elaprase® (idursulfase)

ELAPRASE WEIGHT-BASED DOSING AND INFUSION GUIDE

ELAPRASE Indications and Usage

ELAPRASE® (Idursulfase) 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.

IMPORTANT SAFETY 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.

For Healthcare Professionals

Please see additional Important Safety Information on pages 14–15 and CLICK HERE to see accompanying Full Prescribing Information, including Boxed WARNING for Risk of Anaphylaxis.

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For more information, please visit www.ELAPRASE.com/HCP

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IMPORTANCE OF WEIGHT-BASED DOSING

Hunter syndrome is caused by a deficiency in the activity of the lysosomal enzyme iduronate -2-sulfatase (I2S).[1] In a healthy individual, every cell in the body, except red blood cells, expresses the I2S enzyme.[2]

ELAPRASE is a purified form of the I2S enzyme, designed to replace the deficient or malfunctioning I2S enzyme in Hunter syndrome patients.[1]

The recommended dose of ELAPRASE is dependent on the body weight of the Hunter syndrome patient.[1] It is therefore important to weigh patients before each infusion to ensure correct dosing.

IMPORTANT SAFETY INFORMATION (CONTINUED)

Hypersensitivity Reactions Including Anaphylaxis: Ensure that personnel administering product are adequately trained in cardiopulmonary resuscitative measures, and have ready access to emergency medical services (EMS).

If anaphylactic or other acute reactions occur, immediately discontinue the infusion of ELAPRASE and initiate appropriate medical treatment. 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. 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.

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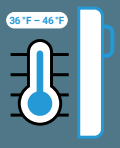
STORING AND HANDLING ELAPRASE VIALS

This guide has been designed to inform you how ELAPRASE vials should be stored and handled correctly.

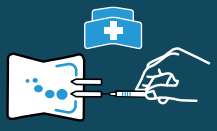
ELAPRASE is supplied as a sterile injection in a 5 mL Type I glass vial and each carton contains a single vial. Elaprase vials are single use.

Pick up the vials of ELAPRASE carefully. Do not shake ELAPRASE.[1]



Store ELAPRASE vials in the carton in a refrigerator at 36°F to 46°F (2°C to 8°C) to protect from light. Do not freeze.[1]

When it is time to use ELAPRASE, check the expiration date on the vial. ELAPRASE should not be used after the expiration date on the vial.[1]



Prior to infusion, the appropriate dose of ELAPRASE will be diluted in a 100 mL bag of 0.9% Sodium Chloride Injection, USP for intravenous infusion. The diluted ELAPRASE is then infused at room temperature.[1]

If immediate use is not possible, the diluted solution should be stored refrigerated at 36°F to 46°F (2°C to 8°C) for up to 24 hours. Any unused product or waste material should be discarded and disposed of in accordance with local requirements.[1]

For more information on storing and handling ELAPRASE vials, please **CLICK HERE** to refer to the Full Prescribing Information.

IMPORTANT SAFETY INFORMATION (CONTINUED)

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.

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DOSE CALCULATION

Recommended dose of ELAPRASE

The recommended dosage regimen of ELAPRASE is 0.5 mg per kg of body weight, administered once weekly as an intravenous (IV) infusion.[1]

Calculation legend

The patient weight: "patient weight" in kg

The recommended dose: 0.5 mg/kg[1]

The concentration of ELAPRASE solution: 2 mg/mL[1]

The volume of one vial: 3 mL[1]

IMPORTANT SAFETY INFORMATION (CONTINUED)

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.

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DOSE CALCULATION (CONTINUED)

Calculation example

Patient weight: 21 kg

- **Step 1:** 21 kg x 0.5 mg/kg = 10.5 mg
- **Step 2:** 10.5 mg ÷ 2 mg/mL = 5.25 mL
- **Step 3:** 5.25 mL ÷ 3 mL/vial = 1.75 vials
- **Step 4:** Withdraw 5.25 mL ELAPRASE, using 2 vials
- **Step 5:** Dispose of unused product

Calculation process

$$\frac{\text{(“patient weight” kg x 0.5 mg/kg)}}{\text{2 mg/mL}} = \text{volume (mL) ELAPRASE solution needed}$$

$$\frac{\text{(“patient weight” kg x 0.5 mg/kg) /2 mg/mL}}{\text{3 mL}} = \text{number of vials required}$$

Visit www.ELAPRASE.com/HCP/dosing-and-administration/dosing-calculation to use the ELAPRASE dose calculator.

IMPORTANT SAFETY INFORMATION (CONTINUED)

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.

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PREPARING ELAPRASE

Supplies for infusion:

1. Required supplies for diluting ELAPRASE solution

- ☐ 100 mL bag of 0.9% Sodium Chloride Injection, USP.[1]
- ☐ Low-protein-binding infusion set equipped with a low-protein-binding 0.2 micrometer (µm) in-line filter.[1]

ELAPRASE should not be infused with other products in the infusion tubing.[1]

2. Additional infusion supplies*

- ☐ Blunt fill or filter needle to withdraw drug from vial(s).[3]
- ☐ 50 mL bag of 0.9% Sodium Chloride Injection, USP (flush infusate).[3]
- ☐ IV needle/catheter and insertion supplies.[3]
- ☐ Infusion control device.

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

IMPORTANT SAFETY INFORMATION (CONTINUED)

Adverse Reactions: 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.

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.

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elaprase® (idursulfase)

PREPARING ELAPRASE (CONTINUED)

Preparation instructions

ELAPRASE is diluted in 0.9% Sodium Chloride Injection, USP for administration by intravenous infusion. The amount of ELAPRASE that is added to the 100 mL bag of 0.9% Sodium Chloride Injection, USP is determined by the patient's weight.[1] Use aseptic technique when preparing and administering ELAPRASE.

1. **Having calculated the volume of ELAPRASE needed (based on the patient's weight), remove the required number of ELAPRASE vials from the refrigerator and allow them to reach room temperature.[1]**

2. **Before withdrawing the ELAPRASE solution from the vials, visually inspect each vial for particulate matter and discoloration:[1]**

- The ELAPRASE solution should be clear to slightly opalescent and colorless.[1]
- Do not use if the solution is discolored or if there is particulate matter in the solution.[1]
- Do not shake the ELAPRASE solution.[1]

3. **Withdraw the calculated volume of ELAPRASE from the appropriate number of vials and add to a 100 mL bag of 0.9% Sodium Chloride Injection, USP for IV infusion.[1]**

- Label the ELAPRASE solution with the patient name, product name, dose, discard date, and time (or as per institution policy).[3]
- ELAPRASE vials are single-use only. Any unused product or waste material should be discarded and disposed of in accordance with local requirements.[1]

4. **Mix gently. Do not shake the solution.[1]**

- ELAPRASE does not contain preservatives; therefore, after dilution with saline, the infusion bags should be used immediately.[1]
- If immediate use is not possible, see Storage and Stability.[1]

IMPORTANT SAFETY INFORMATION (CONTINUED)

Immunogenicity: In clinical trials in patients 5 years and older, 32 of 63 (51%) patients tested positive for anti-idursulfase IgG antibodies (Ab) at least one time. Of the 32 Ab-positive patients, 23 of 32 (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 (neutralizing antibodies, NAb) or enzymatic activity 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.

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, with 16 of 19 (84%) having persistent Ab. In addition, 15 of 19 (79%) Ab-positive patients tested positive for NAb, with 14 of 15 (93%) having persistent NAb.

Please see additional Important Safety Information on pages 14–15 and CLICK HERE to see accompanying Full Prescribing Information, including Boxed WARNING for Risk of Anaphylaxis.

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ADMINISTRATION INSTRUCTIONS

1. **ELAPRASE is intended for IV use only. Obtain or assess IV access.[3]**

2. **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.[1]**

- ELAPRASE should not be infused with other products in the infusion tubing.[1]

3. **Start the infusion control device to regulate the flow of the ELAPRASE solution at the prescribed infusion rate:[3]**

- 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.[1]
- The initial infusion rate should be 8 mL per hour for the first 15 minutes.[1]
- If the infusion is well tolerated, the rate of infusion may be increased by 8 mL per hour increments every 15 minutes.[1]
- The infusion rate should not exceed 100 mL per hour.[1]
- Patients may require longer infusion times if hypersensitivity reactions occur; however, infusion times should not exceed 8 hours.[1]
- The infusion rate may be slowed, temporarily stopped, or discontinued for that visit in the event of hypersensitivity reactions. See Section 5.1 of the Warnings and Precautions section of the Prescribing Information.[1]

IMPORTANT SAFETY INFORMATION (CONTINUED)

Postmarketing 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.

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

Please see additional Important Safety Information on pages 14–15 and CLICK HERE to see accompanying Full Prescribing Information, including Boxed WARNING for Risk of Anaphylaxis.

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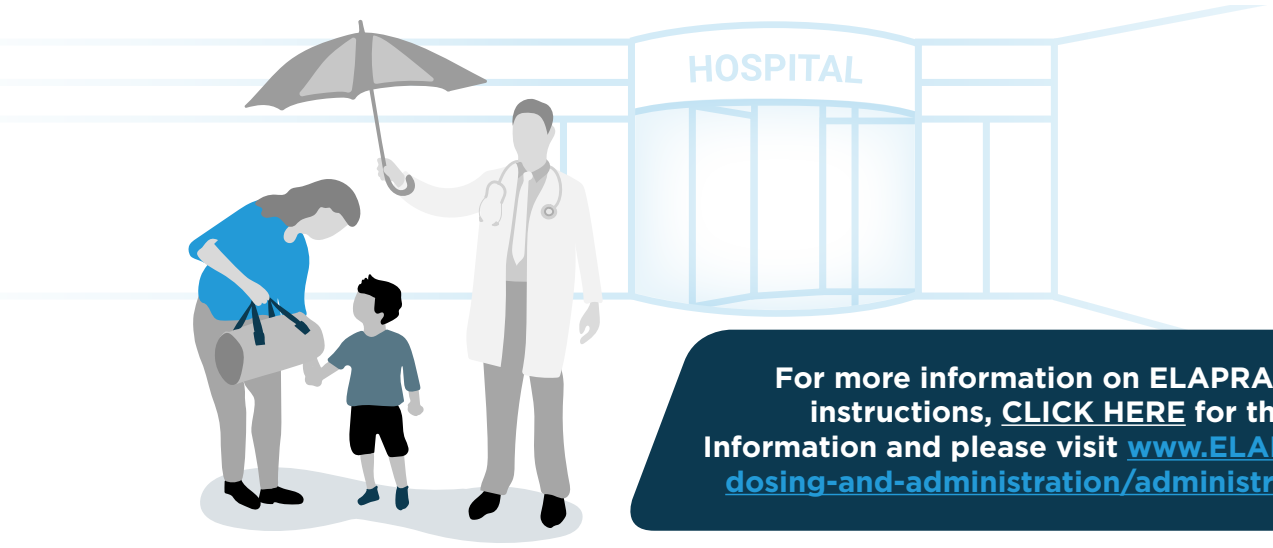
ADMINISTRATION INSTRUCTIONS (CONTINUED)

4. **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.[3]**

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

Physicians can consider whether home infusions may be an option for patients that tolerate ELAPRASE infusions well.



For more information on ELAPRASE administration instructions, CLICK HERE for the Full Prescribing Information and please visit www.ELAPRASE.com/HCP/dosing-and-administration/administration-instructions

IMPORTANT SAFETY INFORMATION (CONTINUED)

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.

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elaprase® (idursulfase)

STORAGE AND STABILITY

Store ELAPRASE vials in the carton at 36°F to 46°F (2°C to 8°C) to protect from light.[1]

Do not freeze or shake. Do not use ELAPRASE after the expiration date on the vial.[1]

ELAPRASE does not contain preservatives; therefore, after dilution with saline, the diluted solution should be used immediately.[1]

If immediate use is not possible, the diluted solution should be stored refrigerated at 36°F to 46°F (2°C to 8°C) for up to 24 hours.[1]

Other than during infusion, do not store the diluted ELAPRASE solution at room temperature.[1]

ELAPRASE vials are single use. Any unused product or waste material should be discarded and disposed of in accordance with applicable requirements.[1]

For more information on storage and stability, CLICK HERE for the Full Prescribing Information and please visit www.ELAPRASE.com/HCP/dosing-and-administration/storage-and-stability

IMPORTANT SAFETY INFORMATION (CONTINUED)

Hypersensitivity Reactions Including Anaphylaxis: Ensure that personnel administering product are adequately trained in cardiopulmonary resuscitative measures, and have ready access to emergency medical services (EMS).

If anaphylactic or other acute reactions occur, immediately discontinue the infusion of ELAPRASE and initiate appropriate medical treatment. 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. 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.

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elaprase® (idursulfase)

HYPERSENSITIVITY REACTIONS, INCLUDING ANAPHYLAXIS

Management of hypersensitivity reactions, including anaphylaxis

If anaphylactic or other acute reactions occur, immediately discontinue the infusion of ELAPRASE and initiate appropriate medical treatment.[1]

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.[1]

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 2–4 month time period. Anaphylactic reactions have been managed by:

- Discontinuing treatment[1]
- Using a slower infusion rate[1]
- Premedication[1]
- Treatment with antihistamines[1]
- Inhaled beta-adrenergic agonists[1]
- Corticosteroids[1]
- Oxygen[1]
- Vasopressors.[1]

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.[1]

Visit www.ELAPRASE.com/HCP/about/safety-information for more information about ELAPRASE safety results.

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elaprase® (idursulfase)

ELAPRASE Indications and Usage

ELAPRASE® (Idursulfase) 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.

Important Safety Information

WARNING: RISK OF ANAPHYLAXIS

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Hypersensitivity Reactions Including Anaphylaxis:

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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.

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.

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elaprase® (idursulfase)

Important Safety Information (continued)

Risk of Acute Cardiorespiratory Failure:

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Adverse Reactions:

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.

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.

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In clinical trials in patients 5 years and older, 32 of 63 (51%) patients tested positive for anti-idursulfase IgG antibodies (Ab) at least one time. Of the 32 Ab-positive patients, 23 of 32 (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.

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Postmarketing Experience:

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

To report SUSPECTED ADVERSE REACTIONS, contact Takeda at 1-877-TAKEDA7 or FDA at 1-866-FDA-1088 or www.fda.gov/medwatch

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1. ELAPRASE Prescribing Information. 2. Martin R *et al. Pediatrics* 2008; 121(2): e377–386. 3. Lilley LL *et al. Pharmacology and the Nursing Process (7th ed.)* Missouri: Elsevier, 2014.

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