

Idursulfase

Idursulfase (Elaprase) was recently reviewed through Ontario's new Drugs for Rare Diseases (DRD) evaluation framework. The outcome of this review has resulted in a change in funding status. Please see below under "status" for additional information.

Product:

IDURSULFASE (Elaprase®) 2 mg/mL vial

Class of drugs:

Enzyme replacement therapy

Indication:

Treatment of Hunter syndrome (Mucopolysaccharidosis II, MPS II)

Manufacturer:

Shire Human Genetics Therapies, Inc.

CED Recommendation

The CED recommended that idursulfase (Elaprase) not be funded through the Ontario Public Drug Programs. Although preliminary data show that the drug demonstrates biological activity, there is no evidence of meaningful benefits (such as improvements in survival, pain, physical function or quality of life). Moreover, the cost of treatment is extremely high.

Executive Officer Decision

Based on the review of Hunter Syndrome and idursulfase (Elaprase) through the Drugs for Rare Diseases (DRD) evaluation framework, the Executive Officer has decided to fund idursulfase (Elaprase) through Ontario Public Drug Programs for specific sub-groups of patients.

Status

Funding is available through the Exceptional Access Program (EAP) according to specific clinical criteria. For further information, please see:

http://www.health.gov.on.ca/english/providers/program/drugs/pdf/elaprase_reimburse.pdf

Highlights of Recommendation:

- ◆ Idursulfase (Elaprase) is a purified form of the iduronate-2-sulfatase enzyme produced by recombinant DNA technology. It is indicated for the treatment of Hunter syndrome, also known as Mucopolysaccharidosis (MPS) II.
- ◆ Idursulfase (Elaprase) has been shown in clinical trials to improve patients' urinary glycosaminoglycans (GAG) levels, liver size and spleen size. Improvements in walking tests were observed but the results were not significant. There is no evidence that the reported biological effects translate into clinically meaningful benefits, such as prolonged survival, improved quality of life, pain reduction or better physical function.
- ◆ Because clinical studies were performed in patients with the milder form of Hunter syndrome, evidence is lacking in patients with the more severe form of the disease (sometimes called Hunter syndrome Type A), which is associated with neurologic involvement.
- ◆ Idursulfase (Elaprase) does not penetrate the brain; therefore, it is unlikely that treatment will prevent the neurological disease seen in patients with Hunter syndrome Type A.
- ◆ Idursulfase (Elaprase) is administered by intravenous injection. The most common side effect with treatment is infusion-related reactions, sometimes leading to severe, life-threatening allergic reactions. Serious side effects, such as irregular heart beats, blood clots in the lung and infections, have also been reported with treatment. Other side effects include headache, rash, abdominal pain, joint pain, anxiety, chest wall pain, back pain, and head injury from falls.
- ◆ Idursulfase (Elaprase) is dosed according to body weight. The drug costs \$4,215 per 6mg vial. The treatment cost is about \$657,000 per year for a child who weighs 35kg. Without any evidence of meaningful benefit to justify the high cost, idursulfase (Elaprase) does not represent value for money.
- ◆ **Overall, the Committee acknowledged the difficulties involved in producing clinical evidence and favourable cost-effectiveness data for rare diseases**

such as Hunter syndrome. These factors were considered by the Committee in making the final recommendation. Given the limitations with the clinical data, the potential for life-threatening reactions to treatment administration, and the lack of cost-effectiveness, the Committee felt that idursulfase (Elaprase) should not be funded.

Background:

Hunter syndrome, also known as Mucopolysaccharidosis (MPS) II, is a rare and progressive genetic disorder in people who do not have enough of an enzyme called iduronate-2-sulfatase. The shortage of this enzyme causes a buildup of glycosaminoglycans (GAG) in cells and tissues. Hunter syndrome affects multiple organ systems in the body.

The disease varies in severity. In its most severe form (sometimes called Hunter syndrome Type A), a buildup of GAG occurs in the brain, causing progressive deterioration of brain cells. Children with the most severe form of the disorder are usually diagnosed when they are between 18 months and 3 years old. They deteriorate mentally, and death generally occurs before age 15. People with the mildest form of the disease (sometimes called Hunter syndrome Type B) are characterized by short stature, stiff joints, osteoarthritis, cardiac valve disease, and hearing impairment. Other people may suffer from an intermediate form of the disease.

Currently, there is no cure for Hunter syndrome. Idursulfase (Elaprase) is a purified form of the enzyme iduronate-2-sulfatase produced by recombinant DNA technology.

continued...

Detailed Discussion:

- ◆ The Committee considered the funding of idursulfase (Elaprase) on two occasions. The first review was initiated prior to Health Canada's approval of this drug and was completed in June 2007. The second review considered additional information provided by the manufacturer and was completed in November 2007.
- ◆ The evidence for effectiveness of idursulfase (Elaprase) comes from two published trials: a small, phase I/II trial involving 12 patients (Muenzer 2007); and a larger, phase II/III trial involving 96 patients (Muenzer 2006).
- ◆ In the Muenzer 2007 study, idursulfase (Elaprase) was shown to decrease urinary levels of glycosaminoglycans (GAG), liver volume and spleen volume. No clear treatment effect was found for other outcomes including forced vital capacity (FVC), global joint range of motion, and sleep quality.
- ◆ The larger study, Muenzer 2006, compared two dose regimens of idursulfase (Elaprase), 0.5mg/kg weekly or 0.5mg/kg every other week, versus placebo. Patients treated with idursulfase (Elaprase) 0.5mg/kg weekly, compared to those on placebo, had a greater improvement in mean distance walked during the 6-Minute Walk Test (6MWT) of 35 meters. However, this difference represented a less than 10% improvement over the baseline mean of over 390 meters at study entry. Patients treated with idursulfase (Elaprase) also experienced statistically significant reductions in measured liver volume, spleen volume and urinary GAG, compared with those on placebo. Improvement in FVC with idursulfase (Elaprase) was not statistically significant. Global joint range of motion, pain and quality of life were not consistently improved.
- ◆ The Committee noted that while idursulfase (Elaprase) has demonstrated treatment effects on 6MWT, urinary GAG, splenomegaly and hepatomegaly, the clinical importance of these reported measures is unknown. Moreover, evidence of benefit is not available for a number of clinically relevant outcomes, such as the need for ventilation, hospitalizations, quality of life, and survival.
- ◆ Evidence is also lacking to support the use of idursulfase (Elaprase) in Hunter syndrome Type A, the more severe variant of the disease. Patients in clinical studies were required to cooperate with pulmonary function tests and, therefore, only patients with the milder form of Hunter syndrome were enrolled. It is unclear whether study results

would be applicable to patients with Hunter syndrome Type A.

- ◆ Idursulfase (Elaprase) does not penetrate the blood brain barrier; therefore, it is unlikely that treatment will prevent the neurological disease seen in Hunter syndrome Type A.
- ◆ In terms of safety, infusion related toxicities were the most common adverse event associated with idursulfase (Elaprase) therapy. Approximately 69% of patients experienced infusion reactions, including anaphylactoid reactions, which may lead to life-threatening respiratory failure. Serious adverse events, such as cardiac arrhythmia, pulmonary embolism and infections, have also been reported with treatment. Other adverse reactions include headache, urticaria, rash, abdominal pain, arthralgia, anxiety, chest wall pain, back pain, and head injury from falls.
- ◆ IgG antibodies to idursulfase (Elaprase) are found in about half of the treated patients; however, their occurrence does not appear to impact the short-term effects of idursulfase (Elaprase). Further long-term data are required to assess the potential effects of anti-idursulfase antibodies.
- ◆ Idursulfase (Elaprase) costs \$4,215 per 6mg vial, or \$657,000 per year for a 35kg child receiving the recommended dose of 0.5mg/kg per week. Without evidence of any clinically relevant benefits that could justify the high cost, idursulfase (Elaprase) does not represent value for money.
- ◆ Overall, the Committee acknowledged the difficulties involved in producing clinical evidence and favourable cost-effectiveness data for rare diseases such as Hunter syndrome. These factors were considered by the Committee in making the final recommendation. However, only preliminary evidence of biological activity currently exists for idursulfase (Elaprase). Data on clinically important measures, such as impact on hospitalization, physical function, quality of life and survival, are lacking. Furthermore, data supporting the use of this drug in the more severe form of Hunter syndrome are not available. Given these limitations with the clinical data, the potential for life-threatening reactions to treatment administration, and the lack of cost-effectiveness, the Committee felt that idursulfase (Elaprase) should not be funded.

CEDAC Recommendation:

(<http://www.cadth.ca/index.php/en/cdr/recommendations>)

The Canadian Expert Drug Advisory Committee (CEDAC) recommended that idursulfase (Elaprase) not be listed.



Ministry of
Health and Long-Term Care
Ontario Public Drug Programs

For more information, please contact:

Ministry of Health and Long-Term Care

Ontario Public Drug Programs

Hepburn Block, 9th Floor

80 Grosvenor Street, Queen's Park

Toronto, Ontario M7A 1R3

or click: http://www.health.gov.on.ca/english/providers/program/drugs/ced_rec_table.html