CDEC FINAL RECOMMENDATION

ELOSULFASE ALFA
(Vimizim — BioMarin Pharmaceuticals [Canada] Inc.)
Indication: Mucopolysaccharidosis IVA

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that elosulfase alfa not be listed.

Reasons for the Recommendation:

1. While one double-blind, phase 3, placebo-controlled randomized controlled trial (RCT) (MOR-004; N = 177) demonstrated that treatment with elosulfase alfa was statistically superior to placebo for improvement in six minute walking distance (adjusted LS mean difference: 22.5 m; 95% CI, 4 to 41 m), the clinical relevance of this finding is uncertain.
2. There was no statistically significant difference between elosulfase and placebo for improvement in the endurance of mucopolysaccharidosis (MPS) IVA patients, as measured by the three minute stair climb test (3MSCT) (adjusted LS mean difference: 1.1 stairs/min; 95% CI, –2.1 to 4.4 stairs/min).
3. Treatment with elosulfase alfa has not been shown to improve other clinical endpoints, including reducing pain, fatigue, disease progression, or the need for surgical intervention.

Background:
Elosulfase alfa is a recombinant formulation of human N-acetylgalactosamine-6-sulfate sulfatase, the enzyme that is deficient in patients with MPS IVA that is responsible for breaking down the glycosaminoglycans keratan sulfate and chondroitin-6-sulfate. Elosulfase alfa has a Health Canada indication as a long-term enzyme replacement therapy in patients with a confirmed diagnosis of MPS IVA (Morquio A syndrome). Elosulfase alfa is the first enzyme replacement therapy to be marketed in Canada for the treatment of MPS IVA.

The recommended dose of elosulfase alfa is 2.0 mg/kg/week administered by intravenous (IV) infusion over four hours. It is available as a sterile solution containing 5 mg elosulfase alfa (expressed as protein content) per 5 mL (extractable volume) solution for infusion.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs focused on the use of elosulfase alfa for the treatment of MPS IVA, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues that are important to individuals living with MPS IVA.

Patient Input Information
The following is a summary of information provided by two patient groups that responded to the CDR call for patient input:

- Reduced endurance and pain from bone and joint disease (e.g., spine, hips, and knees) have a significant impact on the quality of life of those living with MPS IVA.
- Patients expressed a desire to see disease progression stabilized or slowed, with treatment expected to improve mobility and thus increase quality of life, increase (vertical) growth in children with the disease, and reduce the risk of cervical cord compression. Patients anticipated that improvements from treatment would lead to fewer procedures and reduce the time away from school or work.
- Patients indicated a willingness to tolerate serious adverse events in order to experience benefit from therapy.
- Caregiver burden is significant and includes emotional and financial stress related to costly home renovations and devices, supporting demanding medical needs (e.g., frequent appointments with specialists, numerous surgical interventions, long hospital stays), and providing assistance for patients' daily activities due to mobility restrictions and limitations in dexterity.
- Enzyme replacement therapy provides patients and caregivers with a renewed sense of hope regarding their condition.

Clinical Trials
The CDR systematic review included one 24-week, double-blind, three-arm, placebo-controlled RCT. MOR-004 (N = 177) randomized participants (1:1:1) to either a weekly or alternate-weekly regimen of elosulfase alfa 2.0 mg/kg or matching placebo. The CDR review and CDEC's deliberations focused on the Health Canada–approved regimen of weekly administration of elosulfase alfa.

Outcomes
Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Six-minute walking test (6MWT) — change from baseline in the total distance walked in six minutes
- 3MSCT — change from baseline in the number of stairs climbed per minute over three minutes
- Disease progression — assessed by the prevalence of wheelchair dependency; requiring respiratory assistance; or requiring corrective orthopaedic surgery
- Mucopolysaccharidosis Health Assessment Questionnaire (MPS HAQ) — an instrument used to assess changes in health-related quality of life of patients with MPS
- Changes in body weight and standing height

- Pulmonary function — change from baseline in forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and maximum voluntary ventilation (MVV)
- Total adverse events, serious adverse events, and withdrawals due to adverse events.

The primary efficacy outcome in MOR-004 was the change from baseline in 6MWT after 24 weeks.

Efficacy

- At 24 weeks, a statistically significant increase in six-minute walking distance was observed from baseline favouring elosulfase alfa over placebo (adjusted LS mean difference: 22.5 m; 95% CI, 4.0 m to 40.9 m).
- At 24 weeks, there was no statistically significant difference in the 3MSCT between the elosulfase alfa and placebo groups (adjusted LS mean difference: 1.1 stairs/min; 95% CI, –2.1 to 4.4).
- Differences between treatment groups in urine keratan sulfate, pulmonary function tests (FEV, FEV_1, MVV), anthropometry (standing height, weight), and functional status as measured by the MPS HAQ were either statistically non-significant or were not compared between treatments.
- Disease progression, defined in the CDR systematic review protocol as the time to: wheelchair dependency; requiring respiratory assistance; or requiring corrective orthopaedic surgery, was not studied as an efficacy outcome.
- At baseline, wheelchair use was reported in 51.7% (30/58) patients in the elosulfase alfa group and 37.3% (22/59) in the placebo group. At week 24, the total number of patients reporting the use of a wheelchair did not change in the elosulfase alfa group, but increased in the placebo group from 22 to 27 patients.

Harms (Safety and Tolerability)

- The proportion of patients with at least one adverse event was 96.6% in both the elosulfase alfa and placebo groups. The most commonly reported adverse events in elosulfase alfa–treated patients, which also occurred at a higher frequency than placebo, were vomiting (44.8% versus 35.6%), pyrexia (43.1% versus 28.8%), headache (41.4% versus 35.6%), nausea (31.0% versus 20.3%), abdominal pain (24.1% versus 8.5%), diarrhea (20.7% versus 11.9%), oropharyngeal pain (20.7% versus 11.9%), upper abdominal pain (15.5% versus 8.5%), otitis media (15.5% versus 6.8%), dizziness (12.1% versus 5.1%), dyspnea (12.1% versus 5.1%), gastroenteritis (12.1% versus 6.8%), and chills (10.3% versus 1.7%).
- Most study participants experienced at least one infusion-related adverse event (89.7% in the elosulfase alfa group and 91.5% in the placebo group). These adverse events occurred at a consistent rate during the first 24 weeks of the trial. Nearly all infusion-related adverse events were mild to moderate in severity, with severe events being reported for two elosulfase alfa–treated patients (3.4%) and one placebo-treated patient (1.7%). Infusion-related adverse events that resulted in medical intervention were reportedly managed with IV antihistamines and/or IV steroids and none resulted in permanent discontinuation of the study drug.
- The proportion of patients with at least one serious adverse event was 15.5% in the elosulfase alfa group and 3.4% in the placebo group. Infections and infestations classified as serious adverse events occurred in 8.6% of patients in the elosulfase alfa group and none in the placebo group.

- There were no withdrawals due to adverse events reported during the trial.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing elosulfase alfa to best supportive care (BSC; defined as symptomatic management with medications for pain, infections, and surgical interventions) in patients diagnosed with MPS IVA, over a lifetime horizon (i.e., 35 years). The manufacturer's analysis used data from the MOR-004 and MOR-005 clinical trials and the MOR-001 (MorCAP) natural history study. The model included six key health states primarily based on wheelchair status. Patients in all health states except the pre-death health state were eligible for treatment with elosulfase alfa. Based on clinical opinion, the manufacturer implemented a stopping rule and assumed that a proportion of patients whose wheelchair status worsens would discontinue elosulfase alfa treatment after two cycles of the model (two years) due to treatment non-response. The manufacturer reported that elosulfase alfa compared with BSC is associated with an incremental cost-utility ratio (ICUR) of $1,502,641 per quality-adjusted life-year (QALY).

CDR identified a number of limitations with the submitted pharmacoeconomic evaluation:

- Uncertainty regarding transition probabilities beyond 72 weeks (extrapolation based on the 6MWT and FVC levels)
- Double-counting of potential benefits of elosulfase alfa due to different utility values and mortality rates between elosulfase alfa and BSC within the same health state
- Assumption that patients do not gain weight over time
- Inclusion of caregiver disutility values and costs under the Ministry of Health perspective
- Lack of clarity regarding patients who were considered to be "non-responders" to treatment with elosulfase alfa and the associated stopping rule.

CDR reanalysis accounting for the above limitations resulted in an ICUR of $2.96 million per QALY versus BSC and $6.16 million per QALY if no stopping rule is implemented. Based on the CDR reanalysis where the manufacturer's stopping rule is maintained, a 90% price reduction of elosulfase alfa would lead to an ICUR of $308,995 per QALY versus BSC. Elosulfase alfa is priced at $[redacted] per 5 mg vial and the cost will vary based on the patient's weight. At the recommended dose of 2 mg/kg weekly for patients weighing more than 40 kg, the annual cost of elosulfase alfa exceeds $[redacted].

Other Discussion Points:

CDEC noted the following:

- The response to treatment with elosulfase alfa is likely to be heterogeneous, as MPS IVA is a disease associated with substantial genotypic (275 mutations identified at the time of the CDR review) and phenotypic heterogeneity and has a highly variable clinical course. There was insufficient evidence to determine how responders and non-responders would be differentiated in clinical practice and under what circumstances, if any, would treatment with elosulfase alfa be discontinued in the event of an inadequate response to therapy.
- MOR-004 provided relatively short-term efficacy data (i.e., 24 weeks) and focused primarily on the 6MWT, which has not been validated in patients with MPS diseases.
- Patients and caregivers report that this drug provides "a renewed sense of hope for effective treatment of their disease". CDEC considered this input; however, the evidence did not

support the achievement of outcomes known to be clinically relevant to patients and serious adverse events were more frequent with elosulfase treatment and most often classified as infections and infestations.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:

- There were limited or no data regarding the clinical benefit of elosulfase alfa on disease progression, survival, growth, pain reduction, need for surgery, requirement for walking aids, and quality of life.
- The long-term safety profile of elosulfase alfa requires further evaluation.
- The efficacy and safety of elosulfase alfa in patients with MPS IVA who are younger than five years of age have not been assessed.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, and Dr. Adil Virani

January 21, 2015 Meeting
Regrets:

None

Conflicts of Interest:

None

About This Document:
CDEC provides formulary listing recommendations or advice to CDR-participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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