

**elaprase**<sup>®</sup>  
(idursulfase)

# Guidelines for dosing and infusion

Preparation and administration information for healthcare professionals.

## INDICATION

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

### 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.

## Preparation, dosing, and administration

ELAPRASE should be prepared and administered by a healthcare professional. Recommended ELAPRASE dosing is 0.5 mg/kg of body weight, administered intravenously (IV) every week 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. ELAPRASE must be diluted in 100 mL normal saline (0.9% Sodium Chloride Injection, USP) before use.

### HOW TO CALCULATE EACH PATIENT'S ELAPRASE DOSE

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) x 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.

#### Sample calculation

Patient weight: 21.7 kg

**Step 1:** 21.7 kg x 0.5 mg/kg = 10.85 mg

**Step 2:** 10.85 mg ÷ 2 mg/mL = 5.42 mL

**Step 3:** 5.42 mL ÷ 3 mL/vial = 1.8 vials (2 vials are used to withdraw a total volume of 5.4 mL)

**Required dose:** 5.4 mL of ELAPRASE (from 2 vials) for a patient weighing 21.7 kg

These dosing and infusion guidelines are recommendations only. They should be reconciled with appropriate institution policies/procedures, other manufacturers' guidelines, and required regulations and medical judgment.

## IMPORTANT HANDLING AND STORAGE INSTRUCTIONS FOR ELAPRASE

- Vials should be stored under refrigeration at 2°C–8°C (36°F–46°F); protect from light. Do not freeze or shake
- 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 contains particulate matter or is discolored. Do not use ELAPRASE after the expiration date on the vial
- DO NOT mix/administer ELAPRASE with other drug solutions or other IV fluids except 0.9% Sodium Chloride Injection, USP
- Once diluted, the bag containing the ELAPRASE solution should be mixed gently but not shaken
- Since no preservative is present, the diluted ELAPRASE solution should be used immediately. If not used immediately, the diluted solution must be administered within 8 hours if held at room temperature or can be stored refrigerated at 2°C–8°C (36°F–46°F) for up to 48 hours
- Diluted solution should be discarded if not administered or refrigerated within 8 hours of preparation
- ELAPRASE is supplied in single-use vials. The vials contain no preservative. Remaining drug left in the vial should be disposed of in accordance with local requirements

## RECOMMENDED INFUSION SUPPLIES

### Preparation for diluting ELAPRASE solution

- 100 mL bag of 0.9% Sodium Chloride Injection, USP
- Syringe(s) to withdraw drug from vial(s)

### Additional infusion supplies

- 100–250 mL bag of 0.9% Sodium Chloride Injection, USP (primary/emergency infusate)
- 50 mL bag of 0.9% Sodium Chloride Injection, USP (flush infusate)
- IV needle/catheter and insertion supplies
- IV administration set with a 0.2-micrometer (µm) filter (filter may be in-line or a separate add-on device)
- IV administration set with injection/access port (no filter required, as this line will be the primary/emergency line)
- Add-on device(s) as required for a modified piggyback or secondary infusion technique
- Infusion control device
- Supplies required as per institution guidelines

## PREPARATION AND ADMINISTRATION: USE ASEPTIC TECHNIQUES

It is recommended that ELAPRASE not be diluted for administration until the infusion provider has seen the patient and has established IV access. Dilute the total calculated volume of ELAPRASE in 100 mL of 0.9% Sodium Chloride Injection, USP.

Please see Important Safety Information on page 7.

*Follow these steps to dilute ELAPRASE®*

- Step 1:** Remove the cap from a stock bag containing 100 mL of 0.9% Sodium Chloride Injection, USP.
- Step 2:** Wipe the exposed rubber seal injection port with an alcohol pad and allow to dry.
- Step 3:** Remove the flip-off cap from the ELAPRASE vial(s).
- Step 4:** Wipe the exposed rubber seal(s) of the vial(s) with alcohol pads and allow to dry.
- Step 5:** Using sterile syringe(s), withdraw the calculated volume of ELAPRASE from the appropriate number of vials.
- Step 6:** Slowly add the contents of the syringe(s) to the bag containing 100 mL of 0.9% Sodium Chloride Injection, USP. Once diluted into normal saline, gently mix the infusion bag. Do not shake.
- Step 7:** Label the ELAPRASE solution with the patient name, product name, dose, discard date, and time, or as per institution policy. Diluted solution should be discarded if not administered or refrigerated within 8 hours of preparation.

*Intravenous administration*

ELAPRASE is intended for IV use only. The ELAPRASE infusion is given over a period of 1 to 3 hours.

**To administer ELAPRASE, a modified piggyback or secondary infusion technique is recommended:**

1. Obtain IV access and establish a primary/emergency line.
2. Prepare the ELAPRASE solution according to the instructions above.
3. Spike the 100 mL bag of 0.9% Sodium Chloride Injection, USP, containing ELAPRASE with the filtered IV administration set and prime according to the set manufacturer's recommendations.
4. Once the tubing is primed, connect the ELAPRASE drug solution to the primary line's injection/access port (closest to the vascular access device).
5. Start the infusion control device to regulate the flow of the ELAPRASE solution at the prescribed rate. 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.
6. Infuse the ELAPRASE solution.
7. After the ELAPRASE solution has been infused, remove the ELAPRASE drug bag from the IV administration set and replace with the bag containing 50 mL of 0.9% Sodium Chloride Injection, USP. Flush through the volume of drug remaining in the IV tubing to ensure full dosing.

**EXAMPLE**

*3-hour infusion flow regulation*

Time of Infusion	Rate of Infusion	Volume Given During Interval
Start (0-15 minutes)	8 mL/hr	2 mL
15 minutes	16 mL/hr	4 mL
30 minutes	24 mL/hr	6 mL
45 minutes	32 mL/hr	8 mL
60 minutes to end of infusion at 180 minutes	40 mL/hr	80 mL

**Important:** At no time should the infusion rate exceed 100 mL per hour. If the patient appears to be exhibiting any unusual reaction to the infusion (including but not limited to flushing, fever, hives, irritability, rash, respiratory difficulty, and pulse or blood pressure alterations), immediately halt the ELAPRASE infusion and consult the prescribing physician.

**Additional information for ELAPRASE administration**

**ABOUT HUNTER SYNDROME PATIENTS**

Most Hunter syndrome patients have airway abnormalities. Because of this, healthcare professionals administering ELAPRASE should ensure that the treatment area is equipped with a functioning suction and oxygen setup with a face mask. The patient with a tracheostomy will require the proper-sized suction catheter and saline for lavage. It is also recommended that the healthcare professional administering ELAPRASE have available a physician order for ELAPRASE infusion emergency procedures and emergency medication and resuscitation kits. Close monitoring is essential throughout the infusion and observation period.

Many Hunter syndrome patients experience airway obstructions due to narrowed or blocked nasal passages, a large tongue, enlarged adenoids and/or tonsils, abnormal/narrowed trachea, and/or diminished rib movement with breathing. Therefore, prior to infusion, it is important for the physician to assess the patient exhibiting signs of upper respiratory illness, as any additional swelling can significantly compromise the airway. Physicians may want to consider delaying ELAPRASE infusion in patients who present with concomitant acute respiratory and/or febrile illness.

Please see Important Safety Information on page 7.

## INFUSION-RELATED ADVERSE EVENTS

Infusions of protein therapeutics can be associated with infusion-related adverse events that may or may not be immune-mediated. Thus, potential reactions to ELAPRASE® infusions are difficult to predict. The most common infusion-related adverse events in clinical trials included headache, fever, cutaneous reactions (rash, pruritus, erythema, and urticaria), and hypertension.

Hypersensitivity reactions, which may be life threatening, have been observed in some patients during ELAPRASE infusions. Reactions have included respiratory distress, hypoxia, hypotension, angioedema, or seizure. Late-emergent anaphylactoid reactions have been observed after ELAPRASE administration. Patients who have experienced severe and refractory anaphylactoid reactions may require prolonged observation times.

Patients with compromised respiratory function or acute respiratory disease may be at higher risk of life-threatening complications from infusion reactions. Therefore, these patients should be closely monitored and infused with ELAPRASE in an appropriate clinical setting. Consider delaying ELAPRASE infusion in patients with concomitant acute respiratory and/or febrile illness. Patients using supplemental oxygen should have this treatment readily available during infusion in the event of an infusion-related adverse event.

## MANAGEMENT OF INFUSION-RELATED ADVERSE EVENTS

If a severe infusion reaction occurs, immediately suspend the infusion of ELAPRASE and initiate appropriate treatment, depending on the severity of the symptoms. The current medical standards for emergency treatment are to be observed.

ELAPRASE infusion-related adverse events have been managed by slowing the infusion rate, interrupting the infusion, and/or the administration of medications (eg, antihistamines and/or corticosteroids) prior to or during infusions. If, after intervention with medication and altering the infusion rate, the infusions continue without incident, tapering of medications should be considered first, followed by a return to the original infusion rate.

### Modifying the infusion rate

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.

- A 1-hour infusion could be lengthened up to 3 hours
- A 3-hour infusion could be modified by
  - Lengthening the initial ramp-up of infusion rate
  - Slowing the final rate
  - A combination of the above modifications (eg, a slower ramp-up and slower final rate)

At no time should the infusion rate exceed 100 mL per hour. Infusion time should not exceed 8 hours.

### Restarting infusion after interruption

In patients who are clinically stable and have experienced infusion-related adverse events, an interrupted infusion may be restarted based on the clinical judgment of the physician. In some cases, management of the reaction with medication may be needed prior to restarting the infusion (see page 7).

### Administration of medication

Premedication regimens for managing infusion-related adverse events are patient-specific and usually dictated by the severity of prior symptoms. Patients experiencing mild infusion-related reactions may be

premedicated with an antihistamine prior to subsequent infusions. Patients experiencing moderate or severe infusion-related adverse events may be premedicated with both an antihistamine and/or corticosteroid prior to subsequent infusions. Premedication with ibuprofen or acetaminophen may also be considered if fever has occurred.

## FOR MORE INFORMATION

ELAPRASE is supported by OnePath<sup>SM</sup> from Shire Human Genetic Therapies, a comprehensive resource for healthcare professionals, families, and patients with Hunter syndrome (MPS II). For product-related questions, contact OnePath<sup>SM</sup> by calling 1-866-888-0660, 8:30 a.m. to 8:00 p.m. Eastern Time. Medical information is also available 24 hours a day, 7 days a week at this toll-free number.

## Important Safety Information

### Indication

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

### Important Safety Considerations

**Risk of anaphylactic reactions: 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.**

- 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 and 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
- 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.
- 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. If a severe infusion reaction occurs, immediately suspend the infusion of ELAPRASE and initiate appropriate treatment. 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.
- In clinical studies, 51% of patients treated with ELAPRASE developed anti-idursulfase IgG antibodies. These patients had an increased incidence of infusion reactions, including allergic reactions. The relationship between the presence of anti-idursulfase antibodies and clinical efficacy outcomes is unknown.
- In clinical studies, the most common adverse events seen in patients treated with ELAPRASE were pyrexia (63%), headache (59%), and arthralgia (31%). The most common adverse reactions requiring intervention were infusion-related reactions including: headache, fever, cutaneous reactions (rash, pruritus, erythema and urticaria) and hypertension.
- The most frequent serious adverse events related to the use of ELAPRASE were hypoxic episodes. Other notable serious adverse reactions that occurred in ELAPRASE patients but not in placebo patients included one case each of cardiac arrhythmia, pulmonary embolism, cyanosis, respiratory failure, infection and arthralgia.

Please see full Prescribing Information, including Boxed Warning.



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# elaprase<sup>®</sup>

(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 <sub>max</sub> (μg/mL)	1.5 (0.6)	1.1 (0.3)
AUC (min*μg/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)

## 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 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 <sup>a</sup>			Placebo n=32 <sup>a</sup>			ELAPRASE Weekly- Placebo
	Baseline	Week 53	Change <sup>b</sup>	Baseline	Week 53	Change <sup>b</sup>	Difference in Change
<b>Results from the 6-Minute Walk Test (Meters)</b>							
Mean ± SD	392 ± 108	436 ± 138	44 ± 70	393 ± 106	400 ± 106	7 ± 54	37 ± 16 <sup>c</sup> 35 ± 14 <sup>d</sup> (p = 0.01)
Median	397	429	31	403	412	-4	
Percentiles (25 <sup>th</sup> , 75 <sup>th</sup> )	316, 488	365, 536	0, 94	341, 469	361, 460	-30, 31	
<b>Results from the Forced Vital Capacity Test (% of Predicted)</b>							
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 <sup>c</sup> 4.3 ± 2.3 <sup>d</sup> (p = 0.07)
Median	54.9	59.2	2.1	57.4	54.6	-2.5	
Percentiles (25 <sup>th</sup> , 75 <sup>th</sup> )	43.6, 69.3	44.4, 70.7	-0.8, 9.5	46.9, 64.4	43.8, 67.5	-5.4, 5.0	
<sup>a</sup> 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 <sup>b</sup> Change, calculated as Week 53 minus Baseline <sup>c</sup> Observed mean ± SE <sup>d</sup> 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.elaprased.com](http://www.elaprased.com) or call OnePath<sup>SM</sup> 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 ( $\mu$ m) 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.

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

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

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. 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.

NDC 54092-700-01

### Rx Only

ELAPRASE is manufactured for:

Shire Human Genetic Therapies, Inc.  
700 Main Street  
Cambridge, MA 02139  
US License Number 1593

OnePath<sup>SM</sup> phone # 1-866-888-0660

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