

ELAPRASE[®] (idursulfase)

Solution for intravenous infusion

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.

2. DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

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

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

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

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.

2. Before withdrawing the ELAPRASE solution from the vial, visual inspect each vial for particulate matter and discoloration. 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 may be stored refrigerated for up to 24 hours.
5. ELAPRASE is supplied in single-use vials. Remaining ELAPRASE left in a vial after withdrawing the patient's calculated dose should be disposed of in accordance with local requirements.

2.3 Administration Instructions

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.

2.4 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 24 hours. Other than during infusion, do not store the diluted ELAPRASE solution at room temperature.

3.CONTRAINDICATIONS

None.

4.WARNINGS AND PRECAUTIONS

4.1 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].

In clinical trials with ELAPRASE, 16/108 patients (15%) 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 significant allergic 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 post-marketing 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.

4.2 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 3). 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, Adverse Reactions].

4.3 Risk of Acute Respiratory Complications

Patients with compromised respiratory function or acute 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.

4.4 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].

5. ADVERSE REACTIONS

Adverse drug reactions are listed in Table 1. Information is presented by system organ class and frequency (very common $\geq 1/10$; common $\geq 1/100$, $< 1/10$). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Adverse drug reactions derived from post-marketing reports other than interventional clinical trials are printed in italic.

The most common reactions are infusion-related reactions including cutaneous reactions (rash, pruritus, urticaria and erythema), pyrexia, flushing, wheezing, dyspnoea, headache, vomiting, abdominal pain, nausea, and chest pain. An infusion-related reaction was defined as an AE that occurred on the day of the infusion (i.e., within 24 hours after receiving an infusion), began either during or after the infusion, was judged as possibly or probably related to study drug, and was not associated with protocol-defined testing or assessments.

Table 1 Adverse Drug Reactions (ADRs) Reported with Elaprase

System Organ Class	Incidence Category	Adverse Drug Reaction (Preferred Term)
Immune system disorders	Frequency not known	<i>Anaphylactoid/anaphylactic reaction</i>
Nervous system disorders	Very Common:	Headache
Cardiac disorders	Common:	Cyanosis Arrhythmia Tachycardia
Vascular disorders	Very Common: Common:	Flushing Hypertension Hypotension
Respiratory, thoracic and mediastinal disorders	Very common: Common: Uncommon:	Wheezing Dyspnoea Hypoxia Bronchospasm Tachypnoea
Gastrointestinal disorders	Very common: Common:	Vomiting Abdominal pain Nausea Swollen tongue Dyspepsia
Skin and subcutaneous tissue disorders	Very Common:	Urticaria Rash Pruritus Erythema
General disorders and administration site conditions	Very common: Common:	Pyrexia Chest pain Infusion site swelling Face oedema Oedema peripheral
Injury, poisoning and procedural complications	Very common:	Infusion related reaction

5.1 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]

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 studies, 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 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 2 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 2. 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 3 summarizes these findings.

Table 3. 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					
M U T A T I O N S	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*].

5.2 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 3). Of these 15 patients, neutralizing antibodies were observed in 13 (87%) patients. The NAb 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].

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.

5.3 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].

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].

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

6. USE IN SPECIFIC POPULATIONS

6.1 Pregnancy: Teratogenic Effects: Category C

Teratogenicity studies have not been conducted with ELAPRASE. A pre- and postnatal development study in rats showed no evidence of adverse effects on pre- and postnatal development at intravenous doses up to 12.5 mg/kg, administered twice weekly (about 4 times the recommended human weekly dose of 0.5 mg/kg based on body surface area). There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

6.2 Nursing Mothers

ELAPRASE was excreted in breast milk of lactating rats at a concentration higher (4 to 5-fold) than that of the plasma. It is not known whether ELAPRASE 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.

6.3 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).

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

6.4 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.

7.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.

8.DESCRPTION

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 (GAG) 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 U/mg of protein (one unit is defined as the amount of enzyme required to hydrolyze 1 μ mole 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.

9.CLINICAL PHARMACOLOGY

9.1 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 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 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.

9.2 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 and Clinical Studies].

9.3 Pharmacokinetics

Clinical Trials in Patients 5 Years and Older

The pharmacokinetic characteristics of idursulfase were evaluated in several studies 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 ages 7.7 to 27 years (Table 4). There were no apparent differences in PK parameter values between Week 1 and Week 27 regardless of the antibody status in these patients.

Table 4 Pharmacokinetic Parameters in Patients 7.7 to 27 Years of Age (Mean, Standard Deviation)

Pharmacokinetic Parameter	Week 1	Week 27
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} (% BW)	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 5). Idursulfase pharmacokinetics was similar between Week 1 and Week 27 in Ab-negative patients (Table 5).

Table 5. Pharmacokinetic Parameters in Patients 16 months to 7.5 Years of Age

Pharmacokinetic Parameter	Week 1	Week 27	
	(N=27) All Patients Mean (SD)	Anti-idursulfase Antibodies (Ab) [*]	
		(n=9) Negative Ab Mean (SD)	(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.

10. NONCLINICAL TOXICOLOGY

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.

11. CLINICAL STUDIES

Clinical Trials in Patients 5 Years and Older

The safety and efficacy of ELAPRASE were evaluated in 53-week, randomized, double-blind, placebo-controlled clinical study 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 patients' ages ranged from 5 to 31 years. 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 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 6).

Table 6 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.							

Pharmacodynamic assessment 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 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.

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.

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]. 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. Drug Interactions

No formal drug interaction studies have been conducted with ELAPRASE.

13. 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 fluoro-resin coating and an aluminum overseal with a blue flip-off plastic cap.

14. 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, visit www.elaprase.com.

Rx Only

15. MANUFACTURE BY :

Vetter Pharma-Fertigung GmbH&Co. KG, Langenargen, Germany

16. MARKETING AUTHORISATION HOLDER

Sanofi-aventis (Thailand) Ltd. Bangkok, Thailand

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19. DATE OF REVISION

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