

## CEDAC FINAL RECOMMENDATION and REASONS for RECOMMENDATION

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### IDURSULFASE (Elaprase™ – Shire Human Genetics Therapies, Inc.)

#### **Description:**

Idursulfase is the recombinant form of the human lysosomal enzyme, iduronate-2-sulfatase. It is approved for use as enzyme replacement therapy in patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II).

Hunter syndrome is a progressive multi-system disorder due to an inherited deficiency of iduronate-2-sulfatase. There is a broad range of clinical severity and phenotypical involvement with two extremes being recognized. The severe form is characterized by the presence of progressive mental deterioration, is often diagnosed between 18 months and three years and death generally occurs before 15 years of age. The mild form is characterized by normal or relatively normal intelligence, typically presents later (mean of 4.3 years) and has a more prolonged survival (mean age at death of 21.7 years). The phenotypic presentation of Hunter syndrome is variable, reflecting its heterogeneous presentation in affected individuals.

#### **Dosage Forms:**

6 mg vial for intravenous administration. The recommended dose is 0.5 mg/kg every week by intravenous infusion over one to three hours.

#### **Recommendation:**

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

#### **Reasons for the Recommendation:**

1. While idursulfase has been shown to have a biologic effect and improve some outcomes in patients with Hunter syndrome, the clinical significance of its effects is not established. For example, idursulfase improves distance walked in six minutes (6MWD) but the average improvement is less than 10% above baseline values. Idursulfase has not been shown to improve clinically relevant outcomes such as quality of life, pain, rates of hospitalization or the resources required for home care support.
2. It is unlikely that idursulfase enters the central nervous system and therefore, it is not expected to improve the neurological complications of Hunter syndrome.

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### Common Drug Review

3. Idursulfase costs \$4,215 for a 6 mg vial and the cost for treatment of a 35 kg patient (the average weight of patients in the clinical trial reviewed by the Committee) is \$657,000 per year. The Committee did not feel that the high cost was justified given the lack of evidence of improvement in clinically important outcomes.

### **Summary of Committee Considerations:**

The Committee considered a systematic review of clinical trials in patients with Hunter syndrome. Two randomized controlled trials (RCTs) were included in the systematic review.

One RCT compared two dose regimens of idursulfase (0.5 mg/kg weekly or 0.5 mg/kg every other week) versus placebo in 96 patients with Hunter syndrome. Two patients died during the RCT, one treated with placebo and one treated with idursulfase. Compared to placebo, patients treated with idursulfase 0.5 mg/kg weekly had a statistically significant greater improvement in mean change from baseline in the 6MWD (35 meters more at 12 months, on a baseline of 390 meters). Patients treated with idursulfase experienced statistically significant reductions in liver volume, spleen volume, and urinary glycosaminoglycans compared with placebo but there were no statistically significant improvements in pain, quality of life or global passive joint range of motion. Following the completion of the placebo-controlled phase, all 94 surviving patients were transferred to an extension trial and received open-label idursulfase 0.5mg/kg weekly; the results from this trial are not yet available.

The second RCT was a six month trial of 12 patients with MPS II. This trial did not use the approved dose of idursulfase and was reviewed for supportive efficacy and safety information only. The results from this trial were generally similar with those from the larger RCT.

Infusion reactions are the most common adverse event associated with idursulfase, occurring in approximately 69% of patients, and include severe and life-threatening anaphylactoid reactions. Other adverse events reported during idursulfase therapy include headache, urticaria, pruritis, arthralgia, abdominal pain, anxiety, chest wall pain, back pain and head injury. In the largest RCT, serious adverse events that occurred in idursulfase patients but not placebo patients included cardiac arrhythmia, pulmonary embolism, cyanosis, respiratory failure, infection and arthralgia.

Approximately 50% of patients develop antibodies to idursulfase at some point during treatment; although the clinical relevance of these antibodies is unknown they could potentially result in an increased risk of anaphylactoid reactions or tachyphylaxis to idursulfase.

### **Of Note:**

1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.
2. Idursulfase has demonstrated a biological effect in a debilitating disease for which management to date has only included symptomatic therapy. However, it has not been demonstrated to result in improvements in clinically important endpoints and its administration can result in life threatening adverse events. Using conventional criteria, idursulfase is not cost-effective, though this, by itself, is only one of the factors that is used in making a decision about funding. It has been argued that the costs of drugs to treat rare diseases are often high because of the relatively small number of patients for whom the drug is indicated. On the other hand, reimbursement of idursulfase would raise questions about equity, since drugs that have not been shown to be cost-effective for other diseases are not generally reimbursed.

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## **Common Drug Review**

**Background:**

CEDAC provides formulary listing recommendations to publicly funded drug plans. Recommendations are based on an evidence-based review of the medication's effectiveness and safety and an assessment of its cost-effectiveness in comparison to other available treatment options. For example, if a new medication is more expensive than other treatments, the Committee considers whether any advantages of the new medication justify the higher price. If the recommendation is not to list a drug, the Committee has concerns regarding the balance between benefit and harm for the medication, and/or concerns about whether the medication provides good value for public drug plans.