Common Drug Review
Pharmacoeconomic Review Report

July 2015

Drug	elosulfase alfa (Vimizim) (2 mg/kg of body weight)
Indication	For long-term enzyme replacement therapy in patients with a confirmed diagnosis of Mucopolysaccharidosis IVA (Morquio A syndrome, or MPS IVA)
Listing request	As per indication
Manufacturer	BioMarin Pharmaceutical (Canada) Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in the treatment of inherited disorders of metabolism who provided input on the conduct of the review and the interpretation of findings.

Through the Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

6MWT	six-minute walk test
BSC	best supportive care
CDR	CADTH Common Drug Review
EQ-5D	EuroQol 5-Dimensions Questionnaire
FVC	forced vital capacity
HRQoL	health-related quality of life
ICUR	incremental cost-utility ratio
MPS	mucopolysaccharidosis
MPS IVA	mucopolysaccharidosis IVA; Morquio A syndrome
MS	multiple sclerosis
PRO	patient-reported outcomes
QALY	quality-adjusted life-year

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Elosulfase alfa (Vimizim)
Study Question	"What is the cost-effectiveness of Vimizim (elosulfase alfa) relative to BSC for long-term enzyme replacement therapy in patients with a confirmed diagnosis of MPS IVA (Morquio A syndrome)?"
Type of Economic Evaluation	Cost-utility analysis
Target Population	Canadian patients (children and adults) with a confirmed diagnosis of MPS IVA
Treatment	Elosulfase alfa, 2.0 mg/kg, weekly infusion
Outcomes	QALYs, life-years
Comparator	BSC, defined as medications for pain and infections; obstructive sleep apnea management; surgical interventions
Perspective	Ministry of Health and societal
Time Horizon	Lifetime (35 years)
Results for Base Case	ICUR for elosulfase alfa versus BSC: $1,502,641 per QALY (Ministry of Health); $1,522,621 per QALY (societal)
Key Limitations	CDR noted a number of limitations with the structure, parameters and inputs used in the manufacturer's model: • Uncertainty around transition probabilities beyond 72 weeks (extrapolation based on the 6MWT and FVC levels) • Inappropriate equations used to calculate predicted FVC levels (to calculate mortality relative risk), with no identified data source • Double counting of health benefits due to inclusion of different utility values and mortality rates based on treatment effects within the same health state • Assumption that patients do not gain weight over time • Lack of clarity around patients considered "non-responders" to treatment and stopping rule • Inclusion of caregiver disutility values and costs under the Ministry of Health perspective
CDR Estimate	CDR conducted a number of reanalyses to assess the impact of the key identified limitations, but was not able to account for all identified limitations. The following were considered to address the above limitations: • Same utility values and mortality rates for both treatment arms within a given health state • Patients' gain weight up to age 18 • No stopping rule for non-responders • Exclusion of caregiver disutility values and costs from base-case analysis Based on these assumptions, the ICUR increased to $2.96 million per QALY for elosulfase alfa versus BSC. If no treatment stopping rule is operationalized, CDR estimated that the ICUR could be as high as $6.16 million per QALY versus BSC.

6MWT = six-minute walk test; BSC = best supportive care; CDR = CADTH Common Drug Review; FVC = forced vital capacity; ICUR = incremental cost-utility ratio; MPS IVA = mucopolysaccharidosis IVA; QALY = quality-adjusted life-year; RCT = randomized controlled trial.

EXECUTIVE SUMMARY

Background

Elosulfase alfa is being reviewed as a long-term enzyme replacement therapy in patients with a confirmed diagnosis of mucopolysaccharidosis IVA (MPS IVA), also known as Morquio A syndrome.[1] The recommended dose is 2 mg/kg of body weight, administered once a week by intravenous (IV) infusion. The manufacturer submitted a confidential price of $[redacted] per 5-mg vial,[2] which corresponds to an annual cost of approximately:

- $[redacted] for patients aged zero to five years old (assuming an average weight of 13 kg[3])
- $[redacted] for patients aged six to 17 years old (assuming an average weight of 25 kg[3])
- $[redacted] for patients aged 18 years of age (assuming an average weight of 37 kg[3])
- For patients weighing more than 40 kg, the annual cost will exceed [redacted]

The manufacturer is seeking reimbursement in line with the Health Canada indication.

A cost-utility analysis was submitted comparing elosulfase alfa to best supportive care (BSC) — defined as symptomatic management with medications for pain, infections, and surgical interventions — using data from the MOR-004 and MOR-005 clinical trials[4,5] and MOR-001 (MorCAP) natural history study.[6] The reference case time horizon was lifetime (35 years) under the Ministry of Health perspective. The economic submission was based on a Markov model with 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. Long-term disease progression within the model was determined by extrapolating the results of the six-minute walk test (6MWT) and forced vital capacity (FVC) values observed in patients in the key clinical trial.

Summary of identified limitations and key results

The CADTH Common Drug Review (CDR) identified several limitations in the submitted model, such as lack of long-term data on efficacy and uncertain association between 6MWT and disease progression; double counting of elosulfase alfa potential benefits; and an unclear definition of non-responders. It was possible to undertake reanalyses of five key limitations: utility values, mortality rates, patient weight, stopping rule for non-responders, and caregiver disutility. While CDR identified other limitations (long-term clinical efficacy, equations used to predict mortality values), these could not be assessed given the model structure and available data. A combined reanalysis of the first four limitations resulted in an incremental cost-utility ratio (ICUR) of $2.96 million per quality-adjusted life-year (QALY), a significant increase in the ICUR for elosulfase alfa versus BSC from the manufacturer's base case. Upon stratifying by health state, the ICUR ranged from $1.1 million per QALY for the asymptomatic health state to $4.56 million per QALY for the "no use of wheelchair" health state. Further, if no stopping rule is implemented, CDR estimated the ICUR could be as high as $6.16 million per QALY.

Conclusions

The manufacturer-submitted economic evaluation presented a high ICUR in its base-case scenario. Subsequently, CDR reanalyses addressing the key limitations identified resulted in a significant increase in the overall ICUR to $2.96 million per QALY for elosulfase alfa versus BSC, which could be as high as $6.16 million where a stopping rule is not in place for non-responders.

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis comparing elosulfase alfa (Vimizim) to best supportive care (BSC) — defined as symptomatic management with medications for pain, infections, and surgical interventions — in patients diagnosed with mucopolysaccharidosis IVA (MPS IVA), also known as Morquio A syndrome.[1] The reference case time horizon was lifetime (35 years), with a cycle length of one year. The analysis was conducted under the Ministry of Health and societal perspectives.

In the model, patients with MPS IVA transition between six health states based on disease progression and death. The baseline distribution, age, and weight of patients in each health state were based on the MOR-001 natural history study.[6] The six health states are:

- Asymptomatic (6.6% of the cohort; diagnosed MPS IVA patients aged three years or younger who have not yet developed musculoskeletal complications and are not experiencing limitations in endurance or cardiopulmonary function)
- No use of wheelchair (46.4% of the cohort)
- Some use of wheelchair (34.2% of the cohort)
- Wheelchair-dependent (12.8% of the cohort)
- Paraplegic (0%; patients who become paraplegic due to surgical complications)
- Pre-death (0%; patients always in a wheelchair and also requiring mechanical ventilation).

In the four initial health states, patients may undertake surgery to alleviate key disease symptoms. When there are surgical complications, patients can enter the paraplegic health state. Patients enter the pre-death health state from either the wheelchair-dependent or paraplegic health state; this would be the case if they require ventilation support (defined by low forced vital capacity [FVC] values). Patients in all health states except for the pre-death health state were eligible for treatment with elosulfase alfa.

Transition probabilities within the model were based on four outcome measures: 1) time to symptom development (transition from the asymptomatic health state to the primary wheelchair health state), which was based on clinical expert opinion; 2) change in wheelchair use, which is applicable in the first cycle of the model only for the patients in wheelchair health states, due to the absence of long-term data; 3) the six-minute walk test (6MWT), which is applicable from the second cycle onward for patients in the wheelchair health states (excluding the wheelchair-dependent health state); and 4) FVC, which is applicable to all patients in the wheelchair-dependent and paraplegic health states.

In the treatment arm, disease progression in the first cycle was based on data collected in MOR-004 and MOR-005, phase 3 clinical trials that observed changes in wheelchair status over a period of 72 weeks using the mucopolysaccharidosis (MPS) health assessment questionnaire (HAQ) following exposure to treatment with elosulfase alfa. Progression in the second cycle onward was based on clinical expert opinion, where it was assumed that the annual decline in 6MWT and FVC would be 20% that of untreated patients (natural course of the disease). The manufacturer also included delay in time to surgery, faster recovery rates, and differential mortality rates based on exposure to treatment with elosulfase alfa. Data for the natural course of disease progression were obtained from the MOR-001

study,[6] in which clinical outcomes were collected over two years in patients with MPS IVA unexposed to elosulfase alfa.

In the model, patients could either be multi-domain responders (improvement in more than one outcome domain), single-domain responders (improvement in one domain but deterioration in another), or non-responders (no improvement). The manufacturer assumed that a proportion of patients whose progression did not reduce after two cycles would discontinue treatment.

Patient utility values for the wheelchair health states were based on a patient-reported outcomes (PRO) study,[2] which determined health-related quality of life (HRQoL) in treatment-naive patients using the EuroQol 5-Dimensions Questionnaire (EQ-5D) questionnaire. The manufacturer also included differential utility values dependent on treatment effects. Under the Ministry of Health perspective, the model also included caregiver disutility values for each health state, which were based on the average hours of care per day needed and multiple sclerosis (MS) expanded disability status scale (EDSS) states.

The main cost drivers in the model were those associated with elosulfase alfa treatment (i.e., drug and administration costs), the various surgeries, and the costs associated with each health state. These were based primarily on specialist physician visits.

2. MANUFACTURER'S BASE CASE

Under the Ministry of Health perspective, the manufacturer reported that the total cost associated with treatment with elosulfase alfa was $4,553,694.80 — an incremental cost of $4,487,627.21 compared with BSC. Further, treatment would result in 8.97 quality-adjusted life-years (QALYs), and incremental QALYs of 2.99 compared with BSC. Thus, the incremental cost-utility ratio (ICUR) was calculated to be $1,502,641 (Table 2).

TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE (MINISTRY OF HEALTH PERSPECTIVE)

	Total Costs	Incremental Cost of Elosulfase Alfa	Total QALYs	Incremental QALYs of Elosulfase Alfa	Incremental Cost per QALY
BSC	$66,067	$4,487,627	5.98	2.99	$1,502,641
Elosulfase alfa	$4,553,694		8.97		

BSC = best supportive care; QALY = quality-adjusted life-year.
Source: Manufacturer's Pharmacoeconomic submission.[2]

Under the societal perspective, the manufacturer reported the ICUR to be $1.52 million for elosulfase compared with BSC.

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

Uncertainty regarding the parameters chosen for the base-case analysis under the Ministry of Health perspective was addressed by the manufacturer using a one-way deterministic sensitivity analysis and a Monte Carlo simulation probabilistic sensitivity analysis. None of the parameters varied the ICUR by less or more than 25%.

The probabilistic sensitivity analysis showed that in approximately 75% of iterations (payer and societal perspectives), the ICUR was above a willingness-to-pay threshold of $1,000,000 per QALY.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

- **Lack of long-term clinical efficacy data:** Transition probabilities relating to change in wheelchair status beyond 72 weeks were based on extrapolation of the 6MWT and FVC levels. Further, as noted in the CADTH Common Drug Review (CDR) clinical review, the association of 6MWT with outcomes of importance to patients with MPS IVA (such as pain, fatigue, mobility, disease progression, and the need for surgical intervention) is uncertain. This brings uncertainty into the model, and may result in a higher ICUR than what was calculated in the manufacturer's base care scenario.
- **Inappropriate equations used to calculate predicted standard FVC values, resulting in incorrect mortality values:** The manufacturer calculated natural disease progression mortality relative risk values in the model based on absolute FVC values observed in the MOR-001 natural history study,[6] and predicted FVC values based on standards for age and height. Although the predicted standard FVC values do not have a significant impact on the overall results, the equations used to calculate these values were not appropriate as per Canadian standards.
- **Double counting of potential benefit due to use of different utility values and mortality rates between treatment arms within the same health state:** This was based on the observation of a positive correlation between the 6MWT or FVC level and the patient's reported HRQoL, as well as upon observation of a 16.5% improvement in FVC levels versus baseline over three years of treatment with elosulfase alfa.[2] This may lead to double counting of the benefits, as they are already accounted for within each health state.
- **Assumption that patients maintain the same weight over the lifetime horizon:** The manufacturer applied an average patient weight for each health state included in the model, which may be underestimating the true costs associated with the elosulfase alfa treatment. It would be more appropriate to assume patients naturally gain weight as they age.
- **Definition of "non-responders" to treatment and the stopping rule are unclear:** There is a degree of uncertainty regarding the definition of a "non-responder" to treatment. Although the manufacturer defines it by disease progression in terms of moving to a worse health state after two cycles, it is not certain, as the clinical expert identified that they may continue to administer treatment beyond this time frame. Due to this, treatment costs could be much higher, resulting in a higher overall ICUR.
- **Inclusion of caregiver disutility and costs in the base-case analysis:** The manufacturer included these to capture the need for a caregiver in the management of patients with MPS IVA. Although the impact on caregivers may be significant, caregiver utilities and/or costs are not typically included under the Ministry of Health perspective.

5. CADTH COMMON DRUG REVIEW ANALYSES

CDR conducted several reanalyses scenarios considering the key limitations identified. The following reanalyses were conducted:

1. No increase in utility values due to treatment effects within the same health state. Natural disease progression utility values for each health state were applied to both the BSC and treatment arms. Upon changing this, the ICUR increased to $2,187,855 per QALY.

2. No decrease in mortality rates due to treatment effects within the same health state. Natural disease progression mortality relative risk values (determined compared with background mortality risk) were applied to both the BSC and treatment arms. Upon changing this, the ICUR increased to $1,504,641 per QALY.
3. Inclusion of MPS IVA patient natural weight gain as they age. This was conducted using average weight by age observed in patients in the MOR-001 natural history study, as reported in the study by Montaño et al.[3] Patients 18 years and older were assumed to have the same weight. Upon changing this, the ICUR increased to $1,962,921 per QALY.
4. Inclusion of treatment costs (drug and administration) associated with all patients, not just those considered to be "responders." Upon changing this, the ICUR increased to $3,028,932 per QALY. Due to the significant increase in the ICUR, it can be concluded that the definition of who is and is not a responder is crucial, and the lack of clarity over this issue is key.
5. Exclusion of caregiver disutility values and costs. Upon changing this, the ICUR increased to $1,536,242 per QALY.
6. Stratified analysis for each health state, assuming the proportion of patients in each health state at the onset of treatment is 1. Upon conducting this, the asymptomatic health state resulted in an ICUR of $582,067 per QALY; the "no use of wheelchair" health state resulted in an ICUR of $1,744,238 per QALY; the "some use of wheelchair" health state resulted in an ICUR of $1,634,464 per QALY; and the "wheelchair-dependent" health state resulted in an ICUR of $1,351,921 per QALY.

Further, upon conducting a multi-way analysis considering all key limitations identified above, without stratification, the ICUR increased from the manufacturer's base case of $1,502,641 per QALY to $2,956,429 per QALY. With stratification and considering all of the key limitations, the ICUR ranged from $1,090,099 for the asymptomatic health state to $4,561,859 for the "no use of wheelchair" health state.

If no treatment stopping rule is operationalized, CDR estimated that the ICUR could be as high as $6.16 million per QALY versus BSC.

A price reduction analysis was undertaken based on CDR's alternate scenario analysis. This showed that even with a price reduction of 90%, the ICUR for elosulfase alfa compared with best supportive care (BSC) would still be higher than commonly accepted thresholds (Table 3).

TABLE 3: CDR REANALYSIS PRICE REDUCTION SCENARIOS

ICURs of Elosulfase Alfa Versus BSC		
Scenario (Price)	**Base-Case Analysis Submitted by Manufacturer**	**Reanalysis by CDR[a]**
Submitted ($[redacted])	$1,502,641	$2,956,429
10% reduction ($[redacted])	$1,353,223	$2,662,270
20% reduction ($[redacted])	$1,203,805	$2,368,111
30% reduction ($[redacted])	$1,054,387	$2,073,951
40% reduction ($[redacted])	$904,970	$1,779,792
50% reduction ($[redacted])	$755,552	$1,485,633
60% reduction ($[redacted])	$606,134	$1,191,473
70% reduction ($[redacted])	$456,717	$897,314
80% reduction ($[redacted])	$307,299	$603,154
90% reduction ($[redacted])	$157,881	$308,995

BSC = best supportive care; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio.
[a] CDR reanalysis considered utility values, mortality rates, caregiver disutility values and costs, and patient weight gain.

6. ISSUES FOR CONSIDERATION

Although the CDR reanalysis stratified by initial symptom stage showed that the ICUR was lower when patients are in the asymptomatic health state (i.e., in patients three years of age or younger) than in other health states, it is important to note that patients in MOR-004 were aged five years or older. As noted in the product monograph, the safety and efficacy of elosulfase alfa has not been established in children younger than five years of age. However, the clinical expert consulted for the review indicated that the benefits of elosulfase alfa are likely to be greater if treatment is initiated at an early age.

7. PATIENT INPUT

Input was received from two patient groups: the Isaac Foundation for MPS Treatment and Research and the Canadian Society for Mucopolysaccharidosis and Related Diseases Inc. In these inputs, patients noted that effects on endurance and pain have a significant impact on quality of life. They noted that as the condition progresses, patients are increasingly reliant on caregivers and mobility aids. Patients indicated they often experience stress from costly home renovations and devices. They also experience emotional stress from required medical interventions, long hospital stays, many surgical appointments, and repeated appointments with specialists — many of which caregivers sacrifice their time to handle.

Patients noted that they would expect to see an improvement in mobility from treatment, increased growth, and reduced risk of cervical cord compression; this would fill an unmet need and significantly improve their quality of life.

8. CONCLUSIONS

The manufacturer-submitted economic evaluation presented a high ICUR in its base-case scenario. Subsequently, CDR reanalyses addressing the key limitations identified resulted in a significant increase in the overall ICUR to $2.96 million per QALY for elosulfase alfa versus BSC. The reanalysis also found that the ICUR could be as high as $6.16 million where a stopping rule is not in place for non-responders.

APPENDIX 1: COST COMPARISON

Based on consultation with the clinical expert, there are no other comparators currently indicated for this condition.

TABLE 4: COST COMPARISON TABLE FOR MPS IVA TREATMENT

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Daily Drug Cost ($)	Annual Drug Cost ($)
Elosulfase alfa	5 mg/5 mL	Single-use vial	[redacted][a]	2 mg/kg IV infusion once weekly	13 kg: [redacted][b] 25 kg: [redacted][c] 37 kg: [redacted][d] 45 kg:	[redacted]

MPS IVA = mucopolysaccharidosis IVA.
[a] Manufacturer-submitted confidential price.
[b] Assuming an average weight for patients aged 0 to 5 years (13 kg) based on a study by Montaño et al.[3]
[c] Assuming an average weight for patients aged 5 to 7 years (25 kg) based on a study by Montaño et al.[3]
[d] Assuming an average weight for patients aged 18 years (37 kg) based on a study by Montaño et al.[3]

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 5: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS ELOSULFASE ALFA RELATIVE TO BEST SUPPORTIVE CARE?

Elosulfase Alfa Versus BSC	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	N/A
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	$1,502,641 per QALY (manufacturer's base-case scenario) $2,956,429 per QALY (CDR reanalysis scenario, stopping rule applied) $6,156,762 per QALY (CDR reanalysis scenario, no stopping rule)					

BSC = best supportive care; CDR = CADTH Common Drug Review; CE = cost-effectiveness; QALY = quality-adjusted life-year.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 6: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments *Reviewer to provide comments if checking "no"*	None		
Was the material included (content) sufficient?		X	
Comments *Reviewer to provide comments if checking "poor"*	None		
Was the submission well organized and was information easy to locate?		X	
Comments *Reviewer to provide comments if checking "poor"*	There was an inconsistency between the pharmacoeconomic report and the submitted model (e.g., different mortality values reported; lack of clarity regarding proportion of non-responders; starting cohort [birth versus MOR-001, wheelchair costs, adverse events etc.]). There were also many missing data sources and references.		

TABLE 7: AUTHOR INFORMATION

Authors	Affiliations
Colin Vicente Marc Geadah	PIVINA Consulting Inc. PIVINA Consulting Inc.

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	x		
Authors had independent control over the methods and right to publish analysis	x		

APPENDIX 4: REVIEWERS' WORKSHEETS

Manufacturer's Model Structure

The manufacturer's cost-utility analysis was conducted using a cohort-based Markov model where patients with mucopolysaccharidosis IVA (MPS IVA) transition between six health states based primarily on wheelchair use and death. The baseline distribution of patients — in addition to age, weight, and mean six-minute walk test (6MWT)/forced vital capacity (FVC) scores across each of the health states — was based on the MOR-001 (MorCAP) natural history study.[6] The health states were defined as follows:

- **Asymptomatic**: Diagnosed MPS IVA patients aged three years or younger who have not yet developed musculoskeletal complications and are not experiencing limitations in endurance and cardiopulmonary function (6.6% of the cohort)
- **No use of wheelchair**: MPS IVA patients who have started to develop musculoskeletal complications and limitations in endurance, but do not need wheelchair support; mean 6MWT score is 289 metres (46.4% of the cohort)
- **Some use of wheelchair**: MPS IVA patients who have developed pain, fatigue, and musculoskeletal issues that significantly limit their endurance, requiring some wheelchair use; mean 6MWT score is 180 m (34.2% of the cohort)
- **Wheelchair-dependent:** MPS IVA patients who have developed increased pain, fatigue, and musculoskeletal issues, majorly limiting their endurance and leading to wheelchair dependency; mean FVC level is 1.0 litres (12.8% of the cohort)
- **Paraplegic**: MPS IVA patients who become paraplegic due to surgical complications (0%)
- **Pre-death**: MPS IVA patients who are wheelchair-dependent and require mechanical ventilation, defined by low FVC values (0%).

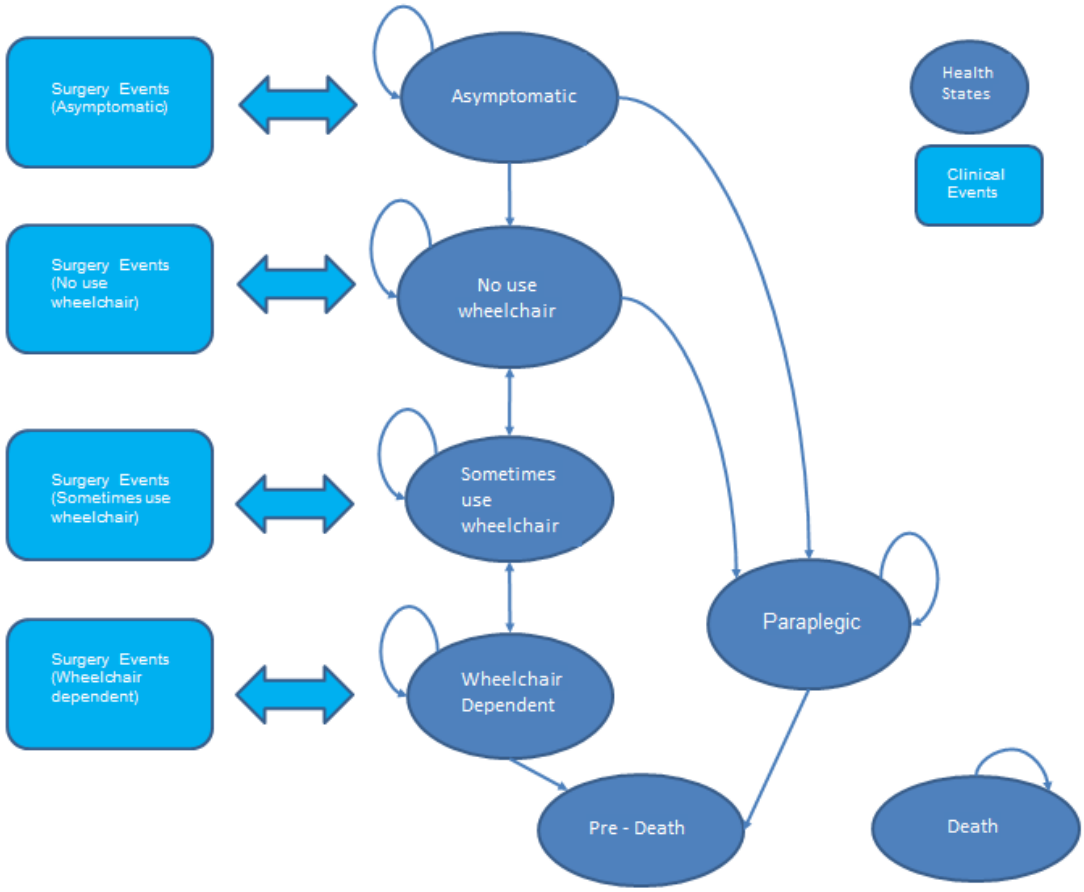
In each of the initial four health states, patients may undertake different types of surgery to manage disease symptoms; these are treated as clinical events and are first-cycle events only.

The primary perspective of the model is the Ministry of Health perspective. The model adopts a cycle length of one year over a lifetime horizon (35 years). It also incorporates differential utility values and mortality risks for each health state, in addition to treatment-dependent utility values and mortality risks.

During natural disease progression, patients progress through the model based on four different outcome measures (Figure 1):

1) Time to symptom development, which is applicable in the asymptomatic health state only, where patients progress to the no-wheelchair-use health state when they reach the age of three
2) Change in wheelchair use, which is applicable for patients in wheelchair health states for the first cycle only (based on observed changes in wheelchair status from the MOR-001 natural history study)
3) 6MWT, which is applicable for the second cycle onward for patients in the no-use-of-wheelchair and some-use-of-wheelchair health states, where patients progress based on a 7.1 m decline in their 6MWT until they reach the wheelchair-dependent health state
4) FVC, which is applicable to all patients in the wheelchair-dependent and paraplegic health states, as they may be unable to perform the 6MWT. At this stage, patients progress based on a 0.1 L decline in FVC.

FIGURE 1: MANUFACTURER'S MODEL STRUCTURE



Source: Manufacturer's Pharmacoeconomic submission.[2]

Patients in all health states except that of the pre-death health state would be eligible for treatment with elosulfase alfa.

The manufacturer considered multi-domain responders, single-domain responders, and non-responders in the submitted model. Multi-domain responders, defined as patients who continue to have improvements across all outcome domains, would see a stabilization of their disease. Single-domain responders, defined as patients who would see an improvement in one outcome domain but become worse in another, would progress at a slower rate compared with untreated patients.[2] Furthermore, as patients would receive a weekly infusion while on elosulfase alfa, it is unlikely they would continue to receive treatment if their disease continued to progress at the same rate as it did prior to initiating treatment. Thus, based on clinical expert opinion, the manufacturer assumed that a proportion of patients whose progression did not reduce after two cycles would discontinue treatment, and would be deemed non-responders.[2]

The manufacturer provided minimal details on the conduction of any model validation, except that the model was checked by a clinical expert.

TABLE 8: DATA SOURCES

Data Input	Description of Data Source	Comment
Natural History		
Baseline distribution of patients; definition of health states (annual average loss in 6MWT/FVC score); progression data	Taken from MOR-001 (MorCAP),[6] a longitudinal study in which clinical outcomes were collected over 2 years under normal settings in patients with MPS IVA unexposed to elosulfase alfa or any other treatment options.	Deemed appropriate, although the wheelchair progression data from the placebo arm of the MOR-004 study may have been a better alternative to populate the BSC arm.
Average age when symptomatic: 3 years	Based on clinical expert opinion.	
FVC decline of 0.1 L in the wheelchair-dependent and paraplegic health states	Based on clinical expert opinion.	
Surgeries associated with each health state (type, proportion, rate of complications, duration, and utility decrement during recovery period)	Based on clinical expert opinion.	Not clear how the utility decrement during the recovery period was applied in the model.
Efficacy		
Delay in the development of musculoskeletal complications by 5 years (i.e., additional years to move from asymptomatic to the never-use-wheelchair health state)	Based on clinical expert opinion. Low-quality evidence sources, such as sibling case studies, were identified by the manufacturer as possible sources of validity for this assumption.[2]	Not supported by evidence. May be overestimating the benefits associated with elosulfase alfa.
Wheelchair progression in treated patients (for the first cycle of the model)	Derived from the MOR-004 and MOR-005 studies. MOR-004 is a phase 3 randomized controlled trial conducted over 24 weeks and extended to 72 weeks (MOR-005). In addition to the primary objective of determining changes in 6MWT following exposure to treatment with elosulfase alfa, this study observed changes in wheelchair status as captured by the MPS HAQ questionnaire.	
Extrapolation of 6MWT and FVC values > 72 weeks	Based on clinical expert opinion and experience with other MPS disorders.[2]	Introduces uncertainty into the model.
Proportion of multi-domain responders, single-domain responders, and non-responders	Determined from the MOR-004 and MOR-005 clinical trials.	Not very clear how multi-domain, single-domain and non-responders were defined.
Annual decline in 6MWT and FVC would be 20% that of untreated patients	Based on clinical expert opinion.	Not clearly stated whether this was applied to all patients or just single-domain responders.
Surgeries per health state (delay in time to surgery after initiating treatment;	Delay in time to surgery under treatment was determined from the MOR-004 and MOR-005 clinical trials.	

Data Input	Description of Data Source	Comment
faster recovery times post-surgery)	Surgery recovery times were based on clinical expert opinion.	
Utilities	Patients' utility values for the wheelchair health states were based on the PRO study conducted by the manufacturer, which determined the HRQoL in treatment-naive patients using the EQ-5D questionnaire.[2] Utility values for patients in the pre-death health state were determined from a subset of wheelchair-dependent patients who required ventilation support in the PRO study.[2] Based on clinical expert opinion, it was assumed that patients in the paraplegic health state would have the same utility values as those in the pre-death health state. The model also included caregiver disutility for each health state, where the MS EDSS state with a similar average hour of care per day was used as a proxy. The average hours of care per day for MPS IVA patients for the wheelchair health states was based on the PRO study.[2] For the asymptomatic, paraplegic, and pre-death states, it was based on clinical expert opinion. MS caregiver disutility values incorporated were taken from a study by Gani et al. (2014).[2] The manufacturer assumed that treated patients would have higher utility values compared with untreated patients. These utility values were based on the EQ-5D questionnaire administered to treated patients during the PRO study (positive correlation between patient's 6MWT and FVC with the HRQoL).[2]	Caregiver disutility values are not typically included under the Ministry of Health perspective. Differential utility values based on treatment effects within the same health state may be double counting the health benefits acquired with treatment with elosulfase alfa. This is not an appropriate modelling method.
Resource use	The type of health care resources utilized depended on the patient's health state. These included (as identified by the manufacturer): visit to the GP, GP nurse visit, neurology, pulmonary complication visits, pain management specialist visits, orthopedics, cardiology specialist visits, ophthalmology, ENT specialist visits, and ventilation. The resources utilized were sourced from a panel of physicians experienced in the management of MPS IVA. The proportion of patients requiring different types of wheelchairs (self or attendant propelled, active user or powered) was assumed to be equal based on the study by Maleki-Yazdi et al. (2012).[7]	

Data Input	Description of Data Source	Comment
Adverse event (anaphylaxis)	The only adverse event considered in the model was anaphylaxis for only a subset of patients (all treated patients were pre-treated with anti-histamines or steroids). The percentage of drug infusions that would result in this adverse event was determined based on the MOR-004 clinical trial.	Inclusion of patients pre-treated with anti-histamines or steroids and patients who experienced adverse events in the model was not very clearly stated.
Mortality	A relative risk of mortality of 1.12 for a 10% decrement in FVC was applied to the mean % FVC for each wheelchair health state (compared with background mortality). This value was obtained from a study by Neas and Schwartz, 1998.[8] The mean % FVC for each wheelchair health state was derived based on the mean % FVC values of all patients in that specific wheelchair health state at baseline observed in the MOR-001 natural history study.[6] The % FVC value for each patient was calculated by dividing the observed (or absolute) FVC value by the predicted FVC value. Predicted FVC values were calculated by the reference equation from the European Community for Steel and Coal study,[9] which was stratified by gender and included patient height and age. Asymptomatic patients were assumed to have 100% FVC and patients in the pre-death health state were assumed to have 10% FVC, both of which were based on clinical expert opinion. The manufacturer assumed that patients treated with elosulfase alfa would have a decreased relative risk of mortality based on a 16.5% improvement in FVC versus baseline over 3 years' treatment. This was based on observation from the MOR-002 and MOR-100 trials.	One of the equations used to calculate the predicted FVC in the pharmacoeconomic report submitted by the manufacturer is not correct; it is not the correct equation from the European Community for Steel and Coal study. Further, the mortality values in the pharmacoeconomic report do not match the mortality values in the economic model. The equations used to calculate the predicted FVC values in the report differ from those used in the models (which have no source identified). Neither is among the most recent equations used as standards in Canada. Differential mortality values based on treatment effects within the same health state may double count the health benefits acquired with treatment with elosulfase alfa. This is not an appropriate modelling method.
Costs		
Drug	The cost of the drug is dependent on the weight of the patient. For the purpose of the analysis, an average weight was assigned to each health state based on natural history data from the MOR-001 study. The manufacturer indicated the confidential price of the drug as $[redacted] per 5 mg vial.	The average patient weight assigned to each health state does not reflect a realistic situation. In reality, patient weight would increase with age.
Administration	The cost of administration ($75) was approximated based on the cost of complex stage drug	

Data Input	Description of Data Source	Comment
	administration for the Ontario Schedule of Benefits.[10]	
Clinical events (surgery)	Different surgeries that patients may incur included (as identified by the manufacturer): cervical fusion operation, genu valgum surgery, spinal decompression surgery, hip surgery, lower spine surgery, aortic valve replacement surgery, tonsillectomy, ear tube replacement, corneal replacement, and cataract surgery. Surgical costs (based on a case-mix group) and the approximate length of stay in the hospital was obtained from the Canadian Institute for Health Information patient cost estimator tool.	
Adverse events	The cost incurred with anaphylaxis was determined from the Ontario Schedule of Benefits and Laboratory Services.[10]	
Resource use	Dependent on the patient's health state, the resources used and related costs differ. These costs are primarily related to physician visits. Unit costs were sourced from the Ontario Schedule of Benefits and Physician Services and the Schedule of Benefits and Laboratory Services.[10] The cost associated with ventilation support was taken from a study conducted by Maleki-Yazdi et al. (2012).[7]	Estimated resource unit costs are overestimated. In reality, these costs would be significantly lower. The source for wheelchair costs was not identified.
Indirect costs	The manufacturer also conducted an analysis under the societal perspective that included indirect costs. This was based on the time lost per health state: half a day (4 hours) lost per physician visit, full day (7.5 hours) lost for each drug infusion and for each day of the length of stay per surgery. The value of time lost was based on the average hourly wage in Canada, which was taken from Statistics Canada.[11] The manufacturer also included the costs incurred by caregiver hours in the base-case analysis. Hourly costs were based on the study by Maleki-Yazdi et al. (2012).[7]	Caregiver costs are not typically included under the Ministry of Health perspective.

6MWT = six-minute walk test; BSC = best supportive care; EDSS = expanded disability status scale; ENT = ear, nose, and throat; EQ-5D = EuroQoL 5-Dimension Questionnaire; FVC = forced vital capacity; GP = general practitioner; HRQoL = health-related quality of life; ICUR = incremental cost-utility ratio; MPS IVA = mucopolysaccharidosis IVA (Morquio A syndrome); MPS HAQ = MPS Health Assessment Questionnaire; MS = multiple sclerosis; PRO = patient-reported outcomes.

TABLE 9: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Natural History	
• Two-year duration in pre-death health state for all patients	According to the clinical expert, a 2-year duration cannot be assumed for all patients in this health state, as a variety of factors would have an impact on the length of time in this health state.
• Patients in the paraplegic health state would have the same utility values as those in the wheelchair pre-death health state	Valid assumption
• Asymptomatic patients were assumed to have 100% FVC and patients in the pre-death health state were assumed to have 10% FVC	Valid assumption
Efficacy	
• Improved clinical outcomes translate into greater HRQoL in treated patients versus untreated patients for each health state	This is an inappropriate modelling method as it will involve double counting utility benefits from treatment, resulting in an underestimate of the overall ICUR.
• Elosulfase alfa–treated patients would have quicker recovery rates from surgery versus untreated patients	According to the clinical expert, this would be a valid assumption if treated patients' pre-surgical health states are better than those of patients not under treatment with elosulfase alfa.
• Assumed improvement trend in 6MWT and FVC would continue past 72 weeks, based on MOR-004 and MOR-005 clinical trials	Uncertainty regarding the use of extrapolation in predicting long-term efficacy. May be underestimating the costs associated with treatment, and therefore, the overall ICUR.
• Annual decline in 6MWT and FVC would be 20% that of untreated patients (second cycle onward)	Not clear how this was operationalized in the model or whether this applies to single-domain and/or multi-domain responders.
• Patients whose wheelchair status worsened would discontinue treatment after 2 cycles (non-responders)	There is a lack of definition and clarity with regard to patients who are responders or non-responders to treatment. May be underestimating the true treatment costs, and therefore, the overall ICUR.

6MWT = six-minute walk test; FVC = forced vital capacity; HRQoL = health-related quality of life; ICUR = incremental cost-utility ratio.
Source: Manufacturer's Pharmacoeconomic submission.[2]

Manufacturer's Results

The manufacturer reported total costs for different parameters for both elosulfase alfa and BSC (Table 10). Drug costs and administration of elosulfase alfa resulted in [redacted] and $27,079 in incremental costs, respectively, compared with BSC. Further, the total cost associated with treatment with elosulfase alfa was $4,553,694, while the total cost associated with BSC was $66,067.

TABLE 10: SUMMARY OF COSTS RESULTS BY RESOURCE TYPE

Cost Parameter	Elosulfase Alfa	No Treatment	Incremental
Elosulfase alfa	[redacted]	$0	[redacted]
Administration	$27,079	$0	$27,079
Pre-treatment	[redacted]	$0	[redacted]
Adverse events	[redacted]	$0	[redacted]
Wheelchairs	[redacted]	$3,042	[redacted]
Surgery	[redacted]	$11,412	[redacted]
Asymptomatic	[redacted]	$180	[redacted]
No use	[redacted]	$4,401	[redacted]
Sometimes	[redacted]	$6,854	[redacted]
Wheelchair-dependent	[redacted]	$3,785	[redacted]
Paraplegic	[redacted]	$118	[redacted]
Pre-death	[redacted]	$1,863	[redacted]
Caregiver	[redacted]	$34,409	[redacted]
Indirect costs	[redacted]	$0	[redacted]
Total	**$4,553,694**	**$66,067**	**$4,487,627**

Source: Adapted from Manufacturer's Pharmacoeconomic submission.[2]

Additionally, the manufacturer reported the total QALYs by health state (Table 6). Treatment with elosulfase alfa would result in 8.97 QALYs gained, while treatment with BSC would result in 5.98 QALYs gained.

TABLE 11: SUMMARY OF QUALITY-ADJUSTED LIFE-YEARS BY HEALTH STATE

Health State	Elosulfase Alfa	No Treatment	Incremental
Asymptomatic	0.48	0.21	0.27
No use	4.65	3.06	1.59
Sometimes	4.16	3.11	1.05
Wheelchair- dependent	0.17	0.19	–0.03
Paraplegic	0.00	0.01	0.00
Pre-death	0.01	0.02	–0.01
Surgery	–0.11	–0.16	0.05
Caregiver burden	–0.39	–0.46	0.06
Total	**8.97**	**5.98**	**2.99**

Source: Adapted from Manufacturer's Pharmacoeconomic submission.[2]

In summary, under the Ministry of Health perspective, over a lifetime horizon, the manufacturer reported the incremental cost and gain in QALYs associated with treatment with elosulfase alfa to be $4,487,627 and 2.99 QALYs respectively, compared with BSC. Treatment would also result in an incremental gain of 1.91 life-years. Thus, the ICUR was calculated to be approximately $1,502,641 (Table 7).

Under the societal perspective, the manufacturer reported the total cost associated with treatment with elosulfase alfa to be $4,640,592.79, an incremental cost of $4,547,296.81 compared with BSC. The incremental QALYs and life-years gained would be similar to those under the Ministry of Health perspective. Thus, the ICUR was calculated to be approximately $1,522,621.

TABLE 12: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

Comparators	Total			Incremental			ICUR	ICER
	Costs	QALYs	Life-Years	Costs	QALYs	Life-Years		
Ministry of Health Perspective								
BSC	$66,067	5.98	12.21	$4,487,627	2.99	1.91	$1,502,641	$2,345,879
Elosulfase alfa	$4,553,694	8.97	14.13					
Societal Perspective								
BSC	$93,295	5.98	12.21	$4,547,296	2.99	1.91	$1,522,621	$2,377,071
Elosulfase alfa	$4,640,592	8.97	14.13					

BSC = best supportive care; QALY = quality-adjusted life-year; ICUR = incremental cost-utility ratio; ICER = incremental cost-effectiveness ratio.
Source: Adapted from Manufacturer's Pharmacoeconomic submission.[2]

Summary of Manufacturer's Sensitivity Analysis

Uncertainty regarding the parameters chosen for the base-case analysis was addressed by the manufacturer using a one-way deterministic sensitivity analysis and a Monte Carlo simulation probabilistic sensitivity analysis, with 1,000 simulations. The manufacturer provided cost-effectiveness acceptability curves at various willingness-to-pay thresholds.

Deterministic Sensitivity Analysis

The parameters varied individually by the manufacturer included:

- Average weight per health state (95% CI from MOR-001 study, except for the asymptomatic health state, which was varied by ± 10%)
- Annual decline in 6MWT (± 25%); annual decline in FVC (± 25%)
- Untreated health state utilities (± 10%)
- Health state costs (± 10%); delay in surgery (+ 10%)
- Delay in becoming symptomatic with treatment (± 10%)
- Discount rates for costs and QALYs (3%, 5%)
- Time horizon (± 15 years)
- Single-domain responder's annual decline in 6MWT and FVC (extreme values)
- Birth cohort was selected at baseline (i.e., assuming 100% of patients are diagnosed and initiate treatment at birth), instead of the population in the MOR-001 study.

The following parameters had the greatest impact on the ICUR: time horizon, discount rate, and selection of the birth cohort at baseline. When these parameters were varied individually, the ICUR ranged from $582,068 to $1,758,604. There were no parameters that increased the ICUR by more than 25%.

Probabilistic Sensitivity Analysis

The variables considered in the probabilistic sensitivity analysis included average weight per health state; annual decline in 6MWT; annual decline in FVC; utilities; costs; delay in surgery; delay in becoming symptomatic with treatment; and wheelchair shift proportions. Under the Ministry of Health perspective, following 1,000 iterations, the median ICUR was calculated to be $1,587,784 and the mean ICUR was calculated to be $1,749,882.

In approximately 75% (payer and societal) of iterations, the ICUR was above a willingness-to-pay threshold of $1,000,000 per QALY.

CADTH Common Drug Review Reanalysis

CDR conducted several reanalyses based on the identified key limitations (i.e., utility values, mortality rates, caregiver disutility values and costs, patient weight gain, and costs associated with non-responders), in addition to two multi-way analyses.

Scenario 1's multi-way analysis used the manufacturer's definition of non-responder; this resulted in an overall ICUR of $2,956,429 per QALY (Table 13).

TABLE 13: SCENARIO 1 — CDR REANALYSIS ICURS FOR ELOSULFASE ALFA VERSUS BEST SUPPORTIVE CARE

		ICUR	Cumulative ICUR — applying manufacturer's stopping rule for non-responders
No treatment effect on utility values		$2,187,855	**$2,956,429**
No treatment effect on mortality values		$1,504,641	
Exclusion of caregiver disutility values and costs		$1,536,242	
Patient natural weight gain		$1,962,921	
Applying manufacturer's stopping rule for non-responders		$3,028,932	
Stratification based on health state[a]	Asymptomatic	$582,067[b]	$1,090,099[c]
	No use of wheelchair	$1,744,238[b]	$4,561,859[c]
	Some use of wheelchair	$1,634,464[b]	$2,840,770[c]
	Wheelchair-dependent	$1,351,921[b]	$2,390,340[c]

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio.
[a] Assuming 100% of patients are in the respective health state.
[b] Based on the manufacturer's base case.
[c] Based on the same parameters used for the cumulative ICUR.

Scenario 2's multi-way analysis considered the limitations related to the lack of clarity regarding the definition of a non-responder and assumed that all patients would continue treatment, even if there was no benefit observed; this resulted in an overall ICUR of $6,156,762 per QALY (Table 14).

TABLE 14: SCENARIO 2 — CDR REANALYSIS OF ICURS FOR ELOSULFASE ALFA VERSUS BEST SUPPORTIVE CARE

		ICUR	Cumulative ICUR — No stopping rule for non-responders
No treatment effect on utility values		$2,187,855	**$6,156,762**
No treatment effect on mortality values		$1,504,641	
Exclusion of caregiver disutility values and costs		$1,536,242	
Patient natural weight gain		$1,962,921	
No stopping rule for non-responders		$3,028,932	
Stratification based on health state[a]	Asymptomatic	$582,067[b]	$1,800,851[c]
	No use of wheelchair	$1,744,238[b]	$10,355,451[c]
	Some use of wheelchair	$1,634,464[b]	$5,796,888[c]
	Wheelchair-dependent	$1,351,921[b]	$4,310,372[c]

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio.
[a] Assuming 100% of patients are in the respective health state.
[b] Based on the manufacturer's base case.
[c] Based on the same parameters used for the cumulative ICUR.

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