Common Drug Review

Pharmacoeconomic Review Report (Resubmission)

May 2016

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
Dosage form	2 mg/kg IV infusion once weekly
NOC date	July 2nd, 2014
Manufacturer	BioMarin Pharmaceutical (Canada) Inc.

Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

6MWT	six-minute walk test
BSC	best supportive care
ESA	elosulfase alfa
CDR	CADTH Common Drug Review
CDEC	CADTH Canadian Drug Expert Committee
FVC	forced vital capacity
HRQoL	health-related quality of life
MPS	Mucopolysaccharidosis
MPS IVA	mucopolysaccharidosis type IVA; Morquio A syndrome
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 best supportive care for long-term enzyme replacement therapy in patients with a confirmed diagnosis of MPS IVA?"
Type of Economic Evaluation	Cost-utility analysis
Target Population	Canadian patients (children and adults) with a confirmed diagnosis of MPS IVA
Treatment	ESA, 2.0 mg/kg, weekly infusion
Outcomes	QALYs, life-years
Comparator	BSC, defined as the need for medications for pain and infections, obstructive sleep apnea management, and surgical interventions.
Perspective	Ministry of Health
Time Horizon	Lifetime (35 years)
Results for Base Case	Incremental cost-utility ratio for ESA versus BSC: $1,720,127 per QALY
Key Limitations	CDR noted a number of limitations with the structure, parameters, and inputs used in the manufacturer's model: • Uncertainty of the 6MWT to model disease progression, as there are no data correlating it with outcomes of relevance and importance to patients with MPS IVA • Uncertainty regarding the assumption that multi-domain responders (patients with any degree of improvement in 6MWT and FVC) would maintain indefinite stabilization of disease (i.e., no progression to wheelchair state) • Uncertainty in the long-term efficacy of ESA; moreover, the proportion of patients who would be responders beyond the 72 weeks of data available from MOR-005 (extrapolation based on 6MWT and FVC levels) • Double-counting of health benefits due to inclusion of different utility values based on treatment effects within the same health state • Incorrect use of treatment-dependent, mortality relative risk values (based on % FVC levels); additionally, the inappropriate assumption that patients in the asymptomatic health state have decreased pulmonary function (and, thus, an increased risk of mortality) • Inappropriate assumption that patients do not gain weight over time
CDR Estimate	CDR conducted a number of reanalyses to assess the impact of the key identified limitations: • Same utility values for both treatment groups within a given health state • Mortality relative risk values based on natural history of disease; patients in the asymptomatic health state assumed to have normal pulmonary function (i.e., 100% FVC) • Patients gain weight up to age 18 Based on these assumptions, the ICUR increased to $3.18 million per QALY for ESA versus BSC.

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

EXECUTIVE SUMMARY

Background

Elosulfase alfa (ESA) is being reviewed as a long-term enzyme replacement therapy in patients with a confirmed diagnosis of mucopolysaccharidosis type 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 and older (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.

ESA was previously reviewed for the same indication by the CADTH Common Drug Review (CDR) and received a "do not list" recommendation by the CADTH Canadian Drug Expert Committee (CDEC) in March 2015.[4] This review is a resubmission based primarily on the availability of new clinical data, including longer-term results collected from the MOR-005 extension trial and results of an open-label, single-group, efficacy, and safety study in patients younger than five years of age (MOR-007). Additionally, the manufacturer submitted a [redacted] for the six-minute walk test (6MWT) to support its clinical relevance. In terms of the pharmacoeconomic submission, the manufacturer made several changes from the original submission, as highlighted in Table 2; however, the submitted price was the same as in the original submission.

Similar to the original submission, a cost-utility analysis was submitted comparing ESA to best supportive care (BSC) — defined as symptomatic management, with medications for pain and/or infections and surgical interventions — using data from the MOR-004/MOR-005 clinical trial[5,6] and the MOR-001 (MorCAP) natural history study.[7] The reference case time horizon was lifetime (35 years), from the Ministry of Health perspective. The economic submission was based on a Markov model with six key health states, primarily based on wheelchair use. Patients in all health states except the pre-death health state were eligible for treatment with ESA. Long-term disease progression within the model was determined by extrapolating the results of the 6MWT and forced vital capacity (FVC) values that were observed in patients in the key clinical trial.

Summary of identified limitations and key results

CDR identified several limitations with the submitted model, such as uncertainty regarding the use of the 6MWT to model disease progression; lack of long-term data on efficacy; strong assumptions regarding long-term disease stabilization among responders; potential double-counting of health benefits; incorrect use of treatment-dependent, mortality relative risk values; and the inappropriate assumption that patients do not gain weight over time. Reanalyses were possible for three key limitations (utility values, mortality rates, and patient weight). CDR identified other limitations, but could not assess them given the model structure and available data. A combined reanalysis of the three limitations resulted in an incremental cost-utility ratio (ICUR) of $3.18 million per quality-adjusted life-year (QALY), a significant increase in the ICUR for ESA versus BSC from the manufacturer's base case. Upon stratifying by health state to determine cost-effectiveness by baseline severity, the ICUR ranged

from $1.54 million per QALY for the asymptomatic health state to $3.45 million per QALY for the "no use of wheelchair" health state.

Conclusions

The manufacturer reported an ICUR of $1,720,127 per QALY for ESA versus BSC in its base-case scenario. CDR reanalyses addressing key limitations of the analysis resulted in a significant increase in the overall ICUR to $3.18 million per QALY. The main observed benefit of ESA compared with BSC in the clinical trial program was improvement in 6MWT distance. In the absence of data correlating 6MWT with key drivers in the economic model, such as progression of wheelchair use and mortality risk, the economic analysis relied heavily upon a number of assumptions regarding the long-term clinical benefits of ESA compared with BSC. Consequently, considerable uncertainty remains regarding the cost-effectiveness of treatment with ESA.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

As part of its resubmission, the manufacturer submitted a cost-utility analysis comparing elosulfase alfa (ESA) (Vimizim) to best supportive care (BSC) (defined as symptomatic management with medications for pain and infections, and surgical interventions) in patients diagnosed with mucopolysaccharidosis type IVA (MPS IVA, also known as Morquio A syndrome).[1] The main differences between the cost-utility analyses provided with the resubmission and the original submission are shown in Table 2.

The reference case time horizon was lifetime (35 years), with a cycle length of one year. The analysis was conducted from the Ministry of Health perspective. 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:[7]

- Asymptomatic (6.6% of the cohort, diagnosed MPS IVA patients younger than three years who have not yet developed musculoskeletal complications or limitations in endurance and cardiopulmonary function)
- No wheelchair use (46.4% of the cohort)
- Sometimes use 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 (e.g., orthopedic complications). Surgeries are treated as clinical events that incur a risk of complications, but are not associated with any clinical benefit. In the case of surgical complications, patients can enter the paraplegic health state. Patients enter the pre-death health state from either the wheelchair-dependent health state or the paraplegic health state once they require ventilation support (defined by low forced vital capacity [FVC] values). Patients in all health states except pre-death were eligible for treatment with ESA.

Disease progression within the model was based on four outcome measures: time to symptom development (transition from the asymptomatic health state to the "no wheelchair use" health state), which was based on clinical expert opinion; change in wheelchair use, which is applicable to patients in any of the wheelchair health states in the first cycle of the model only (due to absence of long-term data on changes in wheelchair use beyond the two years of data available from the MOR-001 [or MorCAP] natural history study);[7] six-minute walk test (6MWT), which is applicable to patients in the first two wheelchair health states (i.e., "no wheelchair use" and "sometimes use wheelchair" health states) in the second cycle onward, where patients progressed based on a 7.1 m annual decline in 6MWT score, based on data from MOR-001;[7] and FVC, which is applicable to all patients in the wheelchair-dependent health state (second cycle onward) and paraplegic health state (all cycles), where patients progressed based on a 0.1 L annual decline in FVC, based on clinical expert opinion.

In the treatment group, transition probabilities in the first cycle were based on data collected in MOR-004/MOR-005, a phase 3 clinical trial that observed changes in wheelchair use over a period of 72 weeks

using the MPS health assessment questionnaire (HAQ). 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% of that of untreated patients (natural course of the disease). The manufacturer also assumed that treatment with ESA would delay time to symptom development and time to surgery, and that it would be associated with faster recovery rates after surgery.

The manufacturer considered different levels of response, including single-domain responders, multiple-domain responders, and non-responders. In the first cycle of the model, the level of response was based upon observation of changes in wheelchair use from baseline to year 2 in MOR-001 and baseline to week 72 in MOR-005. Patients who stayed in the same wheelchair health state were considered single-domain responders, while those with an improvement in wheelchair health state were deemed multi-domain responders. Those who progressed to a health state with greater wheelchair use were deemed non-responders. From the second cycle onward, response for treated patients was based on two outcome domains: endurance (measured by the 6MWT) and pulmonary function (measured by FVC). Patients were considered single-domain responders if they showed any degree of improvement in one domain but worsening in another; multi-domain responders if they showed improvement in both domains; or non-responders if they showed no improvement in either domain.

In the model, the manufacturer assumed [redacted]% of patients would be multi-domain responders and [redacted]% of patients would be single-domain responders, based upon the response rate observed at 72 weeks in MOR-005 among the [redacted]% of patients in the study who did not miss a dose or undergo surgery. There was some uncertainty regarding the fate of multi-domain and single-domain responders in the analysis, although it appears that multi-domain responders were assumed to experience stabilization of disease (i.e., they would stay within the same wheelchair health state indefinitely), while single-domain responders would progress at a 20% lower rate than untreated patients. Thus, the manufacturer assumed all patients would respond to — and, therefore, continue to receive — treatment for the duration of the time horizon. This is different from the original submission, where the proportion of patients in each of the response categories was based on clinical expert opinion. Additionally, in the original submission, the manufacturer included a proportion of patients who were deemed non-responders, all of whom were assumed to discontinue treatment (i.e., a stopping rule was applied).

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 with MPS IVA using the EuroQol 5-Dimensions Health-Related Quality of Life questionnaire (EQ-5D). The manufacturer also included differential utility values dependent on treatment effects, where patients treated with ESA were assumed to have higher utility values in each health state than those on BSC, which was based on the results of a cross-sectional analysis that observed a positive correlation between the 6MWT and FVC and patient-reported HRQoL in 24 German MPS IVA patients.[2,8]

Resource utilization varied by health state, where the frequency of clinical events and need for background care were based on clinical expert opinion.[2] Cost information for the various surgeries, as well as average length of hospital stay, was determined from the Canadian Institute for Health Information Patient Cost Estimator, while unit costs for specialist visits were obtained from the Ontario Schedule of Benefits for Physician Services (2015).[9,10] The main cost drivers in the model included those associated with ESA treatment (i.e., drug and administration costs).

TABLE 2: COMPARISON OF THE COST-UTILITY MODEL PROVIDED IN THE RESUBMISSION WITH THE MODEL IN THE ORIGINAL SUBMISSION

Parameter	Original submission	Resubmission
Proportion of patients who are single-domain, multi-domain, and non-responders to treatment with ESA in subsequent years (i.e., after 72 weeks)	The proportion of patients in different response categories was based on clinical expert opinion; there was a proportion of patients who were considered non-responders to treatment.	The proportion of patients in different response categories was based on the responder analysis at week 72 from MOR-005; it was assumed there would no non-responders. The proportions used in the resubmission were substantially different from the proportions used in the original submission.
Differential rate of mortality between treatments in the same health state	Included in base-case analysis and identified as a limitation by CDR.	Manufacturer correctly assumed the same risk of mortality for treated and untreated patients, by health state.
Risk of mortality in asymptomatic patients (based on % FVC)	Assumed to be no risk of mortality, other than background risk (i.e., 100% FVC).	Assumed to be an excess risk of mortality (i.e., 80% FVC).
Caregiver costs and disutilities	Included in the base-case analysis, and identified as a limitation by CDR.	Manufacturer correctly excluded this from the base-case analysis.
Proportion of patients with successful surgery (i.e., no complications)	Assumed a select proportion of patients would be successful with surgery, based on clinical expert opinion.	The proportion of patients successful with surgery was negligibly smaller (approximately 0.1% difference).
Costs associated with resource use (e.g., pain management specialist visits, ventilation, and wheelchairs)	Assumed lower costs for all 3 resources.	Higher costs for all 3 resources were used; no source was identified for the cost of ventilation.

CDR = CADTH Common Drug Review; ESA = elosulfase alfa; FVC = forced vital capacity.

2. MANUFACTURER'S BASE CASE

The manufacturer reported that the total cost associated with treatment with ESA was $10,851,054, an incremental cost of $10,819,245 compared with BSC. Further, treatment would result in 12.69 quality-adjusted life-years (QALYs), a QALY gain of 6.29 compared with BSC. Thus, the incremental cost-utility ratio (ICUR) was calculated to be $1,720,127 per QALY (Table 3).

In the original submission, the manufacturer calculated an ICUR of $1,502,641 per QALY versus BSC. The incremental costs and benefits of treatment with ESA were $4,487,627 and 2.99 QALYs, respectively. The substantial change from the original submission in the incremental costs and QALYs was driven primarily by the higher proportion of multiple-domain responders in the resubmission ([redacted]%) compared with the original submission ([redacted]%).[2]

TABLE 3: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE-CASE ANALYSIS, PER PATIENT

	Total Costs	Incremental Cost	Total QALYs	Incremental QALYs	ICUR
Best supportive care	$31,809	$10,819,245	6.40	6.29	$1,720,127
Elosulfase alfa	$10,851,054		12.69		

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Source: Adapted from the manufacturer's pharmacoeconomic submission.[2]

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

Uncertainty regarding the parameters chosen for the base-case analysis was addressed by the manufacturer using a one-way deterministic sensitivity analysis, various scenario analyses, and a Monte Carlo simulation probabilistic sensitivity analysis.

Use of a lower discount rate (0%) for the costs and QALYs resulted in the ICUR varying by greater than 25%. None of the other parameters had a high impact on the ICUR (> 25%). The probabilistic sensitivity analysis showed that in approximately 50% of iterations, the ICUR was above a willingness-to-pay threshold of $1.2 million per QALY.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

- **Use of clinical data from MOR-004/MOR-005:** The main benefit observed in the MOR-004 trial and its extension, MOR-005, was improved 6MWT. However, there is substantial uncertainty as to whether the outcome of 6MWT is an appropriate surrogate end point to model disease progression, as there is no strong evidence supporting its correlation to outcomes of relevance and importance to patients with MPS IVA, such as progression in wheelchair use (which was used to structure the pharmacoeconomic model), improvements in quality of life, or overall survival. Although the manufacturer justified the association between improvements in 6MWT and quality of life (based on an observed improvement of 0.2 points on the EQ-5D for every 100 m improvement on the 6MWT in 24 patients with MPS IVA),[8] neither treatment group in MOR-004 achieved this degree of mean improvement on the 6MWT. Thus, the validity of applying these results to model the long-term effects of ESA is uncertain. Additionally, as noted in the clinical review, mean 6MWT appeared to approach MOR-005 baseline values at 120 weeks, thereby also increasing the uncertainty in the long-term trajectory of 6MWT benefits.
  One justification for the resubmission was the availability of more data from the MOR-005 extension trial (i.e., 120 weeks' follow-up data); however, the manufacturer did not use any of these data to inform the pharmacoeconomic model. As in the previous submission, transition probabilities relating to change in wheelchair use beyond 72 weeks, for the duration of the time horizon, were based on extrapolation of the 6MWT and FVC levels, where it was assumed that patients with any degree of improvement in 6MWT and FVC (multiple-domain responders) would see indefinite stabilization of disease (i.e., no wheelchair state progression). Patients with improvement in only one domain (single-domain responders) were assumed to experience annual declines of 20% in 6MWT and FVC compared with untreated patients. This strong assumption regarding disease stabilization among multi-domain responders, which is not directly supported by the clinical data,

was an important driver of the observed QALY gains. Additionally, the manufacturer assumed that the proportion of patients who would be single-domain ([redacted]%) or multi-domain responders ([redacted]%) would stay constant for the duration of the time horizon, and that there would no non-responders to treatment. These were based on the proportions at 72 weeks, and the durability of response over lifetime horizon is uncertain. Furthermore, these proportions were based on the [redacted]% of patients in MOR-005 who did not miss a dose or undergo surgery. It is possible that there were non-responders, or a lower proportion of multi-domain responders, in the remaining [redacted]%.

- **Use of differential utility values for treatment groups within the same health state:** Although the manufacturer claimed to have addressed this limitation in the resubmission, the model still applied different utility weights for treatment with ESA versus BSC, based upon observation of a positive correlation between the 6MWT and FVC level and patient-reported HRQoL in a study by Lampe et al. (2015).[2,8] This may lead to double-counting of the overall health benefits of ESA, as such benefits are already accounted for by the lower probabilities of progression to worse health states. The CDR reanalysis used the same utility weights for each health state, based on the natural history of the disease, regardless of treatment group.
- **Use of treatment-dependent mortality rate**: In this resubmission, the manufacturer corrected the erroneous use of different mortality rates between treatment groups within the same health states employed in the original submission. However, the manufacturer used treatment-dependent, mortality relative risk values, which were based upon observation of a [redacted]% improvement in FVC levels versus baseline over three years of treatment with ESA. It would have been preferable to use the mortality rates based on the natural history of the disease, as the risk of mortality associated with MPS IVA in a given wheelchair state may be independent of treatment. Additionally, the manufacturer assumed that patients in the asymptomatic health state would have an 80% average FVC (and, thus, an increased risk of mortality); this is different from the original submission, in which the manufacturer assumed that asymptomatic patients would have normal FVC (100%). There was no explanation as to why the manufacturer made this change. The CDR clinical expert indicated that patients in this health state would likely have normal pulmonary function. CDR conducted a reanalysis using the relative risk of mortality based on the natural history of the disease and also assumed patients in the asymptomatic health state had no impairment in pulmonary function.
- **Assumption that patients maintain the same weight over the lifetime time horizon**: The manufacturer did not account for this limitation in its resubmission. The same average patient weight was applied for each health state included in the model, which may underestimate the true costs associated with the ESA treatment, given that patients in each health state vary by age and, therefore, by weight. It would have been more appropriate to use varying weights based on the mean age in each health state. CDR conducted a reanalysis using average weight by age observed in patients in the MOR-001 natural history study, as reported by Montaño et al.[3]

5. CADTH COMMON DRUG REVIEW REANALYSES

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

1. No utility advantage ascribed to ESA over BSC within the same health state: Natural disease progression utility values for each health state were applied to both the BSC and treatment groups, based on the results of the PRO study conducted by the manufacturer in treatment-naive patients. With this change, the ICUR increased to $2,347,042 per QALY.

2. No inherent advantage of ESA in terms of mortality risk: Mortality relative risk values based on the natural history of the disease were applied to both the BSC and treatment groups. These were calculated for each health state compared with background mortality risk, based on the percentage decrement in FVC levels. Average percentage FVC levels by health state were based on the MorCAP natural history study. Additionally, it was assumed that patients in the asymptomatic health state had no impairment in pulmonary function (i.e., 100% FVC). With this change, the ICUR increased to $1,720,957 per QALY.
3. Inclusion of age-appropriate mean body weight values for each health state: This was conducted using average weight by age observed in patients in the MOR-001 natural history study, as reported by Montaño et al.[3] Patients 18 years and older were assumed to have the same weight. With this change, the ICUR increased to $2,328,841 per QALY.
4. Stratified analysis for each health state: Assuming that all patients start treatment in the asymptomatic health state, the ICUR for ESA versus BSC was $694,188 per QALY. The ICUR for all patients starting in the "no use of wheelchair" health state was $1,704,464 per QALY; for those in the "some use of wheelchair" health state, the ICUR was $1,854,105 per QALY; and for those in the "wheelchair-dependent" health state, the ICUR was $1,995,458 per QALY.

Upon conducting a multi-way reanalysis incorporating all of the changes previously described, without stratification by health state, the ICUR increased from the manufacturer's base case of $1,720,127 per QALY to $3,179,763 per QALY. With stratification, the ICUR from the multi-way analysis ranged from $1,546,460 per QALY for the asymptomatic health state to $3,449,223 per QALY for the "no use of wheelchair" health state.

A price reduction analysis was undertaken based on CDR's multi-way reanalysis. This showed that even with a price reduction of 90%, the ICUR for ESA compared with BSC would still be higher than commonly accepted thresholds (Table 4).

TABLE 4: CADTH COMMON DRUG REVIEW REANALYSIS PRICE REDUCTION SCENARIOS

ICURs of ESA vs. BSC		
Scenario (price)	**Base-case analysis submitted by manufacturer**	**Reanalysis by CDR[a]**
Submitted ($[redacted])	$1,720,127	$3,179,763
10% reduction ($[redacted])	$1,549,136	$2,863,182
20% reduction ($[redacted])	$1,378,145	$2,546,600
30% reduction ($[redacted])	$1,207,154	$2,230,019
40% reduction ($[redacted])	$1,036,163	$1,913,437
50% reduction ($[redacted])	$865,172	$1,596,856
60% reduction ($[redacted])	$694,181	$1,280,275
70% reduction ($[redacted])	$523,190	$963,693
80% reduction ($[redacted])	$352,199	$647,112
90% reduction ($[redacted])	$181,209	$330,530

CDR = CADTH Common Drug Review; BSC = best supportive care; ESA = elosulfase alfa; ICUR = incremental cost-utility ratio; vs. = versus.

[a] CDR reanalysis considered utility values, mortality rates, and patient weight gain.

Further multi-way reanalyses with larger decrements in price revealed that a price reduction of 97% would be required for the ICUR to approach $100,000 per QALY.

6. ISSUES FOR CONSIDERATION

- Although the CDR reanalysis stratified by health state showed that the ICUR was lowest if treatment was initiated in the asymptomatic health state (i.e., in patients younger than three years old) versus other health states, it is important to note that patients in MOR-004 were aged five years and older. In its resubmission, the manufacturer provided the results of an open-label, single-group, efficacy, and safety study in patients younger than five years of age. However, this study is limited, as there was no comparator included; further, there were no data on outcomes related to disease progression in these patients. However, the clinical expert consulted for the review indicated that the benefits of ESA were likely to be greater if initiated at an early age.
- In the original CADTH Canadian Drug Expert Committee (CDEC) recommendation for ESA, it was noted that due to insufficient evidence, CDEC was unable to identify how responders and non-responders would be differentiated in clinical practice and under what circumstances treatment would be discontinued given inadequate response.[4] In the resubmission, the manufacturer did not provide any evidence to support discontinuation criteria, and assumed a zero probability of non-response in the economic model. As such, CDR was unable to assess the impact of a stopping rule on the cost-effectiveness of treatment with ESA versus BSC.

7. PATIENT INPUT

Input was received from two patient groups: the Isaac Foundation for MPS and the Canadian Society for Mucopolysaccharide and Related Diseases. Patients noted difficulty in walking long distances and climbing stairs, impeding self-care and participation in normal day-to-day activities, such as sports. It was also indicated that patients require substantial medical care (i.e., specialist visits, surgical procedures, and long hospital stays), which can also place a burden on caregivers.

Patients highlighted that as a result of treatment, they would expect to see stabilization of the disease and increased overall endurance, resulting in improved quality of life. As noted in the limitation above, disease progression after the first year is based on the 6MWT outcome. Although the 6MWT indirectly measures endurance and functionality, it is limited by the lack of data correlating it with wheelchair progression (which is associated with disease progression). Thus, there is considerable uncertainty in the predictions of the model with respect to outcomes of importance to patients.

8. CONCLUSIONS

The manufacturer reported an ICUR of $1,720,127 per QALY for ESA versus BSC in its base-case scenario. CDR reanalyses addressing key limitations of the analysis resulted in a significant increase in the overall ICUR to $3.18 million per QALY. The main observed benefit of ESA compared with BSC in the clinical trial program was improvement in 6MWT distance. In the absence of data correlating 6MWT with key drivers in the economic model, such as progression of wheelchair use and mortality risk, the economic analysis relied heavily upon a number of assumptions regarding the long-term clinical benefits of ESA compared with BSC. Consequently, considerable uncertainty remains regarding the cost-effectiveness of treatment with ESA.

APPENDIX 1: COST COMPARISON

Based on consultation with the clinical expert consulted by the CADTH Common Drug Review (CDR), there are no other drugs currently indicated for this condition.

TABLE 5: COST COMPARISON TABLE FOR MUCOPOLYSACCHARIDOSIS TYPE IVA TREATMENT

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Daily Drug Cost ($)	Average 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]	$[redacted] $[redacted] $[redacted] $[redacted]

[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 17 years (25 kg) based on a study Montaño et al.[3]

[d] Assuming an average weight for patients aged 18 years and older (37 kg) based on a study Montaño et al.[3]

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 6: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS ELOSULFASE ALFA RELATIVE TO BEST SUPPORTIVE CARE?

Elosulfase Alfa Versus Best Supportive Care	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					**X**	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	$1,720,127 per QALY (manufacturer's base-case scenario) $3,179,763 per QALY (CDR reanalysis scenario)					

CDR = CADTH Common Drug Review; CE = cost-effectiveness; NA = not available; QALY = quality-adjusted life-year.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 7: 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 some inconsistency between the pharmacoeconomic report and the submitted model. The manufacturer claimed to have addressed some of the limitations previously highlighted in the original submission in their report; however, not all of these were actually addressed in the model (e.g., use of differential utility weights based on treatment effects). Additionally, the total costs reported in the conclusions of the manufacturer's pharmacoeconomic submission and model did not align with the total costs reported when summing the individual costs parameters (Table 12).		

TABLE 8: AUTHORS' INFORMATION

Authors of the Pharmacoeconomic Evaluation Submitted to the CADTH Common Drug Review
☐ Adaptation of Global model/Canadian model done by the manufacturer
☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer
☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer
☐ Other (please specify)

	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: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENT REVIEWS OF DRUG

Three technology appraisals that assessed elosulfase alfa (ESA) were identified. These included appraisals from the National Institute for Health and Care Excellence (NICE), England; the Scottish Medicines Consortium (SMC); and the Pharmaceutical Benefits Advisory Committee (PBAC), Australia. The summaries of the submitted economic models and recommendations are provided in Table 9.

TABLE 9: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS

	NICE (December 2015)[11]	SMC (August 2015)[12]	PBAC (November 2014)[13]
Drug	ESA (Vimizim) 5 mg/5 mL	ESA (Vimizim) 1 mg/mL	ESA (Vimizim) 1 mg/mL (5 mL vial)
Price	£750 per vial (excluding VAT)	Not reported	Not reported
Treatment	2 mg/kg of body weight administered through IV infusion once per week (over 4 hours)		
Comparator	Established clinical management (not defined in report)	Standard medical care (i.e., treatments to address symptoms and complications, including orthopedic surgery, pain management, and treatment of infections)	Placebo in combination with standard medical management (not defined in report)
Population modelled	Patients with MPS IVA with demographic and disease characteristics based on the population in MOR-001	Patients of all ages with MPS IVA	Patients with MPS IVA
Time horizon	Lifetime	Lifetime	24 weeks (in line with MOR-004)
Cycle length	1 year	Not reported	Not applicable
Discount rate	1.5% per year on costs and benefits	3.5% per year on costs and benefits	Not applicable
Type of model	Cost-consequence analysis (e.g., Markov model with 7 health states representing the progression of MPS IVA based on increasing use of a wheelchair)	Cost-utility analysis (e.g., Markov model with 5 health states — asymptomatic, no wheelchair use, sometimes using a wheelchair, wheelchair-dependent, end stage disease requiring ventilation — and death)	Cost-effectiveness analysis
Key outcomes; details of the model	Changes in wheelchair use, 6MWT, and FVC, as seen in MOR-001 and MOR-005 Patients who responded in both the endurance and pulmonary domains were considered multi-domain responders and	Changes in wheelchair use (for the first cycle transitions) and 6MWT or FVC (for subsequent transitions), based on data obtained from MOR-001 and MOR-005 (week 72)	6MWT The key drivers of the model were average patient weight and utility gained from the change in 6MWT results from baseline.

	NICE (December 2015)[11]	SMC (August 2015)[12]	PBAC (November 2014)[13]
	assumed not to have any progression in wheelchair use, while patients who responded in one domain were considered single-domain responders and were assumed to progress at 50% the rate of untreated patients (i.e., the clinical management group).	Patients who were multi-domain responders were assumed to experience a stabilization of their disease, while single-domain responders would have a 6MWT decline at 50% of the rate of untreated patients.	
Results	Base case: Clinical management was associated with £618,812 in costs and 9.75 QALYs over the lifetime of the model; ESA was associated with 27.93 QALYs (incremental 18.18 QALYs compared with clinical management). The acquisition cost of ESA over the lifetime of the model was £14,014,636 (total costs not reported, as they are confidential).	Base case: ICER was calculated to be £829,870, based on an incremental cost of £8,242,197 and 9.91 QALYs gained versus standard medical care.	Base case: The incremental cost ESA is between $15,000 and $45,000 per additional metre in the 6MWT and more than $200,000 per QALY gained.
Key sources of uncertainty	• The assumptions used to model clinical effectiveness were uncertain, as they were based on limited evidence, likely overestimating the benefits of treatment (especially in multiple-domain responders, who were assumed to not progress at all). • Mortality and utility benefits associated with treatment were double counted. • It was uncertain whether the manufacturer's original modelling of survival accurately reflected the mortality risks associated with MPS IVA, such as the risks of cervical complications, trauma, and heart failure.	• Clinical data driving the initial transitions in the model are based on a naive indirect comparison from the MOR-001 natural history and MOR-005 extension study; additionally, the extension study data were from the per-protocol population, and may be subject to bias. • Transition probabilities used after the first cycle of the model assume that the majority of patients on ESA have their disease stabilized (i.e., are multiple-domain responders), and that there is a long-term maintenance of treatment effect; however, given the lack of long-term data on outcomes, this is a key source of uncertainty. • Utility benefits associated with treatment were double counted. • The analysis may not fully reflect increasing patient weight over the	• The results of MOR-004 were applicable to all patients modelled, as the study did not include patients younger than 5 years of age and those who had mild or severe forms of the disease. • The time horizon of the model was too short for the proposed lifelong treatment of patients. • The model assumed a constant treatment effect, which is not applicable given the limited evidence available. • The model did not take into account the heterogeneity of the patient population (e.g., age, mobility). • The costs of managing adverse reactions and pre-treatment medications were not taken into consideration, in addition to other possible resources consumed.

	NICE (December 2015)[11]	SMC (August 2015)[12]	PBAC (November 2014)[13]
		duration of the model; this may result in an underestimate of overall treatment costs of ESA. • The model assumed that no patients were non-responders to ESA, which may lack plausibility in clinical practice.	• There was uncertainty in the reliability and applicability of the utility weights obtained from the unpublished study (Lampe, 2014). • There was an inappropriate assumption that improvements in the 6MWT were associated with survival benefits.
Recommendation	Recommended for funding for treating MPS IVA, within its marketing authorization, according to the conditions in the managed access agreement for ESA.	Not recommended for use within NHS Scotland.	Not recommended.
CDR assessment	The economic evaluation submitted to CDR appears to be similar to the economic evaluations submitted to NICE and SMC, but different from that submitted to PBAC. It appears that the same data were used to inform both the models submitted to NICE, SMC, and CDR. One key difference is the rate at which single-domain responders progress through the model. In the economic evaluations submitted to NICE and SMC, single-domain responders progress at a rate of 50% compared with untreated patients, whereas in the economic evaluation submitted to CDR, patients progress at a much slower rate (20% compared with untreated patients). Both were based on clinical expert opinion. NICE, SMC, and PBAC identified a substantial number of limitations with the submitted models, several of which have been identified within the CDR review of the submitted model.		

6MWT = six-minute walk test; CDR = CADTH Common Drug Review; ESA = elosulfase alfa; FVC = forced vital capacity; ICER = incremental cost-effectiveness ratio; IV = intravenous; MPS IVA = mucopolysaccharidosis type IVA; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; QALY = quality-adjusted life year; SMC = Scottish Medicines Consortium; VAT = value-added tax.

APPENDIX 5: REVIEWER WORKSHEETS

Manufacturer's model structure

The manufacturer's cost-utility analysis was conducted using a cohort-based Markov model in which patients with mucopolysaccharidosis type IVA (MPS IVA) transition between six health states (based primarily on wheelchair use) and death. The baseline distribution of patients — in addition to mean age, weight, and six-minute walk test (6MWT) and forced vital capacity (FVC) scores across each of the health states — was based on the MOR-001 (MorCAP) natural history study.[7] The health states were defined as follows:

- **Asymptomatic**: diagnosed MPS IVA patients younger than three years old who have not yet developed musculoskeletal complications or limitations in endurance and cardiopulmonary function (6.6% of the cohort)
- **No wheelchair use**: 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 m (46.4% of the cohort)
- **Sometimes use wheelchair**: MPS IVA patients who have developed pain, fatigue, and musculoskeletal issues that significantly limit 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 with major limitations in endurance, and leading to wheelchair dependency; mean FVC level is 1.0 L (12.8% of the cohort)
- **Paraplegic**: MPS IVA patients who become paraplegic due to surgical complications (0% of the cohort)
- **Pre-death**: MPS IVA patients who are wheelchair-dependent and require mechanical ventilation, defined by low FVC values (0% of the cohort)

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. These are treated as clinical events that may result in complications, but do not improve the overall health state of the patient. After surgery, patients enter a recovery period (assumed to be six months), during which they have a reduced quality of life. Patients then return to their pre-surgery health state. Thus, surgery was assumed to be associated with no clinical benefit.

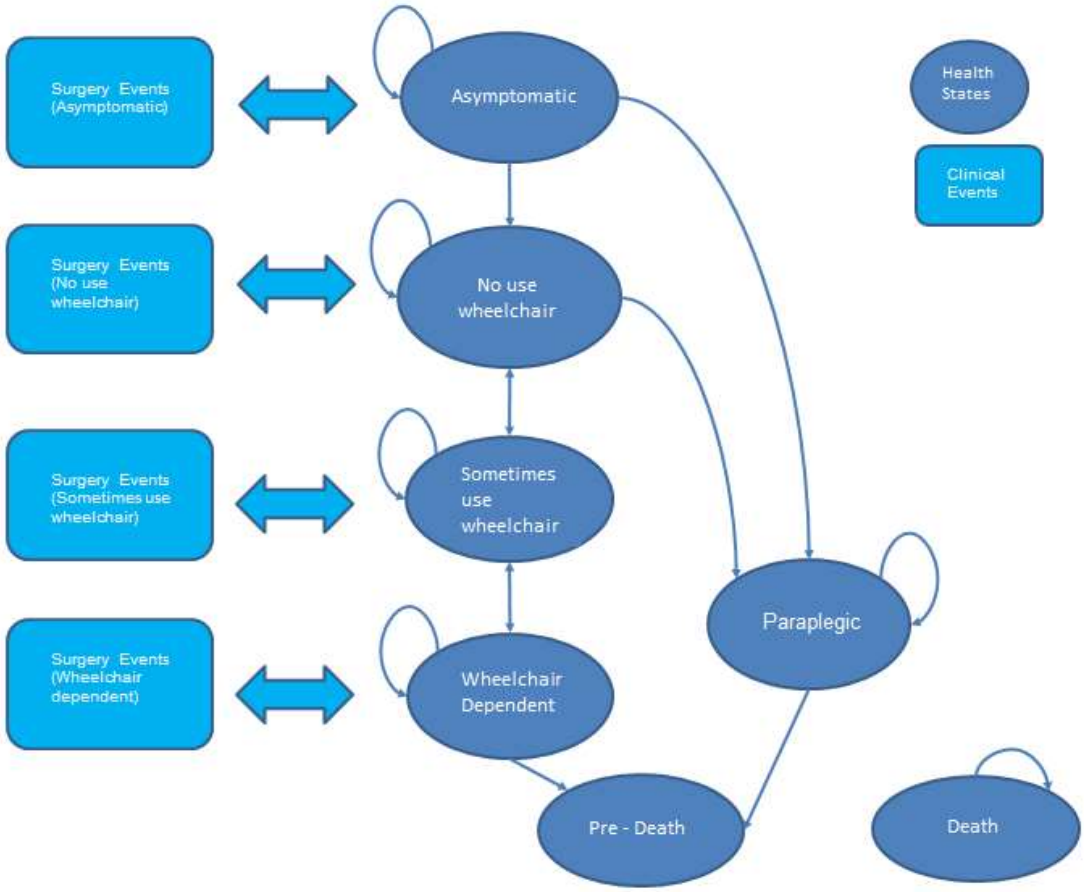
The perspective of the model is that of the Ministry of Health. The model adopts a cycle length of one year over a lifetime horizon (35 years). It also incorporates differential utility values and mortality risks for each health state in addition to treatment-dependent utility values.

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 years
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 use from the MOR-001 natural history study)
3) 6MWT, which is applicable for the second cycle onward for patients in the "no wheelchair use" and "sometimes wheelchair use" health states, where patients progress based on a 7.1 m decline in 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 the pre-death health state would be eligible for treatment with elosulfase alfa (ESA).

The manufacturer considered multi-domain and single-domain responders (for the duration of the time horizon) in addition to non-responders (for the first two years only) in the submitted model. For the first year of the model, the level of response was based on changes in wheelchair use from baseline. Patients who stayed in the same wheelchair health state were considered single-domain responders, while those who went to an improved wheelchair health state were considered multi-domain responders. Those who progressed to a higher wheelchair health state were considered non-responders. For subsequent years, the level of response was based on two outcome domains: endurance (measured by the 6MWT) pulmonary function (measured by FVC levels). Single-domain responders would see an improvement in one outcome domain but worsening in the other; multiple-domain responders would see improvements in both domains; and non-responders would see no improvement.[2] The manufacturer only included

non-response to treatment in the first cycle of the model, but assumed these patients would continue treatment. It was assumed all patients would either be single-domain or multi-domain responders in subsequent cycles, based on 72-week results of MOR-005.

There were minimal details provided regarding validation of the model; however, the authors indicated that it was checked by a clinical expert.

TABLE 10: DATA SOURCES

Data Input	Description of Data Source	Comment
Natural History		
Baseline distribution of patients; definition of health states (annual average loss in 6MWT or FVC score); progression data	Taken from MOR-001 (MorCAP),[7] a longitudinal study in which clinical outcomes have been collected over 2 years under normal settings in patients with MPS IVA unexposed to ESA	Deemed appropriate, although the wheelchair progression data from the placebo group of MOR-004 may have been a better alternative to populate the BSC group
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 The manufacturer made slight changes to the proportion of patients who would be successful following surgery from the previous submission. In the resubmission, the proportion of patients successful with surgery was negligibly smaller than in the original submission (approximately 0.1% difference).	It was not clear how the utility decrement during the recovery period was applied in the model. Surgeries were assumed to provide no clinical benefit (i.e., no QALY increase), only harm (i.e., QALY decrements) during the recovery period.
Efficacy		
Delay in the development of musculoskeletal complications by 5 years with ESA vs. BSC (i.e., additional years to move from asymptomatic to the "never use wheelchair" health state)	Based on clinical expert opinion The manufacturer identified low-quality evidence, such as sibling case studies, to validate this assumption.[2]	Not supported by evidence. May be overestimating the benefits associated with ESA.
Wheelchair progression in treated patients (for the first cycle of the model)	Derived from the MOR-004/MOR-005 studies. MOR-004 is a phase 3 RCT 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 ESA, this study observed changes in wheelchair use as captured by the MPS HAQ.	Time to wheelchair dependency was only assessed descriptively in MOR-004/MOR-005.
Extrapolation of 6MWT and FVC values beyond 72 weeks	Based on clinical expert opinion and experience with other MPS disorders.[2]	Although there was a significant difference in 6MWT observed between ESA-treated patients

Data Input	Description of Data Source	Comment
		versus those on placebo, the clinical significance of this is uncertain. Additionally, there is uncertainty whether this difference extends past 72 weeks. May overestimate benefits of treatment.
Proportion of multi-domain, single-domain	Determined from the MOR-004/ MOR-005 clinical trial (72-week data). This was different from the previous submission, in which the proportion was based on clinical opinion.	Lack of clarity regarding how single-domain and multi-domain responders were defined. It seems there were different definitions used for the first cycle (i.e., based on wheelchair progression) versus subsequent cycles (i.e., based on domains). After the second cycle and onwards, all patients were assumed to be single- or multi-domain responders, which may not be realistic, potentially overestimating efficacy of ESA.
Annual decline in 6MWT and FVC would be 20% of that of untreated patients	Based on clinical expert opinion.	No trial data to support this degree of benefit. May overestimate efficacy of ESA.
Surgeries per health state (delay in time to surgery after initiating treatment; faster recovery times post-surgery)	Delay in time to surgery under treatment was determined from the MOR-004/MOR-005 clinical trial. Surgery recovery times were based on clinical expert opinion	
Utilities	Patient utility values for the wheelchair health states were based on the PRO study conducted by the manufacturer, which determined HRQoL in treatment-naive patients using the EQ-5D-5L 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] The manufacturer assumed that treated patients would have higher utility values compared with untreated patients. These utility values were based on the EQ-5D administered to treated patients during the PRO study (positive correlation between patient's 6MWT and FVC with the HRQoL).[2]	Differential utility values based on treatments within the same health state may be double-counting the health benefits acquired with ESA treatment. This is not an appropriate modelling method.

Data Input	Description of Data Source	Comment
Resource use	The type of health care resources utilized depended on the patient's health state. These included (as identified by the manufacturer): GP visits, GP nurse visits, 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).[14]	
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.	Patients pre-treated with anti-histamines or steroids, and those who experienced adverse events in the model, were not stated very clearly in the report.
Mortality	The mean % FVC for each wheelchair health state was derived based on the mean % FVC values of all patients in that wheelchair health state at baseline observed in the MOR-001 natural history study.[7] 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 using the reference equation from the European Community for Steel and Coal Study,[15] which was stratified by gender and included patient height and age. A relative risk of mortality of 1.12 per 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.[16] The manufacturer assumed that patients treated with ESA would have a decreased	The manufacturer used treatment-dependent, mortality relative risk values instead of mortality rates based on the natural history of the disease. The risk of mortality associated with MPS IVA may be independent of treatment.

Data Input	Description of Data Source	Comment
	relative risk of mortality versus BSC based on a [redacted]% improvement in FVC versus baseline over 3 years' treatment. This was based on observations from the MOR-002/MOR-100 long-term trial.	
Costs		
Drug	The cost of the drug depends on the weight of the patient. For the purpose of the analysis, the same 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.	Application of the same average weight to each health state is not reflective of clinical reality, as patients' weights (and therefore the dose and cost of ESA therapy) would increase with age.
Administration	The cost of administration ($75) was approximated based on the cost of complex drug administration in the Ontario Schedule of Benefits and Laboratory Services.[17]	
Clinical events (surgery)	Surgeries that patients may incur included (as identified by the manufacturer): cervical fusion operation, genus 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 hospital stay was obtained from the Canadian Institute for Health Information Patient Cost Estimator.	
Adverse events	The cost incurred with anaphylaxis was determined from the Ontario Schedule of Benefits and Laboratory Services.[17]	
Resource use	Dependent on the patient's health state, the resources used and related costs differed in the model. These costs were 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.[17] The cost associated with ventilation support was taken from a study conducted by Maleki-Yazdi et. al (2012).[14]	The cost of a specialist visit for pain management, the cost of ventilation, and the cost of the wheelchair was increased from the previous submission, with no justification provided for most of the increases (other than inflation to 2015 prices). Additionally, the source identified for the costs associated with ventilation was not correct, as it did not identify the cost.
Indirect costs	The manufacturer also conducted an analysis under the societal perspective, which included indirect costs. This was	

Data Input	Description of Data Source	Comment
	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.[18]	

6MWT = six-minute walk test; AE = adverse event; BSC = best supportive care; ENT = ear, nose, throat specialist; ESA = elosulfase alfa; EQ-5D-5L = EuroQol 5-Dimensions Health-Related Quality of Life questionnaire, 5 Levels; FVC = forced vital capacity; GP = general practitioner; HRQoL = health-related quality of life; MPS HAQ = mucopolysaccharidosis type IVA Health Assessment Questionnaire; MPS IVA = mucopolysaccharidosis type IVA; PRO = patient-reported outcomes; QALY = quality-adjusted life year; RCT = randomized controlled trial; vs. = versus.

TABLE 11: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Natural History	
2-year duration in pre-death health state for all patients.	According to the clinical expert consulted by CDR, a 2-year duration cannot be assumed for all patients in this health state, as there are a variety of factors that would affect 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 80% FVC and patients in the pre-death health state were assumed to have 10% FVC.	Inappropriate assumption. Patients in the asymptomatic health state would likely not have impaired pulmonary function, as noted by the clinical expert consulted by CDR. The manufacturer assumed normal pulmonary function for asymptomatic patients in its original submission.
Efficacy	
Greater HRQoL in patients treated with ESA versus BSC in each health state	This is an inappropriate modelling method, as it results in double-counting of utility benefits from treatment, resulting in an underestimate of the overall ICUR.
ESA-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 not under treatment with ESA.
Multiple-domain responders were assumed to have no disease progression.	May not be an appropriate assumption, given that multi-domain response was based on "any improvement" in both endurance and pulmonary function, and there are no clinical data to support long-term disease stabilization of such patients.
The proportion of single-domain and multi-domain responders would stay the same for the duration of the time horizon; further, there would be no non-responders to treatment.	Not an appropriate assumption, as there is no evidence to assume that treatment response is maintained past 72 weeks.

CDR = CADTH Common Drug Review; BSC = best supportive care; ESA = elosulfase alfa; 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 ESA and best supportive care (BSC), are shown in Table 12. Drug costs and administration of ESA resulted in $10,729,992 and $63,752 in incremental costs, respectively, compared with BSC. Further, the total cost associated with treatment with ESA was $10,851,054, while the total cost associated with BSC was $31,809.

TABLE 12: SUMMARY OF COST RESULTS BY RESOURCE TYPE

Cost Parameter	Elosulfase Alfa	Best Supportive Care	Incremental
Elosulfase alfa	$10,729,992	$0.00	$10,729,992
Administration	$63,752	$0.00	$63,752
Pre-treatment	$0.00	$0.00	$0.00
Adverse events	$1,292	$0.00	$1,292
Wheelchairs	$3,723	$3,301	$421
Surgery	$4,300	$9,875	($5,575)
Asymptomatic	$464	$203	$261
No use	$9,786	$4,876	$4,910
Sometimes	$10,485	$7,397	$3,088
Wheelchair-dependent	$1,913	$4,068	($2,156)
Paraplegic	$148	$130	$18
Pre-death	$57	$1,958	($1,901)
Caregiver	$0.00	$0.00	$0.00
Indirect costs	$0.00	$0.00	$0.00
Total	$10,825,912[a]	$31,809	$10,794,103

Source: Adapted from the manufacturer's pharmacoeconomic submission.[2]

[a] There is a discrepancy in the manufacturer's analysis in that the total costs reported here are somewhat lower than the total costs reported in the conclusions. This discrepancy has minimal impact on the incremental cost-utility ratio.

Additionally, the manufacturer reported the total quality-adjusted life-years (QALYs) by health state, as shown in Table 13. Treatment with ESA would result in 12.69 QALYs gained, while treatment with BSC would result in 6.40 QALYs gained.

TABLE 13: SUMMARY OF QUALITY-ADJUSTED LIFE-YEARS BY HEALTH STATE

Health State	Elosulfase Alfa	Best Supportive Care	Incremental
Asymptomatic	0.48	0.21	0.27
No use	6.97	3.06	3.91
Sometimes	5.16	3.05	2.11
Wheelchair-dependent	0.11	0.19	–0.08
Paraplegic	0.01	0.01	0.00
Pre-death	0.00	0.02	–0.01
Surgery	–0.04	–0.14	0.10
Caregiver burden	0.00	0.00	0.00
Total	12.69	6.40	6.29

Source: Adapted from the manufacturer's pharmacoeconomic submission.[2]

In summary, over a lifetime time horizon, the manufacturer reported the incremental cost and QALYs gained associated with treatment with ESA to be $10,819,245 and 6.29 QALYs respectively, compared to BSC. Treatment would also result in an incremental 4.29 life-years gained. Thus, the incremental cost-utility ratio (ICUR) was calculated to be approximately $1,720,127 per QALY (Table 7).

TABLE 14: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE-CASE ANALYSIS RESULTS, PER PATIENT

Comparators	Total			Incremental			ICUR	ICER
	Costs	QALYs	Life-Years	Costs	QALYs	Life-Years		
Best supportive care	$31,809	6.40	12.06	$10,819,245	6.29	4.29	$1,720,127	$2,523,976
Elosulfase alfa	$10,851,054	12.69	16.35					

ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Source: Adapted from the manufacturer's pharmacoeconomic submission.[2]

Summary of manufacturer's sensitivity analysis

The manufacturer addressed uncertainty regarding the parameters chosen for the base-case analysis using a one-way deterministic sensitivity analysis, various scenario analyses, 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.

a) Deterministic sensitivity analysis

The parameters varied individually by the manufacturer included:

- Average weight per health state (95% confidence interval from the MOR-001 study, except the asymptomatic health state, which was varied by ± 10%)
- Annual decline in 6MWT, FVC (± 25%)
- Utility weights (± 10%)
- Health state costs (± 10%)
- Delay in surgery (+ 10%)
- Delay in becoming symptomatic with treatment (± 10%)
- Discount rates for costs and QALYs (0%, 3%)

Varying the discount rate was the only parameter that had a substantial impact on the ICUR (± 25%). When a lower discount rate was selected, the ICUR ranged from $728,263 to 3,475,018 per QALY.

b) Scenario analysis

The manufacturer conducted various scenario analyses to assess the impact on the ICUR. The following scenarios were tested:

- Use of a societal perspective incorporating indirect costs and caregiver disutility values
- Utilization of a birth starting cohort
- Utilization of an alternative approach to modelling the utility benefit of treatment (symptom versus correlation analysis).

The utilization of a birth cohort affected the ICUR substantially. The ICUR decreased from the manufacturer's base-case result to $694,188 per QALY.

c) Probabilistic aensitivity 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. Following 1,000 iterations, the median ICUR was calculated to be $2,010,992 per QALY and the mean ICUR was calculated to be $2,020,085 per QALY.

In approximately 50% of iterations, the ICUR was above a willingness-to-pay threshold of $1.2 million per QALY.

CADTH Common Drug Review reanalyses

The CADTH Common Drug Review (CDR) conducted several reanalyses based on the identified key limitations (i.e., utility values, mortality rates, and patient weight gain). The CDR multi-way analysis resulted in an overall ICUR of $3,179,763 per QALY (Table 15).

TABLE 15: CADTH COMMON DRUG REVIEW REANALYSIS OF INCREMENTAL COST-UTILITY RATIOS FOR ELOSULFASE ALFA VERSUS BEST SUPPORTIVE CARE

		ICUR (Based on Manufacturer's Base Case)	Cumulative ICUR (Based on CDR Multi-Way Analysis)
Same utility value for each health state, regardless of treatment		$2,347,042	$3,179,763
Mortality rates based on natural history; no impairment in pulmonary function for patients in the asymptomatic health state		$1,720,957	
Patients gain weight as they progress in the model, based on weight-by-age values reported by Montaño et al.[3]		$2,328,841	
Stratification based on health state[a]	Asymptomatic	$694,188	$1,546,460
	No use of wheelchair	$1,704,464	$3,449,223
	Some use of wheelchair	$1,854,105	$3,183,850
	Wheelchair-dependent	$1,995,458	$3,422,054

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio.

[a] Assuming 100% of patients are in the respective health state.

REFERENCES

1. [Pr]Vimizim™ (elosulfase alfa): solution for intravenous infusion 5 mg/5 mL (1 mg/mL) [product monograph]. Toronto: BioMarin Pharmaceutical (Canada) Inc.; 2014 Jul 2.
2. Pharmacoeconomic evaluation. In: CDR submission: Vimizim (elosulfase alfa), 5 mg/5 mL solution for intravenous infusion. Company: BioMarin Pharmaceutical (Canada) Inc. [**CONFIDENTIAL** manufacturer's submission]. Woodbridge (ON): BioMarin Pharmaceutical (Canada) Inc.; 2015 Nov 6.
3. Montano AM, Tomatsu S, Brusius A, Smith M, Orii T. Growth charts for patients affected with Morquio A disease. Am J Med Genet A. 2008 May 15;146A(10):1286-95.
4. Common Drug Review: CDEC final recommendation: Elosulfase alfa (Vimizim - BioMarin Pharmaceuticals [Canada] Inc.) [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2015 Mar 25. [cited 2015 Dec 22]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/SR0389_complete_Vimizim_Mar-27-15.pdf
5. Clinical study report: MOR-004. A phase 3, randomized, double-blind, placebo-controlled, multinational clinical study to evaluate the efficacy and safety of 2.0 mg/kg/week and 2.0 mg/kg/every other week BMN 110 in patients with mucopolysaccharidosis IVA (Morquio A syndrome) [**CONFIDENTIAL** internal manufacturer's report]. Novato (CA): BioMarin Pharmaceutical Inc.; 2013 Mar 11.
6. Clinical study report: MOR-005. A multicenter, multinational, extension study to evaluate the long-term efficacy and safety of BMN 110 in patients with mucopolysaccharidosis IVA (Morquio A syndrome) [**CONFIDENTIAL** internal manufacturer's report]. Novato (CA): BioMarin Pharmaceutical Inc.; 2013 Mar 18.
7. Harmatz P, Mengel KE, Giugliani R, Valayannopoulos V, Lin SP, Parini R, et al. The Morquio A Clinical Assessment Program: baseline results illustrating progressive, multisystemic clinical impairments in Morquio A subjects. Mol Genet Metab. 2013 May;109(1):54-61.
8. Lampe C, Jain M, Olaye A, Meesen B, Decker C, Mengek E. Relationship between patient-reported outcomes and clinical outcomes in patients with Morquio A syndrome. Journal of Inborn Errors of Metabolism & Screening [Internet]. 2015; -4 [cited 2015 Dec 22]. Available from: http://iem.sagepub.com/content/3/2326409815576188.full.pdf+html
9. Patient cost estimator [Internet]. Ottawa: Canadian Institute for Health Information; 2016. [cited 2016 Feb 12]. Available from: https://www.cihi.ca/en/spending-and-health-workforce/spending/patient-cost-estimator
10. Schedule of benefits: physician services under the Health Insurance Act (October 30, 2015 (effective December 21, 2015)) [Internet]. Toronto: Ministry of Health and Long Term Care; 2015. [cited 2016 Feb 12]. Available from: http://www.health.gov.on.ca/english/providers/program/ohip/sob/physserv/sob_master20151221.pdf
11. Systemic juvenile idiopathic arthritis: canakinumab [Internet]. London: National Institute for Health and Care Excellence; 2014 Mar 18. [cited 2016 Feb 12]. (NICE advice [ESNM36]). Available from: http://www.nice.org.uk/advice/esnm36/chapter/Key-points-from-the-evidence#about-this-evidence-summary

12. Elosulfase alfa, 1mg/mL concentrate for solution for infusion (Vimizim®) [Internet]. Glasgow, Scotland: Scottish Medicines Consortium; 2015 Sep 7. [cited 2016 Feb 12]. Available from: https://www.scottishmedicines.org.uk/files/advice/elosulfase_alfa_Vimizim_FINAL_August_2015_for_website.pdf

13. Pharmaceutical Benefits Scheme. ELOSULFASE ALFA 1 mg/mL concentrate for solution for infusion, 5mL vial; Vimizim®; Biomarin Pharmaceutical Australia Pty Ltd. [Internet]. Canberra, Australia: Australian Government, Department of Health; 2014. [cited 2016 Feb 12]. Available from: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2014-11/files/elosulfase-alfa-psd-11-2014.pdf

14. Maleki-Yazdi MR, Kelly SM, Lam SY, Marin M, Barbeau M, Walker V. The burden of illness in patients with moderate to severe chronic obstructive pulmonary disease in Canada. Can Respir J [Internet]. 2012 Sep [cited 2016 Jan 15];19(5):319-24. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3473007/pdf/crj19319.pdf

15. Hendriksz CJ, Giugliani R, Harmatz P, Mengel E, Guffon N, Valayannopoulos V, et al. Multi-domain impact of elosufase alfa in Morquio A syndrome in the pivotal phase III trial. Mol Genet Metab. 2014 Sep 6.

16. Neas LM, Schwartz J. Pulmonary function levels as predictors of mortality in a national sample of US adults. Am J Epidemiol. 1998 Jun 1;147(11):1011-8.

17. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl. 1993 Mar;16:5-40.

18. Statistics Canada. Average hourly wages of employees by selected characteristics and occupation, unadjusted data, by province (monthly) (Canada) [data table on the Internet]. Ottawa: Statistics Canada; 2016. [cited 2016 Feb 12]. Available from: http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/labr69a-eng.htm Source: CANSIM tables 282-0069 and 282-0073.