CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

ELOSULFASE ALFA RESUBMISSION
(Vimizim — BioMarin Pharmaceutical (Canada) Inc.)
Indication: Mucopolysaccharidosis IVA (Morquio A syndrome)

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that elosulfase alfa be reimbursed for the treatment of mucopolysaccharidosis type IVA (MPS IVA), if the following clinical criterion and conditions are met:

Clinical Criterion:
- Patient has MPS IVA confirmed by diagnostic testing through enzymatic assay for N-acetylgalactosamine-6-sulfate sulfatase (GALNS) activity in peripheral blood leukocytes.

Conditions:
- A substantial reduction in price.
- Treatment should be provided under the care of a specialist with experience in the diagnosis and management of MPS IVA.
- Goals of therapy should be developed on a case-by-case basis prior to the initiation of therapy. If these pre-specified goals are not met at reassessment following a trial of one year of therapy, the treatment should not be continued. Goals of therapy should be clearly documented and measurable. Reassessment of response should be completed annually and be a condition for continued treatment.

Reasons for the Recommendation:
1. There are only approximately 100 patients in Canada living with MPS IVA. MPS IVA is a life-threatening, seriously debilitating disease that is chronic in nature, and no alternative enzyme treatments are available.
2. One double-blind, phase 3, placebo-controlled randomized controlled trial (MOR-004) demonstrated that treatment with elosulfase alfa was statistically superior to placebo for improvement in six-minute walking distance (adjusted least-squares [LS] mean difference: 22.5 m; 95% confidence interval [CI], 4 m to 41 m).
3. CADTH Common Drug Review (CDR) reanalysis accounting for the limitations surrounding utility values, mortality risks, and patient weight over time resulted in an incremental cost-

utility ratio (ICUR) of $3.18 million per quality-adjusted life-year (QALY) versus best supportive care (BSC). With a 90% price reduction, the ICUR was $330,530 per QALY; a price reduction of 97% would be required for the ICUR to approach $100,000 per QALY. However, due to the inherent assumptions in the analysis regarding the long-term clinical benefit of elosulfase alfa compared with the base-case scenario, considerable uncertainty remains regarding the true cost-effectiveness of treatment with elosulfase alfa.

4. Additional evidence on efficacy and outcomes of interest to patients would reduce uncertainty regarding the clinical effects of the new treatment.

Of Note:

1. The six-minute walk test (6MWT) has not been validated as an outcome in MPS disease. MOR-004 provided relatively short-term efficacy data (24 weeks) in the context of a lifelong illness. Therefore, the clinical significance of the trial findings would usually be considered uncertain. However, there is an absence of clinically effective drug or non-drug alternative treatments.
2. Reimbursement should be provided only if patient information is entered into a manufacturer-sponsored international registry to prospectively collect data on patients with MPS IVA who are receiving elosulfase alfa, and health outcomes data are reported on a periodic basis.
3. CDEC noted that the National Institute for Health and Care Excellence (NICE) in the UK has produced a guidance document for the use of elosulfase alfa that can provide additional clinical context for setting parameters for the implementation of this CDEC recommendation, including criteria for setting start/stop criteria, and parameters for monitoring for response and adherence.

Research Gaps:

- CDEC noted there were uncertainties regarding the clinical significance of surrogate outcomes in the clinical trials completed to date on elosulfase alfa in MPS IVA, and additional research is required to understand the impact of drug treatment on outcomes identified as meaningful to patients.

Background:

Elosulfase alfa is a recombinant formulation of human N-acetylgalactosamine-6-sulfate sulfatase, the enzyme responsible for breaking down glycosaminoglycans keratan sulfate and chondroitin-6-sulfate that is deficient in patients with MPS IVA. 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.

Submission History:
The original CDR systematic review of elosulfase alfa included one 24-week, double-blind, three-arm, placebo-controlled randomized controlled trial (RCT). MOR-004 (N = 177) randomized participants (1:1:1) to either a weekly or biweekly 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.
In March 2015, CDEC issued a "do not list" recommendation for elosulfase alfa. Key reasons for the recommendation included uncertain clinical relevance for improvement in 6MWT distance and lack of improvement in other clinical end points, including reductions in pain, fatigue, disease progression, or the need for surgical intervention.

This resubmission of elosulfase alfa is based on manufacturer-provided new clinical data including [redacted], ad-hoc responder analyses based on MOR-004, long-term (120 weeks) results for endurance and pulmonary function from the MOR-005 extension trial, and results from MOR-007 evaluating the use of elosulfase alfa in children younger than five years of age.

Summary of CDEC Considerations:
CDEC considered the following information prepared by CDR: an updated systematic review of the beneficial and harmful effects of elosulfase alfa 2 mg/kg IV once weekly for long-term enzyme replacement therapy in patients with MPS IVA; a critique of additional clinical evidence provided by the manufacturer; a critique of the manufacturer's pharmacoeconomic evaluation; and patient group–submitted information about outcomes and issues important to patients.

Patient Input Information
- MPS IVA has a profound impact on all parts of a patient's life, given the progressive nature of the disease and the range of sequelae of the enzyme deficiency. MPA IVA leads to hernias, chronic ear infections, hearing impairment, corneal clouding, diarrhea, heart disease, respiratory disease, sleep apnea, hyperflexibility of joints, dysostosis multiplex, spinal stenosis leading to spinal cord compression, and short stature.
- Effects on endurance and bone and joint disease are identified as having the most significant impact on a patient's quality of life.
- To date, no specific treatment has been available for MPS IVA — only symptomatic treatment to address the consequences of the disease.
- Patients express a desire to see disease progression stabilized or slowed.
- Patients who received the treatment reported improvements in endurance and stabilization in their condition and did not report any major adverse events.

Clinical Trials
The updated systematic review did not retrieve any new RCTs. One new observational trial was provided by the manufacturer that evaluated elosulfase alfa in pediatric patients.

Additional clinical information (the basis of the resubmission)

1. Clinical relevance of the 6-minute walk test:
In MOR-004, change in 6MWT was the primary efficacy outcome. While a validated outcome in cardiopulmonary conditions, the relevance and validity for MPS IVA patients is uncertain. Furthermore, 6MWT MCID value in MPS IVA patients is unknown. The mean percentage changes from baseline (± standard deviation [SD]) at week 24 were 8.7% (± 28.8), and 23.9% (± 44.8) for placebo and weekly elosulfase alfa, respectively (mean difference of 15.2%). [redacted] However, CDR identified several limitations concerning the manufacturer's estimation. The manufacturer also cited a post-hoc Delphi consensus panel that estimated a more conservative MCID of 15%.

2. Multi-domain responders analysis:
This post-hoc analysis was based on the per-protocol results of MOR-005 at 72 weeks for patients who received weekly elosulfase alfa in MOR-004 and MOR-005. The manufacturer reported that all patients ([redacted]) in the per-protocol population were either single-domain ([redacted]) or multi-domain responders ([redacted]) at 72 weeks.

The main limitation of this analysis was definition of responders; the manufacturer considered patients who had any improvement to be responders. Another limitation was that it excluded [redacted] of patients because they missed doses or had surgeries. The manufacturer did not provide information about these excluded patients who might be considered non-responders.

3. Long-term safety and efficacy profile of elosulfase alfa:
The manufacturer provided new data for up to 120 weeks (96 weeks in MOR-005) of treatment with elosulfase alfa based on endurance and pulmonary function.

Patients treated with elosulfase alfa continued to show improvement in 6MWT distance until 72 weeks of treatment; after this time point, the 6MWT seemed to decline back to values approaching those at baseline of MOR-005. Mean (standard error [SE]) change from baseline in 6MWT distance was [redacted] m at 36 weeks, [redacted] m at 72 weeks, and [redacted] m at 120 weeks.

The improvements in forced vital capacity observed at week 24 had further improved by a mean (SE) increase of 0.08 (0.02) L (8.6%) by week 120. These improvements are not statistically significant compared with MOR-005 baseline.

4. Efficacy and safety of elosulfase alfa in patients younger than five years of age:
The manufacturer reported results of 15 pediatric patients younger than five years old who were included in an open-label, single-arm study (MOR-007). All patients reported at least one adverse event (AE), including 13 (87%) patients reporting drug-related AEs: pyrexia (53%), vomiting (40%), and abdominal pain (27%). Seven patients reported serious AEs, but no patients discontinued treatment due to AEs and there were no reported deaths.

Growth velocity results showed that cumulative growth rate remained positive for patients aged two years and older. The mean height in patients aged two years and older increased by 5.3 (± 2.1) cm from baseline to week 52, and further increased to 7.6 (± 4.0) by week 104.

Cost and Cost-Effectiveness

The confidential submitted price for elosulfase alfa is [redacted] per 5 mg vial. The treatment cost per patient varies based on body weight. At the recommended dose of 2 mg/kg per week, the annual cost exceeds [redacted] for patients weighing more than 40 kg.

The manufacturer submitted a cost-utility analysis comparing elosulfase alfa to BSC (defined as symptomatic management with medications for pain and infections, and surgical interventions) in patients with MPS IVA. The model was based on a lifetime time horizon (35 years) and was conducted from the perspective of a Canadian public payer. The model included six key health states based primarily on wheelchair status. The analysis used data from the MOR-004 and MOR-005 clinical trials and the MOR-001 (MorCAP) natural history study. In the absence of clinical data, the manufacturer made a number of assumptions regarding the long-term efficacy of elosulfase alfa, particularly with respect to the trajectory of long-term disease progression in patients demonstrating a response on one or more clinical domains (i.e., 6MWT, pulmonary function) in the clinical trials. The manufacturer reported that elosulfase alfa compared with BSC is associated with an ICUR of $1,720,127 per QALY.

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

- Uncertainty regarding the validity of 6MWT to model disease progression, given the lack of data correlating improvements in this measure with patient-relevant outcomes
- Uncertainty regarding the assumption that multi-domain responders would maintain lifelong stabilization of disease
- Uncertainty regarding the long-term efficacy of elosulfase alfa, in particular the proportion of patients who would maintain responder status beyond 72 weeks, the longest time point at which this outcome was reported in MOR-004 and MOR-005
- Double-counting of health benefits due to inclusion of different utility values for elosulfase alfa and BSC within the same health state
- Inappropriate use of treatment-dependent, mortality relative risk values rather than mortality risks based on the natural history of MPS IVA
- Inappropriate assumption that patients do not gain weight over time, resulting in underestimation of average elosulfase alfa doses and costs.

A CDR reanalysis accounting for the limitations regarding utility values, mortality risks, and patient weight over time resulted in an ICUR of $3.18 million per QALY versus BSC. A price reduction of 97% would be required for the ICUR to approach $100,000 per QALY, based on the CDR reanalysis. However, due to the inherent assumptions in the analysis regarding the long-term clinical benefit of elosulfase alfa compared with BSC, considerable uncertainty remains regarding the true cost-effectiveness of treatment with elosulfase alfa.

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, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

April 20, 2016 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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