conditions).

ELAPRASE is administered as an intravenous infusion and 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 mL with an idursulfase concentration of 2 mg/mL at a pH of approximately 6. Each vial contains 6 mg idursulfase, sodium chloride (24 mg), sodium phosphate monobasic monohydrate (6.75 mg), sodium phosphate dibasic heptahydrate (2.97 mg), and polysorbate 20 (0.66 mg). ELAPRASE does not contain preservatives. Each vial is for single use only.

12 CLINICAL PHARMACOLOGY

12.1 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 intended to provide exogenous enzyme for uptake into cellular lysosomes. Mannose-6-phosphate (M6P) residues on the oligosaccharide chains allow 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.

12.2 Pharmacodynamics

Decreases in urinary GAG levels were observed following treatment with ELAPRASE. The responsiveness of urinary GAG to dosage alterations of ELAPRASE is unknown, and the relationship of urinary GAG to other measures of clinical response has not been established. Patients who tested positive for anti-idursulfase antibodies (Ab) experienced a less pronounced decrease in urinary GAG levels *[see Adverse Reactions (6.2) and Clinical Studies (14.1, 14.2)]*.

12.3 Pharmacokinetics

Clinical Trials in Patients 5 Years and Older

The pharmacokinetic characteristics of idursulfase were evaluated in 59 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 7.7 to 27 years of age (Table 3). There were no apparent differences in PK parameter values between Week 1 and Week 27 regardless of the antibody status in these patients.

Table 3. Pharmacokinetic Parameters in Patients 7.7 to 27 Years of Age

Pharmacokinetic Parameter	Week 1 Mean (SD)	Week 27 Mean (SD)
C_{max} (mcg/mL)	1.5 (0.6)	1.1 (0.3)
AUC (min•mcg/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} (mL/kg)	213 (82)	254 (87)

Clinical Trial in Patients 7 Years and Younger

Idursulfase pharmacokinetics was evaluated in 27 patients with Hunter syndrome 16 months to 7.5 years of age who received ELAPRASE 0.5 mg/kg once weekly as a 3-hour infusion. The presence of anti-idursulfase antibody (Ab) was associated with a reduced systemic exposure of idursulfase. Eight of the 18 Ab-positive patients had no measurable idursulfase concentrations. An additional 9 Ab-positive patients had decreased C_{max}, AUC, and $t_{1/2}$ at Week 27 compared to Week 1 (Table 4). Idursulfase pharmacokinetics was similar between Week 1 and Week 27 in Ab-negative patients (Table 4).

Table 4. Pharmacokinetic Parameters in Patients 16 months to 7.5 Years of Age

Pharmacokinetic Parameter	Week 1 (N=27) All Patients Mean (SD)	Week 27 Anti-idursulfase Antibodies (Ab)* (n=9) Negative Ab Mean (SD)	Week 27 Anti-idursulfase Antibodies (Ab)* (n=10†) Positive Ab Mean (SD)
C_{max} (mcg/mL)	1.33 (0.817)	1.40 (0.389)	0.706 (0.558)
AUC (min•mcg/mL)	224 (76.9)#	281 (81.8)	122 (92.1)$
$t_{1/2}$ (min)	160 (69)#	134 (19)	84 (46)$
CL (mL/min/kg)	2.4 (0.7)#	2.0 (0. 8)	7.4 (6.0)$
V_{ss} (mL/kg)	394 (423)#	272 (112)	829 (636)$

* Positive anti-idursulfase antibody (Ab) is defined as having at least one serum specimen with measurable antibody during study duration.
† Eight of 18 patients with positive Ab had no measurable concentrations at Week 27.
# N=26
$ N=9

All patients with the complete gene deletion or large gene rearrangement genotype (n=8) developed Ab at Week 27. Five of these eight patients had no measurable idursulfase concentrations at Week 27, and three had a lower systemic exposure at Week 27 compared to Week 1.

13 NONCLINICAL TOXICOLOGY

13.1 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.

14 CLINICAL STUDIES

14.1 Clinical Trials in Patients 5 Years and Older

The safety and efficacy of ELAPRASE were evaluated in a 53-week, randomized, double-blind, placebo-controlled clinical trial of 96 patients with Hunter syndrome. The trial included patients with deficiency in iduronate-2-sulfatase enzyme activity and a percent predicted forced vital capacity (%-predicted FVC) less than 80%. The age of patients ranged from 5 to 31 years. Patients received ELAPRASE 0.5 mg/kg once per week (n=32), ELAPRASE 0.5 mg/kg once every other week (n=32), or placebo (n=32).

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 in six minutes (6-minute walk test) 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 once weekly treatment group (once 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 5).

Table 5. Clinical Trial Results

	ELAPRASE Weekly n=32*			Placebo n=32*			ELAPRASE Once Weekly – Placebo
	Baseline	Week 53	Change†	Baseline	Week 53	Change†	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‡
Median	397	429	31	403	412	-4	35 ± 14§
Percentiles (25^{th}, 75^{th})	316, 488	365, 536	0, 94	341, 469	361, 460	-30, 31	(p=0.01)
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‡
Median	54.9	59.2	2.1	57.4	54.6	-2.5	4.3 ± 2.3§
Percentiles (25th, 75th)	43.6, 69.3	44.4, 70.7	-0.8, 9.5	46.9, 64.4	43.8, 67.5	-5.4, 5.0	(p=0.07)

* 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.
† Change, calculated as Week 53 minus Baseline
‡ Observed mean ± SE
§ ANCOVA model based mean ± SE, adjusted for baseline disease severity, region, and age.

Pharmacodynamic assessments included 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 reduced in the ELAPRASE once 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 once weekly group through Week 53 compared to placebo. There were essentially no changes in liver and spleen volumes in the placebo group.

Extension Trial

Patients who participated in the placebo-controlled trial were eligible to continue treatment in an open-label extension trial. During the extension trial, all patients received ELAPRASE 0.5mg/kg once weekly for 24 months.

Patients who were treated with ELAPRASE once weekly and every other week in the placebo-controlled trial demonstrated improvement in distance walked in the 6-minute walk test for an additional 8 months of treatment in the extension trial. There was no change in mean %-predicted FVC in all Hunter syndrome patients after 6 months of treatment in the extension trial; however, a slight decrease in mean %-predicted FVC was demonstrated through to month 24 of the extension trial. The long-term effect of ELAPRASE on pulmonary function in Hunter syndrome patients is unclear.

There were no further reductions in mean urinary GAG levels in patients initially treated with ELAPRASE once weekly; however, the patients treated with ELAPRASE every other week during the placebo-controlled trial experienced further reductions in mean urinary GAG levels after changing to a more frequent dosing regimen during the extension trial. The persistence of reduced urinary GAG levels did not correlate with the long term effect demonstrated by the 6-minute walk test distance or %-predicted FVC.

14.2 Clinical Trial in Patients 7 Years and Younger

A 53-week, open-label, multicenter, single-arm trial was conducted to assess the safety, pharmacokinetics, and pharmacodynamics of ELAPRASE 0.5 mg/kg once weekly in male Hunter syndrome patients aged 7 years and younger. Safety results demonstrated that patients with complete gene deletion or large gene rearrangement mutations are more likely to develop antibodies, including neutralizing antibodies, and to experience hypersensitivity reactions with ELAPRASE administration *[see Adverse Reactions (6.1, 6.2)]*. In patients who remained antibody negative, the pharmacokinetic profile, reduction in urinary GAG excretion levels, and reduction in spleen volume were similar to those of adults and children 5 years and older. In patients who were persistently antibody positive, the presence of anti-idursulfase antibody was associated with reduced systemic exposure of idursulfase and a less pronounced decrease in urinary GAG levels *[see Clinical Pharmacology (12.2, 12.3)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

ELAPRASE is supplied as a sterile injection 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 carton contains a single vial NDC 54092-700-01

Store ELAPRASE vials in the carton at 2°C to 8°C (36°F to 46°F) to protect from light. Do not freeze or shake. Do not use ELAPRASE after the expiration date on the vial.

17 PATIENT COUNSELING INFORMATION

Information for Patients

Patients should be advised that life-threatening anaphylactic reactions have occurred in some patients during and up to 24 hours after ELAPRASE therapy. 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 hypersensitivity reactions.

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, call Shire Human Genetic Therapies, Inc. at 1-866-888-0660.

ELAPRASE is manufactured by:

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Shire