

## elosulfase alfa, 1mg/mL concentrate for solution for infusion (Vimizim®) SMC No. (1072/15)

### **Biomarin Europe Limited**

07 August 2015

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission considered under the ultra-orphan medicine process

**elosulfase alfa (Vimizim®)** is not recommended for use within NHS Scotland.

**Indication under review:** treatment of mucopolysaccharidosis, type IVA (Morquio A Syndrome, MPS IVA) in patients of all ages.

In a double-blind placebo-controlled study the difference from baseline in the mean distance walked in the 6-minute walking test was significantly longer for elosulfase alfa, given weekly, than placebo at week 24.

The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

This advice takes account of the views from a Patient and Clinician and Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

**Chairman,  
Scottish Medicines Consortium**

## Indication

Treatment of mucopolysaccharidosis, type IVA (Morquio A Syndrome, MPS IVA) in patients of all ages.

## Dosing Information

Elosulfase alfa treatment should be supervised by a physician experienced in the management of patients with MPS IVA or other inherited metabolic diseases. Administration of elosulfase alfa should be carried out by an appropriately trained healthcare professional with the ability to manage medical emergencies.

The recommended dose of elosulfase alfa is 2mg/kg of body weight administered once a week by intravenous infusion. The total volume of the infusion should be delivered over approximately four hours.

Because of the potential for hypersensitivity reactions with elosulfase alfa, patients should receive antihistamines with or without antipyretics 30 to 60 minutes prior to start of infusion.

## Product availability date

28 April 2014.

Elosulfase alfa has been designated an orphan medicine by the European Medicines Agency (EMA) and also meets SMC ultra-orphan criteria.

## Summary of evidence on comparative efficacy

MPS IVA is a rare, inherited disorder caused by mutations of the gene that codes for the lysosomal enzyme N-acetylgalactosamine 6-sulfatase (GALNS) which degrades glycosaminoglycans, including keratan sulfate and chondroitin-6-sulfate. In patients with insufficient GALNS, glycosaminoglycans progressively accumulate in multiple body organs and tissues. Patients with MPS IVA have progressive skeletal dysplasia, require frequent surgical procedures, related mainly to musculoskeletal or respiratory dysfunction, and have significant limitations in mobility, endurance, and respiratory function.<sup>1,2</sup>

Elosulfase alfa, an enzyme replacement therapy, is the recombinant form of human GALNS and is the first medicine licensed for the treatment of MPS IVA, for which only supportive care is currently available.<sup>2</sup>

The pivotal study (MOR-004) was of phase III, multi-centre, double-blind, placebo-controlled design. It recruited patients aged  $\geq 5$  years with a documented clinical diagnosis of MPS IVA (based on clinical signs and symptoms of MPS IVA and documented reduced fibroblast or leukocyte GALNS enzyme activity or genetic testing confirming diagnosis of MPS IVA) and who had a mean 6-minute walking test (6MWT) distance at screening of 30 to 325 metres (m) (inclusive). Patients were randomised in a ratio of 1:1:1 to intravenous infusions of elosulfase alfa 2mg/kg/week (licensed dose), elosulfase alfa 2mg/kg/every other week or placebo for 24 weeks, stratified by screening 6MWT category ( $\leq 200$ m and  $>200$ m) and age (5 to 11, 12 to 18,  $\geq 19$  years old). Patients received pre-treatment with an antihistamine before each study drug infusion and additional treatments ( $H_2$  blockers, leukotriene receptor antagonists, steroids and/or antipyretic medications) were given to patients with known risk factors for infusion administration reactions.<sup>2,3</sup>

The primary outcome was change from baseline to week 24 in the distance walked in a 6MWT, performed according to American Thoracic Society guidelines in the modified intent-to-treat (ITT) population. It was analysed using an analysis of covariance (ANCOVA) model with baseline 6MWT category ( $\leq 200\text{m}$  and  $>200\text{m}$ ) and age (5 to 11, 12 to 18,  $\geq 19$  years) as the covariates. ANCOVA was also used for analysis of secondary endpoints. A total of 58 patients were randomised and treated with elosulfase alfa 2mg/kg/week, 59 patients with elosulfase alfa 2mg/kg/every other week and 59 patients with placebo. Results for elosulfase alfa 2mg/kg/week (licensed dose) and placebo groups only are reported in this document. The mean 6MWT at baseline was 204m and 212m, and at week 24 was 243m and 225m in the elosulfase alfa 2mg/kg/week and placebo groups, respectively. Treatment with elosulfase alfa significantly increased the distance of the 6MWT compared with placebo at week 24; least squares (LS) mean difference 22.5m, 95% confidence interval (CI): 4.0m to 40.9m,  $p=0.017$ .<sup>3</sup>

Secondary endpoints included 3-minute stair climb test (3MSCT), change in normalised keratan sulphate levels, maximum voluntary ventilation (MVV) and forced vital capacity (FVC) at 24 weeks. The LS mean difference in 3MSCT was 1.1 stairs/minute (95% CI: -2.1 to 4.4) and difference in normalised keratan sulphate was -41% (95% CI: -49% to -32%). The LS mean difference in MVV was 10.3% (95% CI: -1.8% to 22.4%), and in FVC was 3.3% (95% CI: -3.1% to 9.6%).<sup>3</sup>

The MPS health assessment questionnaire (HAQ) was used to assess quality of life (QoL) for three domains: self care, caregiver assistance and mobility. Domain scores range from 0 to 20, with decreases in domain scores (negative values) indicating an improvement. At week 24, there were no significant differences between elosulfase alfa and placebo for any domain although differences numerically favoured elosulfase alfa for caregiver assistance and mobility domains.<sup>3</sup>

MOR-005 is an ongoing phase III multi-centre, double-blind and open-label extension study to MOR-004. MOR-005 has two parts; part 1 was double blind and patients originally randomised to elosulfase alfa continued with the regimen, and patients originally randomised to placebo were re-randomised in a ratio of 1:1 without stratification to elosulfase alfa 2mg/kg/week or elosulfase alfa 2mg/kg/every other week. Patients received treatment until the analysis of the final primary efficacy and safety results in MOR-004, in order that the dose for part 2 could be determined. Part 2 is open-label and all patients are receiving elosulfase alfa 2mg/kg/week.<sup>2,4</sup> Unpublished results in the ITT and per protocol (PP) populations are available at the week 72 data cut off (3 September 2013). These are reported in the table below for patients who received elosulfase alfa 2mg/kg/week only.<sup>5</sup>

**Table: Results of MOR-005 study for patients treated with elosulfase alfa 2mg/kg/week<sup>5</sup>**

	Least squares mean change (95% confidence interval) from baseline (of MOR-004 study) to week 72*	
	ITT (n=58)	PP (n=52)
6MWT, metres	30.1; 95% CI: 12.6 to 47.6.	46.0; 95% CI: 27.4 to 64.6.
3MSCT, steps/minute	5.3; 95% CI: 2.3 to 8.2	6.6; 95% CI: 3.3 to 9.8.
Normalised urine keratan sulphate; %	-54%; 95% CI: -58% to -50%	-55%; 95% CI: -60% to -50%
MVV, %	7.2%; 95% CI: -0.7% to 15.1%	9.8%; 95% CI: 0.4% to 19.2%
FVC, %	8.2%; 95% CI: 4.2% to 12.1%	9.0%; 95% CI 4.3% to 13.8%

\*Analysed using ANCOVA model.

ITT=intention to treat, PP=per protocol, 6MWT=6-minute walking test, 3MSCT=3-minute stair climb test, MVV=maximum voluntary ventilation, FVC=forced vital capacity, CI=confidence interval.

Post hoc responder analysis of two domains, endurance (6MWT and 3MSCT) and pulmonary function (MVV and FVC) have been undertaken in the PP population in the cohort of patients who received elosulfase alfa 2mg/kg/week throughout MOR-004/005. At week 24 (baseline for MOR-005), the proportion of multi-domain responders was 67% (33/49), single domain responders was 31% (15/49) and no responders was 2.0% (1/49). At week 72, the proportion of multi-domain responders (improvements in endurance and pulmonary function) was 73% (24/33), and the proportion of single domain responders was 27% (9/33). In addition, a post hoc analysis of wheelchair use suggests that use did not appear to increase at week 72 compared to use at baseline.<sup>5</sup>

MOR-007 is an on-going phase II, open-label study in 15 patients with MPS IVA aged <5 years at the time of first infusion.<sup>6</sup> Patients were treated with elosulfase alfa 2mg/kg/week for 52 weeks. Mean age of patients was 3.1 years. The study's primary objective was to evaluate safety and tolerability of elosulfase alfa treatment in patients aged <5 years with MPS IVA, and secondary objectives were to assess growth velocity and reduction in urinary keratan sulphate levels. The mean increase in height from baseline to week 52 was 5.3cm (standard deviation 2.35), and the mean change was 5.9% (standard deviation 2.53). At week 52, the mean height z-score was -2.2 (standard deviation 1.7) compared to -3.1 (standard deviation 1.4) in an aged-matched untreated cohort from a natural history observational study (MOR-001<sup>7</sup>). The mean change from baseline in urine keratan sulphate was -44% (standard deviation 22.15) at 52 weeks in 10 patients.

## Summary of evidence on comparative safety

In MOR-004 the proportion of patients reporting any adverse event was 97% in the elosulfase alfa 2mg/kg/week group and 97% in the placebo group. Infusion-associated reactions occurred in 90% versus 92% of patients, and hypersensitivity adverse events in 21% versus 12% of patients in the elosulfase alfa 2mg/kg/week and placebo groups respectively. Most adverse events were classed as mild (48% versus 61%) or moderate (45% versus 34%). Study drug-related adverse events occurred in 72% versus 61% of patients in the elosulfase alfa 2mg/kg/week and placebo groups respectively. The proportion of patients treated with elosulfase alfa 2mg/kg/week who had an adverse event which led to infusion interruption/discontinuation requiring medical attention was 22%, although none withdrew or discontinued treatment due to an adverse event. In 1,345 infusions administered to patients in the elosulfase alfa 2mg/kg/week group, the proportion that were interrupted or discontinued and also required medical intervention was 1.3%.<sup>3</sup>

Serious adverse events occurred in 16% of patients in the elosulfase alfa 2mg/kg/week group and 3.4% of patients in the placebo group. Serious adverse events that occurred in the elosulfase alfa 2mg/kg/week group were: pneumonia (two patients [3.4%]), and hypersensitivity, infusion site pain, lower respiratory tract infection, otitis media, urticaria, viral upper respiratory tract infection and vomiting (one patient each). In the placebo group, serious adverse events were cervical cord compression and deafness (one patient each). In the elosulfase alfa 2mg/kg/week group, there were two serious adverse events considered by the investigator to be treatment-related with neither resulting in study discontinuation. These were a hypersensitivity reaction that resolved within 24 hours with symptomatic medical treatment and infusion discontinuation, and one case of severe vomiting that resolved the same day without medication.<sup>3</sup>

In the MOR-007 study safety and tolerability were similar to the MOR-004 study.<sup>6</sup>

## Summary of clinical effectiveness issues

Elosulfase alfa is the first medicine licensed for the treatment of MPS IVA, for which only supportive care is currently available; this includes medications (e.g. NSAIDs and oxygen) and surgical interventions. Most patients with rapidly progressive phenotypes of MPS IVA will live to their second or third decade of life only, although some patients will survive to 60 years. Cardio-respiratory or central nervous system complications (spinal/cervical cord compression) are the main causes of mortality. Mobility problems are common due to skeletal dysplasia, short stature, and joint abnormalities. In addition, respiratory problems, which manifest as dyspnoea and recurrent respiratory infections, may eventually result in respiratory failure. Other symptoms that patients with MPS IVA experience include hearing loss, cataracts, corneal clouding, and heart valve disease.<sup>2</sup> Elosulfase alfa has been designated an orphan medicine by the EMA and also meets SMC ultra-orphan criteria.<sup>2</sup> Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area as there are no therapies that treat the underlying disease and therefore considered elosulfase alfa to be a therapeutic advancement.

In the pivotal study, treatment with elosulfase alfa significantly increased the distance of the 6MWT by 22.5 metres from baseline (of 204m) to week 24, compared with placebo. This is less than an improvement of 40m, which the study was originally designed to detect. The 6MWT provides an indirect assessment of endurance and functionality, but does not provide a direct measure of the effect of treatment on survival.

The minimally clinically important difference (MCID) for the 6MWT in the MPS IVA population is unclear. The authors of the MOR-004 study publication commented that the baseline 6MWT in the study (210m) was lower than that reported for a chronic obstructive pulmonary disease (COPD) population (370m), where a MCID of 54m has been noted, and higher than in a Duchenne muscular dystrophy population (150m), where a MCID of 5.9m has been noted. The authors considered the MCID for MPS IVA should be within the values for the COPD and Duchenne muscular dystrophy populations. The EMA questioned whether clinically relevant differences in 6MWT can be expected in a study of 24 weeks duration. However no other single endpoint which would be more sensitive could be identified when the study was being designed.<sup>2,3</sup> Quality of life related to mobility was not significantly improved with elosulfase alfa treatment.

MOR-004 recruited patients based on genetic testing and the EMA considered this population to be comparable to the population expected to be treated in clinical practice. However, patients with a baseline 6MWT of <30m or >325m were excluded. Therefore the effects of elosulfase alfa in patients unable to walk or those with close to normal 6MWT distances are not known from this study.<sup>2,3</sup>

The submitting company noted that patients who received placebo in the MOR-004 study were not representative of those receiving supportive care in clinical practice as they attended weekly clinic visits and had regular assessments undertaken. The submitting company argued that data from the natural history observation study (MOR-001) are a better reflection of patients receiving supportive care. Data from a subgroup of patients from the MOR-001 study, considered to be matched to patients recruited to MOR-004 study in terms of inclusion criteria, are available. At two years follow-up, the LS mean change in 6MWT was -13.7m from a baseline of 207m.<sup>7</sup> This compares to an increase from baseline to week 24 of 13m for placebo-treated patients in the MOR-004 study.

The pivotal study was of 24 weeks duration, which is short given the life-long nature of the condition. Unpublished results of the extension study are available up to week 72. In a preliminary analysis of the extension study, treatment with elosulfase alfa resulted in significant differences at week 72 (from baseline of the MOR-004 study) in 6MWT, 3MSCT, normalised keratan sulphate and FVC.<sup>5</sup> MOR-004

is the largest placebo-controlled study of patients with MPS, a condition which is considered to have ultra-orphan status. However, long term efficacy and safety data for elosulfase alfa are limited and its effect on survival is unknown. A disease specific registry study for patients diagnosed with MPS IVA and treated with elosulfase alfa was requested by the EMA and is ongoing.<sup>2,8</sup>

The clinical experts consulted by SMC considered that the place in therapy of elosulfase alfa would be at any point following diagnosis of mucopolysaccharidosis, type IVA, although early initiation of treatment may be of most benefit. The introduction of elosulfase alfa is likely to have significant service implications, although the number of patients eligible for treatment will be small. Use of elosulfase alfa will necessitate weekly intravenous infusions which will have implications for patients and carers. Hypersensitivity adverse events occurred in 21% of patients treated with elosulfase alfa 2mg/kg/week in the pivotal study, although only 1.3% of infusions were interrupted or discontinued, requiring medical intervention.<sup>3</sup> Data from 13 patients who received home-based infusions administered by experienced nursing staff suggest that elosulfase alfa was well tolerated with no adverse events resulting in treatment discontinuation or requiring medical interventions.<sup>9</sup> The summary of product characteristics notes that administration of elosulfase alfa should be carried out by an appropriately trained healthcare professional with the ability to manage medical emergencies.<sup>1</sup>

There are limited data in patients less than 5 years of age. Longer treatment duration is required to confirm effect of elosulfase alfa on growth in these patients.

## Summary of patient and clinician engagement

A patient and clinician engagement (PACE) meeting with patient group representatives and a clinical specialist was held to consider the added value of elosulfase alfa, as an ultra orphan medicine, in the context of treatments currently available in NHS Scotland for treatment of mucopolysaccharidosis, type IVA (Morquio A Syndrome, MPS IVA) in patients of all ages.

The key points expressed by the group were:

- MPS IVA is a very rare, progressive inherited condition that has profound effects on many body systems and affects all areas of the lives of patients and their families. It is an utterly devastating diagnosis and average life expectancy is around 25 years.
- Patients suffer from pain, joint stiffness and fatigue. Knee and hip deformities are severe and are likely to lead to use of a wheelchair as the condition progresses. Children start to fall behind their peers in growth severely from about 3 years and stop growing altogether by 8 years old.
- There are currently no treatments for MPS IVA and there is large unmet need in a very small group of patients. Elosulfase alfa is a therapeutic advancement and is the first treatment that addresses the underlying cause of this progressive, incurable genetic condition.
- Elosulfase alfa can give considerable benefits in mobility, endurance and relief from pain and tiredness, enabling patients to maintain independent lives and to engage in all aspects of life. Stamina and energy of children has increased, and there has been evidence of continued growth with less pain and stiffness and wheelchair use was also reduced.
- PACE participants emphasised that the nature of the MOR-004 trial and its short duration did not fully capture the quality of life benefits that elosulfase alfa offered in terms of improved energy, mobility, endurance and relief of respiratory symptoms and pain. They acknowledged that published evidence is lacking and is short term. Clinical experts strongly considered the anecdotal

evidence to be a better reflection of benefit of elosulfase alfa than the clinical trial. There is a large spectrum of effects of this disorder affecting multiple organs which is difficult to assess in a short clinical trial with small numbers of patients.

- PACE participants considered the sum of anecdotal evidence discussed at PACE to be very strong and elosulfase alfa has transformed patients' lives. Without it, clinicians are simply monitoring the decline of patients.

## Summary of ultra-orphan decision-making framework

Elosulfase alfa has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines. Relevant factors under each of the criteria are summarised below:

### **Nature of condition**

Mucopolysaccharidosis type IVA is a very rare inherited lysosomal storage disease. There are currently 9 patients with this diagnosis in Scotland. Patients appear normal at birth but, in the early years of life, significant morbidities and multi-systemic clinical impairments develop. These result in increasing pain, fatigue, diminished functional capacity, decreased endurance and impaired quality of life as a patient gets older, leading to increasing dependence on a wheelchair. Patients with MPS IVA usually have early mortality by the age of 30 years.

### **Impact of new technology**

There is currently no approved treatment for MPS IVA other than palliative or supportive care, which does not treat the underlying cause of the disease so it continues to progress. Enzyme replacement therapy is an entirely new treatment option and elosulfase alfa is the first treatment licensed to treat MPS IVA. Elosulfase alfa is the first and only treatment that has the potential to alter the course of the disease.

Treatment with elosulfase alfa has been shown in the pivotal clinical study, to increase the 6MWT by 22.5 metres from baseline to week 24, compared with placebo. The 6MWT is an indirect measure of endurance and functionality. The minimally clinically important difference for the 6MWT in the MPS IVA population is unclear but no other single endpoint which would be more sensitive could be identified when the study was designed. Quality of life related to mobility in the trial was not significantly improved with elosulfase alfa.

At the PACE meeting, participants felt that limitations with the trial data in terms of duration and outcome measures meant that it did not fully capture the benefits to quality of life that elosulfase alfa could produce. The sum of the anecdotal evidence discussed at PACE was considered to be very strong and elosulfase alfa has transformed the lives of patients.

### **Value for money**

The submitting company presented a cost-utility analysis comparing elosulfase alfa to standard medical care. Standard care consisted of a range of treatments to address the symptoms and complications of MPS IVA e.g. orthopaedic surgery, pain management and treatment of infections. The comparator was appropriate given the range of treatment options currently available for patients. A lifetime horizon was used.

A Markov model was used with health states as follows: asymptomatic, no wheelchair use, sometimes using a wheelchair, wheelchair dependent, end stage disease (in a wheelchair and requiring mechanical ventilation) and death. At baseline, a cohort of patients of different ages, weights and stages of disease was modelled. 5% of patients were asymptomatic with an average age of zero, 48%

of patients were symptomatic but not using a wheelchair (average age of 12), 34% were sometimes using a wheelchair (average age of 17) and 13% were assumed to be wheelchair dependent and have an average age of 19. Patients were then assumed to move through the states on the model dependent on whether they received elosulfase alfa or not. Clinical data to drive the movement through the model were taken from a variety of sources. The key sources were the natural history MOR-001 study for the comparator arm, and the MOR-005 72 week open-label extension study for the elosulfase arm for the first cycle transitions in the model. The key data used from the MOR-005 study related to wheelchair use status and the single/multi-domain responder data. For later transitions in the model, progression was based on changes in 6MWT and FVC. Treatment with elosulfase alfa was assumed to affect progression in a variety of ways. Patients were assumed to have a five year delay in moving from the asymptomatic state to being symptomatic as well as reductions in wheelchair dependency. Patients who were multi-domain responders were assumed to have stabilisation of their disease, and single domain responders would have 6MWT decline at 50% of the rate of untreated patients. In the base case, all patients were assumed to respond to treatment and all patients were assumed to continue on treatment. Excess mortality was allowed for in the model by assuming that once patients reached the end stage disease state, death would occur within 2 years.

Utilities for each health state in the model were estimated from a published study in MPS IVA patients that presented quality of life values according to wheelchair use status. It was also assumed that patients treated with elosulfase alfa would have additional improvements in their symptoms which would result in additional gains in quality of life over and above the common utility value assumed for both arms of the model for each state in the model. The utility values were as follows: asymptomatic 1, no wheelchair use 0.846, sometimes using a wheelchair 0.582, wheelchair dependent 0.057 and end stage disease 0.024. A gain of 0.02 was also added for every 10m gain in 6MWT for elosulfase alfa patients.

Resource use related to the background disease management costs for each state in the model, administration costs for elosulfase alfa, and costs of surgery. These were estimated from a Delphi Panel of clinical experts. Treatment administration costs were included.

A patient access scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was offered on the price of the medicine.

With the PAS, and assuming the standard 3.5% discount rate applied to costs and benefits, the incremental cost-effectiveness ratio (ICER) was £829,870 based on an incremental cost of £8,242,197 and 9.91 incremental QALYs. Around 97% of the incremental cost related to the drug acquisition cost of elosulfase alfa. The vast majority of the QALY gain came from additional time spent in the 'no wheelchair' and 'sometimes wheelchair use' health states.

The results were most sensitive to the choice of discount rate, the utilities attached to the health states, patient weights, the use of a birth cohort, a 50 year time horizon and the use of a 5% progression rate for multi-domain responders (no progression assumed in base case). The relevant ICERs (with PAS, and 3.5% discount rate on costs and benefits) are shown below.

<b>Sensitivity analysis</b>	<b>ICER</b>
50 year time horizon	£870,282
5% progression rate assumed for multi-domain responders	£858,271
Use of a birth cohort (but note concerns about lack of increase in patient weight that might be assumed)	£686,704
No wheelchair weight (25.6kg)	£858,836
All patient weights varied simultaneously to upper case values	£872,100
Annual decline in 6MWT (no wheelchair use, 5.3m)	£856,346
Annual decline in 6MWT (sometimes wheelchair use,5.3m)	£867,443
Sometimes wheelchair utility (0.459)	£876,976
No wheelchair use utility (0.707)	£900,682
Wheelchair dependent utility (-0.165)	£807,173

The results were not sensitive to changes in costs of surgery, asymptomatic health state utility or assuming a 2 year delay to symptom development for asymptomatic patients. Using a societal perspective only reduced the ICER by a small amount to £822,265.

The base case cost per QALY results show a very high cost-effectiveness ratio. In addition, there were a number of weaknesses with the analysis:

- The clinical data driving the initial transitions in the model essentially rested on a naive indirect comparison from the extension study and the natural history study. Additionally, the extension study data were from the per protocol population, which may therefore be subject to some further bias. As such, there is some uncertainty associated with the outcomes of treatment in practice.
- The transition probabilities used after the first cycle of the model appeared to assume that the majority of patients on elosulfase alfa have their disease stabilised, and with repeated application of these transitions in subsequent cycles of the model, there is essentially a long-term maintenance of treatment effect throughout the model for the majority of patients. Given the lack of long term data on outcomes, this is a key source of uncertainty. The company asserted that this was reasonable given the 72 week results of the clinical studies and the patterns seen in other MPS disorders. However, given the lifetime horizon, this still seems optimistic given that such long term data on usage are not available. As the sensitivity analysis results show, changing the assumptions about the assumed rate of progression even by a small amount increased the ICER.
- It could be argued that the additional utility benefit applied for elosulfase alfa treatment may have double-counted some of the benefits of treatment; the source paper was structured around similar states as the model so should capture the benefits of being in these states if wheelchair use is a major determinant of quality of life. An analysis which removed the additional on-treatment gain in utility increased the base case ICER by 29%, or by 13% if the utility gain was reduced by 50%.
- The analysis may not fully reflect increasing patient weight over the duration of the model, which is important given the weight-based dosing regimen. While some account is taken of weight in that increasing weights are linked to successive health states of the model, patients receiving elosulfase alfa appeared to show little progress through the model, meaning that their weight would remain relatively stable over time, and this may result in an under-estimate of overall treatment costs for elosulfase alfa.
- The model appeared to assume that no patients were non-responders to elosulfase alfa, which may lack some plausibility in clinical practice.

Other data were also assessed but remain commercially confidential.\*

### **Patient and clinician engagement**

A Patient and Clinician Engagement (PACE) meeting was held for this submission. Participants at the PACE meeting indicated a range of potential impacts of the new technology for the patient and families/carers.

### **Impact beyond direct health benefits and on specialist services**

MPS IVA has a large impact on both the patient and family, beyond that described by the health outcomes measured. At the PACE meeting, the impact of the disease on patients and families was clearly highlighted, and the need to plan all activities around patients' care needs and their stamina. Patients and carers are often unable to work because of their caring activities. Younger patients may miss school because of clinic appointments and ill health, and older patients may not be able to stay in employment when their disability limits their functionality. Other costs that can be incurred by patients with MPS IVA, carers and families include costs of specialist lightweight wheelchairs, other specialist mobility equipment, travel costs to and from frequent hospital appointments, physiotherapy and hydrotherapy sessions, adaption of home and car and bespoke clothing and shoes (it is difficult to source adult appropriate clothing in children's sizes). At the PACE meeting, participants described evidence of continued growth of patients treated with elosulfase alfa. With treatment, patients suffer less isolation and can maintain a more active life. Reduced wheelchair reliance would relate to an increased independence for patients and less reliance on informal care.

Elosulfase alfa is administered by weekly infusions in hospital but PACE participants suggested it may be delivered at home in the longer term, as is the case for other enzyme replacement therapies.

### **Costs to NHS and Personal Social Services**

The submitting company has estimated that between 9 and 10 patients would be treated with elosulfase alfa per year and that this would be associated with a drug budget impact of £3.35m to £3.72m without the PAS.

The Committee also considered the benefits of elosulfase alfa in the context of the SMC decision modifiers and agreed that the criterion for the absence of other treatments of proven benefit was met. In addition, as elosulfase is an ultra-orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee was unable to accept elosulfase alfa for use in NHS Scotland.

## **Summary of patient and public involvement**

The following information reflects the views of the specified Patient Group.

- A submission was received from the Society for Mucopolysaccharide Diseases (MPS Society), which is a registered charity.
- The MPS Society has received pharmaceutical company funding in the past two years, including from the submitting company.
- MPS IVA is a rare incurable genetic condition. Babies with MPS IVA are born in the normal length and weight range but by 18 months they have dropped from the normal growth curve and usually stop growing altogether by the age of 8 years. The condition dramatically affects the lives of patients due to the bone and joint problems and chronic pain caused by the skeletal dysplasia and

severe fatigue caused by the normal size for age lungs, liver, spleen and heart being squeezed into the tiny abdominal and chest cavity. Most children are using a wheelchair some of the time by the age of ten. Average life expectancy is 25 years.

- There are currently no treatments for MPS IVA that address the underlying cause and patients are managed on best supportive care. This includes medicines such as NSAIDs for pain, and spinal and other surgeries.
- Elosulfase alfa is the first medicine to address the underlying cause of MPS IVA. There is evidence that it can increase patient's endurance and may slow disease progression. This gives patients and their families hope for a happier, healthier, less painful future.

## Additional information: guidelines and protocols

An international expert opinion guideline on the management and treatment of Morquio A syndrome was published in 2014.<sup>10</sup> The guideline is based on the outcomes of two industry sponsored meetings which brought together a multidisciplinary panel of clinical experts in the condition. Management advice consists mainly of symptomatic and supportive care for the multiple possible manifestations of the disease. Two systemic treatment options are also discussed:

### *Elosulfase alfa*

The guideline recommends that treatment with elosulfase alfa should be initiated immediately following a diagnosis of Morquio A.

### *Haematopoietic stem cell therapy (HSCT)*

The panel notes that there is currently insufficient clinical data to assess the efficacy of HSCT in the Morquio A patient population.

## Additional information: comparators

Supportive care.

## Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
<b>elosulfase alfa (&gt;5 years)<sup>‡</sup></b>	<b>2mg/kg intravenous infusion once per week</b>	<b>352,924</b>
<b>elosulfase alfa (2 to 5 years)<sup>‡</sup></b>	<b>2mg/kg intravenous infusion once per week</b>	<b>192,504</b>

Cost of elosulfase is from company's submission. Costs do not take any patient access schemes into consideration.

<sup>‡</sup> based on 27kg weight (mean weight in phase III matched cohort in MOR-001 study at 2 years follow-up)

<sup>‡</sup> based on 14kg weight (mean weight in MOR-007 study).

## Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 9 patients per year, rising to 10 patients in years 4 and 5. The company assumed all eligible patients would be treated.

### Without PAS

The impact on the medicines budget was estimated at £3.35m in year 1 and £3.72m in year 5. As there were no displaced medicines, the net medicines budget impact was the same. If the additional cost of treatment administration was included, the impact rose to £3.44m and £3.83m respectively.

*Other data were also assessed but remain commercially confidential.\**

## References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Elosulfase alfa 1mg/mL concentrate for solution for infusion (Vimizim<sup>®</sup>). Summary of product characteristics. BioMarin Europe Limited. European Medicines Agency [www.ema.europa.eu](http://www.ema.europa.eu). Last accessed 22.4.15
2. European Medicines Agency. European Public Assessment Report. Elosulfase alfa (Vimizim<sup>®</sup>). 20 February 2014. EMEA/H/C/002779/0000.
3. Hendriksz C, Burton B, Fleming 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. *J Inher Metab Dis*. 2014; 37:979-990
4. [www.clinicaltrials.gov](http://www.clinicaltrials.gov) [NCT01415427]
5. *Commercial in Confidence\**
6. Harmatz P, Jones S, Bialer M, et al. Safety and pharmacodynamic activity of elosulfase alfa in pediatric patients less than five years of age with Morquio A syndrome (mucopolysaccharidosis IVA). 2014. Poster presented as SSIEM Annual Symposium 2014 September 2-5, 2014 Innsbruck, Tyrol, Austria.
7. Harmatz, P.R., Mengel, K.E., Giugliani, R., et al. Longitudinal analysis of endurance and respiratory function from a natural history study of Morquio A Syndrome. *Molecular Genetics and Metabolism*. 2014; 114: 186-194.
8. [www.clinicaltrials.gov](http://www.clinicaltrials.gov) [NCT02294877]
9. Santra S, Hendriksz CJ, Vellodi A, et al. Safety of home treatment during a multicenter, open-label, extension study to evaluate the long-term efficacy and safety of elosulfase alfa in patients with mucopolysaccharidosis IVA (MPS IVA, Morquio A Syndrome). Poster presented at SSIEM Annual Symposium, September 2-5, 2014, Innsbruck, Austria.
10. Hendriksz CJ, Berger KI, Giugliani R et al. International guidelines for the management and treatment of Morquio A syndrome. *Am J Med Genet A*. 2015 Jan;167A(1).

This assessment is based on data submitted by the applicant company up to and including 12 June 2015.

*\*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: [http://www.scottishmedicines.org.uk/About\\_SMC/Policy\\_statements/Policy\\_Statements](http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements)*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

**Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*