

7.02 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 re-submission requested Section 100 PBS listing for elosulfase alfa in the treatment of patients with mucopolysaccharidosis (MPS) IVA (Morquio A Syndrome). The first submission was for the November 2014 PBAC meeting.
- 1.2 The re-submission also requested the PBAC consider whether the 'rule of rescue' is applicable.

2 Requested listing

- 2.1 The ESC noted that the requested restriction had been based on the outcomes of the August 2015 stakeholder meeting and might require further consultation. The requested restriction is provided in the Commentary on this item. A summary of the initiation and continuation criteria for patients aged 5 years and over is provided in Table 1 below.
- 2.2 The re-submission proposed that all children under the age of five with MPS IVA could receive elosulfase alfa treatment, without the requirement for continuation rules until the patient turns five years of age. For patients over the age of five years, initial disease severity would need to be recorded and patients could continue treatment if they would meet certain continuation criteria, related to the six-minute walk test (6MWT), forced vital capacity, myocardial dysfunction and sleep apnoea / hypopnoea. The continuation criteria for the 6MWT and forced vital capacity might not be appropriate, as they were based on the mean change in untreated patients. A more appropriate approach might be to use a responder rate criterion for the 6MWT, based on baseline walking distance.
- 2.3 The key difference compared to the previous requested listing is the inclusion of more descriptive initial criteria and continuation criteria for patients aged 5 years and over.

Table 1: Summary of the initiation and continuation criteria for elosulfase alfa in patients aged ≥ 5 years

Criteria	Age, years	Initiation	Continuation		
			6 months	12 months	24 months, then annually
6MWT	≥ 5	Measure (no limits)	-█% change from baseline	-█% from baseline	-█% from previous annual assessment
FVC	5-14	80% of predicted value for height	+█% from baseline	+3.70% from baseline	+█% from previous annual assessment
	>14		-█% from baseline	-█% from baseline	-█% from previous annual assessment
Cardio-vascular	≥ 5	Myocardial dysfunction as indicated by a reduction in ejection fraction <56% or a reduction in fraction shortening to <25%	-	Ejection fraction has not declined by ≥10% from previous annual assessment	
Sleep disordered breathing	≥ 5	Apnoea/Hypopnoea Incidence > five events/hour of total sleep time or >2 severe episodes of desaturation (oxygen saturation <80%) in an overnight sleep study	-	Overnight sleep study has demonstrated that no invasive ventilation is required.	

Source: Compiled during evaluation, using the proposed restrictions
 Ini. = initiation; Cont. = continuation; 6MWT = six-minute walk test; FVC = forced vital capacity

The redacted values in Table 1 show that the proposed continuation criteria for the outcome of 6MWT and FVC should not change by more than that dictated by the natural history of MPS IVA.

- 2.4 The re-submission provided a cost-utility analysis comparing elosulfase alfa with standard medical management.
- 2.5 The sponsor emphasised in the pre-PBAC response that the PBAC may wish to give consideration as to whether all or some of the elements of the Managed Access Agreement now implemented in the UK may be appropriate regarding the uncertain clinical benefit of elosulfase alfa [Pre-PBAC response pp. 2]. The sponsor highlighted that the recently approved NICE Managed Access Agreement may provide an appropriate approach to ensuring patients achieve significant improvements in outcomes.

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

3 Background

- 3.1 TGA status: – elosulfase alfa was TGA registered on 9 December 2014 for the treatment of patients with mucopolysaccharidosis type IVA (MPS IVA; Morquio A Syndrome).
- 3.2 This is the second consideration by the PBAC for elosulfase alfa for the treatment of patients with MPS IVA. The PBAC rejected the November 2014 submission 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.

- 3.3 A Stakeholder meeting was held on 13 August 2015 which included expert clinicians and patient advocacy groups to determine a population who would most benefit from elosulfase alfa treatment. The Stakeholder meeting resulted in consensus initiation and continuation criteria for the treatment of MPS IVA patients with elosulfase alfa.
- 3.4 The following table provides a summary of the previous submission and the current re-submission.

Table 2: Summary of the previous submission and current re-submission

	elosulfase alfa (November 2014)	Current re-submission
Requested PBS listing	<p>•Morquio A Syndrome (MPS IVA)</p> <p>PBAC Comment: 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.</p>	Updated to include initiation and continuation criteria.
Requested price	<p>\$ [redacted] Public (20 vials) - \$ [redacted] (1 vial)</p> <p>\$ [redacted] Private (20 vials) - \$ [redacted] (1 vial)</p>	<p>\$ [redacted] Public (1 vial)</p> <p>\$ [redacted] Private (1 vial)</p>
Main comparator	<p>•Placebo in combination with standard medical management</p> <p>PBAC Comment: reasonable.</p>	Unchanged.
Clinical evidence	<p>• Key trial MOR-04, Elosulfase alfa vs. PBO; N=127 supportive MOR-05, MOR-06, MOR-08 (OL studies N=96)</p> <p>PBAC Comment: The main trial MOR-004 excluded patients younger than five years old and those who were severely disabled (i.e. baseline 6MWT less than 30 metres) or with mild disease (baseline 6MWT more than 325 metres).</p>	Same trial and 3 studies. One additional elosulfase alfa study (BMN110-502, N=13) and one prospective study of untreated patients (MorCAP, n=563).
Key effectiveness data	<p>•6MWT: RD 22.5 metres (95% CI: 4, 41)</p> <p>52% of patients treated with elosulfase achieved a change in 6MWT \geq 20 metres.</p> <p>PBAC Comment: The PBAC considered that the totality of the evidence presented did not establish a clinically significant benefit with elosulfase alfa treatment compared to placebo. (PAR 7.6)</p>	Same data, use of [redacted]% responder rate for 6MWT. [redacted]% vs. [redacted]% RD: 13.7% (-4, 32) Naive comparison at 2 yr, sig difference 6MWT and 3MSCT, not for other outcomes.
Key safety data	<p>RD: SAE: 12% (95% CI: 2, 23)</p> <p>RD moderate to severe IAR: 18% (95% CI: 1, 34)</p> <p>RD pyrexia: 19% (95% CI: 4, 34)</p> <p>RD vomiting 24% (95%CI: 11, 38)</p> <p>PBAC Comment: The PBAC noted that there was no long term safety data available for elosulfase alfa. (PAR 7.7)</p>	Unchanged
Clinical claim	<p>•Superior efficacy</p> <p>Slightly greater incidence of adverse events</p> <p>PBAC Comment: Superior efficacy not accepted, inferior safety accepted</p>	Unaltered

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	elosulfase alfa (November 2014)	Current re-submission
Economic evaluation	<p>•Cost effectiveness analysis, 24 week time horizon. ICER more than \$200,000/QALY</p> <p>PBAC Comment: Economic evaluation resulted in unacceptably high ICER and was unreliable:</p> <ul style="list-style-type: none"> • Applicability trial population • Duration economic evaluation • Cost of AEs excluded • Utility values may not be reliable 	<p>•Cost-utility model (50-yr time horizon): ICER: more than \$200,000/QALY</p>
Number of patients	<p>•less than 10,000 in Year 1 increasing to less than 10,000 in Year 5.</p> <p>PBAC Comment: uncertainty over eligible population size</p>	<p>less than 10,000 in Year 1 increasing to less than 10,000 in Year 5</p>
Estimated cost to PBS	<p>•\$20 - \$30million in Yr 1 increasing to \$20 - \$30million in Yr 5 for a total of more than \$100 million over the first 5 years of listing.</p> <p>PBAC Comment: The submission's financial estimate was uncertain and potentially higher or lower.</p>	<p>Yr 1: \$10 – \$20 million Yr 5: \$10 – \$20 million Yr 1-5: \$30 - \$60 million</p>
Risk sharing arrangements	<p>None</p> <p>PBAC Comment: A re-submission may wish to explore a PBS reimbursement arrangement such as a 'pay-for-performance' proposal.</p>	<p>Pay-for-performance proposal Cap at ■ vials per injection</p>
PBAC decision	<p>•Reject 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.</p>	-

Source: Compiled during the evaluation

MPS IVA = mucopolysaccharidosis IVA; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PBO = placebo; OL = open label; 6MWT = six-minute walk test; RD = risk difference; CI = confidence interval; 3MSCT = three-minute stair climb test; SAE = serious adverse event; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; AE = adverse event; Yr = year; IAR = infusion-associated reactions; sig = significant; PAR = paragraph

For more details 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 enzymopathy results in 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 re-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 details on PBAC's view, see section 7 "PBAC outcome"

5 Comparator

- 5.1 Placebo in combination with standard medical management. This was considered appropriate by the PBAC in November 2014.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item.
The sponsor presented the recently approved NICE guidelines for Morquio A reimbursement in the UK and indicated that these guidelines had been discussed with clinicians in Australia and the patient advocacy group and that they were generally supportive.
The PBAC considered that the hearing was informative.

Consumer hearing

- 6.2 MPS Society Australia requested a consumer hearing for this item. The following points provide a summary of the discussion between MPS Society and the members of the PBAC:
- 6.3 Mucopolysaccharidosis type IVA (Morquio A syndrome) is a rare and serious condition which severely affects the quality of life for patients and their families, and also other factors such as social and economic terms. Without Government subsidy or other assistance (e.g. clinical trials/compassionate access from the sponsor, assistance from the public hospital), the cost of elosulfase alfa would prohibit most patients from accessing the drug.
- 6.4 The MPS Society Australia representatives expressed concern about the translation of outcome measures applied in the key clinical trials of elosulfase alfa (particularly the 6MWT) detecting the real life benefits experienced by treated patients and their carers/families.
- 6.5 They reported that children with Morquio A syndrome experienced a significant improvement in their ability to walk and to engage in school and family activities with elosulfase alfa treatment. They also noted that a gain in height, although not universal in treated patients, was a highly significant result in an illness in which short stature is the main physical feature.

- 6.6 The Committee heard that patients with Morquio A syndrome generally deteriorate without treatment and thus even the prevention of further deterioration would be considered a significant treatment outcome.
- 6.7 It was noted that elosulfase alfa treatment can be intrusive, with the therapy schedule generally requiring weekly infusions delivered in a hospital. It was also noted that elosulfase alfa's clinical benefit varied from patient to patient being greater for younger patients. The MPS society representatives also informed the Committee that the use of the six minute walk test as a measure of elosulfase alfa's efficacy should be considered in the context of the patient's height, as the distance covered will vary due to the different heights of the patient.

Consumer comments

- 6.8 The PBAC noted and welcomed the input from individuals (444), health care professionals (5) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with Elosulfase Alfa including an increase in mobility, stamina and strength, and reduced need for surgery.
- 6.9 The PBAC noted the advice received from Mucopolysaccharide & Related Diseases Society Australia (MPS Australia) clarifying the likely use of elosulfase alfa in clinical practice. The PBAC specifically noted the advice that the use of elosulfase alfa may reduce frequency and length of hospital stays and improve the quality of life of patients.

Clinical trials

- 6.10 The re-submission is based on one head-to-head trial comparing elosulfase alfa to placebo (n=117). This was the same trial as presented in the previous submission. As supportive evidence, the re-submission presented an extended follow-up of patients enrolled in the key trial where all patients were treated with elosulfase alfa, three additional open label elosulfase alfa studies (n=43), and one prospective observational study of untreated patients (n=353). One of the three elosulfase alfa studies (BMN110-502) and the prospective observational study (MorCAP) have not been seen by the PBAC previously.
- 6.11 Details of the trials presented in the re-submission are provided in the table below.

Table 3: Trials and associated reports presented in the re-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). Hendriksz CJ, Burton B, Freming TR et al. 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. Hendriksz CJ, Giugliani R, Harmatz P et al. Multi-domain impact of elosulfase alfa in Morquio A syndrome in the pivotal phase III trial Schweighardt B, Tompkins T, Lau K et al. Immunogenicity of Elosulfase Alfa, an Enzyme Replacement Therapy in Patients With Morquio A Syndrome: Results From MOR-004, a Phase III Trial	Clinical study report. 11 March 2013 J Inherit Metab Dis; 2014; DOI 10.1007/s10545-014-9715-6 Mol Genet Metab 2015; 114 (2): 178-185 Mol Genet Metab 2015; 114 (2015) S105
Supportive elosulfase studies		
BMN110-502	A Multicentre Open-Label, Phase 3B Study to Evaluate the Efficacy and Safety of BMN 110 in Australian Patients With Mucopolysaccharidosis IVA (Morquio A Syndrome)	Executive Summary Final Draft_23JUNE2015
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. Jones SA, Bialer M, Parini R et al. Safety and clinical activity of elosulfase alfa in paediatric patients with Morquio A syndrome (mucopolysaccharidosis IVA) less than 5 years	Clinical study report. 13 May 2014. Interim report Pediatr Res (2015) doi: 10.1038/pr.2015.169. [Epub ahead of print]
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. Burton BK, Berger KI, Lewis GD et al. Safety and physiological effects of two different doses of elosulfase alfa in patients with Morquio A Syndrome: A randomised, Double-blind, Pilot Study	Clinical study report. 5 March 2013. Interim report Am J Med Genet A 2015. 167 (10):2272-81
Supportive non-interventional study		
MorCAP	Harmatz PR, Mengel KE, Giugliani R et al. Longitudinal analysis of endurance and respiratory function from a natural history study of Morquio A syndrome Harmatz P, Mengel KE, Giugliani R et al. The Morquio A Clinical Assessment Program: baseline results illustrating progressive, multisystemic clinical impairments in Morquio A subjects	Mol Genet Metab 2015; 114 (2): 186-194 Mol Genet Metab 2013; 109 (1): 54-61

Source: Table B.2-2, pp47-50 of the re-submission

6.12 The key features of the direct randomised trial and supportive studies are

summarised in the table below.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	MPS IVA Patient population	Key Outcome(s)	Use in modelled evaluation
Elosulfase alfa vs. placebo						
MOR-004	117 ^a	R, DB, MN 24 weeks	Low	≥ 5 years baseline 6MWT 30-325 metres.	6MWT, 3MSCT, UKS and RFT	Used
Elosulfase alfa						
BMN110-502	13	OL, AUS, (ongoing)	High	AUS patients	6MWT, 3MSCT, UKS and RFT	Not used
MOR-005	56 ^b	OL, MN 216 weeks (ongoing)	High	Completed MOR-004.	6MWT, 3MSCT, UKS and RFT	Not used
MOR-007	15	OL, MN 52 weeks	High	≤ 5 years	Urinary GAG and creatinine, anthropometric measurements,	Not used
MOR-008	25 ^c	Pilot R, DB 27 weeks	High	≥ 7 years, baseline 6MWT ≥ 200 metres	6MWT, 3MSCT, UKS and RFT	Not used
Standard medical management studies						
MorCAP	353	Prospective, MN, ongoing	High	-	6MWT, 3MSCT, UKS and RFT	Not used

Source: Compiled during the evaluation

AUS = Australia; DB = double blind; OL = open label; R = randomised; MN = multinational; 6MWT = six-minute walk test; MPS IVA = mucopolysaccharidosis IVA; 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

6.13 The additional studies were an Australian study of 13 patients with MPS IVA (BMN110-502) and a prospective cohort study which included untreated patients with MPS IVA (MorCAP).

6.14 Patients included in the studies had a wide spectrum of age, disease severity and clinical manifestations. The main trial MOR-004 excluded patients younger than five years old, patients who were severely disabled (i.e. baseline 6MWT less than 30 metres), and patients with mild disease (baseline 6MWT more than 325 metres). International data (from the MorCAP study) 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, respectively. This reduces the applicability of the trial results to the economic modelling. The PSCR (p 3) clarifies that severely disabled (non-ambulant) patients would not be treated under the requested restriction. The ESC noted that the wording of the restriction also excludes patients with mild disease (as it requires them to have either organ dysfunction (respiratory or cardiac) or sleep apnoea).

Comparative effectiveness

6.15 Consistent with the previous submission, the main outcome was the improvement in 6MWT at 24-weeks from the randomised controlled trial MOR-004 in patients over 5 years of age. Previously, 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” (Paragraph 7.4, November 2014 PBAC Public Summary Document).

- 6.16 The previous submission reported the results of MOR-004 in terms of an improvement from baseline in 6MWT. At the consideration, the PBAC did not consider the improvement of 22.5 metres observed at 24-weeks for elosulfase alfa compared with placebo in MOR-004 to be clinically relevant improvement (Paragraph 7.5, November 2014 PBAC PSD). The re-submission proposed that an improvement in the 6MWT of 8% was clinically significant and provided responder analyses using this threshold. During evaluation, data were extracted to enable a comparison at a threshold of 15% (defined as response in the CSR) or the baseline specific thresholds discussed by the Delphi panel of experts in the Clinical Study Report. The responder analyses using different thresholds are presented in Table 4.

Table 5: Responder analysis using different levels of the MCID – MOR-004 at 24 weeks

% improvement in 6MWT	Elosulfase alfa	Placebo	OR (95% CI)	RD (95% CI)	NNT (95% CI)
N	■ ^a	■			
Any improvement or decline of less than 8%	■ (■%)	■ (■%)	■ (■)	■% (■)	■ (■)
8%	■ (■%) ^b	■ (■%) ^b	■ (■) ^b	■% (- ■) ^b	(NE)
15% ^c	■ (■%)	■ (■%)	■ (■) ^e	■% (- ■)	(NE)
Baseline specific ^d	■ (■%)	■ (■%)	■ (■) ^e	■% (- ■)	(NE)

Source: Table B.6-1, p109 of the re-submission, extracted from Table 14.2.1.53, p811 and Table 14.2.1.56, p814 of MOR-004 CSR and elosulfase alfa responder analysis.xlsx (Appendix 19)

MCID = minimal clinical important difference; OR = odds ratio; CI = confidence interval; RD = risk difference; NNT = number needed to treat; NE = not estimable; CSR = Clinical Study Report

^a One patient was excluded from the analysis as the patient only received one dose and then had to discontinue due to logistical reasons

^b Data were extracted during evaluation from “elosulfase alfa responder analysis.xlsx”.

^c Defined as responder in the CSR

^d Post hoc analysis presented in the CSR. Responder was defined as 20% for Baseline 6MWT ≥ 30 metres but < 100 metres; 15% for Baseline 6MWT ≥ 100 metres but < 200 metres; and 10% for Baseline 6MWT ≥ 200 metres but ≤ 325 metres

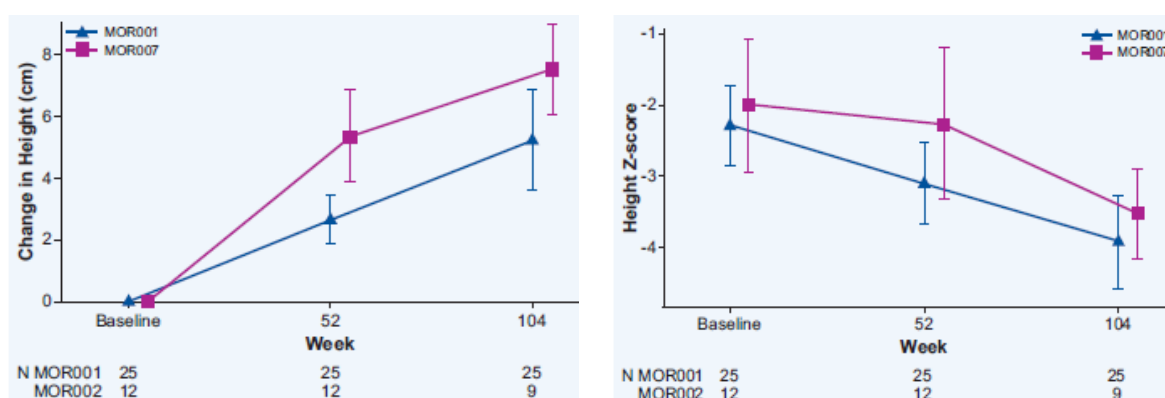
^e Provided in the CSR

- 6.17 The resubmission considered that there was a statistically significantly higher percentage of responders with elosulfase alfa treatment compared with placebo treatment. The values for the 8% responder rates provided in the re-submission could not be verified during the evaluation. The PSCR (pp2-3) clarified that response was defined in this analysis as any improvement or decline of less than 8% from baseline in 6MWT. The ESC considered that the analysis using a definition of response that included patients who had experienced a decline in 6MWT from baseline was not readily interpretable, noting that it was not consistent with the response defined in the CSR, and given the high proportion of responders in the placebo arm under this definition. The ESC considered that the re-analyses performed during the evaluation (8% improvement, 15% improvement and baseline specific definition) were more appropriate. The ESC noted that, across the trial population, an improvement of 8% from baseline would correspond with a median gain of approximately ■ metres. For the ■ patients in the elosulfase alfa arm who experienced equal to or greater than 8% improvement in the 6MWT at 24 weeks the

median gain was approximately ■ metres (compared to a median gain of ■ metres for the ■ placebo responders under the same definition of response).

- 6.18 Using the individual patient data and the various thresholds provided in the re-submission (where response is defined as an improvement of equal to or greater than X%, with X depending on the baseline value), there were non-significant differences in the rates of responders, although the differences favoured elosulfase.
- 6.19 For children under the age of five years, the only relevant outcome presented in the re-submission was the z-score for standing height. The z-score is the number of standard deviations a person is below the average height for their age. Hendriksz (2015) compared the change in z-score of children in MOR-007 (age ≤ 5 years) with an age-matched subgroup of the MorCAP study (no details provided in the accepted manuscript for other variables). The results are shown in the following figure, provided with the PSCR. Patients treated with elosulfase alfa had better z-scores than patients who received standard medical management (i.e. their growth was slightly better). This was a naïve comparison, only a small number of patients were included in both groups and the standard deviations overlapped. The ESC noted that the difference was not statistically significant, and that although the international guidelines recommend commencement of treatment at diagnosis, data in this population are sparse.

Figure 1: Change in height (cm) and change in height z-score; MOR-007 compared with MorCAP



Source: PSCR, p7

- 6.20 The re-submission presented a naïve comparison of the long-term efficacy of elosulfase alfa compared to standard medical management. This approach was required for the longer-term analysis because the double-blind phase of MOR-004 lasted 24 weeks. After this time, patients in the elosulfase alfa arm entered the MOR-005 single-arm extension study. Patients in MorCAP were not matched with the MOR-004/005 study, rather the subgroup analysis for MorCAP were those patients who met two of the inclusion criteria of MOR-004 (age and baseline walking distance). Therefore patients may not be comparable.

Table 6: Comparison MOR-004/005 and MorCAP at approximately two years

	MOR-004/005 Elosulfase alfa		MorCAP Standard Management		
N	56		106 ^a		
	Baseline mean (SE)	Change mean (SE)	Baseline mean (SE)	Change mean (SE)	LSM difference (95% CI)
6MWT, metres	206.8 (10.5)	33.2 (11.6)	206.7 (7.6)	-5.3 (9.3)	38.5 (9, 68)
3MSCT, stairs	28.4 (1.7)	5.4 (1.9)	31.9 (1.3)	0.1 (1.6)	5.3 (0.3, 10.3)
FVC, Litres					
MVV, Litres					

Source: Tables B.6-21 to B.6-23, pp142-144 of the re-submission

SE = standard error; CI = confidence interval; 6MWT = six-minute walk test; 3MSCT = three-minute stair climb test; FVC = forced vital capacity; MVV = maximal voluntary ventilation

^a Those patients who had 2-year data available.

- 6.21 The PSCR (Table 2, p5) presented a re-analysis of these data which stratified the patients in MOR-004/005 and MorCAP to adjust for confounders. This demonstrated statistically different outcomes in favour of elosulfase alfa for 6MWT, FVC, and FEV1 at one year and two years. The ESC noted that 35% of patients in the MorCAP study dropped out in order to receive elosulfase alfa treatment. It is unclear how the decision was made for these patients to commence elosulfase alfa treatment, or for the remaining MorCAP patients not to. It is possible that the patients who remained in MorCAP were those less likely to respond to elosulfase alfa treatment, including those with more severe disease or worse prognosis. This would bias the comparison in favour of elosulfase alfa treatment, as any differences between the treated and MorCAP arms might be increased. The ESC also noted that there were a large number of censored patients after the 12 month follow-up for Mor-004. This might also bias the longer term results.

Table 7: Re-analysis of MOR-004/005 compared with MorCAP

6MWT	Year 1 ^c		Year 2 ^d	
	MOR-001 N=67	MOR004/005 N=123	MOR-001 N=27	MOR004/005 N=117
LS mean change from baseline (SE) ^a 95% CI	-6.4 (8.8) (-23.7, 10.9)	38.8 (6.5) (26.0, 51.6)	-22.0 (12.8) (-47.1, 3.2)	33.2 (6.9) (19.6, 46.8)
LS mean change from baseline difference from MorCAP (SE) ^a 95% CI P-value ^b		45.2 (11.0) (66.8, 23.6) <0.0001		55.1 (14.5) (83.8, 26.5) 0.0002
3MSCT	MOR-001 N=67	MOR004/005 N=123	MOR-001 N=27	MOR004/005 N=117
LS mean change from baseline (SE) ^a 95% CI	0.4 (1.6) (-2.7, 3.5)	6.9 (1.1) (4.6, 9.1)	-1.3 (2.5) (-6.2, 3.6)	6.9 (1.4) (4.2, 9.5)
LS mean change from baseline difference from MorCAP (SE) ^a 95% CI P-value ^b		6.5 (2.0) (10.4, 2.7) 0.001		8.2 (2.8) (13.8, 2.6) 0.0044

Source: PSCR, Table 2, p5

^amodel-based repeated measures ANCOVA including treatment, age group, and baseline 6MWT category; ^bP-value determined by t-test and repeated measure ANCOVA model ^cYear 1 represents data collected from the MOR004/005 week 72 assessment and the MorCAP Year 1 follow-up window, centered at week 63 ^dYear 2 represents data collected from the MOR004/005 week 120 assessment and the MorCAP Year 2 follow-up window, centered at week 111 CI: confidence interval; LS: least square; SE: standard error

- 6.22 The re-submission considered that this comparison between MOR-004/005 and

MorCAP confirmed long-term benefits for elosulfase alfa, as both the 6MWT and the three-minute stair climb test were statistically significantly different. The analyses performed used the last observation carried forward methodology for MOR-004/005 and those who completed two year of follow-up for MorCAP. This might not be appropriate, because a large proportion of the patients in MorCAP discontinued the study as they initiated elosulfase alfa treatment (123/353, 34.8%). These patients who discontinued might be those patients who would be more likely to benefit.

Comparative harms

6.23 The PBAC noted the new safety data from Study BMN110-502, however considered that these data did not raise any new safety concerns.

Benefits/harms

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

Table 8: 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^a							
8% ^b	█ (█%)	█ (█%)	█ (█)	█	█	█% (-, █)	
15% ^c	█ (█%)	█ (█%)	█ ^d	█	█	█% (-, █)	
Baseline specific ^e	█ (█%)	█ (█%)	█ ^d	█	█	█% (-, █)	
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	█ (█)	15.5	3.4	█	
Moderate to severe IAR	█	█	█ (█)	█	█	█	
Pyrexia	█	█	█ (█)	█	█	█	
Vomiting	█	█	█ (█)	█	█	█	

Source: Compiled during the evaluation based on the CSR 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; CSR = Clinical Study Report

* Maximum duration of follow-up = 24 weeks

^a One patient in the elosulfase alfa 2.0 mg/kg/week population discontinued after the first infusion due to withdrawal of consent. The withdrawal was due to logistic difficulties for attending study visits and not because of safety concerns. This patient was excluded from the responder analysis.

^b Values presented in the re-submission could not be verified. Data were extracted during evaluation from "elosulfase alfa responder analysis.xlsx".

^c Defined in the CSR as the responder

^d Provided in the CSR

^e Post hoc analysis presented in the CSR. Responder was defined as 20% for baseline 6MWT ≥ 30 metres but < 100 metres;

15% for baseline 6MWT \geq 100 metres but $<$ 200 metres; and 10% for baseline 6MWT \geq 200 metres but \leq 325 metres

- 6.25 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 at 24 weeks from their baseline 6MWT distance. Based on the longer term data, this could be expected to improve to 45.2m at one year and 55.1m at two years. However, this improvement could be as low as four metres or as high as 41 metres. A large number of patients (■%) are likely to experience an improvement of less than 10% if the baseline walking distance is over 200 metres, less than 15% if the baseline walking distance is between 100 and 200 metres, and less than 20% if the baseline walking distance is less than 100 metres.
- 6.26 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

- 6.27 Similar to the previous submission, the re-submission described elosulfase alfa as superior to placebo in terms of efficacy but associated with a slightly greater incidence of adverse events. In its previous consideration, the PBAC did not accept the clinical claim of superior efficacy and considered an inferior safety claim reasonable. In the context of the consumer input in regard to the outcome measures applied in the key studies and the analysis of the long term response presented in the adjusted MOR-004/005 and MorCAP analysis, the PBAC considered that treatment with elosulfase did result in a small but clinically meaningful improvement in the 6MWT.

Economic analysis

- 6.28 The re-submission presented a cost-utility analysis over a 50-year time horizon, compared to a cost-effectiveness model with a 24-week time horizon in the previous submission. A summary of the model structure and rationale is presented in Table 7. The ESC considered that the time horizon was appropriate in the context of a life-long disease, but that there was considerable uncertainty associated with extrapolation from the 24 week trial data out to 50 years.

Table 9: Summary of model structure and rationale

Component	Summary
Time horizon	50 years in the model base case versus 24 weeks in trial
Outcomes	LYG and QALYs
Methods used to generate results	Cohort expected value analysis,
Health states	responder, non-responder, death
Cycle length	6 months
Transition probabilities	Based on adjusted HR for OS, using galsulfase for MPS VI as a proxy.

Source: compiled during the evaluation

LYG = life years gained; QALYs = quality-adjusted life years; HR = hazard ratio; OS = overall survival; MPS VI = mucopolysaccharidosis VI

- 6.29 The re-submission used the improvement in the 6MWT for elosulfase alfa compared with standard medical management at 24-weeks from MOR-004 as the basis of the model. The response analyses used to support the clinical claim are not used in the model. The re-submission then estimated the overall survival for untreated patients with MPS IVA, using mortality data from the UK. Then it applied a corrected hazard ratio to estimate the overall survival for patients treated with elosulfase alfa and were responding to treatment. This corrected hazard ratio was based on the overall survival with galsulfase compared to standard management in patients with MPS VI. The re-submission adjusted the galsulfase hazard ratio, using the improvement in 6MWT difference between elosulfase alfa and galsulfase.
- 6.30 The ESC noted that all patients treated with standard medical management start in the non-responder health state and either remain in that health state or die. This is not consistent with the placebo response observed in the clinical data and favours elosulfase. The Markov traces presented below demonstrate how this drives the results of the model.
- 6.31 A summary of the key drivers of the model are presented in Table 10.

Table 10: Key drivers of the model

Description	Method/Value	Impact
Time horizon	50 years; assumed from 6 month trial duration	High, favours elosulfase alfa
HR for OS	Use of galsulfase alfa as a proxy, incorrect use of results of 6MWT and adjusted HR linearly	High, favours elosulfase alfa
Utility values	Use of different methodologies for elosulfase alfa responders and standard medical management	Medium, favours elosulfase alfa
Responder rate	Use of 6MWT OR FVC continuation criteria, rather than responder criteria from MOR-004 No responders in the standard medical management arm	Low, favours elosulfase alfa Favours elosulfase

Source: compiled during the evaluation

HR = hazard ratio; OS = overall survival; 6MWT = six-minute walk test; FVC = forced vital capacity

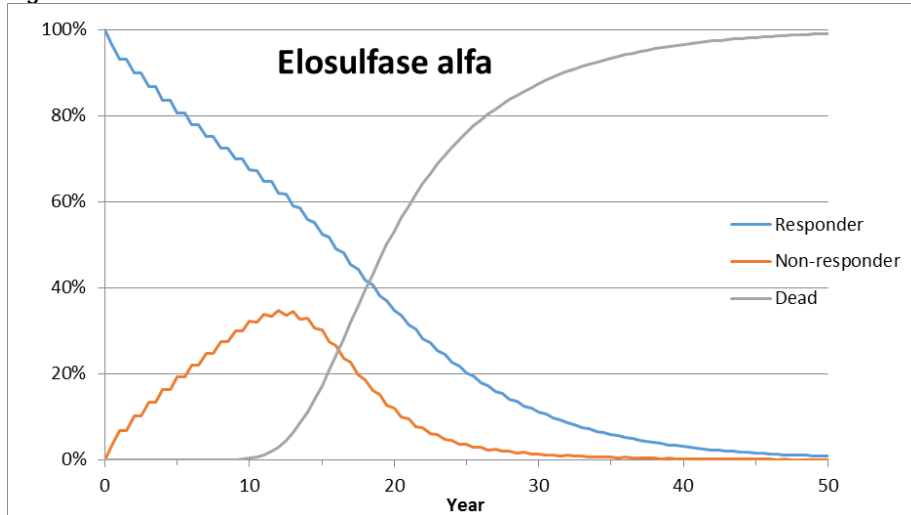
- 6.32 Table 11 presents the results of the stepped economic evaluation.

Table 11: Results of the stepped economic evaluation

Step and component	Elosulfase alfa	Standard medical management	Increment
Step 1: trial-based costs and outcomes			
Costs	\$ [Bar]	\$0	\$ [Bar]
6MWT, metres	[Bar]	[Bar]	[Bar]
Incremental cost/extra metre gained			\$ [Bar]
Upper 95% CI of differences in outcome			\$ [Bar]
Lower 95% CI of differences in outcome			\$ [Bar]
Step 2: trial results and premodelling (extrapolation 50 year, discounting)			
Costs	\$ [Bar]	\$0	\$ [Bar]
Life year gained	[Bar]	[Bar]	[Bar]
Incremental cost/extra life year gained			\$ [Bar]
Step 3: modelled evaluation (incl all resource use and pay-for-performance)			
Costs	\$ [Bar]	\$14,478	\$ [Bar]
Life year gained	[Bar]	[Bar]	[Bar]
Incremental cost/extra life year gained			\$ [Bar]
Step 4: modelled evaluation (incl utilities)			
Costs	\$ [Bar]	\$14,478	\$ [Bar]
QALYs	[Bar]	[Bar]	[Bar]
Incremental cost/extra QALY			\$ [Bar]
Step 4: modelled evaluation (24-week time horizon) – November 2014 submission			
Costs	\$ [Bar]	\$0	\$ [Bar]
QALY	[Bar]	[Bar]	[Bar]

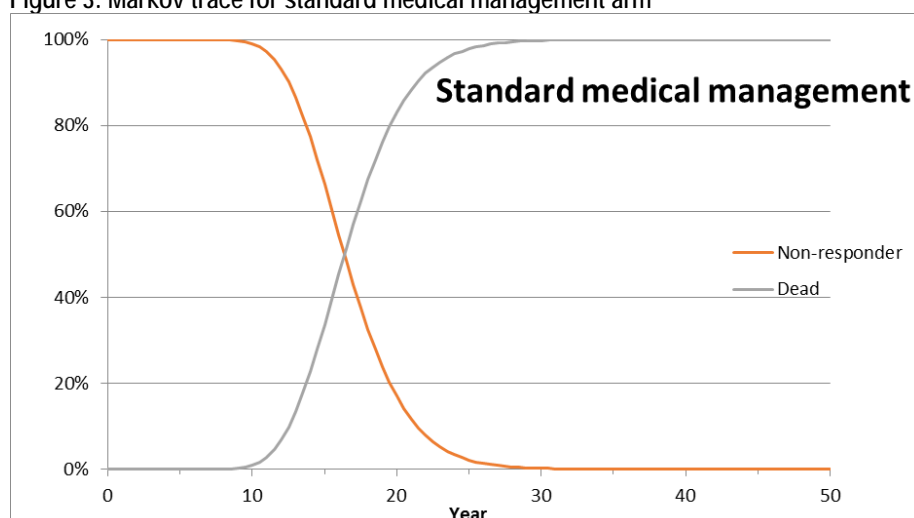
Source: Tables D.5-1 to D.5-4, pp244-246 of the re-submission
 QALY = quality-adjusted life year; 6MWT = six-minute walk test; CL = confidence interval

Figure 2: Markov trace for elosulfase alfa treatment arm



Source: Constructed during evaluation using Elosulfase alfa Section D Economic evaluation.xlsx

Figure 3: Markov trace for standard medical management arm



Source: Constructed during evaluation using Elosulfase alfa Section D Economic evaluation.xlsx

- 6.33 Under the base case assumptions, the incremental cost of elosulfase alfa is more than \$200,000 per quality-adjusted life year (QALY), compared with more than \$200,000 per QALY presented in the previous submission. The key difference was the model duration, with a 50-year time horizon in the current re-submission, compared to a 24-week time horizon presented previously.
- 6.34 The resubmission proposed a pay-for-performance arrangement, and a cap on the maximum annual cost per patient for elosulfase. Both of these assumptions were included in the base-case. Sensitivity analyses showed that these assumptions had only a small impact on the ICER.
- 6.35 The re-submission presented various univariate sensitivity analyses. The economic model was most sensitive to the time horizon, extrapolation methodology, utility gain per 100 metres walked, and body weight. All scenarios resulted in an incremental cost-effectiveness ratio above more than \$200,000 per QALY.

Drug cost/patient/year: \$ [REDACTED]

- 6.36 The yearly costs were based on the body weight of [REDACTED] kg derived from BMN110-502 Study (Australian study including 11 patients), assuming full compliance, [REDACTED] vials per infusion (rounded up), and one infusion per week. Treatment would be ongoing with a discontinuation rate of [REDACTED]% per year from the second year of treatment. The maximum cost per patient per year would be \$ [REDACTED], based on 14 vials per patient per administration (corresponding to a body weight of 35 kg). [REDACTED]

Estimated PBS usage & financial implications

- 6.37 This re-submission was not considered by DUSC.
- 6.38 The re-submission used an epidemiological approach.

Table 12: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated					
Number treated - Nov 2014					
Uptake rate ^a	%	%	%	%	%
Uptake rate Nov 2014	%	%	%	%	%
Prescriptions					
Prescriptions - Nov 2014					
Estimated net cost to PBS/MBS					
Net cost to PBS	\$	\$	\$	\$	\$
Net cost to PBS Nov 2014	\$	\$	\$	\$	\$
Net cost to MBS ^b	\$	\$	\$	\$	\$
Net cost to MBS Nov 2014	\$	\$	\$	\$	\$
Estimated total net cost					
Net cost PBS/MBS ^b	\$	\$	\$	\$	\$
Net cost PBS/MBS Nov 2014	\$	\$	\$	\$	\$

Source: Compiled during the evaluation

MBS = Medicare Benefits Schedule; Nov = November; PBS = Pharmaceutical Benefits Scheme;

^a 100% for < 5 year; 83% for ≥ 5 year; discontinuation rate 3.5% for all patients from year 2 onwards

^b Updated to reflect 75% MBS benefit, rather than 100% MBS benefit presented in the re-submission

The redacted table above shows that at year 5, the estimated number of patients was less than 10,000 and the net cost to the PBS would be \$10 - \$20 million.

- 6.39 The re-submission estimated the net total PBS/MBS cost for elosulfase alfa listing would be \$30 - \$60 million in the first five years of listing, compared to more than \$100 million in the previous submission. This cost may be lower or higher due to:
- Inclusion of costs and rebates for partial patient discontinuations (underestimate); and
 - Assumption of increasing prevalent population of MPS IVA (overestimate).

Quality Use of Medicines

- 6.40 If patients would not meet the continuation criteria, the treating physician can apply to the sponsor to participate in an Australian program for continued treatment of elosulfase alfa. This request should be made if the physician considers that the patient would continue to benefit from treatment based on other clinical parameters.

Financial Management – Risk Sharing Arrangements

- 6.41 The re-submission stated that it is willing to undertake a risk sharing arrangement and proposed two different aspects:
- Pay-for- performance:
 - Maximum cap per patient per year:



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

7 PBAC Outcome

- 7.1 The PBAC did not recommend the Authority Listing Section 100 PBS listing for elosulfase alfa for the treatment of patients with mucopolysaccharidosis (MPS) IVA (Morquio A Syndrome). The PBAC considered that while there was sufficient basis to conclude that treatment with elosulfase alfa results in a small but meaningful clinically improvement, the cost effectiveness of the drug was highly uncertain and unacceptable.
- 7.2 In the context of of the discussion of the impacts of Morquio A syndrome at the consumer hearing the PBAC considered that the benefits captured by the 6MWT are small but likely to be clinically meaningful. In addition the analysis of the adjusted MOR-004/005 and MorCAP analysis suggests that this response is likely to be sustained. The clinical effect of elosulfase alfa treatment in patients under 5 years of age was less certain.
- 7.3 The PBAC agreed with the ESC that the economic model was not informative. The PBAC did not consider that the use of survival data from patients treated with galsulfase was appropriate to be used in the model. In addition the PBAC was uncertain about a survival gain for patients treated with elosulfase alfa.
- 7.4 The PBAC noted the resubmission's proposed pay-for-performance arrangement and [REDACTED]. The PBAC noted that inclusion of these arrangements in the economic analysis did not substantially reduce the ICER. The PBAC also noted that the [REDACTED] complicated the calculation of the financial impact of the drug. Overall, the PBAC did not consider that the resubmission's proposed pay-for-performance arrangement cap would adequately contain the financial risk to the Commonwealth.
- 7.5 The PBAC considered the utilisation estimates included costs and rebates for partial patient discontinuations (potentially reducing the estimates) and assumed an increasing prevalent population of Morquio A Syndrome (potentially increasing the estimates). Overall, the PBAC did not consider the resubmission's utilisation estimates to be reliable.
- 7.6 The PBAC noted the resubmission's request for application of the Rule of Rescue. The four factors of the Rule of Rescue are as follows.
1. No alternative exists in Australia to treat patients with the specific circumstances of the medical condition meeting the criteria of the restriction. This means that there are no nonpharmacological or pharmacological interventions for these patients.
 2. The medical condition defined by the requested restriction is severe, progressive and expected to lead to premature death. The more severe the condition, or the younger

the age at which a person with the condition might die, or the closer a person with the condition is to death, the more influential the rule of rescue might be in the consideration by PBAC.

3. The medical condition defined by the requested restriction applies to only a very small number of patients. Again, the fewer the patients, the more influential the rule of rescue might be in the consideration by PBAC. However, PBAC is also mindful that the PBS is a community-based scheme and cannot cater for individual circumstances.
4. The proposed medicine provides a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition. The greater the rescue, the more influential the rule of rescue might be in the consideration by PBAC.

7.7 Although the PBAC concluded that the improvement in the 6MWT in patients treated with elosulfase alfa was clinically meaningful it was small and not sufficient to qualify as a “rescue” for patient’s with Morquio A Syndrome. The PBAC therefore advised that elosulfase alfa does not meet the Rule of Rescue.

7.8 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 PBAC’s decision, but will continue to work with the Department of Health to make elosulfase alfa available for patients with MPS IVA through the Life Saving Drugs Program.