elaprase® (idursulfase)

DISCUSSING ELAPRASE: YOUR CURRENT PATIENT 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 20–21 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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CONTENTS

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INTRODUCTION

This guide has been designed for healthcare professionals to use and refer to when supporting patients and caregivers with their ELAPRASE treatment.

While every discussion with patients and caregivers will be different, this guide provides information which may be relevant in your discussions.

The topics covered touch on the possible clinical benefits of ELAPRASE and the risks associated with the treatment. Clinical trial designs and outcomes are also displayed here to provide further insight into ELAPRASE's safety and efficacy profile.

If your patient and their caregiver are Spanish-speaking, materials are available in Spanish to aid their understanding.

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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HUNTER SYNDROME MANAGEMENT

Hunter syndrome, also known as mucopolysaccharidosis II (MPS II), is a chronic, progressive metabolic disease. Hunter syndrome is heterogeneous: the multisystemic signs and symptoms have a variable age of onset and variable progression, and there is a wide spectrum of clinical severity.[1,2]

Due to the multisystemic nature of the disease, a multidisciplinary team of specialists may be involved in disease management.[2,3] Inform your patients and caregivers about the healthcare professionals in the multidisciplinary team and the roles they may play. These healthcare professionals may include, but are not limited to:

- Pediatricians
- Specialist nurses
- Metabolic geneticists
- Rheumatologists
- Neurologists
- Cardiologists
- Physiotherapists
- Speech therapists

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.

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 DOSING AND ADMINISTRATION

- ELAPRASE is administered as an intravenous infusion at a recommended dose of 0.5 mg per kg of body weight given once a week.[4] The dose of ELAPRASE depends on the patient's weight, so they will be regularly weighed to calculate the optimal dose.
- To receive ELAPRASE, patients will go to a treatment center every week for an infusion that can last 3 hours, but patients may require longer infusion times if hypersensitivity reactions occur. The infusion time may be gradually reduced to 1 hour if no hypersensitivity reactions occur. There may also be additional time needed for preparation and observation.[4]
- With each infusion, patients are closely monitored. The infusion rate may be slowed, temporarily stopped, or discontinued for that visit in the event of hypersensitivity reactions.[4]
- Patients who tolerate the infusions well may be able to receive infusions at home under the supervision of a healthcare professional. These administration guidelines are recommendations only. They should be reconciled with appropriate institution policies and procedures, required regulations, and medical judgment.

For more information about ELAPRASE dosing and administration, please visit www.elaprase.com/hcp/dosing-and-administration

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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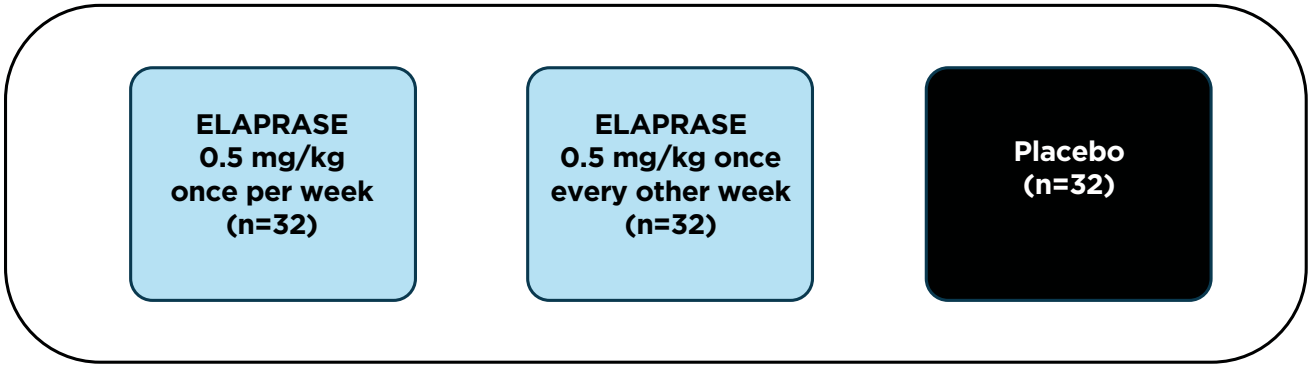
ELAPRASE SAFETY PROFILE AND CLINICAL TRIAL OUTCOMES

Pivotal trial

The safety and efficacy of ELAPRASE were studied in a 53-week pivotal, double-blind, placebo -controlled clinical trial involving 96 Hunter syndrome patients aged 5 years and older.[4]



Trial outcomes

Patients in the ELAPRASE weekly treatment group exhibited a significant improvement, compared with patients who received placebo, in the primary efficacy endpoint: a two-component score based on a statistical analysis of (1) the distance walked during a 6–minute walking test (6-MWT) and (2) a common measure of lung function called % predicted forced vital capacity (% predicted FVC).[4]

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 SAFETY PROFILE AND CLINICAL TRIAL OUTCOMES (CONTINUED)

Pivotal trial

Primary endpoint

The primary endpoint of the trial was a two-component score based on the analysis of:

1 **The distance walked during a 6-minute walking test (6-MWT)**

and

2 **An assessment of lung function called % predicted forced vital capacity (% FVC)**

Patients in the ELAPRASE weekly treatment group exhibited a significant improvement in the primary efficacy endpoint compared with patients who received placebo (p=0.0049)[4]

6-Minute Walking Test[5]

The 6-MWT measured the integrated function of at least 3 separate organ systems that are affected by MPS II: the respiratory, cardiovascular, and musculoskeletal systems.

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.

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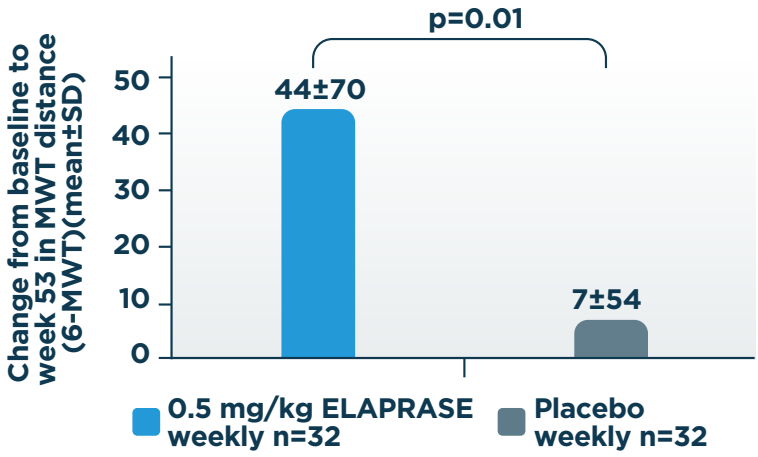
ELAPRASE SAFETY PROFILE AND CLINICAL TRIAL OUTCOMES (CONTINUED)

Pivotal trial

Forced Vital Capacity[6]

Measured by spirometry which assessed the integrated mechanical function of the lung, chest wall, respiratory muscles, and airways.

Change in walking capacity in patients treated weekly with ELAPRASE or placebo[4]



Walking capacity

When the individual components of the composite score were examined separately, patients receiving ELAPRASE for 12 months could walk an average 37* meters more in 6 minutes than patients receiving placebo—this difference was statistically significant (p=0.01).[4]

*Observed mean.

Lung Function

The difference in %-predicted FVC from baseline to week 53 between patients treated with ELAPRASE weekly and those treated with placebo was not statistically significant.[4]

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.

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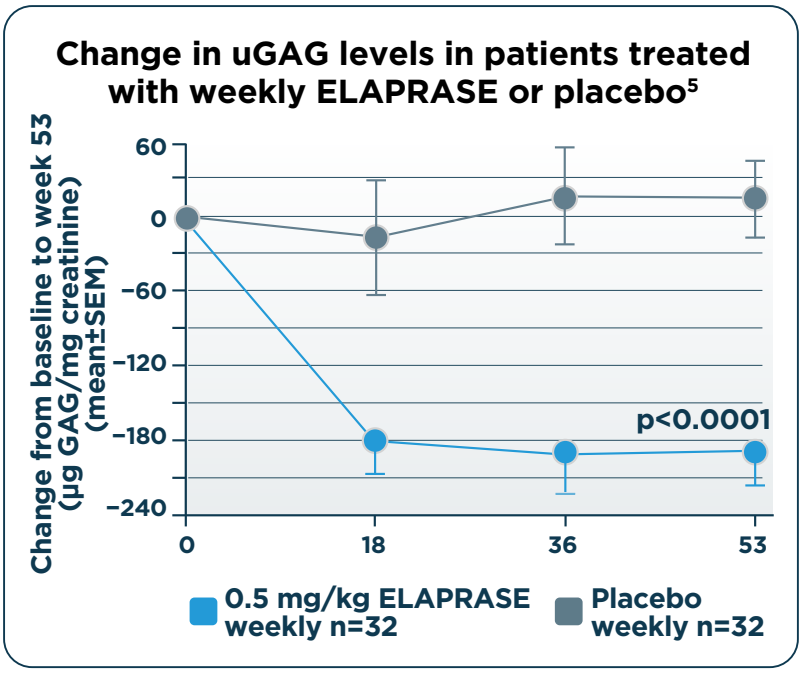
ELAPRASE SAFETY PROFILE AND CLINICAL TRIAL OUTCOMES (CONTINUED)

Pivotal trial

Secondary endpoints



Urinary GAG levels

Following 53 weeks of treatment, mean urinary glycosaminoglycan (GAG) levels were reduced in the ELAPRASE once-weekly group, although GAG levels still remained above the upper limit of normal in half of the ELAPRASE-treated patients. Patients who tested positive for anti-idursulfase antibodies experienced a less pronounced decrease in urinary GAG levels. The responsiveness of urinary GAG levels to dosage alterations of ELAPRASE is unknown, and the relationship of urinary GAG levels to other measures of clinical response has not been established.[4]

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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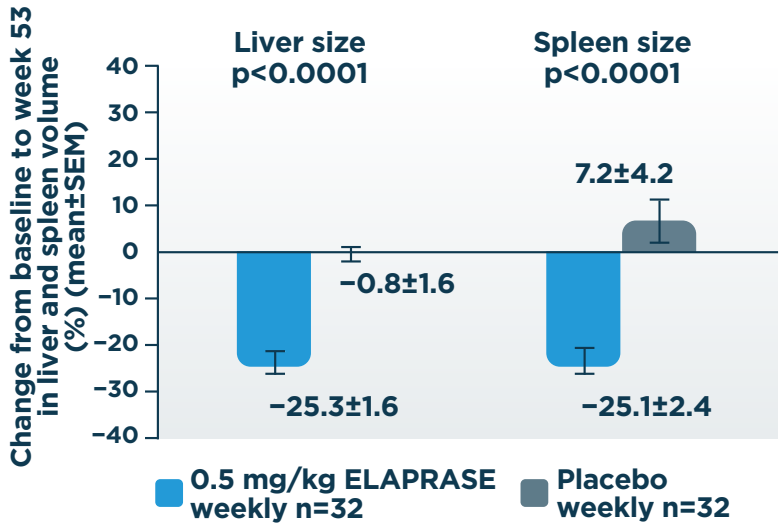
ELAPRASE SAFETY PROFILE AND CLINICAL TRIAL OUTCOMES (CONTINUED)

Pivotal trial

Secondary endpoints

Change in liver and spleen volume in patients treated weekly with ELAPRASE or placebo[5]



Liver volume and spleen volume

ELAPRASE was shown to reduce mean liver and spleen volumes from baseline to week 53 in patients 5 years and older treated with ELAPRASE once weekly. There were essentially no changes in liver and spleen volumes in the placebo group.[4]

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 SAFETY PROFILE AND CLINICAL TRIAL OUTCOMES (CONTINUED)

Pivotal trial

Safety profile

Hypersensitivity reactions were reported in 69% (22 of 32) of patients in the ELAPRASE once-weekly group.[4]

Adverse reactions that occurred in at least three patients (≥9%) in the ELAPRASE once-weekly group, and had a higher incidence than in the placebo group, included:[4]

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 three patients (≥9%) in the ELAPRASE 0.5 mg/kg once every other week group and occurred more frequently than in the placebo group included rash (19%), flushing (16%), fatigue (13%), rapid heart rate (9%), and chills (9%).[4]

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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ELAPRASE SAFETY PROFILE AND CLINICAL TRIAL OUTCOMES (CONTINUED)

Extension trial

Patients in the pivotal trial were eligible to continue treatment in an open-label extension trial; 94 of the 96 patients who were enrolled in the placebo-controlled trial consented to continue treatment in an open-label extension trial. During the extension trial, all patients received ELAPRASE 0.5 mg/kg once weekly for 24 months. The co-primary endpoints were 6-MWT and %-FVC.[4,7]

Trial outcomes

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-MWT for an additional 8 months of treatment in the extension trial.[4]

There was no change in mean %-predicted FVC in all Hunter syndrome patients after 6 months of treatment in the extension trial, followed by a slight decrease for the remainder of the 24-month period. The long-term effect of ELAPRASE on pulmonary function in Hunter syndrome patients is unclear.[4]

Urinary GAG levels

Among patients treated with weekly ELAPRASE, no further reduction in urinary GAG levels was observed during the extension trial. The persistence of reduced urinary GAG levels did not correlate with the long-term effect demonstrated by the 6-MWT or %-predicted FVC.[4]

Safety profile

No new serious adverse reactions were reported during the extension trial[4]

Approximately half (53%) of patients experienced hypersensitivity reactions during the 24-month extension trial.[4]

In addition to the frequently experienced adverse reactions in the pivotal trial (diarrhea [9%], musculoskeletal pain [13%], headache [28%], cough [9%], pruritus [25%], and urticaria [16%]), common hypersensitivity reactions occurring in at least five patients (≥5%) in the extension trial included:[4]

Rash	**(23%)**	**Erythema**	**(7%)**	**Vomiting**	**(5%)**
Pyrexia	**(9%)**	**Nausea**	**(5%)**	**Hypotension**	**(5%)**
Flushing	**(7%)**	**Dizziness**	**(5%)**		

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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ELAPRASE SAFETY PROFILE AND CLINICAL TRIAL OUTCOMES (CONTINUED)

Under 7s trial

Safety profile

Safety results demonstrated that patients aged 16 months to 7.5 years 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.[4]

Patients experienced similar adverse reactions to those observed in clinical trials with patients aged ≥5 years.[4]

The most common adverse reactions following ELAPRASE treatment were hypersensitivity reactions (57%)[4]

A higher incidence of the following common hypersensitivity reactions was reported in this younger age group:[4]

Pyrexia	**(36%)**
Rash	**(32%)**
Vomiting	**(14%)**

The most common serious adverse reactions, occurring in at least three patients (≥10%), included:[4]

Bronchopneumonia/pneumonia	**(18%)**
Ear infection	**(11%)**
Pyrexia	**(11%)**

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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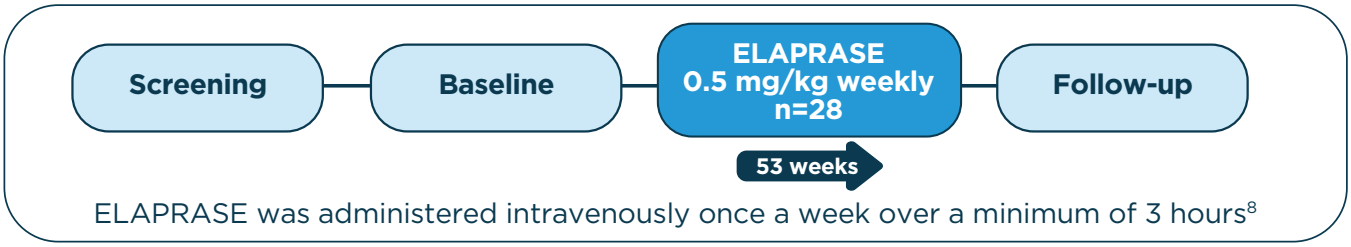
ELAPRASE SAFETY PROFILE AND CLINICAL TRIAL OUTCOMES (CONTINUED)

Under 7s trial

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 28 male Hunter syndrome patients aged 7 years and younger; it did not measure walking ability.[4,8]

Patients were 16 months to 4 years old (n=20) and 5 to 7.5 years old (n=8) at enrollment.[4]



ELAPRASE was administered intravenously once a week over a minimum of 3 hours[8]

Trial outcomes

Similar to the spleen volume reduction seen in the pivotal trial, treatment with ELAPRASE was shown to reduce spleen size in patients who remained antibody negative. A reduction in urinary GAG levels was observed, similar to the urinary GAG reduction seen in the pivotal trial.[4]

In patients who were persistently antibody positive, the presence of anti-idursulfase antibodies was associated with reduced systemic exposure of idursulfase and a less pronounced decrease in urinary GAG levels.[4]

The presence of anti-idursulfase antibodies was associated with a reduced systemic exposure of idursulfase. In contrast, no apparent differences in pharmacokinetic parameter values between week 1 and week 27 were observed in the placebo-controlled trial among patients aged ≥5 years old receiving 0.5 mg/kg ELAPRASE (n=10), regardless of their antibody status.[4]

Discuss whether caregivers of patients aged 7 years and younger are aware of which mutation affects their child, or arrange a consultation with a geneticist for them to find out, as well as to discuss whether the patient is likely to develop antibodies and/or experience hypersensitivity reactions when receiving ELAPRASE.[4]

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 SAFETY PROFILE AND CLINICAL TRIAL OUTCOMES (CONTINUED)

Risk of anaphylaxis

Life-threatening anaphylactic reactions have occurred in some patients during and up to 24 hours after ELAPRASE infusions. Healthcare professionals should closely observe patients during and after ELAPRASE administration, and be prepared to manage anaphylaxis. Patients should seek immediate medical care should symptoms of anaphylaxis occur.[4]

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.[4]

The healthcare professional administering the infusion will be ready to respond appropriately in case of an adverse reaction. Infusions will take place in an infusion center or hospital under close supervision, and a medical professional will be on hand to manage any adverse reactions, if they arise.

Individual experiences may vary. It may be beneficial to discuss this with the patient or caregiver.

Please refer to the Prescribing Information to read more about managing hypersensitivity reactions, and see pages 20–21 for the Full Important Safety Information, including the Boxed WARNING.

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.

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FREQUENTLY ASKED QUESTIONS

1. What product support is available?

*When you prescribe **ELAPRASE** for your patient, Takeda Patient Support is here for them. Our support specialists can help with your patient's questions and concerns, and provide them with the information they need.*

For onboarding, access, and reimbursement assistance, some of our services may include:

- **Benefits investigation** to help determine your patient's insurance benefits and eligibility for certain services
- **Prior authorization (PA), reauthorization, and appeals information**
- **Enrolling your patient in the Takeda Patient Support Co-Pay Assistance Program** if they qualify*
- **Information about financial assistance options** for your patient, if they're eligible

Our additional services include:

- **Specialty pharmacy or site of care triage** and coordination
- **Directing your patient** to community support resources
- **Assistance** during life transitions like relocation, moving to college, or changing jobs, and insurance changes
- **Coordination** between your patient's specialty pharmacy and your site of care, even if they are traveling out of town or relocating

*To be eligible, the patient must be enrolled in Takeda Patient Support, and have commercial insurance. Other terms and conditions apply. Call for more details.

To learn more about Takeda Patient Support, click here

Our support specialists are never more than a tap or a call away — **1-866-888-0660**, Monday through Friday, 8:30 am to 8:00 pm ET.

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.

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FREQUENTLY ASKED QUESTIONS (CONTINUED)

2. Why does the dose of ELAPRASE given vary over time?

The dose of ELAPRASE given depends on the patient's weight,[4] so patients should be regularly weighed to calculate the optimal dose. ELAPRASE is administered at a dose of 0.5 mg per kg of body weight every week, by intravenous infusion.[4]

3. Where do ELAPRASE infusions take place?

Infusions will initially take place at a hospital or infusion center under the supervision of a healthcare professional. Patients who tolerate the infusions well may be able to receive infusions at home under the supervision of a healthcare professional. You may wish to advise the caregiver and patient on the total time needed for an ELAPRASE infusion, including the journey time, infusion time, and any additional time for preparation and monitoring.

4. Who will be involved in my healthcare team and what roles will they play?

The multisystemic and progressive nature of Hunter syndrome means that patients require medical support from a multidisciplinary team of specialists. The specialists involved in each patient's healthcare team may depend on the patient's specific situation and management of the disease. Specialists may include, but are not limited to, orthopedic surgeons, ophthalmologists, cardiologists, pneumologists, neurologists, and physiotherapists.[2]

Please advise the caregiver and patient based on their specific case.

For more frequently asked questions, please visit ELAPRASE.com/HCP/faqs

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.

Please see additional Important Safety Information on pages 20–21 and CLICK HERE to see accompanying Full Prescribing Information, including Boxed WARNING for Risk of Anaphylaxis.

elaprase® (idursulfase)

RESOURCES

Takeda Patient Support is designed for patients who have been prescribed ELAPRASE and their caregivers. Our support specialists can help with your patient's questions and concerns, and provide them with the information they need.

Visit our convenient online enrollment portal here.

ELAPRASE.com/HCP has more information about ELAPRASE, clinical trials, and other resources.

The MPS Society (see mpssociety.org) is a patient organization providing support for families.

There are various social media community pages to help support patients and caregivers living with Hunter syndrome.

Talk through the resources available with the caregiver and patient, allowing them time to write down the information. Remind caregivers or patients that symptoms and experiences may vary widely across patients due to the heterogeneity of the disease.

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)

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

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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.

Please see additional Important Safety Information on page 21 and CLICK HERE to see accompanying Full Prescribing Information, including Boxed WARNING for Risk of Anaphylaxis.

elaprase® (idursulfase)

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.

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 5 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 7 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.

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 in 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%) 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.

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.

To report SUSPECTED ADVERSE REACTIONS, contact Takeda at 1-877-TAKEDA-7 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

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

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1. Martin R *et al. Pediatrics*. 2008; 121(2): e377–386. 2. Scarpa M *et al. Orphanet J Rare Dis*. 2011; 6(72): 1–18. 3. Wraith JE *et al. Eur J Pediatr*. 2008; 167: 267–272. 4. ELAPRASE Prescribing Information. 5. Muenzer J *et al. Genet Med.* 2006; 8(8): 465–473. 6. Pulmonary Function Testing. https://emedicine.medscape.com/article/303239-overview. 7. Muenzer J *et al. Genet Med*. 2011; 13(2): 102–109. 8. Giugliani R *et al. Genet Med.* 2014; 16(6): 435–441.

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