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## **Expert Opinion Update**

**Canadian Expert Opinion:** Recommendations for the use of elosulfase alfa in the management of Morquio A Syndrome (MPS IVA). November 25, 2016

### **Preamble:**

This current document is an update of a previous expert opinion document that was posted June 16<sup>th</sup>, 2014. The rationale for this update relates to the release by the National Institute for Health and Care Excellence (NICE) of the Managed Care Access Agreement (entitled “Elosulfase alfa for treating mucopolysaccharidosis type IVA”) established between NHS England and BioMarin Europe in November 2015 as well as the Canadian Agency for Drugs and Technologies in Health (CADTH) Drug Expert Committee’s recommendation that elosulfase alfa be listed as an approved benefit on provincial drug benefit formularies in Canada at a substantial reduction in price. CADTH suggests that the next step will be reimbursement negotiations between the provinces and the manufacturer.

[www.cadth.ca/sites/default/files/cdr/complete/SR0456\\_complete\\_Vimizim\\_May-26\\_16.pdf](http://www.cadth.ca/sites/default/files/cdr/complete/SR0456_complete_Vimizim_May-26_16.pdf).

The NHS managed care agreement provided specific guidelines for use and assessment of efficacy of elosulfase in MPS IVA patients whereas CADTH provided conditions that “goals of therapy be established on a case by case basis”. Canadian experts in this area felt that the Canadian Expert Opinion should align, where possible, with the NHS document and that augmentation of the discussion of therapeutic goals would align with the CADTH conditions. The original document and this update represent the opinions of Canadian metabolic and genetic physicians who provide comprehensive medical care for individuals suffering from Morquio A syndrome. This document is not intended to provide complete management and treatment guidelines for Morquio A syndrome but rather afford an opinion on the role of elosulfase alfa in the management of this rare disorder within the context of the Canadian health care environment.

The opinions are based on review of elosulfase alfa clinical trial data submitted to the US FDA, published Morquio natural history data, expert experience in the management of Morquio A syndrome patients as well as the UK NHS Managed Access Agreement documentation. BioMarin facilitated this process by bringing Canadian Experts together for 2 meetings; May 2014 and April 2016, where presentation content included clinical trial and trial extension data (published and unpublished) as well as Canadian experts’ personal experiences in the management of MPS IVA. BioMarin had no role in the formulation or phrasing of this opinion piece and the recommendations and opinions reflect solely those of the authors. Elosulfase alpha has been approved for use by the U.S. Food and Drug Administration, FDA, Feb 2014 and the European Commission, April 2014 and CADTH-CDR, May 20, 2016

### **Disease Characteristics:**

*i) Incidence:* Morquio A Syndrome (OMIM #253000) is a rare autosomal recessive lysosomal storage disorder caused by deficiency of the lysosomal hydrolase, N-acetylgalactosamine-6-

sulfatase. Deficiency results in the accumulation of the glycosaminoglycans (GAGs) keratan sulfate and chondroitin-sulfate resulting in a progressive multisystem disease. The disease is extremely rare with incidence rates ranging from 0.48/100,000 in British Columbia (Applegarth, Toone, & Lowry, 2000), 0.16/100,000 in Australia (Meikle, Hopwood, Clague, & Carey, 1999) and 0.22/100,000 in Portugal (Pinto et al., 2004). Based on British Columbia incidence data, approximately 1.8 new cases of Morquio A would be born annually in Canada. There are currently approximately 100 patients residing in Canada.

*ii) Clinical features:* Morquio A syndrome is a clinically heterogeneous progressive multisystem disease characterized by profound skeletal and joint manifestations as well as non-skeletal manifestations which include: corneal clouding, hearing loss, complex respiratory disease as well as cardiac disease. Unlike other MPSs, cognitive impairment is not associated with Morquio syndrome. Although clinically heterogeneous, patients can be broadly classified into early onset “classical” disease and later onset disease. The majority of patients, ~75%, fit a “classical” disease phenotype. The natural history of Morquio A disease is well characterized through detailed observational studies of over 350 patients from the International Morquio Registry (Hendriksz et al., 2013; Montaña, Tomatsu, Gottesman, Smith, & Orii, 2007; Tomatsu et al., 2011) as well as the industry sponsored MorCap study (Harmatz et al., 2013); many patients are represented in both of these observational studies. Pertinent observations from these observational studies include:

**Classical patients** present within the first 5 years of life with short stature and other orthopedic symptoms including genu valgum, kyphosis, abnormal gait and pectus carinatum. After 18 months of age, linear growth is impaired with growth cessation by the age of 8 years. Final height in classical patients is below 120 cm i.e. approximately -8.5 SD as compared to age and sex matched controls. Surgical interventions are common; >70% of patients in the registry required surgery, with many patients requiring multiple surgeries by the early teenage years. Surgeries include; adenoidectomy, ear tube insertion, tonsillectomy, epiphyseal surgery, hip replacement, osteotomy, spinal decompression and spinal fusion. Published longevity data available demonstrate that classical patients die within the 2<sup>nd</sup> to 3<sup>rd</sup> decade usually secondary to progressive cardio-pulmonary compromise (Lavery & Hendriksz, 2014). The natural history of disease is characterized by progressive impairment of mobility and endurance secondary to skeletal and joint disease with associated joint pain as well as pulmonary and cardiac disease. Progressive upper airway and pulmonary disease contributes to decreased endurance and fatigue as well as significant anesthetic risk. Progressive pulmonary disease is caused by intrinsic pulmonary and airway involvement as well as progressive spine and chest wall deformity. This results in patients often requiring CPAP, BiPAP or tracheotomy. Additional morbidity results from hearing loss and corneal clouding; intelligence is not affected in this disorder. Mobility aides including walkers and motorized wheel chairs are required by most patients by the second decade of life. Spinal cord compromise ranging from paraplegia to quadriplegia compounds mobility challenges in many patients.

**Late onset patients:** This group of patients represents a very heterogeneous subgroup of Morquio A patients and are best categorized as fitting a wide disease spectrum. Initial presentation can range from 3 to 5 years of age to well into late childhood. Some patients are initially diagnosed with Legg-Calvé-Perthes disease. Progressive bone deformity, short stature

and abnormal gait are the most common presenting features of disease. The rate of disease progression is highly variable in this group of patients with longevity extending to the normal range. Later onset patients experience similar skeletal and non-skeletal morbidities as experienced in classical patients but at a later age and show a slower disease progression rate.

**Summary of disease impact:** Despite the rarity of Morquio A there is robust natural history/observational data for this disorder. These data indicate that the majority of patients experience significant and profound multisystem progressive morbidity beginning in early childhood. These morbidities significantly impact mobility and lead to the requirement for continued medical and surgical interventions. Despite these interventions, quality of life and life expectancy are severely impaired (Hendriksz et al., 2014b). Endurance is impaired early in this disorder as reflected by performance in the 6-minute walk test (6-MWT) at baseline in the MorCap study (fig 1). The data in figure 1 represent baseline cohort subgroup data for 316 Morquio A patients who participated in the MorCap study and thus does not represent longitudinal data. The 6-MWT indicates a profound early impact of this disease on endurance with affected patients performing 75% less than age-matched controls. MorCap data also reveal significant early pulmonary disease in Morquio A patients (Table 1). Standardization of respiratory function measures in Morquio A patients is problematic as the disease significantly impacts height, weight and chest configuration thus comparison to “predicted” measures are not relevant. Never the less, for patients less than and greater than 18 years of age there is profound reduction in lung volumes in addition to a reduced ability to carry out the work of breathing. The latter is reflected by the severe impairment of maximum voluntary ventilation (MVV) seen in all age groups. Normal MVV for adults is considered to be 80-180 L with values less than 70 L for females and less than 130 L for males considered clinically significant. Note the median MVV of adult Morquio patients is 31.5 L. In addition to the direct impact of this disease on the affected individual, there is considerable social impact related to the requirement for parental involvement and support for activities of daily living for the affected individual as well as the psychosocial impact of the disease on the individual affected. As such there are broader social and economic impacts of this rare disease.

**Clinical Trial Data:** Elosulfase alfa is the first drug available that targets the primary metabolic defect underlying Morquio A. Efficacy of elosulfase alfa in the treatment of Morquio A syndrome was assessed through a phase 3 multinational, randomized, placebo-controlled trial (Hendriksz et al., 2014a). The primary endpoint measure used was improved endurance as demonstrated by the 6-MWT. This phase 3 trial involved 176 patients treated for a 24 week period randomized equally into three treatment arms; placebo, elosulfase alfa 2 mg/kg/wk and elosulfase alfa 2 mg/kg/qow. Patients were stratified into the following age categories; 5-11 yrs., 12-18 yrs., >19 yrs as well as baseline 6-MWT;  $\leq 200$  meters, > 200 meters. Secondary endpoints included; 3-minute stair climb, urine KS, tertiary endpoints included pulmonary function tests.

Compliance in the study was excellent with 175 of the 176 dosed patients completing the study; one patient withdrew prior to dosing. A statistically significant difference was seen in the primary endpoint (6-MWT) for patients receiving elosulfase alfa at the dose of 2 mg/kg/wk as compared to controls. The mean difference was 22.5 meters after 24 weeks in the weekly treated group,  $p < 0.0174$ . No significant difference was seen at the dose of 2 mg/kg/qow. The 6-MWT results are of a similar magnitude to that seen in ERT clinical trials for MPS I and MPS II. For

example, 6-MWT data for 45 MPS I patients in the laronidase phase 3 trial showed a mean difference of 38.1 meters between treated and placebo patients after 24 weeks,  $p=0.039$  (Wraith et al., 2004). Similarly, a longer treatment duration of 53 weeks in the idursulfase phase 2/3 phase trial of 96 MPS II patients resulted in a mean difference in the 6MWT of 37 meters between weekly treated and placebo patients,  $p=0.01$  (Muenzer et al., 2006).

Individual responses to elosulfase reported from the MPS IVA clinical trials indicate that 15% of patients in the weekly treated elosulfase alfa arm had a >100-meter improvement with over 50% having an improvement of > 20-meters. Interestingly, the superior performance in the 6-MWT for the weekly treated patients was apparent at all levels of response. As expected, urine KS decreased significantly in treated patients whereas the other secondary endpoint, 3-minute stair climb showed no significant change. Change in pulmonary function measures (MVV and FVC) showed a trend to improvement in treated patients over 24 weeks but did not reach statistical significance.

Safety data from 6 clinical trials involving 235 patients indicate that approximately 19% of patients who received elosulfase alfa experienced hypersensitivity reactions with 8% of reactions classified as anaphylaxis. Reactions responded to standard management with all patients able to continue to receive drug. No evidence of reduced efficacy has been identified in patients experiencing hypersensitivity reactions.

#### **Opinion statements:**

**a)** Morquio A is a progressive multisystem disease with profound impact on quality of life for affected individuals and their family. Management requires the involvement of a multidisciplinary team with particular involvement of the following specialties; medical genetics/biochemical genetics, orthopedic surgery, neurosurgery, respiratory medicine, ENT and ophthalmology. Anticipatory guidance related to potential disease complications with a plan for early intervention, affords the best long-term outcome for patients. Elosulfase alfa is the only biologic directed to the primary metabolic block in Morquio syndrome; other than symptom management there are no alternative treatments for this disorder.

**b)** There are considerable unmet medical needs for Morquio patients as the current symptom-based approach to the treatment of this complex progressive multisystem disorder has marginal impact on life expectancy. Despite a symptom-based management approach, classically affected patients show progressive decline in mobility and endurance leading to mobility aids/wheel chair requirement in late childhood. In addition, progressive cardio-respiratory compromise leads to significant anesthetic risks and ultimately death by the 2<sup>nd</sup>-3<sup>rd</sup> decade for the classical form. As such affected individuals have significant unmet medical needs

**c)** A 24-week double blind placebo controlled trial of elosulfase alfa in 175 patients with Morquio A demonstrated a significant increase (22.5 meters) in 6-MW in patients receiving elosulfase alfa at a dose of 2 mgs/kg/week as well as reduction in urinary KS excretion. Respiratory measures show a trend for improvement in treated patients. Although the available clinical trial data do not allow for direct evaluation of the long-term impact of elosulfase alfa use,

the fact that weekly elosulfase alfa dosing resulted in a clinically meaningful effect warrants the consideration of elosulfase alfa use in the management of Morquio A patients.

**d) Treatment Considerations: Start Criteria, Treatment Goals, Stop Criteria:** In light of the relentless and predictively progressive course of Morquio A syndrome, treatment should be initiated as early in the clinical course as possible. The clinical heterogeneity of Morquio A syndrome compounded with the variable time point in the disease natural history when individual patients are diagnosed warrants that elosulfase alfa use in individual patients should be paired with personalized, measurable and clinically significant treatment goals. **Treatment goals should take into consideration the burden of disease at the time of treatment initiation and the anticipated benefits over a defined period of time.**

Baseline assessments should include:

- i) Skeletal survey
- ii) Spinal and cranial MRI
- iii) Mobility measure: 6MWT or stair climb (if appropriate for age and disease status)
- iv) Respiratory function testing including sleep study (age appropriate)
- v) Age appropriate quality of life measure (HAQ, PODCI, EQ5D5L or SF36) additional Morquio based scores could be used once validated
- vi) Documentation of mobility aide requirement
- v) Requirement for respiratory aides
- v) Ophthalmologic and ENT assessment
- vi) Urine KS determination: specific KS determination is preferred over total GAGs
- vii) GALNS enzyme activity determination and Morquio A gene mutation analysis.

Both enzyme analysis and mutation analysis are recommended to ensure that the primary diagnosis is correct.

**D1: Start Criteria:**

All are required before treatment start is considered

- Confirmed diagnosis of MPS IVA with **BOTH** N-acetylgalactosamine-6-sulfate sulfatase (GALNS) enzyme determination in either leucocytes or fibroblasts (excluding multiple sulfatase deficiency) **AND** mutation analysis of *GALNS*. Note that not all MPS IVA patients will have 2 known pathogenic alleles identified and that parental mutation analysis to establish the phase of mutations should be performed.
- Baseline evaluations have been completed

Since MPS IVA is a progressive disorder there will be patients in whom the risk benefit ratio of enzyme replacement may not be favorable. This may include patients with significant non-reversible pulmonary compromise from severe chest wall deformity or patients already requiring continuous assisted ventilation.

**D2: Treatment Goals:**

Treatment goals for an individual patient should be established by a multidisciplinary team and should be dependent on where in the natural history of disease the patient is determined to best fit. In that regard, specific treatment goals should be based on disease/functional stabilization and/or prevention of symptom onset. The expected time to reach treatment goals should be within a 1-2 year time interval and new or additional treatment goals should be established therein. The precise time expected to reach treatment goals and the assessment frequency should be agreed upon prior to commencement of treatment and should take into account the patient's disease burden and expected treatment effect. Assessment of treatment goals should take place annually or semiannually dependent upon expected responses. Assessments should take place at an experienced metabolic/genetic treatment center. Clinical trial data suggests that treatment duration of 1 year should be considered the minimal time expected to demonstrate clinically significant treatment effects. Discussions of drug safety, impact of infusion schedules and the strict requirement for participation in frequent monitoring through specialized clinics needs to be discussed with each patient and their families.

The main goal of evaluations and assessments of patients is to demonstrate either disease stabilization, particularly for patients in whom therapy is being initiated early in the natural history of disease or improvement for patients in whom therapy is being initiated when significant disease burden is present. It should be anticipated that due to the progressive nature of this condition that a patient is likely to show improvements once therapy is initiated but will eventually stabilize at a certain clinical level. The team should clearly declare whether disease stabilization or improvement is expected in the treatment period being monitored.

A responder or treatment success will be defined as a patient demonstrating at least 3 of 5 treatment effects. The expected time to reach treatment goals should be within a 1-2 year time interval and new or additional treatment goals should be established therein.

- 6 MWT or Stair Climb test improved or within 5% of baseline measure
- FVC or FEV-1 either parameter improved or within 5% of baseline measure or remaining within 2SD of normal for age
- Improvement or no change (if minimal effect) in age appropriate quality of life measure
- Reduction of urine KSs of 20%
- Stability of cardiac ejection fraction reduction (within 5% of baseline)

Consideration needs to be given to the potential effects that surgical procedures and recovery may have on these assessments. The exact timing of the assessments should take this into account.

For nonambulatory patients, enzyme replacement can be considered as a means to stabilize pulmonary disease. In these cases a treatment success would require demonstrating the pulmonary treatment effect noted below and at least 2 of the remaining 3 treatment effects. The expected time to reach treatment goals should be within a 1-2 year time interval and new or additional treatment goals should be established therein. The precise time expected to reach treatment goals and the assessment frequency should be agreed upon prior to commencement of treatment and should take into account the patient's disease burden and expected treatment effect.

- FVC or FEV-1 either parameter improved or within 5% of baseline measure or remaining within 2SD of normal for age or alternatively reduction in pulmonary support requirements
- Improvement in age appropriate quality of life measure
- Reduction of urine KSs of 20%
- Stability of cardiac ejection fraction reduction (within 5% of baseline)

**D3: Stop criteria:**

- Discontinuation of elosulfase alfa should be considered if treatment goals are not reached within the anticipated time frame. Consideration of a second year of treatment should be considered for treatment naïve patients who do not meet responder criteria within the first year.
- Discontinuation of elosulfase alfa should be considered if patients progress to requiring continuous respiratory support.
- Discontinuation of elosulfase alfa should be considered if more than 6 infusions are missed for any 12 month interval, excluding medically related missed doses or if patients are not compliant with scheduled assessments.
- Final decision to discontinue elosulfase alfa should rest with the treating metabolic and genetic specialist in direct consultation with members of the metabolic team, the patient and/or family and other experts.
- Prior to discontinuing treatment, a supportive and/or palliative care plan should be in place.

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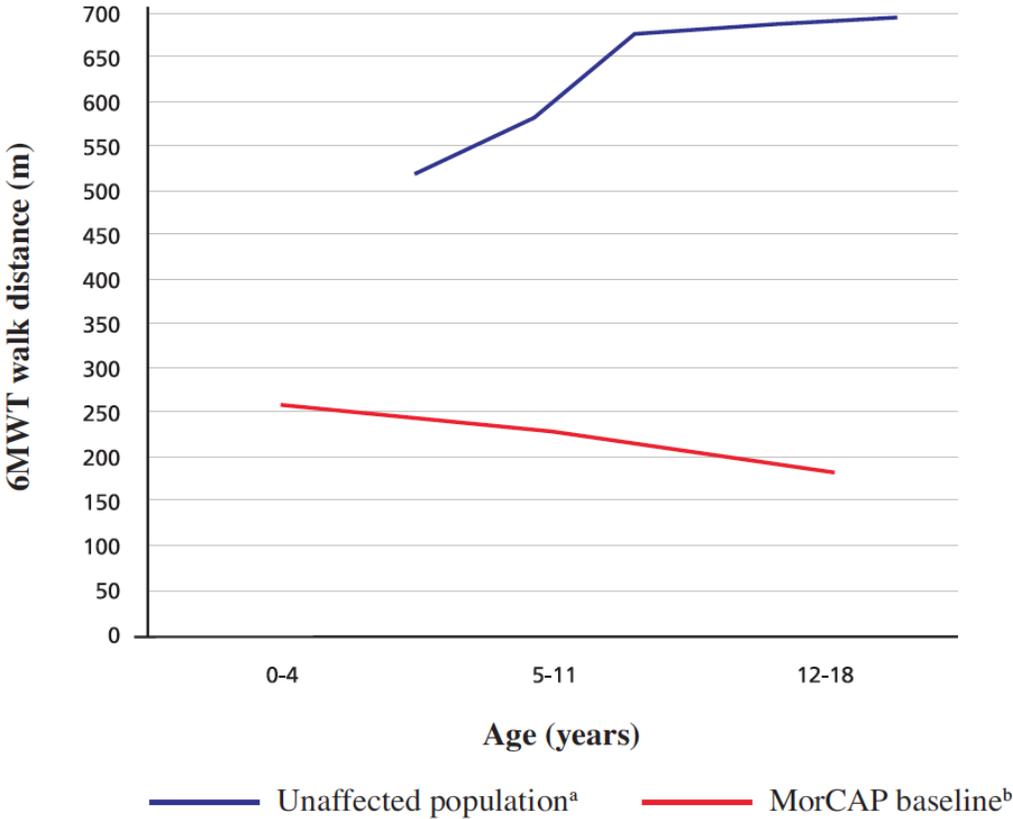
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Figure 1: Mobility MPS-IVA



<sup>a</sup>Adapted from Geiger et al, study provides reference values for 6MWT based on and limited to demographics for 528 healthy children and adolescents ages 3 to 18.  
<sup>b</sup>Baseline data for MorCAP, a multicenter, multinational, cross-sectional longitudinal study of 325 patients with Morquio A.

Table 1: Pulmonary function in Morquio A patients: from (Harmatz et al., 2013)

	<b>FVC</b>		<b>MVV</b>	
	<b>&lt;18 years</b>	<b>&gt;18 years</b>	<b>&lt;18 years</b>	<b>&gt;18 years</b>
<b>N</b>	195	66	178	59
<b>Mean (SD)</b>	1.1 (0.7)	1.5 (1.1)	32.4 (22.1)	42.1 (32.8)
<b>Median</b>	0.9	1.00	25.5	31.5
<b>Min, Max</b>	0.2, 4.5	0.3, 0.5	1.3, 119.0	6.3, 160.0