

## CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

### GALSULFASE (Naglazyme — BioMarin Pharmaceutical Inc.) Indication: Mucopolysaccharidosis VI

#### **Recommendation:**

The CADTH Canadian Drug Expert Committee (CDEC) recommends that galsulfase be listed for long-term enzyme replacement therapy in patients with a confirmed diagnosis of mucopolysaccharidosis VI (MPS VI), if the following clinical criteria and conditions are met:

#### **Clinical criteria:**

- Patients are ambulatory and able to meet minimum mobility parameters.
- Patients do not have another serious and potentially life-limiting intercurrent illness.

#### **Conditions:**

- Patients should be initiated on treatment and followed in a specialized clinic with expertise in the diagnosis and management of MPS VI.
- Goals of therapy should be developed on a case-by-case basis prior to initiation of therapy. If these pre-specified goals are not met at reassessment following a trial of 24 weeks of therapy, the treatment should not be continued.
- Substantial reduction in price

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

1. One double-blind, randomized controlled trial (RCT) (ASB-03-05; N = 39) demonstrated that treatment with galsulfase once weekly was statistically superior to placebo for improvement in 12-minute walking distance (adjusted mean difference [MD]: 92 m; 95% confidence interval [CI], 11 to 172) and a numerical improvement in the three-minute stair climb test (3MSCT; adjusted MD: 5.7 stairs/min;  $P = 0.053$ ).
2. At the current price (\$1,535 per vial) and the recommended dose (1 mg/kg per week), the CADTH Common Drug Review (CDR) estimated that the annual cost of treatment with galsulfase ranges from \$223,496 to \$750,308; therefore, galsulfase is associated with a significantly high cost.
3. Patient groups identified an unmet need in the treatment of MPS VI that, CDEC concluded, could potentially be met by galsulfase.

### Of Note:

- CDEC noted that the patients enrolled in ASB-03-05 were ambulatory and able to walk at least 5 m in a six-minute walk test.
- CDEC noted that a large proportion of galsulfase-treated patients in ASB-03-05 failed to demonstrate a response to treatment based on the 12-minute walking distance (i.e., an improvement of  $\geq 80$  m from baseline).
- CDEC noted that the CDR-participating drug plans and the MPS VI clinical expert community need to establish case-by-case evaluation criteria for the initiation and continuation of galsulfase.

### Background:

Galsulfase is a recombinant form of human *N*-acetylgalactosamine-4-sulfatase, the enzyme that is deficient in patients with MPS VI. Galsulfase has a Health Canada indication as long-term enzyme replacement therapy in patients with a confirmed diagnosis of MPS VI. The recommended dosage of galsulfase is 1 mg/kg/week administered by intravenous (IV) infusion over no fewer than four hours. It is available as a sterile solution containing 5 mg galsulfase per 5 mL solution (1 mg/mL).

In response to a request from the CDR-participating drug plans, the manufacturer of galsulfase indicated that it was not planning to file a CDR submission. Therefore, the current CDR submission was filed by the CDR-participating drug plans in order to address the need for a review of the evidence and a formulary listing recommendation from CDEC on the use of galsulfase for MPS VI.

### Summary of CDEC Considerations:

CDEC considered the following information prepared by CDR: a systematic review of RCTs and pivotal studies, a critique of the manufacturer's pharmacoeconomic evaluation, and information submitted by patient groups about outcomes and issues that are important to individuals living with MPS VI.

### Patient Input Information

Two patient groups (i.e., the Isaac Foundation for MPS Treatment and Research and the Canadian Society for Mucopolysaccharide and Related Diseases) responded to the CDR call for patient input with a single combined submission. Information was obtained from conversations with patients and caregivers, an online survey, and from literature. The following is a summary of key information provided by the patient groups:

- Patients with MPS VI can experience a range of life-altering and life-threatening symptoms that progressively worsen over time. In addition to many respiratory and cardiovascular complications, the impact of MPS VI on the musculoskeletal system results in significant pain, loss of function, and reduced quality of life. Patients lose their ability to participate in many of the normal activities of daily living and childhood.
- Caregivers of patients with MPS VI must cope with extensive care requirements, long hospital stays, multiple surgical interventions, and frequent medical appointments. These can pose significant emotional and financial challenges.

- Patients noted that in the absence of galsulfase, the only condition-specific treatment approved for use in MPS VI, treatment consists of using a long-term supportive approach to managing symptoms.
- Patients and caregivers are seeking a treatment that will lead to stabilization of MPS VI, increased quality of life, and fewer hospital visits, medical interventions, and physician appointments.

### **Clinical Trials**

The CDR systematic review included one double-blind, placebo-controlled RCT. ASB-03-05 was a phase 3, multinational, clinical study conducted in 39 patients with MPS VI. Eligible patients were randomized (1:1) to either 1.0 mg/kg galsulfase or placebo weekly for 24 consecutive weeks. At the end of the RCT, 38 patients entered a 240-week, open-label extension study (ASB-03-06), in which all patients received galsulfase 1 mg/kg per week.

### **Outcomes**

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

- 12-minute walk test (12MWT) — change from baseline in the total distance walked in 12 minutes. [REDACTED]
- 3MSCT — change from baseline in the number of stairs climbed per minute over three minutes.
- Pulmonary function — change from baseline in forced vital capacity (FVC) and forced expiratory volume in one second (FEV<sub>1</sub>).
- Urinary glycosaminoglycan (GAG).
- Disease progression — assessed by a) initiation of wheelchair or walking aid use; b) requirement for corrective orthopaedic surgery; c) the incidence of cardiac failure; or d) the incidence of respiratory failure (e.g., requirement for tracheotomy).
- Total adverse events, serious adverse events, and withdrawals due to adverse events.

The primary efficacy outcome in ASB-03-05 was the change from baseline in 12MWT after 24 weeks. The objective of the extension study was to assess the long-term efficacy and harms of galsulfase.

### **Efficacy**

- Baseline values for the 12MWT differed between the galsulfase group (mean ± standard deviation [SD]: 227 ± 170 m) and the placebo group (mean ± SD: 381 ± 202 m). At 24 weeks, a statistically significant increase in 12-minute walking distance was observed from baseline favouring galsulfase over placebo (adjusted mean difference at 24 weeks: 92 m; 95% CI, 11 to 172). [REDACTED]

- [REDACTED]

Compared with placebo, the adjusted climb rate for patients in the galsulfase group increased by an average of  $5.7 \pm 2.9$  stairs/min ( $P = 0.053$ ).

- Urinary GAG levels were statistically significantly lower than in the placebo group at 24 weeks (mean  $\pm$  standard error [SE]:  $-227 \pm 18$  mcg/mg creatinine; 95% CI,  $-265$  to  $-190$ ,  $P < 0.001$ ).
- There were no statistically significant differences between the galsulfase and placebo groups in FVC or FEV<sub>1</sub>. [REDACTED]
  - [REDACTED]
  - [REDACTED]
- The need for wheelchairs or walking aids and corrective orthopaedic surgery was not reported for either the core or extension phases of the study.
- Cardiac failure and respiratory failure were not studied as efficacy outcomes in study ASB-03-05.
- One patient in the galsulfase treatment group and one patient in the placebo group required a tracheostomy during the 24-week study period.
- There were no statistically significant differences between galsulfase and placebo in shoulder range of motion or joint pain.
- Patients who received placebo during ASB-03-05 demonstrated statistically significant improvements in 12MWT and 3MSCT when they received treatment with galsulfase in the extension study. [REDACTED]
  - [REDACTED]
  - [REDACTED]
- Patients who received galsulfase in the double-blind phase also demonstrated improved endurance during the extension study. [REDACTED]

**Harms (Safety and Tolerability)**

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

**Cost and Cost-Effectiveness**

As the review was initiated by the CDR-participating drug plans, the manufacturer of galsulfase was invited to provide clinical and/or health economic evidence to support the CDR review process. The manufacturer provided a budget impact analysis from the perspective of CDR-participating plans, but indicated that a health economic evaluation of relevance for review such as a cost-utility analysis could not be provided. The CDR assessed the health economic

evidence available in the public domain, as well as budget data provided by the manufacturer, and considered input from the clinical expert consulted by CDR during the review.

A review of the published literature did not identify any relevant published economic literature on galsulfase for the treatment of MPS VI, although one health technology assessment was identified, in which the Australian Pharmaceutical Benefits Advisory Committee concluded that the economic evaluation suggested the incremental cost-effectiveness ratio for galsulfase would be unacceptably high, but that the clinical information met the criteria for listing on Australia's Life Saving Drugs Programme.

Galsulfase was submitted at a marketed price of \$307 per mL (\$1,535 per 5 mL vial). At the recommended dose of 1 mg per kg per week, assuming an average weight similar to the pivotal clinical trial (25 kg), CDR determined the mean annual cost of galsulfase to be \$399,100. Considering that patient weight ranged from 14 kg to 47 kg in the study, this resulted in an annual cost ranging from \$223,496 to \$750,308. CDR noted that galsulfase was administered as an IV infusion over at least four hours, which may lead to additional expenditure associated with the administration of galsulfase. Over 20 years, considering the age and weight ranges from the pivotal study, CDR calculated the total average undiscounted lifetime drug cost of galsulfase per patient to be approximately \$8.0 million.

The pivotal study demonstrated that patients receiving galsulfase plus standard medical management (SMM) had fewer hospitalizations per patient than patients receiving placebo plus SMM (there were approximately four times more hospitalizations in the placebo group than in the galsulfase group).

While no evaluation was provided to CDR that assessed the relative health and economic implications of adding galsulfase to SMM in the Canadian situation, the general findings indicate that treatment with galsulfase appears to lead to improvements on the 12MWT, but at a substantially increased cost.

### **Other Discussion Points:**

CDEC noted the following:

- There are no Canadian guidelines regarding discontinuation of treatment with galsulfase.
- The clinical expert consulted during the review indicated that the observed improvements in walk-test distances were likely clinically meaningful for patients.
- A 10-year follow-up study was also identified during the literature search but did not meet the inclusion criteria for the CDR systematic review. CDEC considered the data from this study and noted several important limitations, including the cross-sectional design of the study, the relatively small control group of untreated patients, and the substantial differences in age and other baseline characteristics between treated and untreated patients. CDEC concluded that these limitations precluded its ability to draw conclusions regarding the long-term effectiveness of galsulfase.

### **Research Gaps:**

CDEC noted that there is insufficient evidence regarding the following:

- There is no evidence that treatment with galsulfase improves survival, pain, fatigue, disease progression, quality of life, or the need for surgical intervention.

- There is limited evidence regarding the benefit of treatment with galsulfase in children who are younger than five years.

### **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 Wijeyesundera.

### **January 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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