# 5.3 ELOSULFASE ALFA
# 1 mg/mL concentrate for solution for infusion, 5mL vial; Vimizim®; Biomarin Pharmaceutical Australia Pty Ltd.

## 1 Purpose of Application

1.1 The major submission sought either a Section 100 PBS listing or consideration of the 'rule of rescue' for elosulfase alfa in the treatment of patients with mucopolysaccharidosis (MPS) IVA (Morquio A Syndrome).

## 2 Requested listing

2.1 The submission's requested restriction is shown below but with additional minor edits proposed by the Secretariat shown in *italics* (additions) and ~~strikethrough~~ (deletions):

| Name, Restriction, Manner of administration and form | Max. Qty | №.of Rpts | Proprietary Name and Manufacturer | |
|---|---|---|---|---|
| ELOSULFASE ALFA<br>5 mg/ 5 mL injection, 5 mL vial | 20 | 5 | Vimizim® | BioMarin Pharmaceutical Australia Pty Ltd |

| | |
|---|---|
| **Category / Program** | Section 100 – Highly Specialised Drugs Program (Private Hospital)<br>Section 100 – Highly Specialised Drugs Program (Public Hospital) |
| **Prescriber type:** | ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives |
| **Episodicity:** | --- |
| **Severity:** | --- |
| **Condition:** | Morquio A Syndrome (MPS IVA) |
| **PBS Indication:** | Morquio A Syndrome (MPS IVA) |
| **Restriction level / method:** | ☐Restricted benefit<br>☒Authority Required - In Writing<br>☒Authority Required - Telephone<br>☒Authority Required – Emergency<br>☒Authority Required - Electronic<br>☐Streamlined |
| **Treatment criteria:** | Must be treated by a ~~paediatrician, physician or health care provider experienced in the management of patients with MPS IVA or metabolic disorders~~ *metabolic physician*<br><br>*AND*<br><br>~~Patients~~ *Must* be treated in a hospital setting for at least 12 months and ~~Patients~~ must be seen at a centre of expertise. |

| | |
|---|---|
| **Clinical criteria:** | Patient must have a confirmed clinical diagnosis of MPS IVA by N-acetylgalactosamine-6-sulfatase (GALNS) enzyme activity assay in leukocytes or skin fibroblasts and/or genetic testing for mutations in GALNS gene (Chromosome 16q24.3) in a NATA accredited laboratory<br><br>AND<br><br>The treatment must be administered over four hours through continuous infusion |
| **Prescriber instruction:** | Pre-treatment with antihistamines or with antipyretics is recommended. |
| **Administrative Advice** | NOTE:<br>Increased maximum quantities may be requested from ~~Medicare Australia~~ *the Department of Human Services* and should be based on a dosing regimen of 2 mg/kg administered once weekly. |

2.2 The ESC noted that the proposed PBS restriction did not limit PBS-subsidy to a specific age group or a patient population with a certain disease severity and that this should be given further consideration because the main randomised controlled trial MOR-004 excluded patients younger than five years and those who are severely disabled (i.e. defined by baseline six-minute walk test (6MWT) less than 30 metres) or who had mild disease (i.e. baseline six-minute walk test more than 325 metres). There are existing Australian patients who are aged less than 5 years of age who may be appropriate to receive treatment. Although one of the submission's 3 supportive studies (MOR-007) included patients younger than five years, the ESC noted that the submission's supportive studies were ongoing, provided interim analyses only and MOR-007 in particular did not measure the same primary outcome (6MWT) as the submission's pivotal trial, MOR-004.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## 3 Background

3.1 TGA status at time of PBAC consideration: Not registered. The submission was made under the TGA/PBAC parallel process provisions. At the time of PBAC consideration, the TGA Delegate's overview and a positive ACPM outcome were available. The ACPM resolved to register elosulfase alfa for the treatment of mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome).

3.2 Elosulfase alfa had not previously been considered by the PBAC.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## 4 Clinical place for the proposed therapy

4.1 Mucopolysaccharidosis IVA **(**MPS IVA), also known as Morquio A Syndrome, is an inherited lysosomal storage disorder characterised by the absence of the enzyme N-acetylgalactosamine-6-sulfatase. This leads to intracellular accumulation of

metabolites such as glycosaminoglycan, keratan sulfate and chondroitin-6-sulfate. The accumulation of these substances causes progressive cellular, tissue and multisystem dysfunction resulting in problems with bone development, growth, mobility, vision, hearing, as well as pulmonary and cardiac function.

4.2 The submission stated that elosulfase alfa provides the exogenous enzyme N-acetylgalactosamine-6-sulfatase which slows the progression of the disease. The current medical management of MPS IVA is focussed on treating symptoms and manifestations of the condition. This includes medications such as non-steroidal anti-inflammatory drugs for joint pain, antibiotics for pulmonary infection, and oxygen supplementation for pulmonary compromise and obstructive sleep apnoea. Patients with MPS IVA may undergo corrective surgeries such as spinal decompression, tonsillectomy, and hip arthroplasty.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## 5 Comparator

5.1 The submission nominated placebo in combination with standard medical management as the main comparator. The main argument provided in support of this nomination was that there is no available pharmacological or non-pharmacological treatment for MPS IVA. The ESC considered this to be appropriate.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## 6 Consideration of the evidence

### Sponsor hearing

6.1 The sponsor requested a hearing for this item. The specialist clinician presenting at the hearing aimed to address the issue of the appropriateness and validity of the 6MWT as a surrogate measure for patient relevant clinical outcomes. The clinician's view was that the 6MWT is a practical test that reasonably captures changes in all affected body systems for MPS IVA (characterised by progressive multi-systemic clinical impairment in respiratory, cardiovascular, musculoskeletal system) and that it is currently the best overall measure of elosulfase alfa's effect on body systems.

6.2 The PBAC considered that the hearing was informative.

### Consumer Comments

6.3 The PBAC noted and welcomed the input from individuals (91) and organisations (2) via the Consumer Comments facility on the PBS website. The individuals' comments described a range of benefits of treatment with elosulfase alfa including:

- Reduced pain, resulting in a reduction in the requirement for pain treatments;
- Improvement in endurance, energy, mobility, sleep, growth, breathing, quality of life for the individual and family members/caregivers;
- Reduced need for mobility aids and major surgeries; and

- Improved access to the drug.

6.4 Rare Voices of Australia and the Mucopolysaccharide & Related Diseases Aust. Ltd both commented that there are currently no other treatments for MPS IVA other than elosulfase alfa and that a lack of public subsidy for elosulfase alfa would be inequitable for patients with MPS IVA compared to other MPS patients. Further comment was made that elosulfase alfa would be beneficial in terms of improving skeletal growth/short stature, reducing pain and joint contractures, improving respiratory function, mobility, endurance, and reducing tongue size which in turn improves swallowing and talking functionality, and, reducing liver size which in turn reduces pressure on the lungs and returns body size to a more 'normal shape'.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## Clinical trials

6.5 The submission was based on one head-to-head randomised trial MOR-004 (n=173) comparing elosulfase alfa (2 mg/kg/week or 2 mg/kg/every other week) to placebo. Patients who completed the MOR-004 trial were eligible to enrol in the ongoing open-label extension study MOR-005 (n=169). Two additional supportive studies were included: MOR-007 (n=15) and MOR-008 (n=25).

6.6 Details of the trials presented in the submission are provided in the table below.

**Trials and associated reports presented in the submission**

| Trial ID/First Author | Protocol title/ Publication title | Publication citation |
|---|---|---|
| **Direct randomised trial** | | |
| 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). | Clinical study report. 11 March 2013 |
| Hendriksz | Efficacy and safety of enzyme replacement therapy with BMN 110 (elosulfase alfa) for Morquio A syndrome (mucopolysaccharidosis IVA): a phase 3 randomised placebo-controlled study. | *J Inherit Metab Dis*; 2014; DOI 10.1007/s10545-014-9715-6 |
| **Supportive trials** | | |
| MOR-005 | A Multi-center, Multinational, Extension Study to Evaluate the Long-Term Efficacy and Safety of BMN 110 in Patients with mucopolysaccharidosis IVA (Morquio A Syndrome). Data cut-off 04 January 2013. | Clinical study report. 18 March 2013. Interim report. |
| MOR-007 | A phase 2, open-label, multinational clinical study to evaluate the safety and efficacy of BMN 110 in paediatric patients less than 5 years of age with Mucopolysaccharidosis IVA (Morquio A Syndrome). Data cut-off at 52 weeks. | Clinical study report. 13 May 2014. Interim report |
| MOR-008 | A randomised, double-blind, pilot study of the safety and physiological effects of two doses of BMN 110 in patients with Mucopolysaccharidosis IVA (Morquio A Syndrome). Data cut-off 14 September 2012. | Clinical study report. 5 March 2013. Interim report |

Source: Table B.2-2, p24 of the submission.

6.7 The key features of the clinical trials are summarised in the table below.

**Key features of the included evidence**

| Trial | N | Design/ duration | Risk of bias | Patient population | Outcome(s) | Use in economic evaluation |
|---|---|---|---|---|---|---|
| **Elosulfase alfa versus placebo** | | | | | | |
| MOR-004 | 127 [a] | R, DB,MN 24 weeks | Low | MPS IVA patients ≥ 5 years with an average baseline 6MWT distance ≥30 and ≤325 metres. | 6MWT, 3MSCT, UKS and RFT | Used |
| **Supportive studies** | | | | | | |
| MOR-005 | 56 [b] | OL,MN 216 weeks (ongoing) | High | MPS IVA patients who completed MOR-004. | 6MWT, 3MSCT, UKS and RFT | Not used |
| MOR-007 | 15 | OL, MN 52 weeks | High | MPS IVA patients ≤ 5 years, no 6MWT restriction. | Urinary GAG and creatinine, anthropometric measurements, | Not used |
| MOR-008 | 25 [c] | Pilot R, DB 27 weeks | High | MPS IVA patients ≥ 7 years, baseline 6MWT≥200 metres | 6MWT, 3MSCT, UKS and RFT | Not used |

Source: compiled during the evaluation DB = double blind; OL = open label; R = randomised; MN = multinational; 6MWT = six-minute walk test; MPS = mucopolysaccharidosis; 3MSCT = three-minute stair climb test; UKS = urine keratan sulfate; GAG = glycosaminoglycan; RFT = respiratory function test. [a] Number of patients in the 2 mg/kg/week and placebo arms. [b] Number of patients who continued the 2 mg/kg/week from MOR-004 [c]Patients randomised to elosulfase 2 mg/kg/week or elosulfase 4 mg/kg/week

6.8 Patients included in the studies had a wide spectrum of age, disease severity and clinical manifestations. As noted under 'Requested Listing', the main trial MOR-004 excluded patients younger than five years old and those who were severely disabled (i.e. baseline six-minute walk test less than 30 metres) or with mild disease (baseline six-minute walk test more than 325 metres. This excluded potentially more than 50% of the proposed PBS population, since worldwide data indicate that severely disabled patients who use wheelchairs and those with the mild form of the disease represent 37% and 20% of MPS IVA patients (Hendriksz 2013) respectively, thereby reducing the applicability of the trial results to the economic modelling.

## Comparative effectiveness

6.9 The primary outcome in the main trial MOR-004 was the 6MWT as a measure of endurance and functionality. Survival was not an outcome in any of the included trials.

6.10 The main issue with the clinical evidence was whether the six-minute walk test (6MWT) is an appropriate and valid surrogate measure for patient relevant clinical outcomes with respect to elosulfase alfa's clinical efficacy. Patient relevant outcomes include quality of life, a reduction in MPS IVA related complications such as musculoskeletal deformities, cardiovascular, respiratory and neurological complications, normal growth rate in paediatrics, ability to mobilize and function independently. The ESC noted that there was no standard therapeutic outcome in patients with MPS IVA because the disease affects multiple body organs. The 6MWT has been used in studies of pulmonary hypertension patients and subsequently in other cardiovascular, musculoskeletal and neurological diseases. Patient characteristics and the minimal clinically important difference in the 6MWT varied across the studies depending on the disease. Whilst the 6MWT may be of relevance in measuring changes in endurance and mobility, the ESC noted the multisystem nature of MPS IVA and considered that there are other important aspects of MPS IVA such as skeleton and joint deformity, growth impairment, and neurological

complications which cannot be directly quantified with the 6MWT. Therefore, the ESC considered that the 6MWT is one of several outcome measures that should be considered in an assessment of elosulfase alfa's clinical efficacy.

6.11 Results of primary and secondary outcomes of MOR-004 are summarised in the table below.

**Results of key primary and secondary outcomes in MOR-004 trial at Week 24**

| | Elosulfase alfa 2mg/kg/week n=58 | | | Placebo n=59 | | | LSM of change or % change (95%CI) |
|---|---|---|---|---|---|---|---|
| | Base (SD) | Change (SD) | % change (SD) | Base (SD) | Change (SD) | % change (SD) | |
| 6MWT, metres | 203.9 (76) Med:216.5 | 36.5 (59) Med:20.0 | 23.9 (45) Med:10.0 | 211.9 (70) Med:228.9 | 13.5 (51) Med:9.9 | 8.7 (29) Med:3.8 | **22.5 (4, 41)** |
| 3MSCT, stairs/min | 29.6 (16) | 4.8 (8) | [redacted] | 30.0 (14) | 3.6 (9) | [redacted] | 1.1 (-2, 4) |
| UKS, µg/mg | 26.9 (14) | -12.6 (10) | -45.1 (20) | 25.7 (15) | -2.8 (8) | -4.4 (27) | **-40.7% (-49, -32)** |
| MVV, Litre/minute | 28.3 (17) | [redacted] | 10.8 (26) | 34.8 (27) | [redacted] | 2.4 (21) | 10.3% (-2, 22) |
| FVC, Litre | 0.9 (1) | [redacted] | 4.9 (12) | 1.2 (1) | [redacted] | 1.5 (14) | 3.3% (-3, 10) |
| Composite z-score[a] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 0.1 (-0, 0.3) |

Source: Table B.4-2, p53, Table B.6-1, p85, Table B.6-5, p91 of the submission and extracted from MOR-004 Clinical Study Report, Appendix 3 in the submission [a] Composite measure of 6MWT, 3MSCT and MVV 3MSCT = 3-minute stair climb test; 6MWT = 6-minute walk test; FVC = forced vital capacity; UKS = urine keratan sulfate; MVV = maximum voluntary ventilation; SD = standard deviation; LSM = least square mean difference compared to placebo; CI = confidence interval; Med = median; bold = statistically significant.

6.12 At Week 24 of the MOR-004 trial, there was a statistically significant difference between elosulfase alfa and placebo in the improvement in the 6MWT distance from the baseline of 22.5 metres (95% CI: 4 to 41). The submission claimed that the change in the 6MWT represented an 11% improvement, which is greater than the literature-based minimal clinically important difference (MCID) of [redacted]% using the submission's reported 'Anchor-based method' and therefore, the results were clinically significant. The evaluation identified that the mean improvement of 22.5 metres over 24 weeks in the 6MWT between elosulfase alfa and placebo may not be clinically significant. The evaluation noted that this incremental distance was below the 40 metres distance used to determine the sample size in the MOR-004 trial and the 15% change recommended by a Delphi Panel of nine experts in the treatment of MPS IVA as a minimal clinically meaningful distance (p119, MOR-004 Clinical Study Report). Further, the MCID of [redacted]% described in the literature was mostly for cardiac and respiratory improvement and not in terms of metres in distance. The ESC noted the PSCR's (p.3) further clarification of the Delphi Panel responder definitions, and the assertion that clinicians consider any gain in the 6MWT to be significant (p.2) but remained unconvinced that an improvement of 22.5 metres in the 6MWT from baseline was clinically significant, particularly given that there was considerable heterogeneity in the change from baseline in the 6MWT in the trial population.

6.13 When the changes in 6MWT from baseline are broken down by increments of 20 metres, the results are as follows:

**Responder analysis for the change in 6MWT in MOR-004 at 24 weeks**

| 6MWT change from baseline | Elosulfase alfa 2 mg/kg/week n=58 | Placebo n=59 | Absolute risk difference (95%CI) | Relative risk (95%CI) | NNT (95%CI) |
|---|---|---|---|---|---|

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ≥ 0 metres | | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] | |
| ≥ 20 metres | | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] | |
| ≥ 40 metres | | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] | |
| ≥ 60 metres | | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] | |
| ≥ 80 metres | | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] | |

Source: constructed during evaluation based on Figure 10.4.1.1.3.3: Responder Analysis for six-Minute Walk Test, p151 in the Clinical Study Report of MOR-004, Appendix 3 of the submission; 6MWT = six-minute walk test; CI = confidence interval; bold = statistically significant; NE = not evaluable; NNT = number needed to treat

6.14 Only [redacted]% of the patients treated with elosulfase alfa achieved a change in the 6MWT equal to or greater than 20 metres and [redacted]% had an increment of 40 metres or more. None of these comparisons resulted in a statistically significant difference between the two groups, although it was noted that sample sizes for these comparisons were small.

6.15 The table below shows the change in six-minute walk test from baseline for the subgroups of patients stratified according to their baseline six-minute walk test and age.

**ANCOVA of six-minute walk test change from baseline to Week 24**

| Subgroup | Elosulfase alfa 2 mg/kg/week | | | Placebo | | | LSM of change (95%CI) |
|---|---|---|---|---|---|---|---|
| | n | Baseline (SD) | LS mean change (SD) | n | Baseline (SD) | LS mean change (SD) | |
| **Baseline distance in six-minute walk test** | | | | | | | |
| ≤ 200 m | [redacted] | | | | | | **40.4 (11, 70)** |
| > 200 m | [redacted] | | | | | | 10.8 (-13, 34) |
| **Age** | | | | | | | |
| 5-11 years | [redacted] | | | | | | 13.8 (-12, 39) |
| 12-18 years | [redacted] | | | | | | **48.2 (12, 84)** |
| ≥ 19 years | [redacted] | | | | | | 10.4 (-31, 52) |

Source: Tables 14.2.1.26-35 the Clinical Study Report of MOR-004, Appendix 3 of the submission
ANCOVA = analysis of covariance; 6MWT = six-minute walk test; SD = standard deviation; CI = confidence interval; bold = statistically significant.

6.16 The response to elosulfase alfa in MOR-004 appeared to be dependent on the patient's baseline 6MWT result and age. Patients with a baseline 6MWT of 200 metres or less or those between 12-18 years of age achieved the greatest benefit. The evaluation considered there was great heterogeneity in the population of this trial in terms of age, baseline endurance and disease severity; therefore, the reported improvement in the six-minute walk test may not be applicable to all subgroups. The evaluation noted that patients older than [redacted] years appeared to have more severe musculoskeletal manifestations that are unlikely to be reversed or improved significantly - this was apparent from their baseline distance. Patients younger than [redacted] years tend to have better baseline six-minute walk test compared to older patients and thus the improvement from their baseline may not be significant. The ESC considered that the sample sizes in the subgroups above were too small to reliably identify a subgroup in which a clinical benefit is clearly established and in which cost-effectiveness (and possible PBS-subsidy) should be further examined.

Because patients younger than five years were excluded from the MOR-004 trials, the submission presented interim results from the ongoing MOR-007 study on paediatric patients younger than five years as summarised in the table below.

**MOR-007 efficacy outcomes of paediatric patients treated with elosulfase alfa at 2 mg/kg/week**

| | Baseline, mean (SD) | Change in week 52, mean (SD) |
|---|---|---|
| Urine Keratan Sulfate in µg/mg, | [redacted] | [redacted] |
| Normalised Standing Height, z-score, | [redacted] | [redacted] |
| Cumulative Growth Rate (per year), z-score | [redacted] | [redacted] |

Source: Table B.6-6, p 93 in the submission

6.17 The submission stated that the interim results of MOR-007 showed sustained reduction in urine keratan sulfate at Week 52 with a mean decrease from baseline of [redacted] micrograms/mg (SD:[redacted]). The effect of elosulfase alfa on growth was evaluated by anthropometric measurements and radiographs of the lower extremities. The normalised standing height z-score showed that at baseline subjects in MOR-007 were between [redacted] and [redacted] standard deviations below the normal age adjusted standing height z-scores with a mean z-score of [redacted] (SD [redacted]). The Week 52 mean normalised standing height z-score was [redacted] (SD [redacted]) with a mean change from baseline of [redacted] (SD [redacted]). The submission considered this slight decrease from baseline a favourable outcome because the mean z-score did not significantly worsen as expected in MPS IVA patients. Cumulative growth rate change was the combined historical and on-study normalised standing height z-scores. The mean change from baseline to week 52 was [redacted] (SD [redacted]) suggesting that elosulfase alfa slows the progression MPS IVA musculoskeletal symptoms. The ESC agreed with the evaluation that these benefits could not be confirmed due to the absence of a control arm and the interim nature of the analysis. Further, the MOR-007 study did not evaluate endurance outcomes such as the 6MWT to show how the growth benefits from elosulfase alfa translates into better functionality in this population. Therefore, it was debatable if the available evidence is sufficient to support the claimed efficacy of elosulfase alfa in patients younger than five years with respect to improving growth or stopping disease progression in paediatric patients.

6.18 The PBAC considered whether there is evidence from the results other than from the 6MWT outcome measure, to support a clinical benefit with elosulfase alfa treatment. In terms of secondary outcomes, there was a statistically significant reduction in urine keratan sulphate concentration. However, there were no statistically significant differences for the three-minute stair climb test, respiratory function, and the composite measure. The ESC noted that 4 out of the 5 secondary efficacy outcome measures (the 5 secondary measures were: 3-minute stair climb test (3MSCT), urine keratan sulphate levels, maximum voluntary ventilation (MVV), forced vital capacity and a composite measure of 6MWT, 3MSCT and MVV) failed to demonstrate statistical significance and therefore the evidence base presented does not establish a clear clinical benefit for elosulfase alfa treatment.

6.19 The long-term efficacy of elosulfase treatment (beyond 52 weeks) was unknown.

**Comparative harms**

6.20 In MOR-004, there were more serious adverse events in the elosulfase alfa group compared to placebo (15.5% versus 3.4%). More moderate or severe infusion associated reactions were reported for elosulfase compared to placebo ([redacted]% vs. [redacted]%) as well as moderate drug-related adverse events (27.6% vs. 6.8%). Adverse events leading to infusion interruption or discontinuation requiring medical intervention were higher in the elosulfase group compared to placebo (22.4% versus 0%). All patients treated with elosulfase alfa developed anti-drug antibodies. The

ESC considered the significance of these antibodies to be unknown. In the extension study MOR-005, there was no death or permanent drug discontinuation from adverse events at Week 48. A summary of adverse events in MOR-004 is shown in the following table.

**Summary of adverse events in MOR-004**

| | Elosulfase alfa 2mg/kg/week n = 58 | Placebo n = 59 | RR (95% CI) |
|---|---|---|---|
| Any AE | 56 (96.6%) | 57 (96.6%) | [redacted] |
| Mild | 28 (48.3%) | 36 (61.0%) | [redacted] |
| Moderate | 26 (44.8%) | 20 (33.9%) | [redacted] |
| Severe | 2 (3.4%) | 1 (1.7%) | [redacted] |
| Number of AEs per subject Mean/Median | 14.3/12.0 | 10.4/10.0 | |
| Any study drug-related AE | 42 (72.4%) | 36 (61.0%) | [redacted] |
| Mild | 24 (41.4%) | 32 (54.2%) | [redacted] |
| Moderate | 16 (27.6%) | 4 (6.8%) | [redacted] |
| Severe | 2 (3.4%) | 0 (0.0%) | [redacted] |
| Any SAE | 9 (15.5%) | 2 (3.4%) | [redacted] |
| Mild | 2 (3.4%) | 0 (0.0%) | [redacted] |
| Moderate | 6 (10.3%) | 1 (1.7%) | [redacted] |
| Severe | 1 (1.7%) | 1 (1.7%) | [redacted] |
| Number of SAEs per subject Mean/Median | 0.2/0.0 | 0.0/0.0 | [redacted] |
| Any study drug-related SAE | 2 (3.4%) | 0 (0.0%) | [redacted] |
| Mild | 0 (0.0%) | 0 (0.0%) | [redacted] |
| Moderate | 1 (1.7%) | 0 (0.0%) | [redacted] |
| Severe | 1 (1.7%) | 0 (0.0%) | [redacted] |
| Subjects with a Least 1 Hypersensitivity AE | 12 (20.7%) | 7 (11.9%) | [redacted] |
| Subjects with any infusion associated reaction | 52 (89.7%) | 54 (91.5%) | [redacted] |
| Mild | [redacted] | [redacted] | [redacted] |
| Moderate | [redacted] | [redacted] | [redacted] |
| Severe | [redacted] | [redacted] | [redacted] |
| Any AE leading to infusion interruption or discontinuation requiring medical intervention | 13 (22.4%) | 0 (0.0%) | [redacted][a] |
| Any AE leading to permanent study drug discontinuation | 0 (0.0%) | 0 (0.0%) | [redacted] |
| Death | 0 (0.0%) | 0 (0.0%) | [redacted] |

Source: Table B.6-7, p95 of the submission and Table 11.3.3.2.1, p 231 in the MOR-004 Clinical Study Report, Appendix 5 of the submission; AE =adverse event; SAE = serious adverse event; RR = relative risk; **bold** = statistically significant; *italics* = corrected during evaluation; NE = not evaluable.

[a] *Added [redacted] to both values to calculate the relative risk*

## Benefits/harms

6.21 A summary of the comparative benefits and harms for elosulfase alfa versus placebo is presented in the table below.

**Summary of comparative benefits and harms for elosulfase alfa and placebo**

| MOR-004 | Elosulfase | Placebo | RR (95% CI) | Event rate/100 patients* | | RD (95% CI) |
|---|---|---|---|---|---|---|
| | | | | Elosulfase | Placebo | |
| **Benefits** | | | | | | |
| **Responders in the 6MWT** | | | | | | |
| ≥ 20 metres | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ≥ 40 metres | [redacted] | | | | | | |
| **Change from baseline 6MWT** | | | | | | | |
| | **Elosulfase** | | | **Placebo** | | | **Mean difference*: Elosulfase vs. placebo (95% CI)** |
| | **n** | **Mean Δ baseline, metres** | **SD** | **N** | **Mean Δ baseline, metres** | **SD** | |
| 6MWT | 58 | 36.5 | 59 | 59 | 13.5 | 51 | **22.5 (4, 41)** |

| **Harms** | | | | | | |
|---|---|---|---|---|---|---|
| **AE** | **Elosulfase** | **Placebo** | **RR (95% CI)** | **Event rate/100 patients*** | | **RD (95% CI)** |
| | | | | **Elosulfase** | **Placebo** | |
| Any serious AE | 9/58 | 2/59 | [redacted] | 15.5 | 3.4 | [redacted] |
| Moderate to severe IAR | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Pyrexia | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Vomiting | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Source: Compiled during the evaluation based on the Clinical Study Report of MOR-004, Appendix 3 of the submission
RD = risk difference; RR = risk ratio; 6MWT = 6-minute walk test; SD = standard deviation; CI = confidence interval; AE = adverse event; IAR =infusion associated reaction
* Maximum duration of follow-up = 24 weeks

6.22 On the basis of direct evidence presented by the submission, a person treated with elosulfase alfa compared to placebo could expect an average improvement of 22.5 metres from their baseline 6MWT distance. However, this improvement could be as low as 4 metres or as high as 41 metres. A large number of patients ([redacted]%) are likely to experience an improvement of less than 20 metres.

6.23 On the basis of direct evidence presented by the submission, for every 100 patients treated with elosulfase alfa in comparison to placebo for 24 weeks:

- Approximately 12 additional patients will experience a serious adverse event.
- Approximately 18 additional patients will experience a moderate to severe infusion associated reaction.
- Approximately 19 additional patients will experience pyrexia.
- Approximately 24 additional patients will experience vomiting.

**Clinical claim**

6.24 The submission described elosulfase alfa as superior to placebo in terms of efficacy but associated with a slightly greater incidence of adverse events.

6.25 The ESC advised that this claim may not have been adequately supported for the following reasons:

- The ESC considered that the 6MWT does not capture all clinically relevant health outcomes.
- The ESC remained unconvinced that a 22.5-metre improvement in the 6MWT between elosulfase alfa and placebo was clinically significant.
- A large number of patients ([redacted]%) were likely to experience an improvement of less than 20 metres.
- The ESC noted that 4 out of the 5 secondary efficacy outcome measures failed to demonstrate statistical significance.
- The evidence in patients aged less than 5 years of age came from outside the main MOR-004 trial, lacked a control arm, did not evaluate endurance outcomes and the results were from an interim analysis.

- There was an absence of data on the long-term safety and efficacy of elosulfase alfa beyond 52 weeks.
- The number of serious adverse events were statistically significantly higher with elosulfase alfa compared to placebo, especially infusion associated reactions.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## Economic analysis

6.26 The submission presented a cost-effectiveness analysis based on the direct randomised trial MOR-004. Utility values were obtained from the unpublished study by Lampe et al (2014).

**Summary of model structure and rationale**

| | |
|---|---|
| Time horizon | 24 weeks as reported in MOR-004 |
| Outcomes | Step 1: metres gained in the 6MWT at Week-24<br>Step 2: incremental cost per quality-adjusted life year gained |
| Methods used to generate results | Directly trial based (MOR-004) |
| Cycle length | Not applicable |
| Transition probabilities | Not applicable |
| Discount rate | Not applicable because the time horizon is shorter than one year (24 weeks) |
| Software package | MS Excel |

Source: Constructed during the evaluation
6MWT = six-minute walk test

6.27 Key drivers of the economic evaluation are summarised in the following table.

**Key drivers of the economic evaluation**

| Description | Method/Value | Impact |
|---|---|---|
| Average patient weight | Average patient weight = [redacted] kg from MOR-004 trial, this is higher than Australian patients average in BMN 100-502 ([redacted] kg) | High, favours placebo |
| Utility gained from the change in the 6MWT from baseline | Utility gained per 100 m in 6MWT= [redacted] | High, favours elosulfase alfa |

Source: compiled during the evaluation
6MWT = six-minute walk test

6.28 The results of the economic evaluation were driven by the cost of elosulfase treatment, which was dependent on the average patient weight, and the utility gained from the change in the 6MWT from baseline.

6.29 Results of the stepped economic evaluation are in the table below.

**Results of the stepped economic evaluation**

| Step and component | Elosulfase alfa | Placebo | Increment |
|---|---|---|---|
| **Step 1: trial-based costs and outcomes** | | | |
| Total costs [a] | [redacted] | [redacted] | [redacted] |
| Change in baseline 6MWT, metres | 36.5 | 13.5 | 22.5 (CI: 4, 40) |
| **Incremental cost/ metres gained** | | | [redacted] |
| **Upper 95% CL of differences in outcome** | | | [redacted] |
| **Lower 95% CL of differences in outcome** | | | [redacted] |

| Step and component | Elosulfase alfa | Placebo | Increment |
|---|---|---|---|
| **Step 2: trial results and including utilities** | | | |
| Costs | [redacted] | [redacted] | [redacted] |
| QALY | [redacted] | [redacted] | [redacted] |
| **Incremental cost/ QALY gained** | | | [redacted] |

Source: Table D.5-1 and Table D.5.2, p228 of the submission
6MWT= six-minute walk test; QALY = quality adjusted life year; bold = corrected during evaluation; CI = confidence interval
[a] Drug cost at 2 mg/kg/dose based on average patient weight of [redacted] kg plus administration cost

6.30 Under the base case assumptions, the incremental cost of elosulfase alfa is between $15,000 - $45,000 per additional meter in the 6MWT and more than $200,000 per quality adjusted life year gained.

6.31 The submission presented the results of univariate sensitivity analyses. During evaluation, the incremental cost of elosulfase alfa treatment based on the weighted average weight of patients in the Australian study BMN 100-502 ([redacted] kg) would be $[redacted] resulting in incremental cost-effectiveness ratio of more than $200,000 per quality adjusted life year gained.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

**Drug cost/patient/year:**

6.32 The drug cost/patient/year was estimated to be $[redacted]. The ESC raised concerns that this cost appeared to be significantly higher (approximately double) than the cost found in the United States of America ($US [redacted][1]) and the United Kingdom (£[redacted][2]) and potentially contrary to the information displayed in the table below.

6.33 The submission assumed the average patient weight is [redacted] kg. At a dose of 2 mg/kg/week and a dose of 5 mg per vial (1 mg/mL, vial size 5 mL), this resulted in [redacted] vials per week. The submission noted that vials cannot be re-used; therefore it applied [redacted] vials per week, resulting in a weekly cost of $[redacted], which corresponded to an annual cost of $[redacted].

6.34 The submission also presented the price of elosulfase alfa in the United States and Germany.

**Elosulfase reimbursement status and prices**

| Country | Subsidised (Y/N) | Pack size | Price ex-manufacturer | Effective ex-manufacturer price | Price in AUD$[a] |
|---|---|---|---|---|---|
| USA | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Germany | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Australia | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Source: Table 7, p xxxii of the submission
[redacted]
[a]August 2014 prices: [redacted]

**Estimated PBS usage & financial implications**

6.35 This submission was not considered by DUSC

[1] http://www.genengnews.com/keywordsandtools/print/3/34133/
[2] http://www.ukmi.nhs.uk/applications/ndo/record_view_open.asp?newDrugID=5313

6.36 The submission used an epidemiological incidence approach to estimate the total number of patients with MPS IVA over the analysis period of 2015 to 2019. Patients who commence treatment with elosulfase alfa were expected by the submission to experience improved survival. As new patients were diagnosed with MPS IVA each year the total number of prevalent patients with MPS IVA estimated by the submission increased over time.

**Estimated use and financial implications**

| | Year 1 2015 | Year 2 2016 | Year 3 2017 | Year 4 2018 | Year 5 2019 |
|---|---|---|---|---|---|
| **Estimated extent of use** | | | | | |
| Number treated | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Scripts [a] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Estimated net cost to PBS/RPBS/MBS** | | | | | |
| Net cost to PBS/RPBS | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Net cost to MBS | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Estimated total net cost** | | | | | |
| **Net cost to PBS/RPBS/MBS** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Source: Tables E.4-1 and E.4-2, p243 of the submission.
[a] Assuming each scripts covers four weeks of treatment

*The redacted table above shows that at Year 5, the estimated total number treated would be less than 10,000.*

6.37 The submission estimated a net total PBS cost for elosulfase alfa listing increasing to between $20 - $30 million per year in 2019, a cost between $105,000 - $200,000 for the MBS in year 5 of listing and a total cost to the Government of more than 100 million in the first five years of listing.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## 7 PBAC Outcome

7.1 The PBAC rejected the submission to list elosulfase alfa on the PBS as a Section 100 (Highly Specialised Drugs Program) benefit on the basis that a clear clinically significant clinical benefit with elosulfase alfa treatment had not been demonstrated and on the basis that the estimated incremental cost/QALY gained with elosulfase alfa treatment was unreliable but also unacceptably high.

7.2 The PBAC noted the consumer comments received on this submission and acknowledged the sentiment expressed in these comments that a clinical need exists for an effective treatment in this rare condition. The PBAC noted that the current medical management of MPS IVA is focussed on treating symptoms and manifestations of the condition and that the submission's positioning of elosulfase alfa as a first-line drug treatment option for patients with MPS IVA was consistent with comments from the specialist clinician presenting at the hearing that early treatment with elosulfase alfa in a patient's life is far better than initiating treatment later in life. Treatment with elosulfase alfa would be initiated early in a patient's life to ideally prevent or slow the manifestations of MPS IVA disease. Therefore, consideration to what therapy would be most likely replaced by elosulfase alfa

focused on either no treatment or standard medical management as the appropriate comparator.

7.3 The submission's nominated comparator of placebo in combination with standard medical management was considered to be reasonable by the PBAC as this was a reflection that there are no current pharmacological or non-pharmacological treatments specifically indicated for MPS IVA but that specific symptoms of the disease are treated for as they arise.

7.4 The PBAC noted that the main clinical evidence presented in the submission focused on the health outcome of improved mobility as measured by the 6MWT. The Committee also noted the ESC discussion of whether this sole measure would accurately capture the proposed benefits of the drug, given that the disease symptoms afflicting patients vary widely due to multiple body organ systems being simultaneously affected. The PBAC considered that the use of the 6MWT as a measure of elosulfase alfa's efficacy was debatable but on balance, accepted that the measure is clinically relevant as a patient's level of mobility would be influenced to a certain extent by their freedom from pain, respiratory capacity, musculoskeletal functioning and presence of neurological deficits. Therefore, the PBAC viewed the 6MWT as a somewhat indirect surrogate measure that might quantify an improvement in these various symptoms in the context of treating MPS IVA. Leaving the clinical relevance of the 6MWT aside, the PBAC then gave consideration to the magnitude of benefit with elosulfase alfa treatment.

7.5 The submission's estimate of an average gain of 22.5 metres at 24 weeks in the 6MWT from the MOR-004 trial was not considered by the PBAC to establish that elosulfase alfa treatment provides a clinically significant health benefit for patients. The PBAC noted in particular that the reported improvements in the 6MWT in the MOR-004 trial patients were highly variable and that the results were possibly overestimated due to skewing of the data, given the outliers in the observed data that inflated the estimate of the mean. The PBAC noted that [redacted]% of elosulfase alfa treated subjects and [redacted]% of placebo treated subjects gained more than 20 metres which in turn meant that a significant number of subjects gained less than 20 metres. Whilst it was accepted that elosulfase alfa treatment was more likely than placebo to improve mobility to some extent as measured by the 6MWT, the evidence provided to the PBAC did not establish that improvement in a person's ability to walk an extra 22.5 metres in 6 minutes translates into a meaningful difference in that person's quality of life.

7.6 In addition to the 6MWT, the PBAC noted that the effect of elosulfase on 4 out of the 5 secondary efficacy outcome measures was not statistically significant. The Committee also considered that the analysis of the effect of elosulfase on growth and disease progression in patient younger than five years of age was extremely difficult to interpret given that there were no control data and the analysis was an interim report. In addition the MOR-007 trial did not evaluate how endurance outcomes such as the 6MWT relate to potential effects on growth, or how it translates into better functionality in this paediatric population. As there was no long term data on survival gain or other comparative outcomes data examining changes in mobility or important outcomes such as hospitalisations or major procedures avoided, the PBAC considered that the totality of the evidence presented did not establish a clinically significant benefit with elosulfase alfa treatment compared to placebo.

7.7 In terms of comparative safety, the PBAC noted that there were more serious adverse events in the elosulfase group compared to placebo. The PBAC also noted that there was no long term safety data available for elosulfase alfa.

7.8 With respect to the submission's clinical claim, the PBAC was not prepared to accept the submission's claim of superior efficacy for elosulfase alfa compared to placebo on the trial data presented. The claim of inferior safety compared to placebo appeared reasonable.

7.9 The PBAC noted that the results of the cost-effectiveness analysis produced an incremental cost of [redacted] per additional meter gained in the 6MWT following elosulfase treatment and a base case ICER of more than $200,000 per quality adjusted life year gained. The PBAC considered this to be unacceptably high as well as unreliable for the following reasons as advised by ESC and the evaluation:

- The results of the MOR-004 trial were not applicable to all intended PBS patients, given that the MOR-004 excluded patients less than 5 years of age and those who were severely disabled or had mild disease.
- The duration of the economic evaluation (24 weeks) was too short compared to the proposed life-long use of the medication. The model effectively assumed a constant treatment effect over time and did not take account of the heterogeneity in the patient population (including age, mobility etc.).
- The costs of managing adverse reactions and pre-treatment medications (the submission's proposed restriction suggested antihistamines and antipyretics) had not been taken into account and other health system resource use (either as cost offsets or additional costs) may not have been fully captured by the short 24-week model duration.
- Estimates of the changes in quality of life from a change in the 6MWT test from baseline were obtained from a small unpublished study of German subjects (Lampe 2014), thereby making it difficult to assess the reliability of these results as well as raising applicability considerations for an Australian population. In addition, it was evident that the estimate was based on a sub-sample of the patients in the Lampe 2014 study for whom 6MWT and EQ-5D results were available. The submission did not attempt to estimate a survival benefit but assumed that there was a relationship between improvements in 6MWT and survival benefits based on other studies in different disease populations which involve the use of the 6MWT.

7.10 The PBAC noted the estimated PBS usage and financial implications as estimated by the submission. The Committee agreed with the evaluation's observation that the estimated increasing patient prevalence with MPS IVA would be appropriate if elosulfase alfa treatment results in an extension of life, but that this benefit was not supported by the evidence provided. The submission's financial implications of more than $100 million over the first five years of listing were noted in the evaluation to be uncertain and potentially higher or lower due to:

- Uncertainty over the eligible population size;
- Overestimation of the average patient weight used to calculate drug costs;
- Non-inclusion of pre-medication costs and costs associated with the treatment of adverse events;
- The assumption of 100% uptake and that all patients will continue treatment

despite potential efficacy concerns and the possibility of adverse events to occur.

7.11 The PBAC further noted that the price of elosulfase alfa is higher in Australia than in other similarly developed countries.

7.12 The PBAC considered that a future re-submission would need to further establish the clinical benefit of treatment with elosulfase alfa as the PBAC was not convinced that a gain of 22.5 metres in the 6MWT is a clinically meaningful improvement. A re-submission may wish to give consideration to targeting PBS subsidy to a more specific patient population in which cost-effectiveness might be significantly improved compared to the current submission's proposed patient population. This may involve identifying certain patient age groups that may respond better to treatment compared to other age groups, as well as consideration of clinical criteria in the PBS restriction that mandate that a clinical improvement is demonstrated for continued PBS subsidised treatment. The PBAC further considered that a re-submission may wish to explore a PBS reimbursement arrangement such as a 'pay-for-performance' proposal. This would mean that if a specified level of clinical improvement is not shown in the Australian patient population after PBS listing, the sponsor reimburse the Commonwealth an amount commensurate with the difference between the expected and realised clinical outcomes. The PBAC recognised the challenges posed in the collection of clinical trial data in rare conditions and considered that alternative approaches to data collection might be informative.

7.13 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**
Rejected

## 8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

## 9 Sponsor's Comment

BioMarin is disappointed with the outcome and will continue to work with the PBAC to make elosulfase alfa available for patients with MPS IVA