

A GUIDE TO ELAPRASE[®] REIMBURSEMENT

Information for
healthcare providers,
patients, and families

WARNING: RISK OF ANAPHYLAXIS

Important Safety Information

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.¹



elaprased
(idursulfase)

Please see the accompanying full Prescribing Information,
including the Boxed Warning.

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Information about ELAPRASE® (idursulfase)

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

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

The safety and efficacy of ELAPRASE have not been established in pediatric patients less than 16 months of age.¹

When considering treatment, it's important to learn as much as possible about the reimbursement process. In doing so, you'll be prepared to provide the necessary information to the insurer or state Medicare, Medicaid, or Medicaid managed care office. While this process may seem unfamiliar at first, OnePath can help you navigate potential coverage issues.

This booklet reviews some key issues pertaining to ELAPRASE coverage and reimbursement.

WARNING: RISK OF ANAPHYLAXIS

See full prescribing information for complete boxed warning

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

Please see the Important Safety Information for ELAPRASE on pages 9–11, and the accompanying Full Prescribing Information, including Boxed Warning.

Key facts about ELAPRASE® (idursulfase) coverage

There are several potential sources of coverage

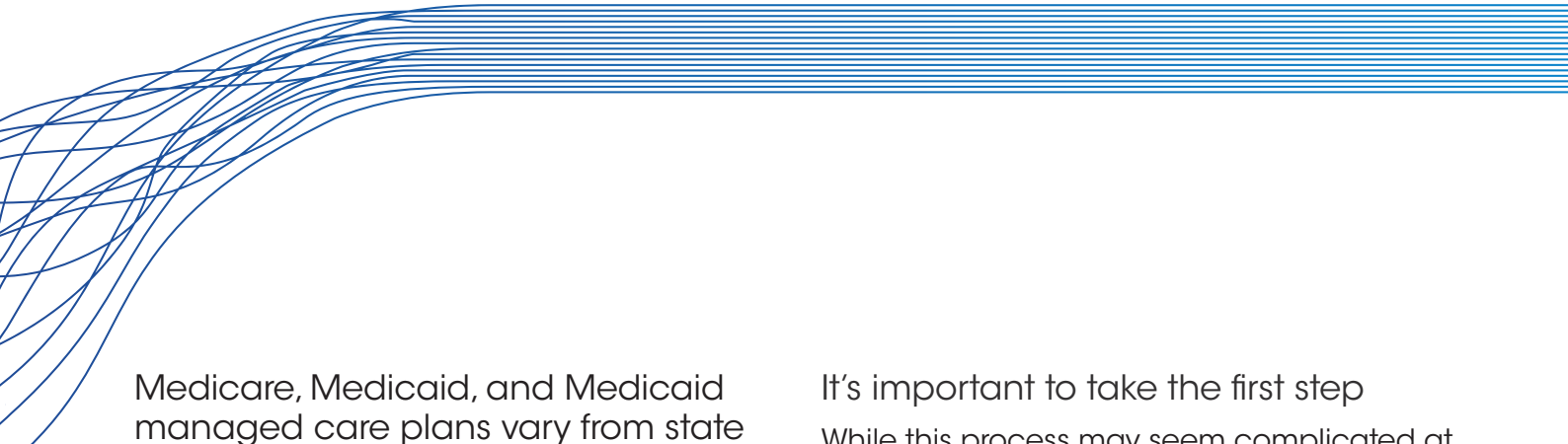
A patient's insurance benefits for ELAPRASE will depend on his or her coverage. Some sources of coverage include private insurance companies, preferred provider organizations (PPOs), health maintenance organizations (HMOs), Medicare and Medicaid. There may also be other sources of coverage available to a patient or family.

Each insurer may have different coverage policies

Because each plan can be different, be sure to check with the plan about its specific guidelines and requirements for ELAPRASE coverage. Most insurers require some kind of prior authorization and/or statement of medical necessity for ELAPRASE therapy. Coverage also differs depending on the site of care — hospital, inpatient, outpatient, physician office, or at home. Insurers may require completion of forms such as a Statement of Medical Necessity or a Letter of Intent to Treat, prior to establishing coverage for ELAPRASE treatment.

Each insurer determines how it will cover ELAPRASE; for example, it may choose the physician who will administer and monitor therapy, as well as the facility for treatment. The insurer may also require periodic reauthorization or recertification for continued treatment. The Affordable Care Act prohibits health care plans from putting a lifetime

limit on essential health benefits. The ban on lifetime dollar limits applies to every health plan — whether you buy coverage for yourself or your family, or you receive coverage through your employer.² Be sure to check with the insurance carrier before beginning ELAPRASE treatment. That way you can determine the information and action necessary to avoid potential issues and delays in beginning treatment and obtaining reimbursement.



Medicare, Medicaid, and Medicaid managed care plans vary from state to state

For those who are covered under a Medicare, Medicaid, or Medicaid managed care program, it's important to find out the coverage options and regulations pertaining to the patient's state of residence.³ In most cases, ELAPRASE must be considered medically necessary to be covered under Medicare, Medicaid, or Medicaid managed care.⁴ Some states require prior approval by the state Medicare, Medicaid, or Medicaid managed care program to begin ELAPRASE; for example, a state may require a Letter of Intent to Treat or provider referrals before beginning ELAPRASE therapy.

Be aware that each state's Medicare, Medicaid, or Medicaid managed care office may have different policies regarding ELAPRASE therapy, including the location where it can be provided. To be certain of coverage guidelines, please call the state's local Medicare, Medicaid, or Medicaid Managed Care office. You can find the number of each state's Medicaid office at the back of this booklet (Appendix B, page 14).

Call the OnePath support service at **1-866-888-0660** to learn more. If you are enrolled in OnePath, contact your OnePath Patient Support Manager to locate resources and information about Medicare, Medicaid, and Medicaid managed care programs and receiving ELAPRASE in a state in which you are not a resident.

It's important to take the first step

While this process may seem complicated at first, try not to be discouraged. There are many ways to obtain reimbursement — and there are many people who are available to help you and provide the information you need. To get started, please visit **www.onepath.com** or call the OnePath support service at **1-866-888-0660**. If you are enrolled in OnePath, Patient Support Managers are available Monday through Friday, from 8:30 a.m. to 8:00 p.m. Eastern Time.

OnePath® can help

OnePath® from Shire — a product support service for ELAPRASE® reimbursement information

OnePath, Shire's product support service, can help you with many aspects related to ELAPRASE. OnePath offers product support to patients and their families. If you are enrolled in OnePath, your dedicated Patient Support Manager is available at **1-866-888-0660** and can assist with questions you may have about accessing ELAPRASE. Patient Support Managers are available from 8:30 a.m. to 8:00 p.m. Eastern Time. You may also visit the OnePath website for more information at **www.onepath.com**.

When you enroll with OnePath, your dedicated Patient Support Manager can connect you with many important resources, including your local Patient Access Manager, and can address questions or concerns associated with insurance and accessing ELAPRASE. Your OnePath Patient Access Manager is available to provide dedicated reimbursement education and help you understand insurance options and coverage, and assist with access-related challenges if they arise.

OnePath can also provide information and assistance with specialty pharmacy distribution of ELAPRASE to the site of care. Two of our distribution partners are Accredo Health Group, Inc. and CVS Caremark Speciality Pharmacy. Both are familiar with supporting patients with chronic conditions and distribution of biological products such as ELAPRASE. If insurance requires that a different specialty pharmacy be used, then OnePath will coordinate with that pharmacy to ensure timely distribution of medication for those enrolled in the program.

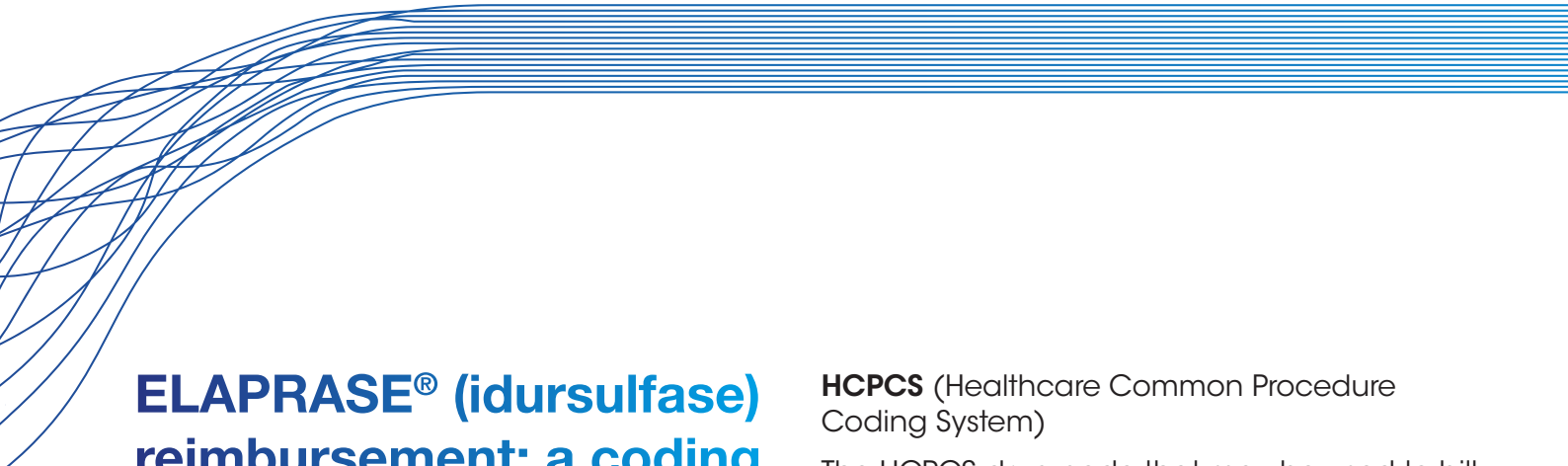
Shire is committed to supporting ELAPRASE patients and their families. To learn more, simply call OnePath toll-free at **1-866-888-0660**, or visit **www.onepath.com**.



1-866-888-0660

www.OnePath.com

elaprase®
(idursulfase)



ELAPRASE® (idursulfase) reimbursement: a coding guide for healthcare providers

Completing forms with the appropriate codes is a necessary part of the reimbursement process and is the responsibility of the healthcare providers who are administering ELAPRASE therapy. The accompanying table describes some of the codes that may be required for billing. Please be aware that codes and billing procedures sometimes change. Before completing a reimbursement form, be sure to obtain the most up-to-date information.

Key Codes and Services for Billing

ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification)

- 277.5 — Diagnosis code for all mucopolysaccharidosis (MPS) disorders⁵

ICD-10-CM (International Classification of Diseases, 10th Revision, Clinical Modification)

Please note, ICD-10-CM replaces ICD-9-CM in October 2015

- E76.1 — Mucopolysaccharidosis, type II⁶
- E76.3 — Mucopolysaccharidosis, unspecified⁶

NDC (National Drug Code)

- 54092-700-0¹
- 54092-0700-01 (11-digit code is required by some payers)⁷

HCPCS (Healthcare Common Procedure Coding System)

The HCPCS drug code that may be used to bill for ELAPRASE is:

- J1743 — Injection, Idursulfase 1mg⁸

CPT-4 (CPT – Current Procedural Terminology)*

- 96365 — IV infusion for therapy/prophylaxis, administered by physician or under direct supervision of physician; up to 1 hour⁹
- 96366 — Each additional hour, up to 8 hours⁹
- Q0081 — Non-chemotherapeutic infusion (hospital only)¹⁰
- S9357 — Home infusion therapy, enzyme replacement intravenous therapy (e.g. imiglucerase); administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately) per diem¹¹

Revenue Codes

Hospitals must use the following revenue code on Form UB-04:

- 0636 — Drugs and biologicals requiring an HCPCS code¹²

Other revenue codes that may be used by hospitals include:

- 0258 — IV solutions¹³
- 0260 — General IV therapy service¹⁴
- 0261 — Infusion pump¹⁵

*CPT is a registered trademark of the American Medical Association.

Please see the Important Safety Information for ELAPRASE on pages 9–11, and the accompanying Full Prescribing Information, including Boxed Warning.

What is ELAPRASE® (Idursulfase)?

ELAPRASE is a prescription medicine for patients with Hunter syndrome.

ELAPRASE has been shown to improve walking ability in patients 5 yrs and older.

In patients 16 months to 5 yrs old, ELAPRASE did not show improvement in disease-related symptoms or long term clinical result; however, treatment with ELAPRASE has reduced spleen size similarly to patients 5 yrs and older.

It is not known if ELAPRASE is safe and effective in children under 16 months old.



Important Safety Information

Risk of serious allergic reactions:

Some patients have experienced serious allergic reactions (including life-threatening anaphylactic reactions) during and up to 24 hours after treatment, regardless of how long they were taking ELAPRASE. Anaphylactic reactions are immediate and include breathing problems, low oxygen levels, low blood pressure, hives and/or swelling of the throat or tongue.

If a patient (you or your child) has experienced an anaphylactic reaction, the patient may require an extended period of observation by the patient's healthcare team.

If you or your child has breathing problems, a fever, or a respiratory illness, you or your child may be at risk of life-threatening worsening of those conditions due to allergic reactions from ELAPRASE. Your healthcare team should be advised of those conditions before treatment with ELAPRASE because the information may affect the timing of ELAPRASE treatment.

You or your child should be closely watched during and after ELAPRASE treatment and you should confirm with your healthcare team in advance of treatment that it is prepared to manage serious allergic reactions, including anaphylactic reactions.

Tell your healthcare team immediately if any signs of an allergic reaction happen.

Those signs may include breathing problems, low blood pressure, rash, hives, itching, flushing, fever and/or headache.

When serious allergic reactions happened during clinical trials, later ELAPRASE treatments were managed with allergy-controlling drugs before or during treatment, a slower rate of ELAPRASE treatment, and/or early discontinuation of treatment.

Children with serious genetic mutations may be at risk for allergic reactions, serious side effects and antibody development.

In a clinical study of children 7 years and younger, patients with certain types of genetic mutations experienced a higher number of allergic reactions, serious side effects, and development of an immune response to treatment. This immune response may interfere with the effectiveness of ELAPRASE. Talk to your healthcare team about whether you or your child may be at risk.

If you or your child has breathing problems, other respiratory illness, heart problems, or susceptibility to fluid overload, you or your child may be at higher risk of fluid overload during ELAPRASE treatment.

Your healthcare team should be advised of those problems before treatment and you should confirm with your healthcare team in advance of treatment that it is appropriately trained to watch for signs of fluid overload and provide the necessary medical support. Patients at risk for fluid overload may require longer observation time.

What are possible side effects of ELAPRASE?

The most common side effects of ELAPRASE include:

- **In patients aged 5 and older:**
 - Headache
 - Itching
 - Muscle and bone pain
 - Hives
 - Diarrhea
 - Cough
- **In patients aged 7 years or younger:**
 - Fever
 - Rash
 - Vomiting
 - Hives

The most common side effects needing medical attention were allergic reactions, and included rash, hives, itching, flushing, fever, and headache. **Tell your healthcare team immediately if any signs of an allergic reaction happen.** These are not all the possible side effects of ELAPRASE.

For additional safety information, please click [here](#) for Full Prescribing Information, including Boxed Warning for Risk of Anaphylaxis, and discuss with your doctor.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.



GLOSSARY – Key reimbursement terms used inside

Specialty pharmacy

A type of pharmacy that provides a variety of specialized services for people with complex, chronic, or rare conditions. Medications offered by specialty pharmacies are often high cost, available with limited distribution, or require special storage, handling or administration.¹⁶

Site of care

A location where a patient receives health care, such as a hospital, physician office, or the patient's home.

Lifetime limits

Insurance companies cannot set a dollar limit to what they spend on essential health benefits for your care during the entire time you're enrolled in that plan.² This applies to all health plans whether you receive coverage through your employer or buy it yourself.² Insurance companies can still put a dollar limit on health care services that are not considered essential health benefits.²

HMO

Health Maintenance Organization. A HMO is a type of health insurance plan that usually limits coverage to care from doctors who work for or contract with the HMO network. Out-of-network care is usually not covered except in emergency. A HMO may require you to live or work in its service area to be eligible for coverage. HMOs often provide integrated care and focus on prevention and wellness.¹⁷

PPO

Preferred Provider Organization. A PPO is a type of health care plan where you pay less if you use providers in the plan's network. You can use doctors, hospitals, and providers outside of the network without a referral for an additional cost.¹⁷

Managed Care

Managed Care is a health care delivery system organized to manage cost, utilization and quality. Medicaid managed care provides the delivery of Medicaid health benefits through contracted arrangements between the state Medicaid agencies and managed care organizations.³ Approximately 70% of Medicaid enrollees are served through managed care delivery systems.³

Medicaid

Medicaid is a federally and state-funded health insurance program for some low-income people, families and children, pregnant women, the elderly, and people with disabilities. Coverage and costs vary from state to state. Some Medicaid programs pay for care directly while others use private insurance companies to provide Medicaid coverage.¹⁸

Medicare

Medicare is a federally funded health insurance program for people who are age 65 or older and certain younger people with disabilities. Medicare also covers people with End-Stage Renal Disease.¹⁹

The information contained in this guide has been developed to help you understand insurance benefits and the process of submitting claims. Shire cannot guarantee that the information in this guide will result in coverage or payment. As payer policies may change, please consult with those policies to get the most up-to-date information.

Please see the Important Safety Information for ELAPRASE on pages 9–11, and the accompanying Full Prescribing Information, including Boxed Warning.

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Appendix A – Sample coding for ELAPRASE®

The following coding information for ELAPRASE (idursulfase) is an example only. Specific codes will vary based on payer guidelines, patient-specific treatment, and diagnosis.

CMS-1500 - Physician Office Setting

17. NAME OF REFERRING PROVIDER OR OTHER SOURCE		17a.	18. HOSPITALIZATION DATES RELATED TO CURRENT SERVICES	
19. RESERVED FOR LOCAL USE		17b. NPI	FROM MM DD YY	TO MM DD YY
21. DIAGNOSIS OR NATURE OF ILLNESS		19. RESERVED FOR LOCAL USE		20. OUTSIDE LAB? \$ CHARGES
24B. PLACE OF SERVICE		List the product name, dose administered, route of administration, and NDC #.		24E. DIAGNOSIS POINTER
Office 11		• Elaprased NDC: 54092-700-01		Specify the diagnosis code position from Box 21 that relates to the code listed in Box 24D (e.g., 1,2,3).
Home 12				
Other 99				
21. DIAGNOSIS CODE		24D. PROCEDURE CODE		24G. UNITS
Document the primary diagnosis on line 1 and the secondary diagnosis on line 2 using ICD-9 diagnosis codes.		Document the drug administration with an appropriate CPT code and the product administered with the HCPCS code (J-code). Some Medicaid plans and managed care plan may require the NDC # to be listed here.		For each HCPCS or CPT code, insert the number of units administered.
<ul style="list-style-type: none"> • Elaprased ICD-9 code: 277.5 for all Mucopolysaccharidosis (MPS) disorders (Hunter syndrome) • Elaprased secondary ICD-9 code: 99.29 injection or infusion of other therapeutic or prophylactic substances 		<ul style="list-style-type: none"> • Elaprased HCPCS J-Code: J1743 		<ul style="list-style-type: none"> • Elaprased: For Medicare and Medicaid, multiply the number of vials by 6. For example, 1 vial = 6 units. For private payers, enter the number of vials. For example, 1 vial = 1 unit. For drug administration up to 1 hour, enter 1 unit

CMS-1450 (UB-04) - Hospital Outpatient Setting

42 REV. CD.	43 DESCRIPTION	44 HCPCS / RATE / HPCS CODE	45 SEPR. DATE	46 SERV. UNITS	47 TOTAL CHARGES	48 NON-COVERED CHARGES	49
42. REVENUE CODE		43. DESCRIPTION		44. PRODUCT AND PROCEDURE CODE		46. UNITS	
See payer's requirements. Medicare and most other payers require a revenue code for each procedure executed, so one line is required for the product and another line for the procedure.		Provide the description associated with the HCPCS J-Code or the revenue code entered in Box 42.		Enter the HCPCS J-Code on the product line and enter the CPT code on the procedure line.		Enter the number of units.	
		<ul style="list-style-type: none"> • For the product: <ul style="list-style-type: none"> - Elaprased (idursulfase for injection) - IV solution (for 0258) • For the procedure: <ul style="list-style-type: none"> - IV therapy, general (for 0260) - Infusion therapy (for 0261) 		<ul style="list-style-type: none"> • For the product: <ul style="list-style-type: none"> - Elaprased HCPCS J-Code: J1743 • For the procedure: <ul style="list-style-type: none"> - For intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour, administered by physician or under direct supervision of physician, enter: 96365 - For IV infusion therapy each additional hour, up to 8 hours, enter: 96366 - For non-chemotherapeutic infusion, enter: Q0081 		<ul style="list-style-type: none"> • On the product line, enter the number of units administered - Elaprased: For Medicare and Medicaid, multiply the number of vials by 6. For example, 1 vial = 6 units. For private payers, enter the number of vials. For example, 1 vial = 1 unit. For drug administration up to 1 hour, enter 1 unit. • On the procedure line, enter 1 unit for 1 hour 	
69. DIAGNOSIS CODE		68. ADDITIONAL DIAGNOSIS		90. REMARKS			
Enter the appropriate ICD-9 diagnosis codes as documented in the patient's clinical record.		Enter the appropriate ICD-9 codes for additional diagnoses.		This field is used to report additional information to support claims review and payment. Record the product name, NDC #, dose administered and route of administration.			
<ul style="list-style-type: none"> • Elaprased ICD-9 Code: 277.5 for all Mucopolysaccharidosis (MPS) disorders (Hunter syndrome) 				<ul style="list-style-type: none"> • Elaprased NDC: 54092-700-01 			

Appendix B – State Medicaid offices*

CMS Headquarters

Centers for Medicare and Medicaid Services (CMS)
7500 Security Boulevard
Baltimore, Maryland 21244-1850
Toll-Free: 877-267-2323
Local: 410-786-3000
TTY Toll-Free: 866-226-1819
TTY Local: 410-786-0727

Regional Contacts

Region One – Boston

Connecticut, Maine, Massachusetts,
New Hampshire, Rhode Island, and Vermont
Richard McGreal
JFK Federal Building, Suite 2325
Boston, MA 02203-0003
617-565-1299; ROBOSDMCH@cms.hhs.gov

Region Three – Philadelphia

Delaware, District of Columbia, Maryland,
Pennsylvania, Virginia, and West Virginia
Francis McCullough
150 S. Independence Mall West
Philadelphia, PA 19106
215-861-4155; ROPHIDMCH@cms.hhs.gov

Region Five – Chicago

Illinois, Indiana, Michigan, Minnesota, Ohio,
and Wisconsin
Ruth Hughes
233 North Michigan Avenue, Suite 600
Chicago, Illinois 60601
312-353-1133; R5DMCH@cms.hhs.gov

Region Seven – Kansas City

Iowa, Kansas, Missouri, and Nebraska
James Scott
601 E. 12th Street, Suite 355
Kansas City, MO 64106
816-426-5925; ROKCMMCH@cms.hhs.gov

Region Nine – San Francisco

Arizona, California, Hawaii, Nevada, Pacific Territories
Henrietta Sam-Louie
90 – 7th Street, Suite 5-300
San Francisco, CA 94103-6706
415-744-3568; ROSFOMCD@cms.hhs.gov

Region Two – New York

New Jersey, New York, Puerto Rico, and Virgin Islands
Michael Melendez
26 Federal Plaza, Room 3811
New York, NY 10278-0063
212-616-2400; RONYDMCH@cms.hhs.gov

Region Four – Atlanta

Alabama, Florida, Georgia, Kentucky, Mississippi,
North Carolina, South Carolina, and Tennessee
Shantrina Roberts
61 Forsyth Street, SW, Suite 4T20
Atlanta, Georgia 30303-8909
404-562-7359; ROATLMCD@cms.hhs.gov

Region Six – Dallas

Arkansas, Louisiana, New Mexico, Oklahoma, Texas
Bill Brooks
1301 Young St. Suite 714
Dallas, TX 75202
214-767-6495; RODALDMCH@cms.hhs.gov

Region Eight – Denver

Colorado, Montana, North Dakota, South Dakota,
Utah, and Wyoming
Richard Allen
1961 Stout Street, Room 08-148
Denver, CO 80294
303-844-0634; RODENDMCH@cms.hhs.gov

Region Ten – Seattle

Alaska, Idaho, Oregon, and Washington
David Meacham
701 Fifth Avenue, Suite 1600
Seattle, WA 98104
206-615-2326; SEARODMCH@cms.hhs.gov

*Validated as of 01/08/19



HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

WARNING: RISK OF ANAPHYLAXIS

See full prescribing information for complete boxed warning.

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

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

- None (4)

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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

See 17 for PATIENT COUNSELING INFORMATION.

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ELAPRASE® (idursulfase) injection, for intravenous use

FULL PRESCRIBING INFORMATION

WARNING: RISK OF ANAPHYLAXIS

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

1 INDICATIONS AND USAGE

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

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

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

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

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

2.2 Preparation Instructions

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

- 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.

- Before withdrawing the ELAPRASE solution from the vial, visually inspect each vial for particulate matter and discoloration. The ELAPRASE solution should be clear to slightly opalescent and colorless. Do not use if the solution is discolored or if there is particulate matter in the solution. Do not shake the ELAPRASE solution.
- Withdraw the calculated volume of ELAPRASE from the appropriate number of vials.
- Add the calculated volume of ELAPRASE solution to a 100 mL bag of 0.9% Sodium Chloride Injection, USP for intravenous infusion.
- Mix gently. Do not shake the solution.

2.3 Administration Instructions

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

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

2.4 Storage and Stability

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions Including Anaphylaxis

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

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

In clinical trials with ELAPRASE, 16 of 108 (15%) patients experienced hypersensitivity reactions during 26 of 8,274 infusions (0.3%) that involved adverse events in at least two of the following three body systems: cutaneous, respiratory, or cardiovascular. Of these 16 patients, 11 experienced anaphylactic reactions during 19 of 8,274 infusions (0.2%) with symptoms of bronchospasm, cyanosis, dyspnea, erythema, edema (facial and peripheral), flushing, rash, respiratory distress, urticaria, vomiting, and wheezing.

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

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

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

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

5.3 Risk of Acute Respiratory Complications

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

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5.4 Risk of Acute Cardiorespiratory Failure

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

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

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

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

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

Clinical Trials in Patients 5 Years and Older

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

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

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

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

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

Extension Trial

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

Clinical Trial in Patients 7 Years and Younger

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

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

Safety results demonstrated that patients with complete gene deletion, large gene rearrangement, nonsense, frameshift, or splice site mutations are more likely to experience hypersensitivity reactions and have serious adverse reactions following ELAPRASE administration, compared to patients with missense mutations. Table 2 summarizes these findings.

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

			Anti-idursulfase antibodies (Ab)		Anti-idursulfase neutralizing antibodies (Nab)		
		Total	Positive	Negative	Positive	Negative	
Antibody Status Reported (patients)		28	19	9	15	13	
Serious Adverse Reactions* (patients)		13	11	2	9	4	
Hypersensitivity (patients)		16	12	4	10	6	
Patients with genotype data		27					
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 (6.1)].

6.2 Immunogenicity

Clinical Trials in Patients 5 Years and Older

As with all therapeutic proteins, there is potential for immunogenicity. In clinical trials in patients 5 years and older, 63 of the 64 patients treated with ELAPRASE 0.5 mg/kg once weekly or placebo for 53 weeks, followed by ELAPRASE 0.5 mg/kg once weekly in the extension trial, had immunogenicity data available

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for analysis. Of the 63 patients, 32 (51%) patients tested positive for anti-idursulfase IgG antibodies (Ab) at least one time (Table 2). Of the 32 Ab-positive patients, 23 (72%) tested positive for Ab at three or more different time points (persistent Ab). The incidence of hypersensitivity reactions was higher in patients who tested positive for Ab than those who tested negative.

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

Clinical Trial in Patients 7 Years and Younger

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

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

The immunogenicity data reflect the percentage of patients whose test results were positive for antibodies to idursulfase in specific assays, and are highly dependent on the sensitivity and specificity of these assays. The observed incidence of positive antibody in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to idursulfase with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ELAPRASE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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

A seven year-old male patient with Hunter syndrome, who received ELAPRASE at twice the recommended dosage (1 mg/kg weekly) for 1.5 years, experienced two anaphylactic events after 4.5 years of treatment. Treatment has been withdrawn [see *Overdosage* (10)].

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Data

Animal Data

In a pre- and post-natal development study, idursulfase was administered to pregnant rats twice weekly, intravenously, from gestation day 6 through lactation day 19. No significant adverse effects on pre- and post-natal development of the offspring were observed at twice weekly intravenous doses up to 12.5 mg/kg

(about 4 times the recommended human weekly dose of 0.5 mg/kg based on body surface area).

8.2 Lactation

Risk Summary

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

Data

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

8.4 Pediatric Use

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

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

8.5 Geriatric Use

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

10 OVERDOSAGE

One patient with Hunter syndrome, who received ELAPRASE at twice the recommended dosage for one and a half years, experienced two anaphylactic reactions over a 3-month period 4.5 years after initiating ELAPRASE treatment.

11 DESCRIPTION

ELAPRASE is a formulation of idursulfase, a purified form of human iduronate-2-sulfatase, a lysosomal enzyme. Idursulfase is produced by recombinant DNA technology in a human cell line. Idursulfase is an enzyme that hydrolyzes the 2-sulfate esters of terminal iduronate sulfate residues from the glycosaminoglycans dermatan sulfate and heparan sulfate in the lysosomes of various cell types.

Idursulfase is a 525-amino acid glycoprotein with a molecular weight of approximately 76 kilodaltons. The enzyme contains eight asparagine-linked glycosylation sites occupied by complex oligosaccharide structures. The enzyme activity of idursulfase is dependent on the post-translational modification of a specific cysteine to formylglycine. Idursulfase has a specific activity ranging from 46 to 74 units/mg of protein (one unit is defined as the amount of enzyme required to hydrolyze 1 micromole of heparin disaccharide substrate per hour under the specified assay conditions).

ELAPRASE is administered as an intravenous infusion and supplied as a sterile, nonpyrogenic clear to slightly opalescent, colorless solution that must be diluted prior to administration in 0.9% Sodium Chloride Injection, USP. Each vial contains an extractable volume of 3 mL with an idursulfase concentration of 2 mg/mL at a pH of approximately 6. Each vial contains 6 mg idursulfase, sodium chloride (24 mg), sodium phosphate monobasic monohydrate (6.75 mg), sodium phosphate dibasic heptahydrate (2.97 mg), and polysorbate 20 (0.66 mg). ELAPRASE does not contain preservatives. Each vial is for single use only.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Hunter syndrome (Mucopolysaccharidosis II, MPS II) is an X-linked recessive disease caused by insufficient levels of the lysosomal enzyme iduronate-2-sulfatase. This enzyme cleaves the terminal 2-O-sulfate moieties from the glycosaminoglycans (GAG) dermatan sulfate and heparan sulfate. Due to the missing or defective iduronate-2-sulfatase enzyme in patients with Hunter syndrome, GAG progressively accumulate in the lysosomes of a variety of cells, leading to cellular engorgement, organomegaly, tissue destruction, and organ system dysfunction.

ELAPRASE is intended to provide exogenous enzyme for uptake into cellular lysosomes. Mannose-6-phosphate (M6P) residues on the oligosaccharide chains allow binding of the enzyme to the M6P receptors on the cell surface, leading to

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cellular internalization of the enzyme, targeting to intracellular lysosomes and subsequent catabolism of accumulated GAG.

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

Clinical Trials in Patients 5 Years and Older

The pharmacokinetic characteristics of idursulfase were evaluated in 59 patients with Hunter syndrome. The serum concentration of idursulfase was quantified using an antigen-specific ELISA assay. The area under the concentration-time curve (AUC) increased in a greater than dose proportional manner as the dose increased from 0.15 mg/kg to 1.5 mg/kg following a single 1-hour infusion of ELAPRASE. The pharmacokinetic parameters at the recommended dose regimen (0.5 mg/kg ELAPRASE administered weekly as a 3-hour infusion) were determined at Week 1 and Week 27 in 10 patients 7.7 to 27 years of age (Table 3). There were no apparent differences in PK parameter values between Week 1 and Week 27 regardless of the antibody status in these patients.

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

Pharmacokinetic Parameter	Week 1 Mean (SD)	Week 27 Mean (SD)
C _{max} (mcg/mL)	1.5 (0.6)	1.1 (0.3)
AUC (min·mcg/mL)	206 (87)	169 (55)
t _{1/2} (min)	44 (19)	48 (21)
CL (mL/min/kg)	3.0 (1.2)	3.4 (1.0)
V _{ss} (mL/kg)	213 (82)	254 (87)

Clinical Trial in Patients 7 Years and Younger

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

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

Pharmacokinetic Parameter	Week 1 (N=27) All Patients Mean (SD)	Week 27	
		Anti-idursulfase Antibodies (Ab)*	
		(n=9) Negative Ab Mean (SD)	(n=10) [†] Positive Ab Mean (SD)
C _{max} (mcg/mL)	1.33 (0.817)	1.40 (0.389)	0.706 (0.558)
AUC (min·mcg/mL)	224 (76.9) [‡]	281 (81.8)	122 (92.1) [§]
t _{1/2} (min)	160 (69) [‡]	134 (19)	84 (46) [§]
CL (mL/min/kg)	2.4 (0.7) [‡]	2.0 (0.8)	7.4 (6.0) [§]
V _{ss} (mL/kg)	394 (423) [‡]	272 (112)	829 (636) [§]

* Positive anti-idursulfase antibody (Ab) is defined as having at least one serum specimen with measurable antibody during study duration.

[†] Eight of 18 patients with positive Ab had no measurable concentrations at Week 27.

[‡] N=26

[§] N=9

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential or studies to evaluate mutagenic potential have not been performed with ELAPRASE.

ELAPRASE at intravenous doses up to 5 mg/kg administered twice weekly (about 1.6 times the recommended human weekly dose based on body surface area) had no effect on fertility and reproductive performance in male rats.

14 CLINICAL STUDIES

14.1 Clinical Trials in Patients 5 Years and Older

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

The primary efficacy outcome assessment was a two-component composite score based on the sum of the ranks of the change from baseline to Week 53 in distance walked in six minutes (6-minute walk test) and the ranks of the change in %-predicted FVC. This two-component composite primary endpoint differed statistically significantly between the three groups, and the difference was greatest between the placebo group and the once weekly treatment group (once weekly ELAPRASE vs. placebo, p=0.0049).

Examination of the individual components of the composite score showed that, in the adjusted analysis, the weekly ELAPRASE-treated group experienced a 35 meter greater mean increase in the distance walked in six minutes compared to placebo. The changes in %-predicted FVC were not statistically significant (Table 5).

Table 5. Clinical Trial Results

	ELAPRASE Weekly n=32*			Placebo n=32*			ELAPRASE Once Weekly - Placebo Difference in Change
	Baseline	Week 53	Change [†]	Baseline	Week 53	Change [†]	
Results from the 6-Minute Walk Test (Meters)							
Mean	392	436	44	393	400	7	37 ± 16 [‡] 35 ± 14 [§] (p=0.01)
± SD	± 108	± 138	± 70	± 106	± 106	± 54	
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	55.3	58.7	3.4	55.6	56.3	0.8	2.7 ± 2.5 [‡] 4.3 ± 2.3 [§] (p=0.07)
± SD	± 15.9	± 19.3	± 10.0	± 12.3	± 15.7	± 9.6	
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	
* One patient in the placebo group and one patient in the ELAPRASE group died before Week 53; imputation was by last observation carried forward in the intent-to-treat analysis.							
[†] Change, calculated as Week 53 minus Baseline							
[‡] Observed mean ± SE							
[§] ANCOVA model based mean ± SE, adjusted for baseline disease severity, region, and age.							

Pharmacodynamic assessments included urinary GAG levels and changes in liver and spleen size. Urinary GAG levels were elevated in all patients at baseline. Following 53 weeks of treatment, mean urinary GAG levels were reduced in the ELAPRASE once weekly group, although GAG levels still remained above the upper limit of normal in half of the ELAPRASE-treated patients. Urinary GAG levels remained elevated and essentially unchanged in the placebo group. Sustained reductions in both liver and spleen volumes were observed in the ELAPRASE once weekly group through Week 53 compared to placebo. There were essentially no changes in liver and spleen volumes in the placebo group.

ELAPRASE® (idursulfase) injection, for intravenous use

Extension Trial

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

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

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

14.2 Clinical Trial in Patients 7 Years and Younger

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

16 HOW SUPPLIED/STORAGE AND HANDLING

ELAPRASE is supplied as a sterile injection in a 5 mL Type I glass vial. The vials are closed with a butyl rubber stopper with fluororesin coating and an aluminum overseal with a blue flip-off plastic cap.

Each carton contains a single vial NDC 54092-700-01

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

17 PATIENT COUNSELING INFORMATION

Information for Patients

Patients should be advised that life-threatening anaphylactic reactions have occurred in some patients during and up to 24 hours after ELAPRASE therapy. Patients who have experienced anaphylactic reactions may require prolonged observation. Patients with compromised respiratory function or acute respiratory disease may be at risk of serious acute exacerbation of their respiratory compromise due to hypersensitivity reactions.

A Hunter Outcome Survey has been established in order to understand better the variability and progression of Hunter syndrome (MPS II) in the population as a whole, and to monitor and evaluate long-term treatment effects of ELAPRASE. Patients and their physicians are encouraged to participate in this program. For more information, call Shire Human Genetic Therapies, Inc. at 1-866-888-0660.

ELAPRASE is manufactured by:

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