CHANGING THEIR HORIZONS

INDICATIONS AND USAGE[1]

ELAPRASE is indicated for the long-term treatment of patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II). Heterozygous females were not studied in the clinical trials.

Treating patients with MPS II for more than 10 years, we have improved life expectancy*.

elaprase® (idursulfase)

* Based on 10 years of Hunter Syndrome Outcome (HOS) data.
This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 of the product SmPC for how to report adverse reactions.

Takeda

Takeda Pharmaceuticals FZE
Shire is now part of Takeda
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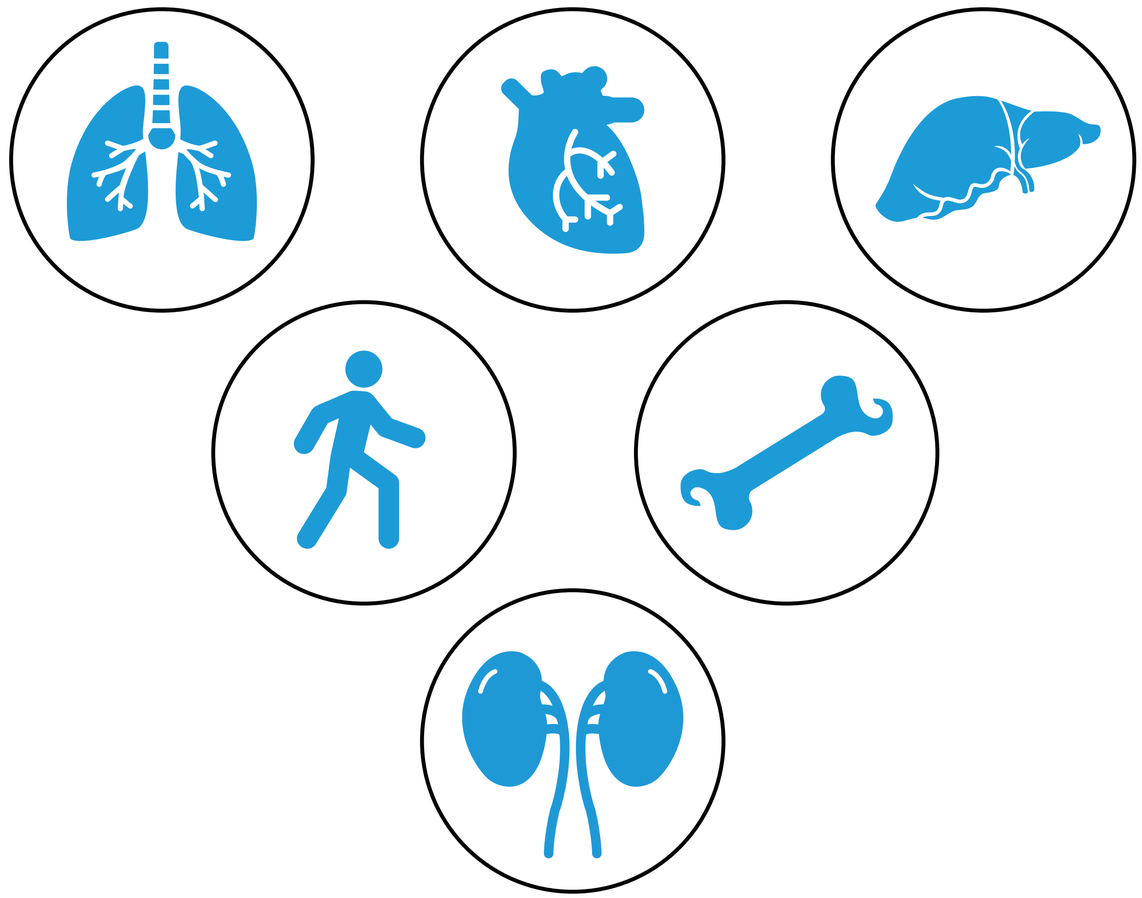
Expiry Date: 25/12/2024 C-APROM/SA/ELA/0006

HUNTER SYNDROME

MPS II is a chronic, multisystemic, progressive metabolic disease[2-5]

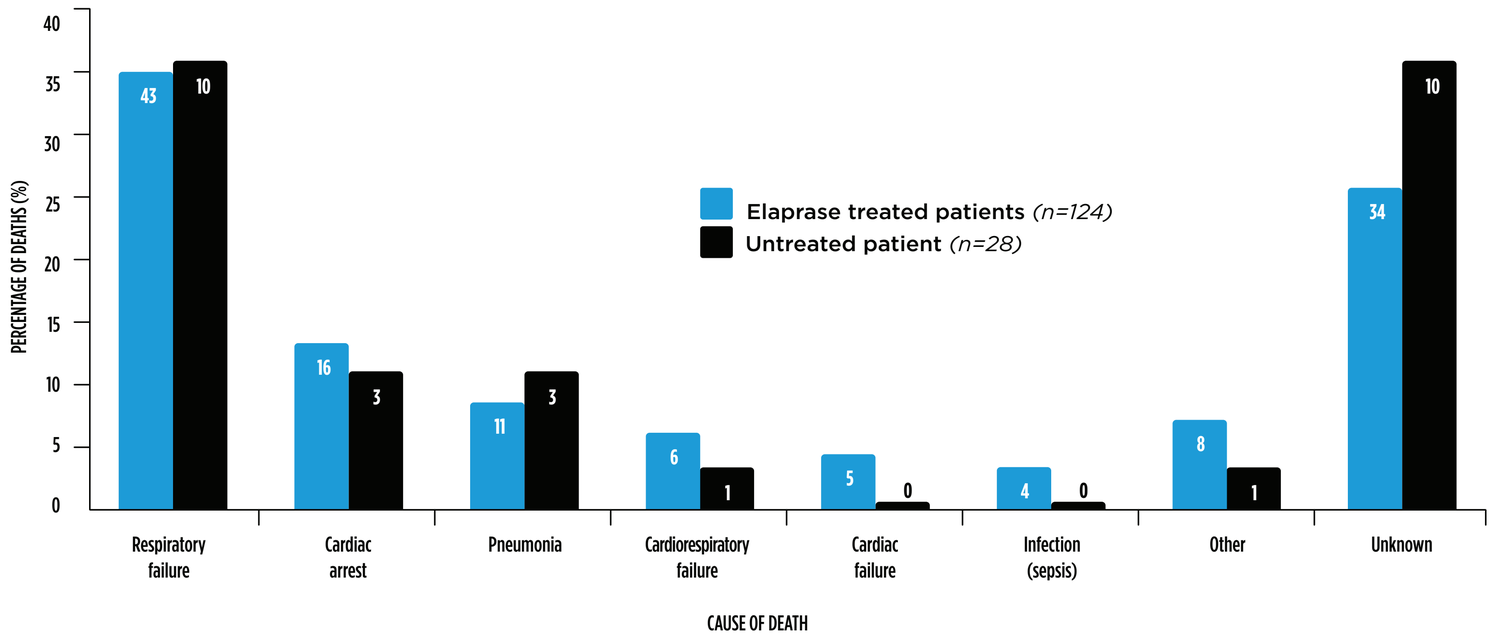
- Hunter syndrome can present as a variety of signs and symptoms due to the multisystemic nature of the disease.[2-5] Many different parts of the body can be affected including, but not limited to, the respiratory, cardiovascular, skeletal systems. This disease can also affect the growth and development of individuals suffering from the disease.[2-5]



- The symptoms of MPS II can lead to increased mortality.[5]
  Patients with Hunter syndrome have been shown to have an increased risk of mortality and death can occur in the second decade of life if left untreated.[5]

Somatic aspects of MPS II contribute to mortality, as demonstrated by the positive impact of treatment on survival[1]

The most common cause of death in MPS II patients was respiratory failure



N=895 (800 treated, 95 untreated) included in overall study analysis.

The main causes of death were:*

- **respiratory failure** (34.7% of treated and 35.7% of untreated patients)
- **cardiac arrest** (12.9% of treated and 10.7% of untreated patients)
- **pneumonia** (8.8% of treated and 10.7% of untreated patients)[6]

*a large number of unknown causes of death were recorded (25% of treated and 35.7% of untreated patients). Unknown was a category of death that could be selected as a pre-specified field in the Hunter Outcome Survey database.

Study design[6]

OBJECTIVE - Compare the survival in ELAPRASE-treated and untreated MPS II patients using data collected by the Hunter Outcome Survey (HOS).

METHOD - Observational, therefore no predetermined assessments.

PATIENT POPULATION - All confirmed (genetically or biochemically) MPS II patients were enrolled in the Hunter Outcome Survey, including those receiving intravenous (IV) idursulfase, a bone marrow transplant (BMT) or those not being treated. Patients were excluded if they were receiving treatment with a product other than IV idursulfase. Both prospective (alive at the time of enrollment) and retrospective patients (deceased at enrollment) can be included.

ANALYSES - Kaplan-Meier analyses were used to estimate survival probability. Multivariate Cox regression modelling was used to generate the hazard ratio for survival (HR).

BENEFITS OF ELAPRASE

INCREASED SURVIVAL

ELAPRASE has been shown to positively affect the survival and a number of somatic parameters of MPS II patients[6]

SOMATIC IMPROVEMENTS

ELAPRASE demonstrated improvement of the somatic parameters of MPS II patients[1, 7-9]

INITIATED EARLY

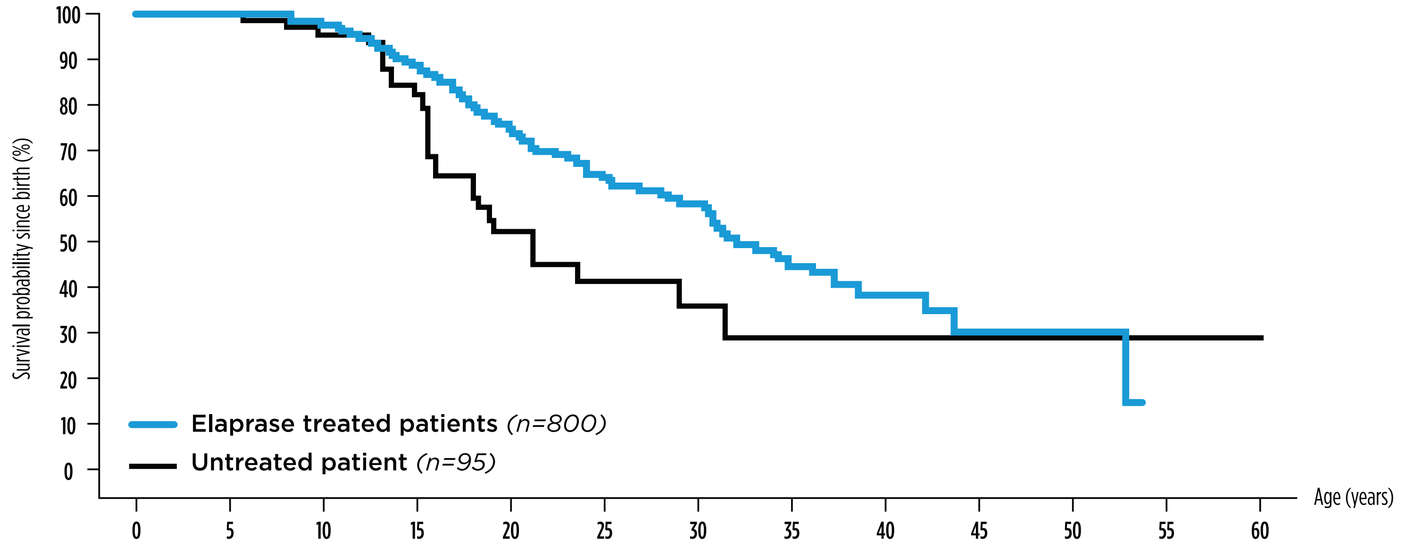
ELAPRASE was shown to effectively treat paediatric patients[10, 11]

ELAPRASE 10 YEAR SURVIVAL DATA

ELAPRASE has been shown to positively affect the survival and a number of somatic parameters of MPS II patients[6]

ELAPRASE increased survival of MPS II patients

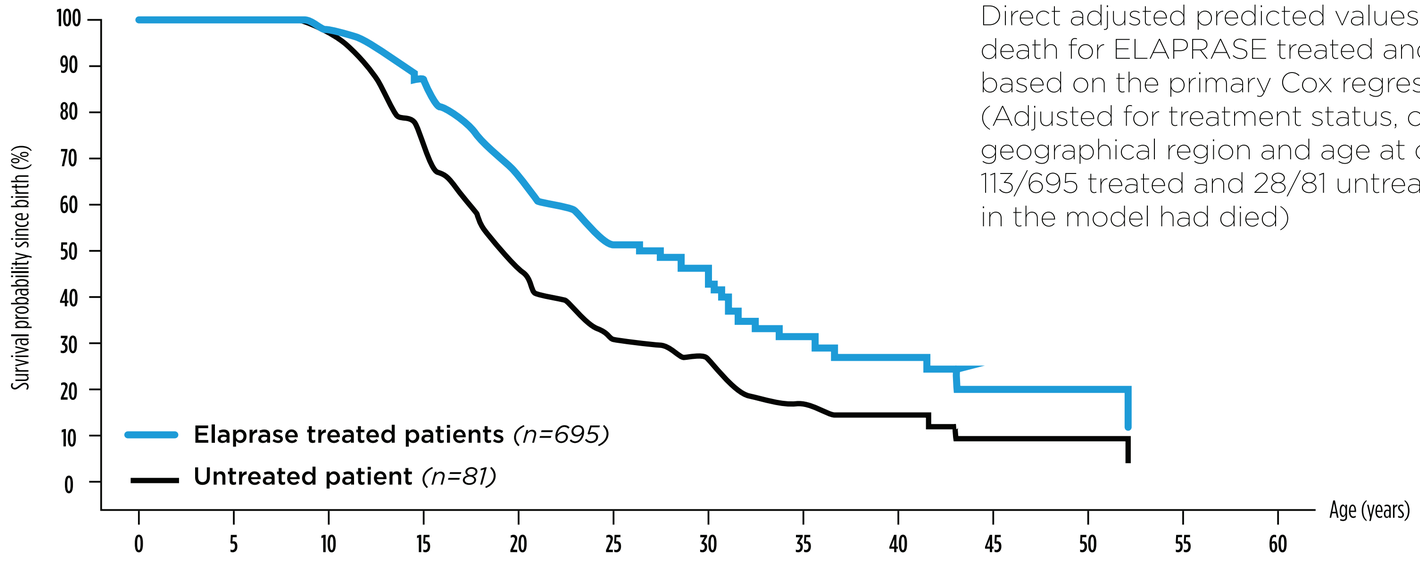
Kaplan-Meier survival analysis for ELAPRASE treated and untreated patients[6]



NUMBER OF PATIENTS AT RISK													
Treated	800	724	509	305	157	90	58	26	14	7	3	0	
Untreated	95	79	58	39	19	10	6	3	3	3	2	2	1

ELAPRASE treatment extended the patients' lifespans by an average of 11.8 years compared to untreated patients'[6]

Adjusted survival curve for ELAPRASE treated and untreated patients[6]



Direct adjusted predicted values for the risk of death for ELAPRASE treated and untreated patients based on the primary Cox regression model. (Adjusted for treatment status, cognitive impairment, geographical region and age at diagnosis. 113/695 treated and 28/81 untreated patients included in the model had died)

ELAPRASE treated patients had a 54% lower risk of death compared with untreated patients[6]

BENEFITS – ELAPRASE INCREASED SURVIVAL

Study design[6]

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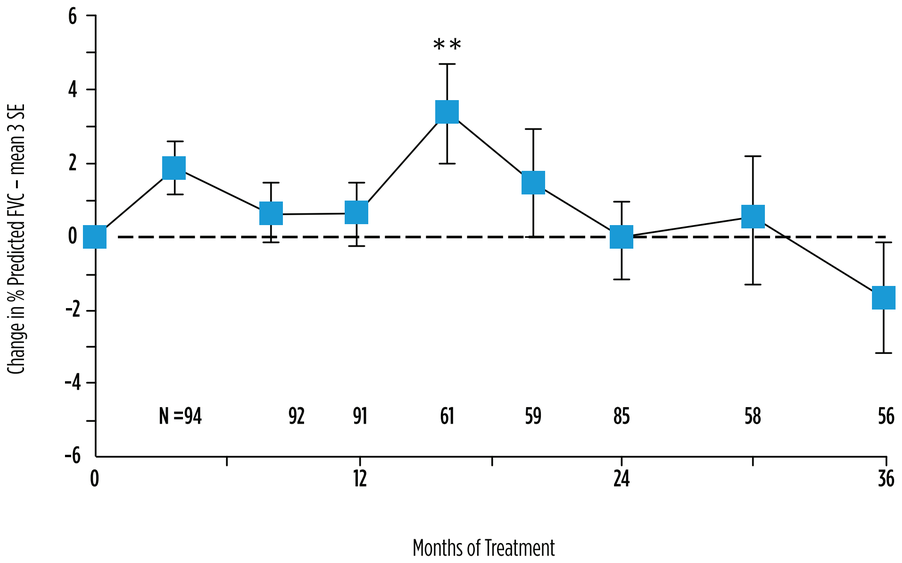
ANALYSES - Kaplan-Meier analyses were used to estimate survival probability. Multivariate Cox regression modelling was used to generate the hazard ratio for survival (HR).

ELAPRASE IN CLINICAL PRACTICE[7, 8]

ELAPRASE demonstrated improvement of the somatic parameters of MPS II patients

ELAPRASE sustained pulmonary function

The effect of ELAPRASE on percentage predicted forced vital capacity[8]



Baseline % predicted FVC = 56.2% 3 1.5% (mean 3 SE).

**P<0.01.

Patients, aged 5-31 years, treated with ELAPRASE experienced no change in %FVC over 3-year period[8]

ELAPRASE improved cardiac outcomes

- In the pivotal and extension trial analysis in patients aged 5-31 years, cardiac LVMI remained stable throughout 3 years of ELAPRASE treatment[1, 8]

Study design[7]

THE PIVOTAL PHASE II/III STUDY

OBJECTIVE - To determine the efficacy and safety of ELAPRASE in MPS II patients aged ≥5 years.

METHOD - Randomised (1:1:1), double blind, placebo controlled, 53-week trial.

PATIENT POPULATION - Age 5-31 years. N=96 treatment naïve male MPS II patients.

PRIMARY ENDPOINT - Two-component composite score based on the sum of the ranks of the change from baseline to week 53 in 6MWT as a measure of endurance and %FVC as a measure of pulmonary function.

SECONDARY ENDPOINTS - 6MWT distance, %FVC, absolute FVC, liver and spleen volumes, uGAG excretion and passive JROM.

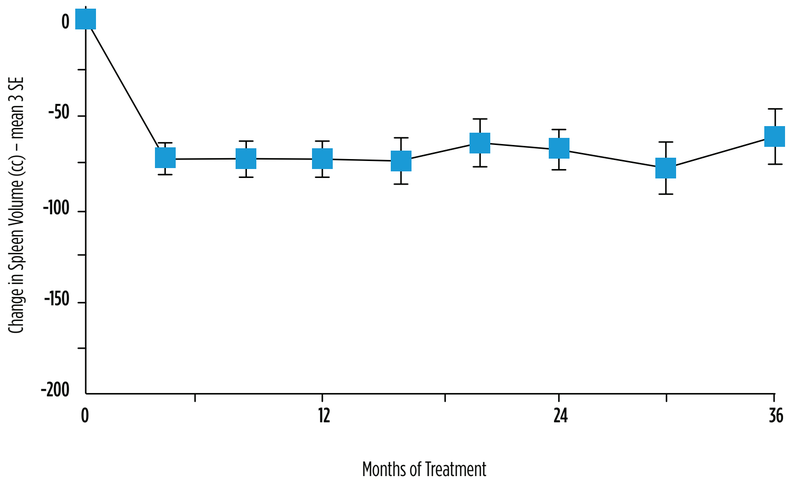
SAFETY ASSESSMENT - Physical exam, serum chemistry, complete blood count, urinalysis, measurement of vital signs, height and weight, and ECG.

AEs monitored and recorded throughout the study. The total number of AEs was similar in each treatment group and the majority were mild to moderate. The most common AEs possibly related to treatment were IRRs; a similar number of patients in the placebo and weekly ELAPRASE groups experienced ≥ IRR. The number of patients that experienced SAEs was similar between treatment groups; all except three SAEs were considered unrelated to the study group.

AE: Adverse event; JROM: Joint range motion; % FVC: % predicted forced vital capacity; 6MWT: 6 minute walk test.

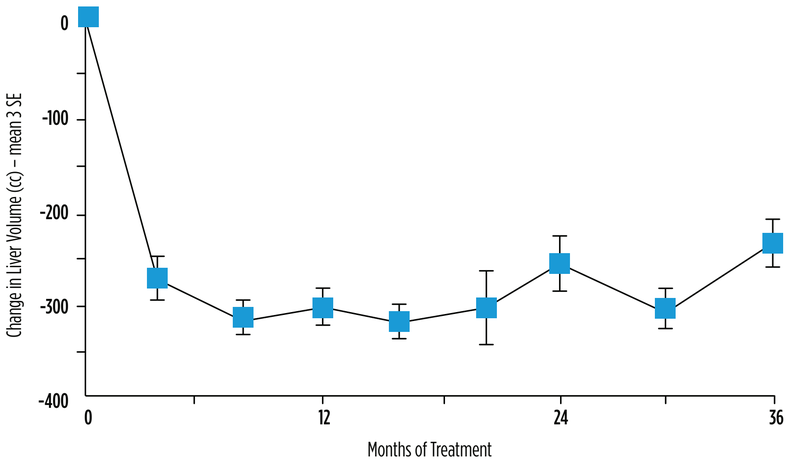
ELAPRASE reduced hepatosplenomegaly as early as 4 months

The effect of ELAPRASE on liver and spleen volumes[8]



Baseline spleen volume = 292 3 19 L
(mean 3 SE).

P<0.001 compared to baseline for all points (n=88)



Baseline liver volume = 1213 3 30 L
(mean 3 SE).

P<0.001 compared to baseline for all points (n=88)

In the pivotal extension study, in patients aged 5-31 years, ELAPRASE significantly improved liver and spleen volumes as early as after 4 months of treatment[8]

Study design[8]

THE PIVOTAL PHASE II/III EXTENSION STUDY

OBJECTIVE - To determine the efficacy and safety of long-term treatment with ELAPRASE in MPS II patients aged ≥5 years.

METHOD - Open label, 24 month extension trial for patients who completed the 53-week Phase II/III pivotal trial.

PATIENT POPULATION - Age 5-31 years. N=94.

PRIMARY OUTCOME MEASURE - Safety, 6MWT distance and FVC.

SECONDARY OUTCOME MEASURES - Liver and spleen volume, uGAG excretion, cardiac mass, JROM, linear growth velocity and functional status.

SAFETY ASSESSMENT - Clinical assessment of treatment safety at each study visit AEs were monitored and recorded throughout the study. Presence of anti-idursulfase antibodies was assayed. The most common AEs possibly related to treatment were IRRs; a similar number of patients in the placebo and weekly ELAPRASE groups experienced ≥ IRR. The number of patients that experienced SAEs was similar between treatment groups; all except three SAEs were considered unrelated to the study group.

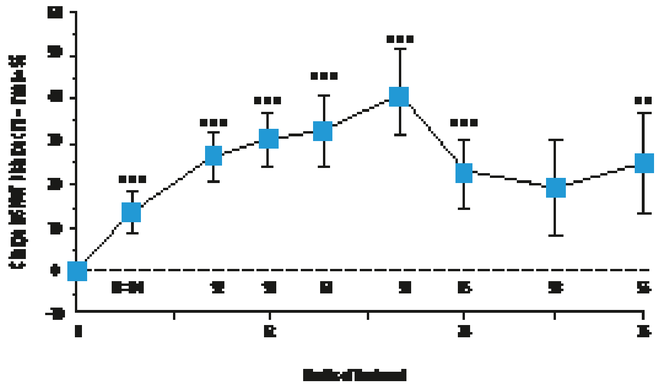
AE: Adverse event; JROM: Joint range motion; % FVC: % predicted forced vital capacity; 6MWT: 6 minute walk test.

BENEFITS – ELAPRASE LED TO SOMATIC IMPROVEMENTS

ELAPRASE IN CLINICAL PRACTICE[7,8]

ELAPRASE improved 6MWT

The effect of ELAPRASE on 6-minute walking test (6MWT) distance[8]



Baseline 6MWT distance = 400 3 10m (mean 3 SE).

The dotted horizontal line represents the baseline.

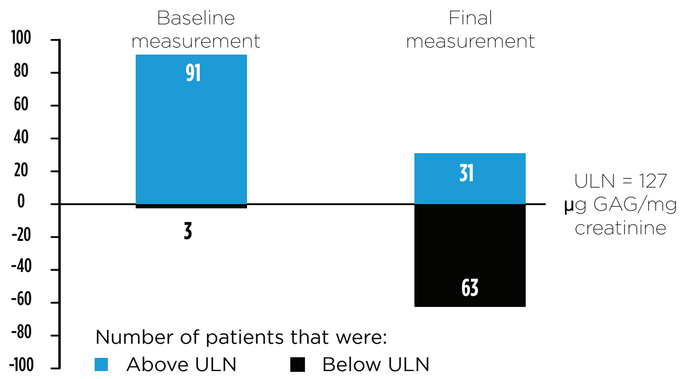
** P<0.01;

***P<0.001.

ELAPRASE significantly increased 6MWT distance vs. baseline after 3 years in patients aged 5-31 years[8]

ELAPRASE reduced uGAG excretion

The effect of ELAPRASE on uGAG levels[8]



Baseline was defined as the most recent assessment before beginning of treatment with ELAPRASE. At final measurement, patients in the active treatment groups had received ELAPRASE for a total of 36 months; patients in the placebo group received ELAPRASE for 24 months.

Baseline-normalised levels of uGAG in patients aged 5-31 years was 362 3 14 µg/mg creatinine (mean 3 SE).

P<0.0001.

ELAPRASE significantly reduced and sustained uGAG levels over 3 years in patients aged 5-31 years[8]

Study design[7]

THE PIVOTAL PHASE II/III STUDY

OBJECTIVE - To determine the efficacy and safety of ELAPRASE in MPS II patients aged ≥5 years.

METHOD - Randomised (1:1:1), double blind, placebo controlled, 53-week trial.

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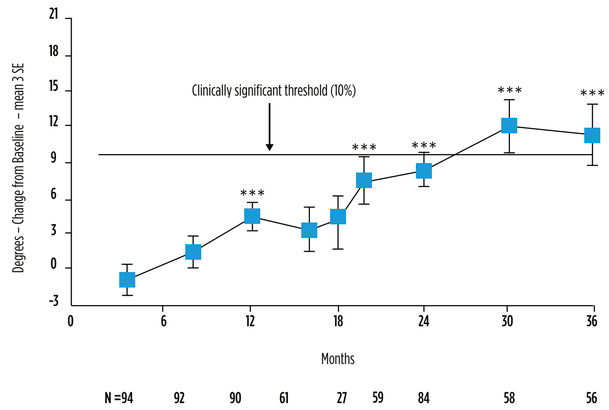
AE: Adverse event; JROM: Joint range motion; % FVC: % predicted forced vital capacity; 6MWT: 6 minute walk test.

ELAPRASE IMPROVED JOINT MOBILITY

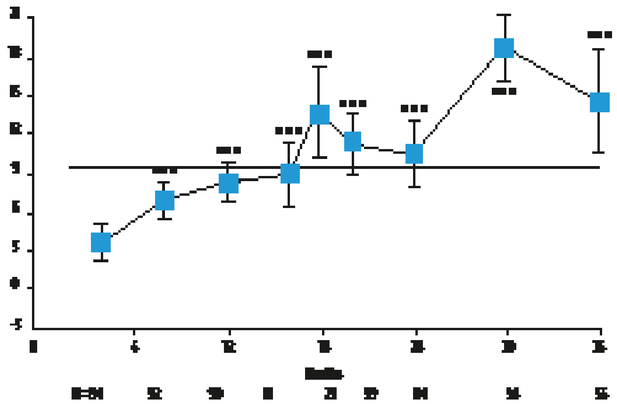
The effect of ELAPRASE on shoulder abduction[7, 8]



***P ≤ 0.005 compared with baseline.

ELAPRASE significantly improved shoulder abduction of patients aged 5-31 years[8]

The effect of ELAPRASE on shoulder flexion-extension[7, 8]



***P ≤ 0.005 compared with baseline.

ELAPRASE significantly improved flexion-extension of patients aged 5-31 years[8]

BENEFITS – ELAPRASE LED TO SOMATIC IMPROVEMENTS

Study design[8]

THE PIVOTAL PHASE II/III EXTENSION STUDY

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PATIENT POPULATION - Age 5-31 years. N=94.

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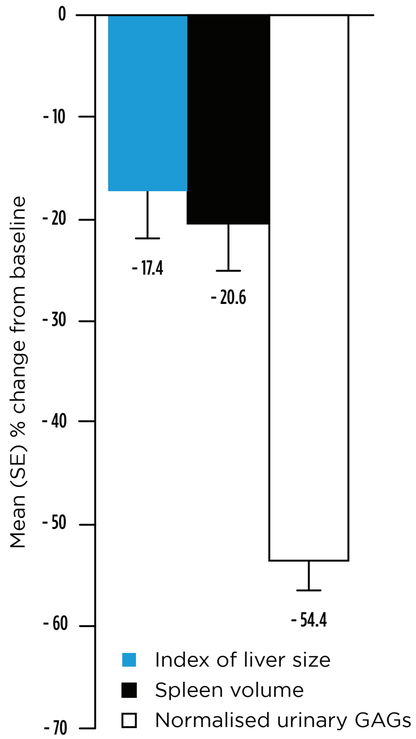
AE: Adverse event; JROM: Joint range motion; % FVC: % predicted forced vital capacity; 6MWT: 6 minute walk test.

INITIATING ELAPRASE EARLY[10,11]

ELAPRASE was shown to effectively treat paediatric patients[10, 11]

ELAPRASE reduced hepatosplenomegaly and uGAGS

Mean percentage change from baseline in index of liver size, spleen volume and urinary GAGs over 53 weeks[10]



Baseline index of liver size was 118.9 3 30.9 cm^2.
Baseline spleen volume was 160.0 3 56.6 cm^2 (mean 3 SD).
Baseline-normalised uGAG level was 738.3 3 165.2 µg/mg creatinine (mean 3 SD) (n=27).

In an open-label study of paediatric patients aged 16 months to 7.5 years, ELAPRASE led to reductions in liver size, spleen volume and uGAG levels compared to baseline over 53 weeks[10]

BENEFITS – INITIATE ELAPRASE EARLY

Study design[10]

OBJECTIVE - Determine the safety of ELAPRASE in Hunter syndrome patients aged ≤5 years.
METHOD - Open-label, 53-week safety study.
PATIENT POPULATION - Age 1.4-7.5 years. N=28 male MPS II patients.
PRIMARY ENDPOINT - Safety and tolerability assessed through TEAEs, concomitant medications and surgical procedures, vital signs physical examinations, clinical laboratory testing, 12-lead ECG and anti-idursulfase antibodies.
SECONDARY ENDPOINTS - Mean change from baseline to week 52 in uGAG levels and single-dose and repeat-dose PK parameters at weeks 1 and 27, respectively.
EXPLORATORY VARIABLES - Liver and spleen volume, routine developmental milestones and growth indices (height, weight and head circumference).
SAFETY ASSESSMENT - ELAPRASE was well tolerated in patients aged ≥16 months. All 28 patients experienced > 1 AE, all of which were mild to moderate except two cases of sleep apnoea, which did not cause treatment disruption. Most common AEs probably or possibly related to treatment were fever, rash, urticaria and vomiting.

TREATMENT OPTIMISATION[1]

ELAPRASE is dosed according to the weight of the patient with Hunter syndrome[1]

Dosing calculation

$$\frac{\text{Patient weight (kg)} \times 0.5\ \text{mL/kg}}{2} = \text{mL of Elaprase required}$$

Recommended supplies for infusion

For diluting ELAPRASE[1]

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

For ELAPRASE infusion[1, 12]

- Blunt fill or filter needle to withdraw drug from vial(s)
- 50 mL bag of 0.9% Sodium Chloride injection, USP (flush infusate)
- IV needle/catheter and insertion supplies
- Add-on device(s) as required for a modified piggyback or secondary infusion technique
- Infusion control device

These additional infusion supplies are recommendations only. They should be reconciled with appropriate institution policies and procedures, required local regulations and medical judgment.

PATIENT PROFILES

Non-neuronopathic or neuronopathic

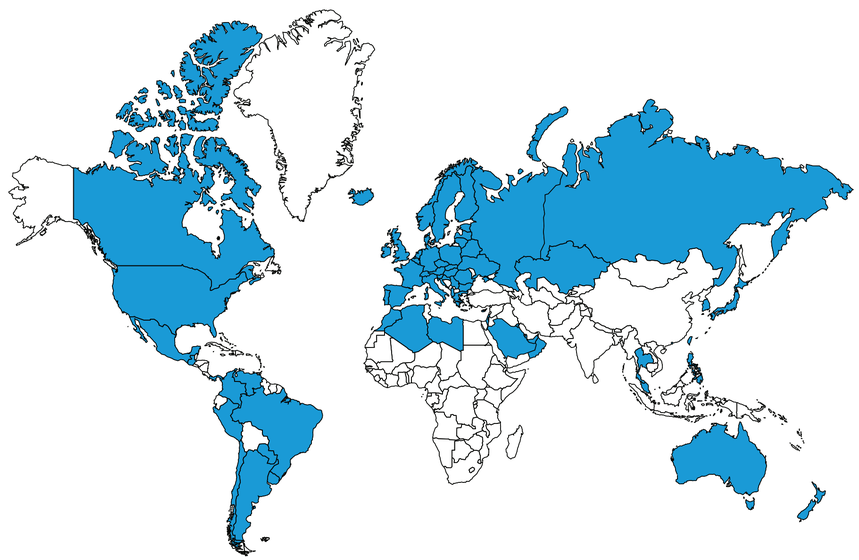
BRYCE
AGED 13 YEARS

KAYQUE
AGED 11 YEARS

ARTHUR
AGED 2 YEARS

OUR COMMITMENT TO HUNTER SYNDROME

Elaprase has more than 10,000 patients-years of exposure worldwide, in more than 70 countries[13, 14]



Elaprase is currently available for the treatment of Hunter syndrome patients in Canada, United States, European Union, Iceland, Liechtenstein, Norway, Switzerland, Albania, Algeria, Bahrain, Belarus, the Gulf co-operation council, Israel, Kazakhstan, Saudi Arabia, Kuwait, Libya, Morocco, Oman, Qatar, Russia, Serbia, Ukraine, Argentina, Brazil, Chile, Colombia, Guatemala, Mexico, Panama, Paraguay, Peru, Uruguay, Venezuela, Australia, Hong Kong, Japan, Macau, Malaysia, New Zealand, Philippines, Singapore, South Korea, Taiwan, Thailand.

SAFETY INFORMATION

Brief Safety Information

Please consult the Elaprase® Summary Product Characteristics (SmPC) before prescribing.

Elaprase® treatment should be supervised by a physician or other healthcare professional experienced in the management of patients with MPS II or other inherited metabolic disorders.

Contraindication
Severe or life-threatening hypersensitivity to the active substance or to any of the excipients if hypersensitivity is not controllable.

The most commonly observed adverse events with Elaprase treatment were infusion-related reactions, which included cutaneous reactions (rash, pruritus, urticarial, and erythema), pyrexia, flushing, wheezing, dyspnea, headache, vomiting, abdominal pain, nausea, and chest pain.

Very common adverse reactions (frequency ≥1/10) included headache, flushing, wheezing, dyspnoea, abdominal pain, nausea, diarrhoea, vomiting, urticaria, rash, pruritus, erythema, pyrexia, chest pain, infusion-related reactions.

ABBREVIATED PRESCRIBING INFORMATION

ELAPRASE™ (idursulfase)

(Please consult the Summary of Product Characteristics (SmPC) before prescribing)

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See Section 4.8 of the SmPC for how to report adverse reactions.

Product Name: Elaprase 2 mg/ml concentrate for solution for infusion. **Indication:** Elaprase is indicated for the long-term treatment of patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II). Heterozygous females were not studied in the clinical trials. **Dose and Administration:** Elaprase treatment should be supervised by a physician or other healthcare professional experienced in the management of patients with MPS II or other inherited metabolic disorders. Elaprase is administered at a dose of 0.5 mg/kg body weight every week by intravenous infusion over a 3-hour period, which may be gradually reduced to 1 hour if no infusion-associated reactions are observed. Infusion of Elaprase at home may be considered for patients who have received several months of treatment in the clinic and who are tolerating their infusions well. Home infusions should be performed under the surveillance of a physician or other healthcare professional. **Contraindications:** Severe or life-threatening hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SmPC, if hypersensitivity is not controllable. **Special warnings and precautions for use:** Infusion-related reactions: Patients treated with idursulfase may develop infusion-related reactions.

No patient discontinued treatment due to an infusion reaction during clinical studies. Special care should be taken when administering an infusion in patients with severe underlying airway disease. Delaying the infusion in patients who present with an acute febrile respiratory illness should be considered. Patients using supplemental oxygen should have this treatment readily available during infusion in the event of an infusion-related reaction. Anaphylactoid/anaphylactic reactions: These have the potential to be life-threatening and have been observed in some patients treated with idursulfase up to several years after initiating treatment. Late emergent symptoms and signs of anaphylactoid/anaphylactic reactions have been observed as long as 24 hours after an initial reaction. If an anaphylactoid/anaphylactic reaction occurs, the infusion should be immediately suspended and appropriate treatment and observation initiated. Patients who have experienced anaphylactoid/anaphylactic reactions should be treated with caution when re-administering idursulfase, and appropriately trained personnel and equipment for emergency resuscitation (including epinephrine) should be available during infusions. Severe or potentially life-threatening hypersensitivity is a contraindication to rechallenge, if hypersensitivity is not controllable. Patients with the complete deletion/large rearrangement genotype: Paediatric patients with this genotype have a high probability of developing antibodies, including neutralizing antibodies, in response to exposure to idursulfase. Patients with this genotype have a higher probability of developing infusion-related adverse events and tend to show a muted response compared to patients with the missense genotype. Management of patients must be decided on an individual basis. **Sodium:** Elaprase contains 0.482 mmol sodium (11.1 mg) per vial. This is equivalent to 0.6% of the WHO recommended maximum daily intake of 2 g sodium for an adult. Interactions: No formal medicinal product interaction studies have been conducted. Based on its metabolism in cellular lysosomes, idursulfase would not be a candidate for cytochrome P450 mediated interactions. Fertility, Pregnancy and Lactation: There are no data or limited data from the use of idursulfase in pregnant women. As a precautionary measure, it is preferable to avoid the use of Elaprase during pregnancy. Use of idursulfase during breastfeeding should only occur when the potential benefit is judged by the physician to justify the risk.

Driving: Idursulfase has no or negligible influence on the ability to drive and use machines. Undesirable Effects: In a Phase II/III 52-week placebo-controlled study where 32 patients were treated with idursulfase, adverse drug reactions were almost all mild to moderate in severity. The most common adverse reactions (ARs) were infusion-related reactions, which included cutaneous reactions (rash, pruritus, urticaria), pyrexia, headache, hypertension and flushing. Frequency of infusion-related reactions decreased over time with continued treatment. Very common (≥1/10) ARs: headache, flushing, wheezing, dyspnoea, abdominal pain, nausea, diarrhoea, vomiting, dyspepsia, urticaria, rash, pruritus, pyrexia, chest pain, infusion-related reactions, infusion-site swelling, hypertension. Common (>1/100, <1/10) ARs: dizziness, tremor, cyanosis, arrhythmia, tachycardia, hypotension, hypoxia, tachypnoea, bronchospasm, cough, swollen tongue, arthralgia, erythema, face oedema, oedema peripheral. Uncommon (≥1/1,000 to <1/100) ARs: Tachypnoea. Description of selected adverse reactions: Across clinical studies, serious adverse reactions were reported in a total of 5 patients who received 0.5 mg/kg weekly or every other week. Four patients experienced a hypoxic episode during one or several infusions, which necessitated oxygen therapy in 3 patients with severe underlying obstructive airway disease (2 with a pre-existing tracheostomy). The most severe episode occurred in a patient with a febrile respiratory illness and was associated with hypoxia during the infusion, resulting in a short seizure. In the fourth patient, who had less severe underlying disease, spontaneous resolution occurred shortly after the infusion was interrupted. These events did not recur with subsequent infusions using a slower infusion rate and administration of pre-infusion medicinal products, usually low-dose steroids, antihistamine, and beta-agonist nebulisation. The fifth patient, who had preexisting cardiopathy, was diagnosed with ventricular premature complexes and pulmonary embolism during the study. There have been post-marketing reports of anaphylactoid/anaphylactic reactions. **Immunogenicity:** Across 4 clinical studies 53/107 patients (50%) developed anti-idursulfase IgG antibodies at some point. The overall neutralising antibody rate was 26/107 patients (24%). In a further study in paediatric patients, 67.9% (19/28) developed anti-idursulfase IgG antibodies, 54% (15/28) tested positive for neutralising antibodies. **Paediatric Population:** Adverse reactions reported in the paediatric population were, in general, similar to those reported in adults. **Overdosage:** There is no experience with overdoses of Elaprase.

Marketing Authorisation Holder: Shire Human Genetic Therapies AB, Vasagatan 7, 111 20 Stockholm, Sweden.

Further information is available on request:

Suspected Adverse Events should be reported to Takeda at: ae.middleeast@takeda.com

Date of Preparation of the API: Feb/21

SMPC

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1. Elaprase, Summary of Product Characteristics. Feb 2021.
2. Martin R, Beck M, Eng C, ***et al.*** Recognition and diagnosis of mucopolysaccharidosis II (Hunter syndrome). ***Pediatrics.*** 2008;1221(2):e377-86.
3. Muenzer J, Beck M, Giugliani R, ***et al.*** Idursulfase treatment of Hunter syndrome in children younger than 6 years: Results from the Hunter Outcome Survey. ***Genet Med.*** 2011;13(2):102-109.
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